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ICE salvage therapy with autologous PBSCT – a safety and effective therapy of patients with adult nephroblastoma and tumorprogression during adjuvant chemotherapy-a case report of a 40 years (y) old female

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Introduction: In the last decades, survival of children with nephroblastoma has dramatically improved through risk - adapted treatment stratification based on tumour stage and histology. Nephroblastoma in adults is a rare disease and diagnosed in advanced stage.
Patient and methods: During a routine check up in 12/07 a tumour on the right kidney was discovered in a 40 y old female. Suspicious for renal cell cancer, a laparoscopic nephrectomy was performed. Histology detected an adult type nephroblastoma pT3, pNx, M0, L1, V0, and the tumor was graded according to SIOP as intermedium risk, stage II, with R0 resection. In 02/08, adjuvant systemic therapy started according to the SIOP 2001/GPOH protocol with repeated applications of Vincristine in combination with either Doxorubicin or Actinomycine D for 28 weeks. Radiatio of the primary tumor area with 14, 4 Gy was performed from the 2nd week simultaneously to chemotherapy. The restaging examinations after completion of therapy revealed a metastasis in the chest wall (4 x 2,5 cm) and multiple pulmonary and bone metastases. Due to instability of BWK a laminectomy was performed. Immediately after the surgical procedure, salvage chemotherapy with ICE (Ifosfamide 3g/m2 d1-3, Carboplatin 200mg/m2 d1-3, Etoposide 100mg/m2 d1-3) was started. Peripheral stem cells were collected after the 2nd course. Restaging after 4 courses ICE revealed a completely regression of the chest wall metastasis, a partial regression of the bone metastases and two suspect new bone manifestations. In 03/09, an autologous PBSCT after conditioning with Melphalan, Carboplatin and Etoposide was performed without significant complications. A local radiatio of two active bone manifestations was performed in 04/09. After completion of this therapy, the patient had reached a clinical complete remission with no disease activity in the restaging examinations. Eleven months after the autologous PBSCT a rapid disease progression with multiple metastases was detected. Radiatio of the cerebral metastases and palliative chemotherapy with Trofosfamide were given without success and the patient died due to rapid disease progression in 04/10.
Conclusion: ICE salvage therapy followed by autologous PBSCT induced a complete remission in this refractory patient with progressive metastatic disease during adjuvant therapy.

Disclosure: No conflict of interest disclosed.

P229

Hepatotoxicity of 5-FU: a case report

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Introduction: We report the rare case of severe hepatotoxicity after neoadjuvant application of 5-fluorouracil (5-FU) in a patient with rectal adenocarcinoma.
The case: A 70 year old female patient was diagnosed with rectal adenocarcinoma (uT3, N+, M0) in July 2009. The patient had been treated for arterial hypertension, and a chronic renal insufficiency was known; there was no prior history of any liver abnormalities. The patient received preoperative radiotherapy (50,4 Gy) and 2 cycles of 5-FU. Dihydropyrimidine dehydrogenase (DPD)- insufficiency was excluded prior to chemotherapy. The first cycle of 5-FU was administered with 1000 mg/sqm (8100 mg/5 days), the second cycle was started on day 29 with a dose reduction to 80% (6400 mg/5 days) due to mucositis after the first cycle. Four weeks later the patient was admitted to the hospital due to a painless icterus and itching of the whole body. The patient had received no other drugs during this period, except her daily medication for arterial hypertension.
Results: Parameters of cholestasis and transaminases were elevated (bilirubin 7.2 mg/dl, AP 499 U/l, GGT 696 U/l, ALT 236 U/l). Abdominal ultrasound showed cholecystolithiasis. ERCP revealed no intra- or extrahepatic cholestasis; a papillotomy was performed for initially suspected papillary stenosis. Cholestasis parameters and transaminases further increased during the following nine days (bilirubin 17.2 mg/dl, direct bilirubin 15.2 mg/dl, AP 981 U/l, GGT 1073 U/l, ALT 142 U/l) without a significant reduction of liver synthetic function. MRT/MRCP scan of the liver showed no significant findings. Viral and autoimmune hepatitis were excluded by serologic testing. Liver biopsy showed portal hepatitis and cholangitis probably due to drug toxicity. The acute hepatitis subsided over a period of four months, but AP (502 U/l) and GGT (626 U/l) were still elevated. A second liver biopsy two months later confirmed the initial histological findings with reduced inflammatory changes. Tumor resection was performed 11 weeks after the onset of acute hepatitis (pT2, pN1, M0, R0, Grade 2). No postoperative chemotherapy was administered. Follow-up up to four months after resection showed no tumor recurrence.
Conclusion: After exclusion of other etiologies and because of histology results, we conclude that the acute icteric hepatitis was caused by treatment with 5-FU. Regular monitoring of liver function tests during and after 5-FU therapy is therefore recommended.

Disclosure: No conflict of interest disclosed.

Posterdiskussion

Infektiologie

P230

Late arterial CT is superior to the portal venous CT for initial diagnosis and follow-up of hepatic candidiasis during the treatment of acute leukemia

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Background: Hepatic candidiasis is a frequent complication in patients receiving intensive chemotherapy for acute leukemia. Hepatic lesions can be detected by computerized tomographic (CT) scans, but there is no standardized CT protocol for the diagnosis and follow-up of hepatic candidiasis.
Methods: We retrospectively analyzed the number and the volume of hepatic fungal lesions in 24 thoraco-abdominal CT of 20 consecutive patients treated for acute leukemia during late arterial phase (chest-CT) and portal venous phase (abdomen-CT).
Results: The mean number of lesions per patient was 31 (3-105) in the late arterial and 26 (3-81) in the portal venous CT (p=0.026). The mean total volume of all lesions was 6.45 mL in the late arterial and 4.07 mL in the portal venous CT representing a 1.6-fold difference between the two CT scans (p=0.008). The total volume of the lesions negatively correlated to the absolute contrast difference between liver parenchyma and liver vein (Pearson correlation, r=-0.62; p=0.002).
Conclusion: The chest-CT provides a superior distinction of hepatic lesions due to a delayed perfusion of the outer rim of the fungal lesions resulting in an extended visibility. The chest-CT is superior to the abdomen-CT for initial diagnosis and follow-up of hepatic candidiasis.

Disclosure: No conflict of interest disclosed.

P231

In vitro interaction of human natural killer NK cells with *Aspergillus fumigatus*

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Introduction: Invasive Aspergillosis (IA) is a major cause of morbidity and mortality in patients with haematological malignancies. Aspergillus fumigatus (AF) is the most common cause of this disease. Effector cells of the innate immune system, like the alveolar macrophages and the neutrophils provide the first line of host defense against AF invasion. In our study, we investigated the possible interaction of AF with another potent component of the innate immunity, the Natural Killer (NK) cells.
Methods: Human NK cells were isolated after magnetic depletion of the peripheral blood of volunteers and were used after 24h priming with 500 U/ml recombinant human interleukin 2, rhIL2. Interferon gamma (IFN-g) and Tumor Necrosis Factor- alpha (TNF-a) regulation were assessed after NK- AF co-culture. Fungal damage was investigated via plate killing and XTT assays. To explore the influence of rhIL2 on NK cells, experiments were performed with resting and primed NK cells. Transwell permeable membranes, NK cell granule depletion (treatment with strontium chloride), calcium chelating (treatment with EGTA), surface expression of degranulation markers CD107a/b and neutralization of NK death ligands (TNF- related apoptosis- inducing ligand [TRAIL] and FasL) by blocking antibodies were used to evaluate the means of this interaction.
Results: AF induced towards NK cells a Th1-like immune response with up-regulation of IFN-g and TNF-a ($p< 0.05$). NK cells displayed strong fungicidal effects against AF germlings ($p< 0.05$), but were inactive against conidia. Priming with rhIL2 ($p< 0.05$) and direct effector-pathogen contact ($p< 0.001$) were required for this interaction. Cytotoxicity was mediated at least by a soluble factor, which was not contained in the NK cell granules. Cytotoxicity was also not attributed to the engagement of NK cell death ligands.
Conclusions: Human NK cells are stimulated *in vitro* only by AF germinated morphologies, triggering a Th1-like immune response and causing significant fungal damage. Prerequisites for this interaction are the priming of NK cells with rhIL2 and the direct contact between NK cells and the fungus. Interestingly, NK cells mediate their cytotoxic effect via a soluble factor, other than perforin and granzymes, suggesting an alternative pathway to be involved in the NK cell - AF interplay.

Disclosure: No conflict of interest disclosed.

P232

Intracellular concentrations of echinocandins in different compartments of the peripheral blood

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Introduction: While serum and plasma concentrations of antifungal drugs are usually measured during routine therapeutic drug monitoring, little is known about the concentrations in other compartments of the peripheral blood, i.e. peripheral blood mononuclear cells (PBMCs), polymorphonuclear leucocytes (PMNs), and red blood cells (RBCs). Interactions with these cells might well influence the efficacy of antifungal drugs. We developed a method to quantitate most clinically relevant antifungal drugs in different compartments of the peripheral blood and recently presented data showing that the intracellular concentration of posaconazole (PSC) in PBMCs and PMNs was significantly increased compared to the plasma concentrations. Based on the same method we also determine the intracellular concentrations of anidulafungin (ANF), caspofungin (CAS), micafungin (MCF), and voriconazole (VRC).
Methods: We developed a liquid chromatography tandem mass spectroscopy (LC-MS/MS) assay allowing the quantitation of ANF, CAS, isavuconazole (ISC), MCF, PSC, and VRC in different compartments of the peripheral blood. The lower limits of quantitation [ng/mL] were: ANF 64, CAS 108, ISC 4.5, MCF 160, PSC 10, and VRC 4.2. Samples: Whole blood from patients receiving antifungal treatment was collected in two EDTA salt containing tubes (2x8 mL). The blood was separated by double discontinuous Ficoll Hypaque density gradient centrifugation. The cells were extracted with acetonitrile containing internal standard by sonication, vortexing and centrifugation.
Results: Data on the intracellular concentrations of echinocandins is pending. Preliminary data suggests that the intracellular concentrations of CAS (PMN 71.1 µg/mL, PBMC 29.7 µg/mL) and MCF (PMN 7.8 µg/mL, PBMC 14.1 µg/mL) are increased compared to the plasma concentrations (CAS 16.2 µg/mL, MCF 2.9 µg/mL). However, the magnitude seems to be less than for PSC.
Conclusion: We established a method to determine the concentration of azole and echinocandin antifungals within one sample and in different compartment of the peripheral blood and we present data on the intracellular concentrations of those drugs.

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P233

Epidemiology of bacterial blood stream infections in hemato-oncological patients before and after introduction of quinolone prophylaxis

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Objectives: Empiric antibiosis is a common strategy and often necessary, especially for patients with fever in neutropenia. The choice of antimicrobial agents depends on the expected spectrum of possible causal microorganism. Introduction of antibiotic prophylaxis might have an influence on rate of blood stream infections but also on distribution of bacterial species. Here we investigate the bacterial epidemiology before and after the introduction of quinolone prophylaxis.
Methods: In this single center retrospective study we analyzed all blood stream infections between January 2003 and June 2009 from patients hospitalized at our hemato-oncological department (without stem cell unit). Number of positive blood cultures and strains were extracted from the microbiological database. Positive specimens with an identical differentiation from the same patient were counted once within 30 day.
Results: From 2003 to June 2009 there have been 109 to 138 bacteremias per year and in total 794 blood stream infections in 11698 hospitalizations. Rate of gram positive strains have been 57,6% for 2003, 52,5 for 2004, 62,3% for 2005, 72,5% for 2006, 59,6 for 2007, 67,2% for 2008 and 72,4% in the first half of 2009. *Stapholoccous aureus*, coagulase negative staphylococci and *Escherichia coli* have been the most often isolated bacteria accounting for a range of 1,3% to 8,5% (*Staph. aureus*),28,8% to 52,6% (coagulase negative staphylococci) and 9,2% to 20,8% (*E. coli*) of blood stream infections.
Conclusions: Introduction of levofloxacin had no significant impact on general bacterial epidemiology and rate of gram positive or negative blood stream infections. Further differentiation of patient population and a longer period of investigations might be necessary.

Disclosure: No conflict of interest disclosed.

P234

Results from an observational study on primary prophylaxis of invasive fungal disease with posaconazole in patients with acute myelogenous leukemia

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Introduction: Patients with acute myelogenous leukemia (AML) and neutropenia after chemotherapy are at high risk of getting a life-threatening invasive fungal disease (IFD). The aim of the study was to provide real-life data on characteristics, risk factors, complications and additional antifungal treatment of AML patients receiving posaconazole prophylaxis (PP) after chemotherapy in a clinical setting.
Methods: A retrospective single-center observational study on primary prophylaxis in 40 AML patients was conducted at a German university hospital. Data were abstracted over a two-year period (12/2006 to 1/2009). PP 200mg three times daily was given routinely.
Results: After 76 cycles of remission induction chemotherapy followed by PP (median duration: 31 days, range 6 to 61 days), no fatal case occurred. In the majority of cycles (93%) patients had at least one additional risk factor for IFD, during 61 cycles (80%) three or more risk factors were present. Fever of unknown origin occurred during 40 therapy cycles (53%). After eleven cycles sepsis occurred (13%). Pneumonia was diagnosed after 23 cycles (30%), thereof 13 cases of probable IFD (17%) and one case of proven IA (1%). PP was interrupted in a total of 25 cycles (33%) and was followed by systemic antimycotic therapy, median duration 15 days (range 6 to 32 days). Monotherapy was given in 17 cycles, sequential therapy in six cycles and combination therapy in two cycles.
Conclusions: PP appears to be an effective and well tolerated protection against IFD for AML patients under real-life conditions. Further research is desirable to demonstrate the effectiveness of PP in comparison to other prophylactic treatment regimens.

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Anthony D. Ho: No conflict of interest disclosed.

P235

Efficacy and toxicity of amphotericin B lipid complex as prophylaxis of invasive fungal infections in patients after allogenic stem cell transplantion

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Prophylaxis of invasive fungal infections (IFI) in patients after allogenic stem cell transplantation (SCT) is indispensable. However, there is discussion about the optimal drug choice.
Adult patients after allogenic SCT received antifungal prophylaxis with amphotericin B lipid complex (ABLC) at a dose of 1mg/kg once daily, if they were unable to take oral prophylaxis with a triazole antifungal drug. In a retrospective analysis, efficacy and toxicity were evaluated.
A total of 103 patients received ABLC prophylaxis for a median of 9 days (range: 1-30 days). In 24 patients (23%) ABLC had to be discontinued after a mean of 6 days (range: 1-20 days) because of infusion related acute side effects (mainly fever and/or chills), despite premedication with an antihistamine ± acetaminophen. In a subgroup of patients who received ABLC at least 7 days (n=60), nephrotoxicity and efficacy were analysed: In 14 patients (23%) serum creatinine increased under treatment with ABLC to levels ≥ 2-times higher compared to baseline. Patients receiving ≥ 5 nephrotoxic drugs concomitantly, had significantly higher risk for impaired renal function according to Bearman's criteria: creatinine in normal range 66.7 (< 5 other nephrotoxic drugs) vs. 40.7% (≥ 5 nephrotoxic drugs), p=0.04. Regarding efficacy, 13 patients (22%) fulfilled the EORTC-criteria for IFI (proven: n=2, probable: n=4, possible: n=7).
Regarding efficacy and nephrotoxicity, our results are in good accordance with the results of other studies using different amphotericin lipid formulations or prophylaxis with azoles. However, to our opinion the high rate of infusion related acute side effects makes ABLC only the drug of second choice for antifungal prophylaxis in high risk patients

Disclosure: No conflict of interest disclosed.

P236

Delayed-onset neutropenia due to parvovirus B19 in a patient treated with rituximab

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Introduction: Delayed-onset neutropenia is a known complication after rituximab treatment and affected patients are prone to develop severe infections. Parvovirus B19 infection has been described as the causative agent for neutropenia. Diagnosis of acute and persistent parvovirus B19-infection is usually made by detection of parvovirus B19 DNA in the peripheral blood. Treatment of neutropenia is limited to symptomatic therapy and, if persistent, by administering granulocyte-colony-stimulating-factor (G-CSF).
Case report: A 64 year old woman diagnosed with diffuse large B-cell lymphoma was treated with rituximab-combined chemotherapy (6x R-CHOP 14 + 2x Rituximab). After completion of treatment she developed a delayed-onset neutropenia. Bone marrow examination excluded recurrence of lymphoma or therapy-associated myelodysplasia. PCR amplification for nucleic acid sequences of several viruses revealed an isolated bone marrow infection with parvovirus B19. Because of persistent G-CSF refractory neutropenia and recurrent severe infections with need of broad-spectrum anti-infectious therapy intravenous immunoglobulins were administered to treat the parvovirus B19-infection. Within days a dramatic neutrophil recovery was observed and filgrastim treatment could be stopped. The patient subsequently had normal peripheral white blood cell count, parvovirus B19 genomes could not be amplified in a control biopsy of the bone marrow.
Conclusion: It is important to consider that parvovirus B19 in bone marrow cells is a possible reason for delayed-onset neutropenia in patients treated with rituximab-combined chemotherapy. Therefore, PCR-testing for parvovirus B19 should be performed in the bone marrow, since the infection can successfully be treated by immunoglobulins as demonstrated in this case.

Disclosure: No conflict of interest disclosed.

P237

Comparison of caspofungin versus liposomal amphotericin B as antifungal prophylaxis following allogeneic hematopoietic stem cell transplantation in paediatric patients

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Introduction: Paediatric patients undergoing hematopoietic stem cell transplantation (HSCT) are at high risk of acquiring fungal infections due to extensive immunosuppression. Paediatric patients (< 18 years) often receive empirical antifungal prophylaxis with liposomal amphotericin B after allogeneic HSCT. Caspofungin could be an effective alternative antifungal prophylaxis with reduced nephrotoxicity.
Design and methods: In a retrospective single center trial, we assessed safety, feasibility and efficacy of liposomal amphotericin B in comparison with caspofungin as primary antifungal prophylaxis immediately after allogeneic HSCT in pediatric patients (< 18 years).
Results: The fifty paediatric patients who received caspofungin as antifungal prophylaxis for a median of 24.5 days after allogeneic HSCT and the seventy paediatric patients who received liposomal amphotericin B as antifungal pro-

phylaxis for a median duration of 23 days after HSCT, experienced no proven breakthrough fungal infections. One (1.4%) of the seventy paediatric patients in the liposomal amphotericin B group had a probable invasive fungal infection with candida during therapy, and seven (10%) had a possible invasive fungal infection (7% aspergillosis, 3% candidiasis). In the caspofungin group, no patient had a probable invasive fungal infection and seven patients (14%) had a possible invasive fungal infection, all of which candidoses. During the observation period, there was an significant increase in aspartat-aminotransferase, alanin-aminotransferase, gamma-glutamyl-transferase, creatinin, urea, and a significant decrease of potassium. In the patient group that received antimycotic prophylaxis after allogeneic HSCT with liposomal amphotericin B, patients additionally experienced a significant increase in bilirubin. At the end of the intravenous antimycotic prophylaxis, the phosphate and potassium requirement was higher in the liposomal amphotericin B group than in the caspofungin group.
Interpretation and Conclusion: Caspofungin is an effective antifungal monoprophylaxis after allogeneic HSCT in paediatric patients with the same efficacy as liposomal amphotericin B.

Disclosure: No conflict of interest disclosed.

P238

Use of systemic antifungal agents in patients with acute leukemia: a prospective analysis covering clinical parameters, side effects, drug interactions and costs

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Introduction: Invasive mycoses show high morbidity and mortality rates among immunocompromised patients (pts), and have multiplied the use of systemic antifungal drugs (SAD). This challenges physicians, as various drug-related aspects have to be considered and medication costs have enlarged. As side by side comparisons in unselected high-risk pts with different SAD are lacking, we prospectively analysed the frequency, clinical relevance and severity of SAD-related problems in consecutive pre- and acute leukemic pts, a ´typical´, rather than highly-selected study cohort, in order to improve the efficacy and safety of SAD treatment.
Methods: SAD-analysis was performed by daily participation on ward rounds, consultation of ward physicians and review of pts´ medication charts and laboratory values. Pt characteristics, development of kidney- and liver toxicity, potential drug interactions (DI), treatment outcome and costs were assessed. SAD were given according to EORTC guidelines.
Results: Currently, data from 71 consecutive pts have been obtained (AML n=48, ALL n=16, MDS n=7) with a median age of 57 years (range 19-75). Administered SAD included fluconazole (n=39), liposomal amphotericin B (amb, n=27), voriconazole (n=19), posaconazole (pos, n=17), and caspofungin (cas, n=9). The frequency of 1, 2 or 3-5 SAD regimens/pt was 41, 20 and 10, respectively, with SAD combination therapy rarely being applied (3%). Pts with initial leukemia diagnosis (n=52) vs. at relapse (n=19) received more than one subsequent SAD in 34% vs. 63%, respectively. The importance of detailed DI analyses was stressed with substantial number of concomitantly administered medications (median 20; range 1-50). Organ function deterioration by means of eGFR decline, comparing median eGFR values with SAD-initiation vs. after SAD-medication-end, revealed a considerable eGFR decrease of 15.4% for amb, whereas cas and azole SAD had no major effects on renal function. In 2009, SAD accounted for 20% of our department´s inpatient drug expenses, including chemotherapeutics. Additionally, we are further optimizing our previously published HPLC method for the serum quantification of pos [Neubauer W. J Chromatogr B 2009], in order to obtain more information about pharmacokinetics of this increasingly used drug in high-risk pts.
Conclusions: This ongoing project suggests to valuably contribute to a safe, efficient and economically appropriate SAD use. Subsequent data will be presented at the meeting.

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P239

Use of tigecycline in patients (pts) with neutropenic hematological diseases or hematopoietic stem cell transplantation (HSCT)

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Introduction: Tigecycline is the first antibiotic in the class of glycylcyclines and is approved for the treatment of intraabdominal infections and complicated skin and soft tissue infections in adults. However, its efficacy and safety profile in immunocompromised pts is largely unknown.
Methods: We retrospectively evaluated the use of tigecycline at our center. Demographic, microbiological data, indications for tigecycline and outcomes were analysed.
Results: Overall, 29 pts treated with tigecycline for 3 - 43 days (median 10) were identified. Underlying conditions included allogeneic (13) or autologous (3) HSCT, hematological malignancies (12) and aplastic anemia (1). The indications for use of tigecycline were pneumonia (n=11), fever of unknown origin (n= 10), soft tissue infections (n=2), sinusitis (n=2), cholecystitis (n=1), urinary tract infection (n=1) and central venous line infection (n=1). At initiation of tigecyclin treatment, 18 pts had neutropenia (WBC< 1.5/nL). Except for a single pt, all pts had previously received antibiotics consisting of glycopeptide or clindamycin (18), carbapenems (17), aminoglycosides (10), broad-spectrum beta-lactams (9), quinolones (5) and daptomycin (1). Antifungal agents had previously been administered in 24 pts. Isolates were recovered from 18 pts, including gram +ve bacteria (12), gram -ve bacteria (5) and *C. tropicalis* (1). Susceptibility testing was available for 15 bacterial isolates. Except for a single *S. maltophilia* strain, all tested isolates showed in vitro susceptibility to tigecycline. Overall, 22 (76%) of 29 pts achieved defervescence within a median of 5 days. Three pts were afebrile at baseline, but showed a 50% reduction of the C-reactive protein. The remaining 4 pts had persistent fever despite tigecycline therapy with equivocal variations of the C-reactive protein. Tigecycline was well tolerated and no toxicities attributable to tigecycline were recorded.
Conclusions: Persistent infections in heavily pre-treated, immunocompromised patients remain a challenge for clinicians. In our series of pts, tigecycline has shown excellent tolerability and promising efficacy. Thus, future studies should explore the use of tigecycline in this particular subgroup of patients.

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P240

Meningoencephalitis and sepsis caused by *Listeria monocytogenes* after consumption of contaminated cheese in a patient with lymphoplasmacytic lymphoma

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Introduction: Listeriosis is a relatively rare bacterial infection caused by the grampositive, motile bacteria *Listeria monocytogenes*. It occurs mainly in newborn infants, elderly and immunocompromised patients. Here we present

a case of meningoencephalitis and sepsis caused by *Listeria monocytogenes* in a patient with lymphoplasmacytic lymphoma.
Case: A 57 year old female patient was diagnosed with stage IV lymphoplasmacytic lymphoma in July 2009. She underwent six courses of immunochemotherapy with rituximab, fludarabine and cyclophosphamide until January 2010 and reached a good partial remission. Two weeks after the last chemotherapy cycle she presented to the emergency room with fever, diarrhea and headaches. Clinical examination revealed dehydration, hypotension, cognitive deceleration and poor performance status with no sign of menigism or focal neurological symptoms. Lab results showed elevated inflammatory parameters and creatinine but no neutropenia. After microbiological sampling of blood, urine and stool an antibiotic therapy with piperacilline/tazobactam and intravenous rehydration was started. A cranial computertomography showed no abnormalities. A lumbal puncture was performed and cloudy spinal fluid was drawn which demonstrated leucocytosis of 1640 Mpt/l, the gram stain of the spinal fluid showed no bacteria possibly due to the ongoing antibiotic treatment. Meanwhile *Listeria monocytogenes* was cultured from the blood. The antibiotic therapy was changed to ampicillin and gentamycine according to the resistogram. Further radiological diagnosis showed liver abscesses as a sign of hematogenic spreading. The patient reported consumption of a raw milk cheese brand which had already caused several infections and deaths in Austria and Germany. After three weeks of intravenous antibiotic treatment the patient could be discharged fully recovered.
Discussion: Listeriosis is a rare and usually symptomless or mild infection in humans. In immunocompromised patients however it can be a lifethreatening condition especially when meningoencephalitis or sepsis occur. Early detection and antibiotic treatment are essential. As the main route of a acquisition is through the ingestion of contaminated food as raw milk products, patients at risk should be advised to avoid these aliment.

Disclosure: No conflict of interest disclosed.

P241
HEXA*FIL*: Non-interventional study for supportive treatment of chemotherapy induced neutopenia with Filgrastim HEXAL®

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Background: Chemotherapy induced neutropenia (CIN) are common complications in the course of systemic antineoplastic chemotherapy of different tumour entities. For the development of CIN, different factors are held responsible for. The human Granulocyte-Stimulating Factor (G-CSF) is a peptide hormone and haematopoietic growth factor that promotes the proliferation and differentiation of progenitor cells into mature neutrophils. The collection of data from intended use of the biosimilar Figrastim HEXAL® will allow for a more comprehensive data collection of efficacy and safety of Filgrastim HEXAL®.
Methods: Planned patient enrolment is 500 patients within 6 months at 100 study centres in Germany. Patient data will be documented for up to 3 consecutive chemotherapeutic cycles supported by Filgrastim-HEXAL®. Patients complete a questionnaire focussing on common G-CSF related adverse events, assessment of self-administration of Filgrastim HEXAL® (s.c.) and handling of the innovative needle protection system. In addition to efficacy and safety data, oncological data sets and comorbidity scores will be correlated to supportive G-CSF therapy. Patient's individual risk to develop neutropenia and intention of G-CSF treatment will be valuated by the investigator before start of supportive therapy. An overall rating for efficacy and tolerability of Filgrastim-HEXAL® will be documented by investigators. Inclusion Criteria: Patients undergoing antineoplastic therapy and that are treated either prophylactically or interventionally with Filgrastim HEXAL® in case of emerging neutropenia; Male and female patients at least 18 years old; signed informed consent. Exclusion criteria: Contraindication according to SmPC Filgrastim HEXAL®; patients who have been treated with G-CSF in the current line of chemotherapy treatment (details see http://register.germanctr.de).
Results: The study started in 01/2010. Until 04/2010 about 80 patients were enrolled. The interim analysis (intended no. of patients: 300) focusses on Filgrastim-HEXAL® dosing schemes, duration of treatment necessary to support systemic chemotherapies, safety profile of Filgrastim-HEXAL® and self application and handling of the injection needle featuring a protection system.
Conclusion: The systematic collection of data from the intended use of biosimilar Figrastim HEXAL® combined with data gained from patient questionnaires will allow for a comprehensive data collection of efficacy and safety of Filgrastim HEXAL®.

Disclosure: Hans Tesch: Employment or Leadership Position: Niedergelassener Onkologe in der Onkologischen Gemeinschaftspraxis am Bethanien-Krankenhaus; Advisory Role: Sanofi Aventis, Roche Pharma AG, Novartis, Glaxo Smith Kline, Pfizer, HEXAL; Honoraria: Honorare von u.a. Sanofi Aventis, Roche Pharma AG, Novartis, Glaxo Smith Kline, Pfizer, HEXAL
Ulrike Hartmann: Employment or Leadership Position: Angestellte der HEXAL AG; Stock Ownership: Amgen, Novartis, Takeda, Teva, PharmaFond; Expert Testimony: Keine extern von HEXAL

Posterdiskussion
Querschnittsthemen

P242
Bridging theory and therapeutic practice: From generalized disease models to particular patients

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Introduction: The traditional problem of the poor presentability as well as diagnostic and therapeutic practicability of individual patient care is still unresolved.
Methods: Biomodulatory therapies for metastatic tumors bring transparency into tumor systems by breaking into a tumor's holistic communicative world, and by dissecting the tumor for practical purposes, such as attenuation of tumor growth, in comprehensible evolutionary processes.
Results: Biomdulatory therapies show that the holistic communicative structures of a tumor are now an experimentally and therapeutically accessible entity: Communication within systems - which is self-content to some degree - works with the implicit understanding that (1) the validity and denotation of particular systems objects (proteins, cells etc.) is always context-dependent, (2) the validity and denotation of the systems objects may be therapeutically redeemed by systems-immanent communication rules, which are determined by descriptively accessible communicative systems textures including intersystemic exchange processes. The difference between theory and practice may be decisively attenuated (1) by giving reductionistically derived systems features an internal communicative context (formal-pragmatic communication theory), (2) by introducing a novel and scientifically accessible perspective, i.e. the tumor's 'living world', which is defined as a tumor's holistic communicative world, and (3) finally by binding the systems features to tumor-immanent evolutionary processes (modularity of biochemical and cellular processes, rationalization of tumor functions).
Conclusion: The newly discovered tumor-associated systems architectures, which are built on the capability of tumor systems to modularly rearrange the validity and denotation of systems objects, clearly differ from the reductionistically derived systems comprehension:
1) Communicatively-derived systems structures offer new insights into evolutionary processes, promoting tumor development and expansion into the 'metabolism' of tumor evolution.
2) Based on the perception of a systems participator, we ultimately leave behind typical reductionistically derived teleological systems features.
3) Both, reductionist and holistic understanding are exerted to reproduce a situational stage of tumor disease: Differential perspectives of therapeutic interaction are entangled with various levels of knowledge and consecutively with different therapy strategies.

Disclosure: No conflict of interest disclosed.

P243

Budgeting staff costs to conduct a clinical trial at the site

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Introduction: A crucial aspect in managing a clinical trials unit (CTU) is adequate reimbursement of staff costs. CTU have to pre-estimate costs in advance of the trial for financial negotiations. Underestimation of costs leads to insufficient financing. In the course of the trial this causes lack in motivation of the study team affecting data-quality and recruitment efforts. It involves delay in overall recruitment, postponement of timelines and higher costs for the overall study.
Methods: On the basis of MS Excel© we created an instrument to structure the tasks for a trial and define expenditures of time. We established a task-group of physicians and study nurses from different departments of the University Hospital Cologne to ensure the versatile applicability of the calculation tool.
The bases for calculation comprise the number of patients, duration of the study and the expected general condition of the patients to be enrolled, with that setting the number of adverse events and changes in medication and therefore time for documentation. The detailed description of tasks is divided in one-time costs, costs per patient and continuous costs. One-time costs for initiation and close-out of the trial sum up to a start-up fee. Costs associated with study visits are grouped to screening and baseline visits, visits during intervention- and follow-up-phase. These costs are reimbursed on a per-patient basis. Time expenditures are defined for the list of required tasks (e.g. ECG, blood sampling). Continuous tasks depend on trial duration. Required costs for the overall duration are distributed to all visit-fees as a surcharge.
The tool was tested and refined for several month by the task-group. Afterwards round robin tests were performed by several physicians and research nurses to ensure the sensitivity and practicality of the tool.
Results: Use of the tool requires an initial instruction. Information to be entered has to be collected from experienced study nurses, investigators specialized in the specific treatment of the trial and the sponsor. The calculated sums can be reallocated according to negotiations.
Conclusions: The calculation tool provides CTU with reference values for required fees to conduct a clinical trial. Negotiations are facilitated and adequate reimbursement is ensured.

Disclosure: No conflict of interest disclosed.

P244

Promise and potential with 'Chemo-AS', the department´s electronic chemotherapy (CTx) ordering and prescription system (eCOP), based on the 'Blue Book' ('Das Blaue Buch'/BB), generates CTx-orders and – charts and efficiently avoids CTx errors in cancer patients (pts)

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Introduction: Our standardized CTx manual (BB) contains >300 CTx-protocols, is updated daily and used extensively within our university. Chemo-AS is an eCOP-system, programmed by our IT-specialists´ in cooperation with the CIO team, that includes all BB-protocols, allows correct CTx-ordering and generation of CTx-charts.
Methods & results: Chemo-AS is a web-based database application, written in PHP and running on the apache web server and SAP MaxDB database. For CTx-orders, the ward physician uses this ordering system by a web browser. The CTx-order form is stored as a HTML document on the server and is sent automatically by E-mail or fax to the CIO and pharmacy. Upon receipt, a clinical accuracy check is performed simutaneously by both teams. If any error is detected, this is immediately reported to the ward physician and instantly corrected via eCOP. If the CTx-order is entirely flawless, the CIO creates a detailed, pt-individual treatment schedule through Chemo-AS, using a pre-planned scheme which is available for each CTx protocol. These templates are generated in our database through a protocol editor module. Immediately after any order has been transformed into an exact CTx schedule, this pt-specific plan is sent through the network printer onto the ward. The ward physicians acknowledge this CTx plan for each pt with their signature on the print-outs. Only then, the prescription is regarded ready for application. Using our CTx database, basic pt demographics can also be generated through the hospital´s central clinical information system via the HL7 protocol. In a prospective study of consecutive cancer pts who received CTxs in our department between 1/2005 and 12/2006, 22,216 CTx orders were analysed, of which 83.5% were completely error free, whereas detected and corrected medical and administrative errors were observed in 17.1%: in 3.8%, these errors involved the CTx itself, in 4.5% pt data, and in 8.7% missing written informed consent forms. CTx errors - with implementation of Chemo-AS - were effectively reduced from 4.2% in 2005 to 3.6% in 2006, and to 1.9% in 2007. Of note, due to Chemo-AS and our CIO-team, errors were avoided in >99.9% (Markert A et al. Int J Cancer 124:722-728, 2009).
Conclusions: We identified our surveillance system as an important safety check, thereby ensuring that CTxs are delivered error-free. We recommend this efficient control system to other institutions that administer CTxs to cancer pts.

Disclosure: No conflict of interest disclosed.

P245

The organization, structure and support of clinical trials (CTs) in Hematology and Oncology (H&O) through the "Center of Clinical Investigations, Optimization, Standardization and Safety in Hematolgy and Oncology" (CIO) at the University Medical Center Freiburg

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Introduction: CTs in H&O are broadly performed due to enormous drug advances and medical progress being generated in this field, making the organization and logistics of phase I-III CTs, most of which test novel agents within AMG-restraints, a daily challenge.
Methods: We report of our organization, structure and support of CTs through a departmental ´CIO team´.
Results: The CIO is responsible for 1. all CTs conducted within our department, 2. the documentation of patients (pts) within (and outside) CT using an electronic tumor base documentation system (eTBD) and 3. chemotherapy (CTx) support and logistics. In close cooperation with the attendings and PIs, our CT office coordinates various trial tasks: from first contacts (with sponsors/CRO, ethic committees, BfArM, PEI), to the evaluation of CTs of interest, trial initiation logistics and CRF-documentation. In order to estimate highly realistic pt recruitment numbers, we employ our eTBD: this includes demographic data, cancer diagnoses, specific cancer histologies, relevant comorbidities, given CTx regimens, CTx-side effects, date of progression and, when applicable, death. Almost 21.000 tumor pts are recorded within the eTBD since its initiation in 1997. At least 500 detailed analyses for CT logistics are performed per year. Another useful CT-support tool is our protocol study and review board (PSRB), that organizes and discusses newly proposed CTs with the clinic director, attendings and PIs, naming pro and cons of planned CTs, feasibility questions and logistics. Aspects like a) are there sufficient pts to enroll, b) is there an overlap to currently active trials, and c) how are the regulatory and financial aspects, are discussed in detail. Within CTs, close collaborations have been proven valuable, e.g. with the CCCF, ZKS, clinical pharmacy, Regierungspräsidium, BfArM, PEI, as well as various others treating cancer pts whole-heartedly. In order to enhance pt recruitment into CTs, we offer brief intranet-based trial synopses. Entity-specific ´CT-outpt-

clinics´ are another useful tool to efficiently enroll pts in active CTs. Patient´ feedback reviews regularly demonstrate complete satisfaction to the above efforts. For our achievements, the CIO has been awarded first prize winner of the QM-initiative 2009.
Conclusions: In times of increasingly tight daily physicians´ schedules and with enormous CT-logistics, our CIO structure is highly valuable for efficient trial performance in H&O clinics.

Disclosure: No conflict of interest disclosed.

P246
Quality management systems for investigator sites – a model with future?

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Introduction: Clinical trials underlie high ethically legal, methodical and scientific requirements in an increasing international competition. At investigator sites an optimal execution of clinical trials are very important for quality and speed. The loss of quality endanger the essential goals of GCP regulation for patient protection and data validity and results. As an answer, a model of a quality management system (QMS) for investigator sites has been developed.
Methods: Investigator sites stand in context with QMS health care and clinical research. These systems have been analysed and evaluated regarding four prospects (university hospital, hospital, investigator site, clinical trial/sponsor) on the basis of DIN EN ISO 9001:2008. Afterwards a visualisation of an analysis document was established with the help of an evaluation scale. The results of the analysis were the basis for an optimized QMS model.
Results: Both QMS are not able to provide a complete and sufficient quality management for clinical trials. The QMS health care is mainly in line with primary patient care and its basic processes and definition of quality. Clinical Trials have other basic processes and definition of quality. This leads to isolation and in this connection a control mechanism like Deming (PDCA-cycle) is missing. Quality management cannot really take place. In contrast to this a sponsor is obligated to implement a QMS for clinical trials. But he is not an organisational part of an investigator site. Therefore he has limited influence on quality. A self-contained QMS for clinical trials will bridge a gap between primary patient care and clinical research. The basic elements of the model are the administrative coordination as a control and processing mechanism, the QM commission as a centre of operative and strategic decision making, the clinical trial centre as the primary practice area and the fixed working and flexible project groups as a source of creativity. Through networking with QMS health care and clinical research interaction will be ensured.
Conclusions: The model fulfilled the requirements of clinical trials and ISO 9001:2008. A separate certification for an investigator site is possible. Furthermore the basic structure offers a flexible internal and hospital overlapping adaptation and thus it is adaptive for a comprehensive cancer centre. Finally, it is important to implement a functional self-contained control mechanism for clinical trials.

Disclosure: No conflict of interest disclosed.

P247
Development of structures for a cancer centre

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Our hospital consists of three existing oncological centres: a breast, a gynaecologic and a colorectal cancer centre. To concentrate the basic structures the decision was made to establish a cancer centre in the Ev. Waldkrankenhaus in Berlin.
Tumour documentation: The first step was to investigate the number of the new diagnosed cancer patients of primary disease. The number patients in the existing centres were well known, because for the certification process the data have to be presented to the auditors for the breast (n=500), the gynaecological (n=99) und the colorectal (n=70) centre for the year 2009.
In order to estimate the number of other cancer entities three different approaches were made. Approach 1 was to search the data of our pathological institute of all investigations per year (ca. 20.000) and to select die malignant diagnoses using the icd-o code, ending /3, /6 or /9, resulting in ca. 1000 hits. Approach 2 was to look in the administration data for patients admitted with a primary or secondary diagnosis or C00 until C99 for ICD-10. This approach resulted in 3.500 items. Approach 3 was to scan the data of the tumour conferences regarding decisions of therapeutic relevance for tumour patients. Approach 3 produced 90 items.
Quality assurance: The second step was the compilation of different guidelines published by the German Society of Haematology, the German Cancer Society and the ESMO Clinical or recommendations. These guidelines were translated into clinical pathways suited for our hospital. The pathways consist of a definite structure: introduction, diagnosis, staging, therapy and literature. For relevant diseases a checklist was created to demand data required for decision made in the tumour conference (Performance status, histology, TNM etc).
Clinical Studies: For the certification process the fraction of patients in studies is stipulated for breast by 20%, for gynaecologic by 10% and for colorectal cancer by 10%. Although enough patients were proposed for a study only 7% could be finally included. Efforts have to be made to improve the achievement.

Disclosure: No conflict of interest disclosed.

P248
Supportive therapy in haematology/oncology

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At least 25% of patients with malignant diseases are already hypermetabolic at diagnosis. Depending upon the nature of the disease and the subsequent intensity of chemotherapy treatment with the known side-effects, this leads to a further increase in the loss of substance. This has a negative influence on the outcome (Pirlich et al. 2006) of the therapy and hence the patient´s chances of recovery. In order to prevent this loss of substance to the greatest possible extent, a nutrition team has been set up at the Klinikum Frankfurt (Oder) GmbH.
Its functions include the recording of the nutritional state and the documentation of follow-ups. Particular emphasis is being placed on an early identification of malnutrition. They recommend dietetic approaches, offer a consultation service and organise home enteral and parenteral care. The goal is improved nutritional therapy and maximum quality. Successes in standardisation and quality assurance of nutritional therapy deserve a particular mention.
All in all the nutrition team in Klinikum Frankfurt (Oder) GmbH is very well received. They are developing in-house standards and are being recruited increasingly frequently by surgical units, radiotherapists and ENT clinics.

Disclosure: No conflict of interest disclosed.

Posterdiskussion
Supportive Therapie / Sonstiges

P249
Implementation of standardized parenteral nutrition support in cancer patients during chemotherapy: a prospective observational study

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Introduction: Unintentional weight loss as the most obvious manifestation of cancer cachexia is a common problem among tumour patients. It is associated with decreased qualitiy of life and a poorer prognosis. We performed a prospective observational study in tumour patients receiving adjuvant, neoadjuvant or palliative chemotherapy. We report interim results regarding the impact of early parenteral nutrition therapy during chemotherapy on nutritional parameters, quality of life, toxicity of chemotherapy and survival.

Methods: From 02/09 - 02/10, 31 patients (median age 64 years) provided informed consent. Inclusion criteria were: malignant tumours scheduled for chemotherapy, unintentional weight loss over 10% within the last 6 months and estimated life-expectancy greater than 6 months. Baseline examinations included bio-impedance analysis (BIA) to determine body composition, subjectiv global assessment (SGA), body mass index (BMI), Karnofsky index and laboratory tests. Visits were scheduled at 4-week intervals to collect longitudinal data on changes in parameters, adverse events, chemotherapy toxicity according to NCI- criteria, catheter and metabolic complications. Dependent on the body weight at the time of inclusion, patients received daily doses of 1265 to 2530 kcal over 12 to 16 hours. Parenteral nutrition support was finished when oral calory intake was sufficient, weight gain occurred and Karnofsky index improved by more than 20%.
Results: Median body weight at baseline was 62 kg, median BMI was 21.3 kg/m², median Karnofsky index was 70%. Median oral energy intake before nutrition support was 900 kcal. Median weight loss before nutrition treatment was 13 kg. During nutrition therapy, Karnofsky index values remained essentially constant between 50 and 70%. During the parenteral nutrition period, median oral calory intake rose from 900 to 1700 kcal. The median time of parenteral support was 49 days. In all patients the planned number of cycles could be applied.
Conclusion: In this prospective study we show that unintentional weight loss over 10 percent is a reliable factor to initiate parenteral nutrition support. It seems to be important to start parenteral nutrition early, because in all patients chemotherapy was well tolerated. This suggests that in patients during chemotherapy early parenteral nutrition support is important to improve general condition, to reduce toxicity of chemotherapy and thus, to potentially influence survival.

Disclosure: No conflict of interest disclosed.

P250

Treatment of tumor induced iron deficiency with ferric carboxymaltose (FCM, ferinject®)

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Introduction: Cancer patients often suffer, as a consequence of disease and cytotoxic therapy, from iron deficiency and anemia, resulting in decrease of patient´s quality of life. Iron in conjunction with erythropoiesis stimulating agent (ESA) has been demonstrated to improve hemoglobin (Hb) levels and decrease need for ESA. Intravenous (iv) iron is considerably more efficacious than oral iron supplementation.
Methods: We performed a non-interventional study across 110 sites in Germany aiming to include a total of 450 cancer patients suffering from iron deficiency and anemia who received iv iron in form of ferric carboxymaltose (FCM, ferinject®) treatment.
Results: Initiated in December 2008, to date almost 380 cancer patients of all ages (≥ 18 years) have consented to the non-interventional study, until 04/2010 167 men and 201 women (45% men, 54% women, 1% missing) were enrolled. Among those patients most frequent tumor indications were colorectal (24%), breast (22%) and stomach (9%) cancer. 204 cancer patients already completed FCM therapy and terminated observation period. Median age of those patients was 64. Approximately 67% of patients were receiving cytotoxic chemotherapy during 12-week observation period. Weekly doses of FCM ranged from 50mg - 1.500mg iv iron. Half of patients were receiving median weekly FCM-doses ≥ 500mg iv iron. Patients with baseline ferritin < 100 ng/mL (TSAT 20% - 30%) showed higher Hb increases than patients with baseline ferritin ≥ 100 ng/mL (TSAT > 30%). Approximately 70% of patients receiving ESA up to 4 weeks before beginning of FCM therapy (n=24) were not in need of further ESA therapy during the 12-week observation period. Less than 5% of safety population (n=347) suffered from adverse drug reactions, mainly gastrointestinal side effects. The two reported serious adverse events were considered to be unlikely related to FCM (tachycardia) and possibly related (respiratory insufficiency).
Conclusions: This non-interventional study provides new verified data regarding usage of FCM in correction of anemia secondary to iron deficiency in cancer patients.

Disclosure: No conflict of interest disclosed.

P251

The patients' perspective on maintanance therapy: Intial results of a survey applying a semi-structured interview

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Introduction: Palliative systemic chemotherapy is usually applied for a limited number of cycles. Afterwards, the patients (pts) are followed without further treatment until a second line of therapy is initiated due to progression. Maintenance therapy (MT) is considered a treatment option instead of therapy-free follow up. Currently, MT is approved in low grade non Hogdkin's lymphoma, colorectal cancer and lung cancer (LC). Pts undergoing MT trade a period undisturbed by any anti-tumor treatment for a limited gain in overall survival (OS). We here assessed pts' preference regarding treatment with MT versus follow-up without any treatment, the side effects pts were willing to tolerate and the gain in survival that would subjectively be worth the effort.
Methods: After approval by the institutional review board, pts suffering from lymphoma, LC or gastrointestinal cancer (GIC) were surveyed by a semi-structured interview. The survey was purely hypothetical, individual MT was not discussed within this context. The pts' preferred route of therapy application and their willingness to tolerate side effects were assessed. In addition, patients were asked which prolongation of life they would require to accept MT. Pts were interviewed in their 4th or a subsequent cycle of chemotherapy.
Results: So far, 50 pts with a median age of 64 years were included. Pts suffered from lymphomas (n=17), GIC (n=17), or LC (n=16). 45 pts (90%) would be willing to accept a MT. Under the assumption of intense side effects, this value dropped to 22 pts (44%). Eight pts (16%) would prefer the oral route and 17 (34%) an i.v. application, while the remaining had no preference. Without side effects, 8 pts (16%) would accept MT assuming a prolongation in OS of 3 months or less, 12 pts (24%) in case of 1-2 years and 28 pts (56%) in case of 3 years or more. 2 patients did not answer. With more intense side effects, the prolongation of survival had to be considerably longer to make MT acceptable for the pts.
Conclusion: The majority of pts are willing to accept a MT given mild or absent side effects without a clear preference for the oral route of application. Of note, the majority of pts expects a prolongation of OS that currently is hardly realistic. Thus, when discussing the issue of MT, it is important to inform the pts openly and precisely about the expected benefit and side effects of MT to enable them to make an informed choice about a MT based on a realistic benefit-risk assessment.

Disclosure: No conflict of interest disclosed.

P252

Osteoporosis, 25-OH-D-level, and substitution of vitamin D in cancer patients

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Introduction: Cancer patients are known to have an increased BMD-loss. Nevertheless data about prevalence of osteoporosis in this population based on DXA-measurement are rare in Germany. Therefore we conducted a survey (02/2006 - 09/2009) among cancer patients attending our clinic..
Methods: BMD and T-Scores were measured with DXA (LWS- and femur-scan) in 1035 patients. Mean age was 57.0 (11.0) years, BMI 27.6 (5.3) kg/m²,

and mean interval between cancer diagnosis and DXA-Scan was 22.4 (36.9) months. 78.1% (n=808) of the patients were women and 21.9% (n=227) were men. Among the women 66.3% were postmenopausal, 19.2% had ovarian dysfunction caused by therapy and 9.8% were premenopausal.
About one half of the patients suffered from breast cancer (51.0%), the others had cancers at following sites: 10.8% gynecological (others than breast cancer), 14.6% gastro-intestinal tract, 5.3% urogenital tract, 12.2% malignant systemic diseases (without M. Myeloma) and 6.5% others (e.g. sarcoma, skin,…). According to the high percentage of women with breast cancer we found that more women had CT respectively RT than men (CT: 60.8% vs. 48.2%; RT: 67.7% vs. 29.9%).
In addition we measured 25-OH-D-levels in 101 patients suffering from breast, colon or prostate cancer from 04/ - 11/2009.
Statistics were done in a descriptive manner with means (SD) and percentages [95%-CI].
Results: We found in 22.7% [14.5;30.9] of the cases 25-OH-D-levels < 10ng/ml and in 68.3% [54.2;77.4] levels of 10 - 32 ng/ml. Only 8.9% [4.8;16.1] had levels >32 ng/ml which is considered as sufficient concerning bone health.
In the greater population about 16% had osteoporosis according to the WHO definition (w: 15.6% [13.3;18.3]; m: 15.9% [11.7;21.2]) and 44.3% had osteopenia. Among women we found 10.1% [8.0;12.2] having vitamin D supplementation. In men this rate was even lower (4.5% [2.5;8.0]).
Conclusions: In our survey the number of cancer patients having vitamin D supplementation in order to prevent BMD-loss in this high-risk population was very low. With regard to the high rate of patients suffering from osteoporosis / osteopenia and the small number shown to have sufficient 25-OH-D levels more attention must be paid to vitamin D supplementation in clinical routine. We recommend a generous substitution of vitamin D among cancer patients in particular since this is considered to be safe and there are several hints in the literature of vitamin D having a positive impact on cancer.

Disclosure: No conflict of interest disclosed.

P253

The Viv-Arte training program supplemented by whole-body vibration training in the treatment of chemotherapy-induced sensorimotor polyneuropathy

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Background: Peripheral sensorimotor polyneuropathy (PNP) is a frequent toxicity observed after combination intensive chemotherapy but also after single agent treatment with IMiDs or proteasom inhibitors. Chemotherapy-induced PNP (ciPNP) is characterized by an enormous interference with daily activity of life, in that pain, severe disturbance of fine motor skill and insomnia result in loss of independency and in consequence the need of care. The therapeutic benefit of gabapentin or pregabalin in ciPNP is uncertain and therefore new options are needed.
Methods: In a pilot study patients with ciPNP at least NCI CTC grade 3 were treated with Viv-Arte® training program including whole-body vibration with Galileo® training device (SKMT) for 15 training sessions in a time period of 12 to 15 weeks. The SKMT was composed of 4 parts, i) manual therapy including passive mobilization, massage and active three-dimensional complex movements, ii) whole-body vibration training, iii) gymnastics and iv) training of specific individualize functional tasks to regain self control in activity of daily life. Patients were evaluated before, two times during and after treatment using locomotoric- and sensoric multidimensional tests.
Results: 20 patients were included (n=16 multiple myeloma, n=1 diffuse large B-cell lymphoma, n=1 Sézary-syndrome, n=1 acute myeloid leukemia, n=1 follicular lymphoma). Median age was 62 years, n=12 were male. In all patients treatment was well tolerated. With regard to locomotoric- and sensoric multidimensional tests large difference were observed between pre- and post-treatment. Pre-treatment paresthesia of the feet measured on a scale of 1 to 10 (worst) was most prominent (median 8, range 1-10) resulting in an impairment of climbing stairs measured on a scale from 1 to 6 (worst) (median 4, range 3-6) and plane walking distance measured as steps per day (median < 1000, range < 1000-7000). After treatment these measures improved markedly, paresthesia (median 2, range 0-7), climbing stairs (median 1, range 1-4), plane walking distance (median 5250, range 2000-7000). In parallel, physical fitness measured with the chair rising test improved significantly from pre-treatment (median 17 seconds (s), range 13-21s) to post-treatment values (median < 10s, range < 10-18s).
Conclusions: Based on these data SKMT seems to be very effective in the treatment of ciPNP. To evaluate the relative impact of the vibration training we initiated a randomized study.

Disclosure: No conflict of interest disclosed.

P254

Assessment of Quality of Life (QoL) during treatment holidays or treatment deescalation in patients with 1st line treatment for metastatic colorectal cancer (MCRC): A complimentary study of the German AIO Group

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Introduction: Traditionally, assessments of the benefit of cancer treatments have focused on outcome parameters like disease-free or overall survival and toxicity. However, during the last years, the growing interest in "patient reported outcomes" (PROs) underlines the need to develop instruments to assess the multidimensional issues of quality of life (QoL). In MCRC, current data shows that distribution of chemotherapy impacts on QoL, and so far, only treatment intensification is prospectively assessed. However, treatment holidays have become a common practise in MCRC, which are believed to improve QoL. However, there are no prospective data available whether this really interacts with the multidimensional concept of QoL.
Method: AIO KRK 0207 is a large randomized 3 arm trial in order to assesses the non-inferiority of deescalated treatment arms after 24 weeks "induction". This QoL study is designed as an add-on, with the primary objective to assess whether treatment stop (after an "combination chemotherapy with bevacizumab) and watchful waiting leads to relevant differences in QoL when compared to any "maintenance" therapy, either consisting of bevacizumab as single agent, or the combination of a fluoropyrimidine and bevacizumab. Therefore, Qol will be examined throughout all treatment phases. In addition, following secondary endpoints will be assessed:
1) Evaluation of the prognostic impact of the QoL and comparison to performance status.
2) Correlation between response rate and QoL and between symptomatic/asymptomatic patients and QoL. Instruments for analysis will include the EORTC QLQ-C30 and the colorectal cancer specific module QLQ-CR29. Additionally, the short version of the Fear of Progression Questionnaire (FoP-Q, Herschbach et al.) will be used to address the issue of anxiety. About 130 patients per treatment group are necessary. Nearly 120 centers will be participating.
Results: Recruitment started in October 2009. Until know, 114 patients are included, as anticipated. Compliance at baseline is nearly 85%. First results for maintenance treatment are expected in October 2010.
Conclusion: To our knowledge, this trial is the first to assess a potential benefit in QoL throughout discontinuation of treatment in MCRC. Adherence to the evaluation is currently high, although final results will not be available before 2012. However, the innovation of the examination yet justifies a methodologic discussion.

Disclosure: Julia Quidde: No conflict of interest disclosed.
Dirk Arnold: Advisory Role: Roche, Sanofi-Aventis; Honoraria: Roche, Sanofi-Aventis

P255

Experiences of nursing staff in dealing with the patient`s living will and their attitude to euthanasia. A descriptive semi-structured study of nursing personnel at a University Hospital in Austria

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Background: Since 2006, there is a law regulating the handling of patient`s living wills in Austria. However, the experience of the nursing staff handling these very situations has not yet been documented. Therefore it is of interest to determine the opinion of Austrian NS for euthanasia and for their own end of life. The displayed results are part of a larger investigation of the nursing staff role in ethical end of life decisions.
Objective: The objective of this study is the collection and presentation of the nurse's role in ethical end of life decisions and the currently established practice in the use of the patient's living will in an Austrian University Hospital, as well as the determination of the training needs for this complex subject from the nurse's side.
Methods: A semi-structured questionnaire was distributed to 341 nurses working in several divisions (intensive care, oncological, palliative and emergency unit) engaged in terminal life care. 51.6% (n=) of questionnaires were returned for evaluation.
Results: Nurses play a significant role in ethical end of life decisions. Regarding the patient's living will, in practice still many uncertainties exist because currently the handling is unstructured and not institutionalized. Interdisciplinary conflicts arise due to the informal communication and insufficient documentation. 68.8% of the surveyed nurses support the legalization of euthanasia according to the Dutch model, but 43.2% of those with reservations only.
Relevance to practice / conclusion: The study suggests the need for development of concepts and guidelines in the interdisciplinary cooperation about how to handle the patient's living will in practice. The number of nurses agreeing to a legalization of euthanasia reflects the international trend. A broad and public discussion within the profession of nursing staff on this subject would be useful.

Disclosure: No conflict of interest disclosed.

P256

The Austrian BMT/SCT nurses group – A platform for information and cooperation

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Allogeneic and autologous stem cell transplantation is still associated with morbidity and mortality and high level nursing care is essential for adult and paediatric patients. To increase knowledge of nursing practices and exchange information on transplantation specific topics a national network was established in March 2007.The Austrian BMT/SCT NG members represent 14 centres and the group is a sub-organization of AHOP (Austrian Working group of haemato-oncological nurses). It is also an active member of the EBMT nurses group.The primary aims are exchange of knowledge and distribution of standards for clinical care. Workshops are held twice a year.To identify the local standards of care a questionnaire on current practice in isolation, nutrition and hygiene measures was sent out. Twelve/14 centers responded and the results were evaluated in September 2008. It turned out that wide variation exists in isolation practice, infection prophylaxis, hygiene management and nutrition. Intensive and critical discussion on the different policies led to a restructuring of different nursing procedures. Old structures were challenged, adapted or partly exchanged.Willingness to reconsider our own position and looking over the rim of our tea cup will ensure high quality of care at a reasonable cost.

Disclosure: No conflict of interest disclosed.

P257

Pain management in patients (pts) with advanced cancer (excluding breast and prostate) or multiple myeloma (MM): Results from a randomised phase 3 clinical trial of denosumab versus zoledronic acid (ZA)

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Introduction: Historically, pts with advanced cancer or MM and bone metastases have been treated with bisphosphonates to prevent osteoclast-mediated skeletal-related events (SREs) and improve pain. In a previous presentation, the fully human monoclonal antibody against RANKL, denosumab, was shown to be noninferior to ZA in preventing SREs in this solid tumour and MM pt population. We present pain outcomes from this study herein.
Methods: Eligible pts (no prior IV bisphosphonate) received subcutaneous denosumab 120mg or intravenous ZA 4mg every 4 weeks in a double-blind, double-dummy, active-controlled design. Supplementation with vitamin D and calcium were recommended. Pts were required to complete the Brief Pain Inventory to measure pain severity at baseline (BL), day 8, and before each monthly visit. Data shown are for all randomised pts (N=1,776) through week 45, when ≥ 50% of pts had dropped out due to death, disease progression, or withdrawl of consent. Analyses included clinically significant delay in worsening of pain (≥ 2-point increase from BL) in all pts and in pts with no/mild pain at BL, and the percentage of pts with no/mild pain at BL reporting moderate/severe pain on-study.
Results: Pts receiving denosumab experienced a delay in clinically significant pain worsening compared with those pts receiving ZA, median of 169 days and 143 days, respectively (HR=0.85, 95% CI: 0.73-0.98, p=0.02). Among the

Table 1. Percentage of pts with no/mild pain at BL reporting moderate/severe pain (worst pain score >4) by study week (for Abstract P257)

Study Week	5	9	13	17	21	25	29	33	37
Denosumab (N=361)	21.7	28.3	27.9	26.6	28.3	26.5	29.8	30.4	24.0
ZA (N=317)	24.1	29.7	30.0	29.9	29.9	29.9	26.5	27.0	28.6

Table 1. Percentage of pts with no/mild pain at BL reporting moderate/severe pain (worst pain score >4) by study week (continued) (for Abstract P257)

Study Week	41	45
Denosumab (N=361)	23.8	25.3
ZA (N=317)	29.3	29.7

group of pts with no/mild pain at BL (n=678), median time to moderate/severe pain was also delayed in the denosumab group compared with ZA group (144 days vs 102 days; HR=0.81, 95% CI: 0.67-0.99, p=0.04). Furthermore, the proportion of pts with BL scores of no/mild pain who reported moderate/severe pain on-study was lower for denosumab than for ZA at most time points (Table).
Conclusions: In this patient population denosumab prolonged time to worsening of pain compared with ZA. Furthermore, among pts with BL scores of no/mild pain, fewer pts reported moderate/severe pain with denosumab versus ZA.

Disclosure: Roger von Moos: Advisory Role: Amgen, Novartis, Roche; Honoraria: Amgen, Roche
Karen Chung: Employment or Leadership Position: Amgen Inc; Stock Ownership: Amgen Inc

P258

Assessment of fever of unknown origin: Whole body diffusion weighted imaging and continuous table movement MRI in comparison to leucocyte scintigraphy / FDG-PET CT

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Purpose: To evaluate whole body (WB)-MRI using diffusion weighted imaging (DWI) and continuous table movement (CTM) STIR and contrast enhanced GRE sequences as a new specific modality for the etiologic workup of fever of unknown origin (FUO) without radiation exposure and less technical effort in comparison to scintigraphy and PET-CT.
Material and methods: 20 patients (11 f, mean age 49 y) with FUO (fever > 38.3º C for ≥ 3 weeks of which the cause is not found despite adequate diagnostics or fever during neutropenia< 3 weeks duration) were examined at 3 and 1.5 T (Siemens Magnetom Trio/Avanto, Siemens Healthcare, Germany) using a combined protocol with coronal WB DWI, axial WB CTM HASTE STIR sequences and axial contrast-enhanced T1-weighted GRE-sequences (examination time 35 min). In 8 patients ^{67}Gallium-scintigraphy (Ecam, Siemens) was performed as current standard of reference, in 5 patients 18F-FDG-PET-CT after installation of the PET-CT-scanner (Biograph mCT, Siemens). Scintigraphy / PET-CT exams were assessed by a nuclear medicine physicist and radiologist, WB MRI was read by two experienced radiologists in consensus blinded to the results of scintigraphy/PET-CT. Sensitivity/specificity of WB DWI was assessed. Results were compared, findings were clinically assured (biopsy, follow up, lab test) and modalities were re-evaluated after diagnosis.
Results: In 14 patients 17 fever foci / fever causing entities found were found by WB-MRI. In 6 patients no focus was found by WB-MRI and scintigraphy /PET-CT and clinical follow up was negative. In 4 patients (20%) with positive MRI (pneumonia, polymyositis, extended hepatic metastastic disease, peritoneal carcinosis) scintigraphy was negative, in these patients clinical assessment confirmed the MR diagnosis. Sensitivity of DWI was 94 % (DWI false negative in 1 pt. with pneumonia), specificity 100%, PPV 100%, NPV 80 %. In 3 patients negative DWI ruled out suspected infection suspected from STIR and contrast enhanced GRE images.
Conclusion: WB-MRI excellently depicts fever foci and shows higher detection rates than the current standard of reference. The presented first results using WB-DWI and fast morphological sequences are promising for the workup of FUO. This combined MR-protocol should replace leucocyte scintigraphy as diagnostic standard of reference in the future and adds to PET-CT-diagnostic as new potent modality without radiation exposure.

Disclosure: No conflict of interest disclosed.

P259

Fertility preservation in young female lymphoma patients: initial experience with a specialized outpatient clinic

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Introduction: The cure of women suffering from Hodgkin's disease or aggressive non Hodgkin's lymphoma is often achieved at the cost of impaired ovarian function or infertility. Different approaches are thus being employed to protect fertility. Here, early experiences with the implementation of a specialised fertility preservation clinic were analysed with the aim to assess need and acceptance of the clinic and the delay of treatment caused by different approaches.
Methods: Retrospective analysis of data regarding the underlying malignancy and fertility preservation measures of women in childbearing age treated for aggressive lymphoma and Hodgkin´s disease in curative intent between November 2006 and January 2010.
Results: Among 111 female lymphoma patients, 30 were eligible for counselling, and 19 accepted the offer. The main reason for declining was a completed family planning (n=6). In two patients, immediate initiation of chemotherapy was required due to symptomatic compression of the superior vena cava. In addition to these 19 patients, eight further patients were referred from outside. 96% of counselled patients decided to pursue at least one protective strategy, 39% chose an invasive procedure. The most commonly performed fertility preservation method was the administration of a gonadotropin-releasing-agonist (GnRH-a) in all but one patient (96%) whose diagnosis was made during pregnancy. Laparoscopic removal of ovarian tissue was performed in 7 patients (27%). Median time from presentation to the fertility preservation clinic to surgery was 2 days (range 1-8). After surgery, systemic treatment was started after a median of 6 days (range 1-30). Oocytes were aspirated following hormonal stimulation in 6 patients (23%). Median interval between counselling and completion of oocyte retrieval was 17.5 days (range 13-23). Systemic treatment was started 4.5 days later (range 1-15). The latter patients were all in a stable relationship, and their oocytes could therefore be fertilised by intracytoplasmatic sperm injection (ICSI).
Conclusion: Female lymphoma patients have a large demand for counselling about measures to protect fertility. In a proper setting, counselling and intervention can be offered without undue delays menacing the chance for cure.

Disclosure: No conflict of interest disclosed.

P260

The influence of cisplatin on porphyrin-metabolism: A pilot study based on a case observation

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Background: A 67 year old patient developed a first episode of porphyria 9 days after treatment with cisplatin (Cis). Urine excretion of d-aminolaevulinic acid (Ala) and porphobilinogen (Pbg) were transiently increased 20fold and 6.5fold, respectively. In vitro studies have shown that the enzyme activity of aminolaevulinic acid dehydratase (Ala-D) can be inhibited by Cis in concentrations of 0.5 mM. In a rat model, a time- and dose dependent inhibition of ALA-D by Cis was demonstrated with a maximum of Ala-D inhibition after 96 hours. Data from human patients about the interaction of Cis with porphyrin-metabolism are rare. Therefore a pilot study was designed to elucidate the influence of Cis on porphyrin-metabolism.
Methods: In patients (pts) receiving Cis in a dose of > 60 mg/m2 intravenously, the urine concentrations of creatinine (Crea), Ala, Pbg and other cumulative prophyrin metabolites (Por) were measured before and on day 5 after Cis. The ratios of the urine concentration of Crea to the urine concentrations of Ala, Pbg and Por were calculated.
Results: A total of 12 pts were included. Mean Ala/Crea before Cis was 1.7 umol/mmol (SD 0.6) before and 1.96 umol/mmol (SD 0.6) on day 5 after

ciplatin, p=0.34. Mean Pbg/Crea was 0.5 umol/mmol (SD 0.2) before and 0.48 umol/mmol (SD 0.25) after Cis, p=0.71. Mean Por/Crea decreased from 21.2 umol/mmol (SD 17.3) to 15.1 (SD 7.2), p=0.21.
Discussion: Mean ALA/Crea increased by 15% after Cis, which was not statistically significant. The reduction in urine excretion of Pbg (-4%) and of Por (-29%) was not statistically significant. All changes in urine excretion of porphyrine metabolites remained below the normal reference limits (Ala/Crea < 2.8 nmol/mmol; Por/Crea < 0.7 nmol/mmol). The discrepancy of our results to the results in the animal model is likely explained by the Cis doses used: In humans, the Cis dose is 1-2mg/kg body weight, and hence 5-10fold lower than the doses used in the animal model (up to 10 mg/kg).
Conclusion: Cis in doses commonly used in clinical practice does not cause significant alterations of porphyrine-metabolism and does not result in a pathologically increased urine excretion of porphyrine metabolites. An acute episode of prophyria after chemotherapy with cisplatin is very rare. In our patient other factors such as glutathion depletion in conjunction with fasting and septicaemia might have contributed to the clinical manifestation.

Disclosure: No conflict of interest disclosed.

P261
Extravasation with liposomal doxorubicin (Myocet®)

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Introduction: Extravasation of anthracyclines is a severe complication in the treatment of malignancies. Most cases necessitate surgical intervention to prevent from permanent impairment. Non-surgical treatment options as local cooling, topical dimethyl sulfoxid (DMSO), corticosteroids or hyaluronidase have widely been used with less success. Actually, Dexrazoxane (Savene®) demonstrated highly efficiency in treating anthracycline extravasation in two randomized trials.
Liposomal formulations of doxorubicin exhibit a better safety profile with less cardiotoxicity while maintaining antitumor efficacy comparable to conventional anthracyclines. Myocet® is classified as a non-vesicant agent and extravasation causes generally a mild reversible cutaneous reaction. A series of eight drug extravasations with liposomal doxorubicin resulted in none of the cases in clinically apparent tissue damage. Here we report a case of extravasation into the chest wall and breast with liposomal doxorubicin which resulted in a large necrosis needing surgical intervention.
Case report: A 68-year-old woman with relapsed breast cancer was treated with an anthracycline containing immunochemotherapy regimen. Liposomal doxorubicin at a dose of 60 mg/m^2 and trastuzumab at a dose of 6 mg/kg bodyweight were infused at 21 day intervals by using a central venous access (port-catheter). Five days after the third administration the patient reported about feeling of tension and breast-swelling. Physical examination revealed a distinct edema and erythema with hydrous blisters of the right breast below the intravenous port-catheter. The diagnosis of an extravasation with liposomal doxorubicin was made. Sterile dressings, local cooling and oral antiinflammatory and prophylactic antibiotic therapy were administered and a surgeon was consulted. Four weeks after the extravasation edema was slightly recurrent, but pain and rigidification of the breast tissue increased. The blister had burst showing a partial superinfection. A referral to a plastic-surgeon resulted in a watch-and-wait policy. Specific treatment contained sterile local dressings and oral analgesia. Twelve weeks later the patient's right breast-tissue was indurated and the surface of the skin was coloured with partially weeping areas. Finally the patient was treated by breast ablation and a skin graft.
Conclusion: To prevent extensive necrosis we recommend treatment with Dexrazoxane in case of liposomal doxorubicin extravasation.

Disclosure: No conflict of interest disclosed.

P262
Chinese Medicine after exhaustion of existing standard treatments

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Introduction: For most tumors a limited number of treatment options has been established with conclusive data. From Chinese Medicine several drugs, that influence tumor growth, have been developed.
Methods: A male patient (59 years) suffering from squamous cell carcinoma of the palatine tonsil (pT3, pN2c, cMo, G3, R1) was treated with surgery, radiotherapy and Cisplatin / 5-Fluorouracil in 2008. In 2009 he developed a local relapse and pulmonary metastases. Despite Carboplatin and Docetaxel in sequence, combined with Cetuximab, the disease showed a significant progression at CT- Staging after 3 and 2 months. During this time the patient´s general state deteriorated (Karnofsky- Index 50%, ECOG 3). After discussion of further treatment options he opted for Chinese medical treatment.
A second patient (female, 67 years) was treated for adenocarcinoma of the colon (pt4, pN2, cM0, G2, R0) since 2004. Primary treatment was surgery, adjuvant treatment could not be administered because of postoperative complications. In 3/08 she developed pulmonary metastases, was operated and received chemotherapy (FOLFOX4 regimen x12 until 2/09). In 5/09 new pulmonary metastases were diagnosed and chemotherapy with the FOLFIRI regimen plus bevacizumab was started. Because of serious side effects, (Karnofsky- Index 60%, vomiting grade 2, neuropathy grade 3 swelling of her neck with nearly complete loss of voice), she denied further chemotherapy and asked for treatment with Chinese Medicine.
Results: The first patient is now treated with decoctions since 6 months. Simultaneously two painful supraclavicular lymph nodes were treated with radiotherapy. We have no objective measurements of the tumorgrowth due to missing consequences. Clinically he shows a slow tumorprogression. He claims to fell better and the general state has improved (Karnofsky- Index 60%, ECOG 2-3).
The second patient receives decoctions since 7 months now. The metastases show a slow progression on CT scans. Her general state has improved (Karnofsky- Index 70%), she eats normally, neuropathy has improved to grade 2, the swelling of the neck is completely resolved and she speaks only slightly hoarsely now.
Conclusion: The two patients demonstrate, that after standard treatments had to be stopped for objective or subjective reasons, decoctions according to Chinese Medicine can improve the general state of the patients. Tumor progression was at least not more aggressive than under standardtherapy.

Disclosure: No conflict of interest disclosed.

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V263
Selected Abstract
Expression of the embryonic self-renewal protein NANOG predicts higher tumor aggressiveness in human breast cancer samples

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Introduction: Cancer stem cells (CSC) are tumor cells capable of initiation and propagation of the malignant disease. Stem-cell like features (e.g. expression of protein pumps such as MDR) can be used for isolating CSC from the tumor mass. On the molecular level, embryonic stem cell regulators including

NANOG have been shown to be expressed and possibly play a pathogenetic role in human tumors (Ben-Porath et al. 2008; Jeter et al, 2009). However, while much is known on the role of embryonic regulators in embryonic stem cells, their role during tumorigenesis needs to be further explored.
Methods: We used $CD24^{-}/CD44^{+}$ staining and/or the Aldefluor assay detecting aldehyde dehydrogenase activity to isolate CSC via flow-cytometry from primary human breast tumor samples. Isolated cell fractions were functionally analysed in mammosphere assays and for RNA expression by quantitative PCR. Furthermore, primary samples from a cohort of 88 patients with breast cancer and, if available, samples from matched lymph-node metastases underwent immunohistochemical staining for NANOG protein.
Results: We detected various levels of *NANOG* mRNA expression in several primary breast cancers and cell lines. *NANOG* expression is increased in the putative breast cancer stem cell compartment. Up to now NANOG protein expression has been evaluated in 40 of the 88 samples of primary early breast cancers included in our cohort. NANOG was detected in 24 out of 40 samples of different histological type. Interestingly, NANOG expression was associated with an invasive phenotype (p=0.024) and presence of lymph node metastases. Tumors of all patients with lymph node metastases, and all samples from metastatic lymph nodes (n=5) showed focal NANOG expression. NANOG expression was more frequent among large (T3-4) and less differentiated tumors, with all grade 3 tumors falling into the NANOG-positive group, and appears associated with HER2 positivity and negative estrogen and progesteron receptor-expression status.
Conclusion: We demonstrate that NANOG is commonly expressed in primary breast cancer tissue and enriched in the putative CSC compartment. Our data suggest NANOG expression is associated with high tumor invasiveness and metastatic potential in early breast cancer. Analysis of larger numbers of samples is ongoing and will be presented at the meeting.

Disclosure: No conflict of interest disclosed.

V264
Effect of bisphosphonates and RANKL-antibodies upon ostelytic lesions and tumor cells

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Bone metastases (BM) from solid tumors induce local bone destruction by increasing osteoclast (OC) activity, result in skeletal complications like fractures, and may cause hypercalcemia. Adjuvant therapies for early breast cancer are associated with substantial decreases in bone mineral density. Bisphosphonates (BP) are antiresorptive agents that are widely used in the treatment of diseases involving excessive bone resorption, including osteoporosis, tumor-associated bone disease and hypercalcaemia. They also have an established role in preventing skeletal morbidity in patients with BM from solid tumors and in patients with multiple myeloma (MM). In animal models of breast cancer BM, animals that were treated with BP, the trabecular bone could be preserved because the BP is blocking bone resorption. The same effect has been observed in preclinical models of MM using a cellular antagonist of receptor activator of RANKL, RANK-Fc. When mice are treated with RANK-Fc, the trabecular bone is preserved as a result of inhibition of OC activity. These previous findings led to the concept of the vicious cycle that exists between tumor cells and OC in the bone marrow microenvironment. The cycle involves a bidirectional interaction between tumor cells and OC, in which the tumor cells produce factors that activate OC, thereby stimulating them to resorb bone and release growth factors from bone that, in turn, influence the aggressive behavior of the tumor cells, causing them to release additional OC-activating factors. Interruption of this cycle with drugs that block OC resorption, such as BP, or OC formation, function and survival, such as denosumab, blocks OC activity and some of the resulting bone loss while decreasing the supply of growth factors to the tumor cells. BP are potent inhibitors of OC-mediated bone resorption and have been shown to reduce tumor-induced osteolysis in patients with malignant bone disease. New bone-targeted therapies are currently under investigation. The fully human monoclonal antibody denosumab inhibits RANKL, a key mediator of OC activity, and has also shown activity compared to zoledronic acid in patients with BM in large phase 3 trials of different tumor types, including breast cancer. Data from clinical trials has shown limited influence of BP or denosumab therapy on patient survival thus far. Treatment regimens may need optimization to realize their full anti-tumor potential as well as their efficacy in preventing skeletal-related events.

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V265
Antiangiogenic therapies in the management of breast cancer

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Introduction: The growing knowledge of the role of angiogenesis in tumor biology has led to the development of a variety of antiangiogenic therapies, resulting in the approval of bevacizumab (Bev) in the treatment of metastatic breast cancer (MBC). This abstracts offers an overview of clinical trial data of antiangiogenic agents with the greatest potential for clinical use in breast cancer in the near future.
Recent findings: Bevacizumab (Bev), a monoclonal anti-VEGF antibody is the first antiangiogenic agent approved in MBC. It significantly improves response rates and progression free survival in combination with taxanes, anthracylclines as well as capecitabine in the first line treatment of MBC. Yet, this has failed to translate into a longer overall survival in any of these trials as well as a recent pooled analysis. It is unclear if this is due to cross over, further lines of therapy or a rebound phenomenon. A recent phase III trial demonstrated a benefit also in the second line treatment of MBC. Bev is currently investigated in phase III studies in the adjuvant and neoadjuvant setting.
Multikinase inhibitors (TKIs) might, due to their lesser specificity, yield a broader range of activity, yet at the risk of inducing off-target toxicities. Sunitinib (SU) and sorafenib (SO) are the TKIs which are most advanced in clinical development. Both exhibit only limited acitivity as monotherapies in MBC.
Sunitinib (SU) has been investigated in a row of four large phase III trials, known as the SUN studies, including capecitbine, pacli- and docetaxel. Neither of these studies has met their primary end point (PFS). Yet, the addition of SU to chemotherapy (CHT) lead to significantly higher toxicities and dose holds, despite the reduced chemotherapy dosage in the combination arms. Sorafenib thus far has showed more promising results in two phase IIb trials with an improved PFS when added to paclitaxel or capecitabine, yet also at the cost of increased toxicity.
A variety of further antiangiogenic TKIs are currently in clinical development. Low dose metronomic CHT and vascular disrupting agents are further approaches targeting the tumor vasculature that hold promise for the future.
Conclusions: Antiangiogenic therapies offer an additional therapeutic option in MBC, with Bev as the first approved agent. Further agents, such as TKIs and vascular disrupting agents are in clinical development.
Predictive factors for better patient selection require intensified research.

Disclosure: Frederik Marmé: Advisory Role: Fresenius Biotech; Honoraria: ROCHE, Sanofi-Aventis, Essex, Fresenius Biotech, Amgen

Fortbildung
MDS

V268
Diagnosis of MDS – with or without cytogenetics?

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An adequate diagnostic work up in cases of suspected MDS is an inalienable precondition for differential diagnosis, classification, prognostic estimation and therapeutic stratification.
The most relevant theoretical reasons to renounce a given diagnostic method are a lack of diagnostic reliability and clinical relevance, a negative cost-benefit analysis and an unacceptable burden for the patient to obtain examination material. Is any of these points relevant for cytogenetics of MDS which might vote for a diagnosis of MDS without cytogenetics?

Within the complex of diagnostic tools in MDS, cytogenetics is one of the most relevant diagnostic and prognostic components. In the frame of the new WHO classification system cytogenetic findings are of special relevance to define the subtypes of cases with isolated 5q-deletion and of cases with unclassifiable MDS.
The IPSS comprises the three parameters: bone marrow blast counts, cytopenias and cytogenetics. There is now clear evidence that the prognostic weight of cytogenetics vs. blast counts is undervalued. Within the more recently developed WPSS cytogenetics already has gained a higher prognostic weight. However there are still other unsolved problems such as prognosis of double abnormalities and of cytogenetic subgroups within complex abnormal cases and prognosis of most rare abnormalities. To overcome these shortcomings of the old IPS-system we currently are developing a new cytogenetic prognostic scoring system based on an international dataset of nearly 3000 pts. with MDS which allows for a further improved estimation of individual prognosis and will serve as one module of an IPSS revision.
Our recently developed method of CD34+-FISH from peripheral blood is representative for the clonal situation in the bone marrow. It thus can improve diagnostics in situations where a bone marrow aspiration is not possible or refused. It also can be used for a close-meshed monitoring of a disease evolution over time and response to therapy. In relation to modern therapeutic strategies including allogeneic stem cell transplantation, cytogenetics not only causes a small fraction of costs but furthermore is a reliable and relevant parameter for treatment decisions.
Taken together, nowadays there are no valid arguments against the routine use of cytogenetics for the diagnosis of MDS. MDS diagnosis without cytogenetics clearly is not state-of-the art and significantly reduces the quality of clinical management.

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V269
MDS in elderly: Treatment algorithms and the relevance of comorbidities

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Myelodysplastic syndromes (MDS) represent a complex group of clonal hematopoietic stem cell disorders characterized by a dysplastic hematopoiesis and the potential to transform to acute myeloid leukemia (AML). Due to ineffective hematopoiesis patients often present with symptoms caused by anemia, thrombopenia or granulopenia. MDS represent a typical disease of the elderly as the median age at diagnosis is around 75yrs in most epidemiological analyses. The incidence of MDS increases dramatically with advanced age revealing age specific incidences of 9, 25, and 31/100.000/year for the age groups 60-70, 71-80, and 80+, respectively. Moreover, therapy-related MDS (t-MDS) is observed preferentially in elderly cancer survivors following chemotherapy and/or radiation therapy. The large and increasing proportion of elderly MDS patients and the availability of more and effective treatment options like immunomodulating drugs (IMiDs), epigenetic agents and effective iron chelators, imposes an urgent need to develop strategies and algorithms for individualized management in elderly. Based on the IPSS, patients are divided into low-risk and high-risk MDS. These prognostic subgroups differ significantly in survival and rates of leukemic transformation and maintain their prognostic significance even in MDS patients aged 70+. As shorter overall survival in aged persons is logical, prognostication in the elderly should include age-adjusted parameters like the standardized mortality rate (SMR) or the age-adjusted relative survival, thus designing age and risk-adapted treatment strategies. Whereas prognostic scores established so far are based on disease-specific prognostic factors like bone marrow blasts or karyotype, patient-related factors like performance status, functional capacities and most importantly comorbidities are less well defined. To assess these dimensions the integration of assessment scores has just started. An example to be mentioned is the prospective registry of the European Leukemia Net (ELN) for newly diagnosed MDS. Likewise, the hematopoietic stem-cell transplantation-specific comorbidity index (HCT-CI), was found to be a significant prognostic factor for overall and event-free survival as well as for non-leukemic death in MDS. The systematic evaluation and integration of the various aspects of geriatric assessment in MDS will improve individualized therapy-planning and definition of treatment goals in clinical studies and in daily practice.

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V270
Disease-specific therapy or allogeneic HSCT in MDS

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Because myelodysplastic syndromes (MDS) are a disease of the elderly population, there are potential risks from intensive treatment approaches. Whereas in low-risk MDS supportive care only can be considered in many patients, in high-risk MDS the considerable rate of AML transformation as well as mortality from infectious complications make therapeutic approaches desirable, which can alter the disease history.
In low-risk MDS supportive therapy with growth factors like erythropoietin yields erythroid responses in up to 20-30% of selected patients. Additionally, thrombopoetin receptor agonists seem to be a potent strategy in reducing the risk of bleeding in patients with severe thrombocytopenia. The innovative use of immunomodulatory drugs like lenalidomide potentially offers the greatest potential to achieve long-term transfusion independence for selected karyotypes. Other therapeutic approaches include the use of HDAC-inhibitors.
In high-risk MDS treatment with DNA-methyltransferase inhibitors (MTI) such as 5-azacytidine, has changed the natural course of the disease and prolonged survival compared to supportive care only. However, with the rare exception of patients who achieve long lasting remissions with chemotherapy, allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only modality with proven curative potential. Although improvements in donor selection, post-grafting immunosuppression and supportive therapy have been achieved, allogeneic HSCT after standard conditioning remains restricted to a small minority of younger patients. The development of reduced intensity conditioning regimens may allow patients with higher age or comorbidities to undergo this procedure. Published reports suggest that allogeneic HSCT can be successful in elderly patients and possibly provide a survival advantage compared to non-transplant approaches. However, a reduction in the intensity of the preparative regimen is associated with a higher risk of relapse after HSCT. Identification of clinical markers, which might help in selecting older patients who are likely to benefit from HSCT and in determining the optimum time point for HSCT would be helpful. Current approaches focus on the relevance of pre-transplant therapy with additional efforts to integrate preemptive strategies post transplantation in order to improve outcome of patients undergoing allogeneic HSCT.

Disclosure: Uwe Platzbecker: Advisory Role: Amgen, Celgene, GSK, Novartis; Honoraria: Amgen, Celgene, GSK, Novartis; Financing of Scientific Research: Celgene, Novartis

Fortbildung
Qualitätsindikatoren in der Onkologie - Qualitätsmessung und Versorgungssektoren

V272
Quality indicators in outpatient cancer care

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Background: Measuring and comparing quality of care at the level of individual institutions requires exactly defined measurement parameters, so-called quality indicators. Apart from a few exceptions concerning application of systemic therapies, though, there is a lack of quality indicators for outpatient cancer care in Germany. Within a project sponsored by the German Cancer Aid, the Scientific Institute of Hematologists and Oncologists in Office Practices - WINHO - aims at developing both generic and tumor entity specific indicators. Regarding the latter, health care for patients with breast and colorectal cancers, respectively, is initially envisaged.
Methods: At the start of a multi-stage developmental process, major aspects of outpatient cancer care from the view of both patient representatives and oncologists were explored in semi-structured interviews. Concurrently, inter-

nationally available indicators were identified in a comprehensive search in the internet as well as in scientific literature data bases. The resulting preliminary indicator list was, beneath other relevant materials, used as a basis for specifying quality indicators for outpatient cancer care in Germany. Subsequently, within a two-step rating procedure, these indicators were assessed with regard to their clarity, unambiguousness as well as various criteria concerning their relevance and meaningfulness. The ratings of the first round, yielded from a total of 25 domain experts, were used to refine indicator specifications which were afterwards rated a second time.
Results: The preliminary indicator list encloses a total of 207 quality indicators. However, on the one hand, these indicators are in parts substantially redundant; on the other, they differ greatly in the precision of their respective specifications. Altogether, a number of 67 indicators have been developed for outpatient cancer care in Germany. From these, a large majority (n=52) concern generic aspects of cancer care (e.g., documentation, pain management). While 37 indicators were consistently positively evaluated in the first round, a total of 30 indicators yielded heterogeneous ratings. Results of the second round will be reported as well.
Conclusions: After developing a first set of quality indicators relevant for outpatient cancer care in Germany, the next step consists of examining the feasibility of assessing these indicators based on data abstraction from patient charts.

Disclosure: Gudrun Klein: Employment or Leadership Position: Angestellte des Wissenschaftlichen Instituts der Niedergelassenen Hämatologen und Onkologen (WINHO) GmbH
Walter Baumann: Employment or Leadership Position: Geschäftsführer des Wissenschaftlichen Instituts der Niedergelassenen Hämatologen und Onkologen (WINHO) GmbH; Advisory Role: siehe 1.; Honoraria: in seltenen Fällen.

V274

Qualitätsmessung in der Onkologie – deutlich schwerer als gedacht

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Die Darstellung von Versorgungsqualität wird von verschiedenen gesetzlichen Grundlagen auch in der Onkologie gefordert. Daneben sind zunehmend Qualitätsberichte, Rankinglisten, Webportale und Patientenführer zu finden, die sich ebenfalls der Darstellung onkologischer Versorgungsqualität verschrieben haben. Die Ziele dieser Darstellungen reichen von reinem Marketing über ökonomische Druckinstrumente, von gesundheitspolitischen Überlegungen und unabhängiger Patienteninformation bis zu wissenschaftlichen Interessen. Die Qualität dieser Darstellungsformen ist sehr unterschiedlich. Methodische Überlegungen treten in vielen Darstellungen aus Unkenntnis oder bewußt hinter die Ziele zurück.
Häufig kommt es zur Vermischung von Kennzahlen und Qualitätsindikatoren. Letztere wurden bisher vor allem in der Onkologie nur wenig systematisch entwickelt. Insbesondere die Bewertung, Risikoadjustierung, Interpretationsrichtlinien sind selten vorhanden. Dieses Defizit trifft auch nicht unerheblich für die in den aktuellen Leitlinien geforderten Kennzahlen zu.
Für die Weiterentwicklung der Qualitätsmessung in der Onkologie ist daher zu fordern, dass Qualitätsindikatoren systematisch entwickelt und bewertet werden. Der Einsatz muss zielgruppenspezifisch erfolgen und entsprechenden Veröffentlichungskriterien unterliegen. Eine „GCP“ als „Good Communicative Practice“ sollte in die publikatorische Arbeit mit Qualitätsindikatoren Einzug halten. Anforderungen an die Außendarstellung von Qualitätsindikatoren sind

- Definition der Zielgruppe(n), für die der Indikator entwickelt und geprüft wurde, und diese erhält eine zielgruppenspezifische Darstellung der Ergebnisse
- Verständlichkeit der Gesamtdarstellung für die jeweilige Zielgruppe
- Eindeutige Kennzeichnung und Trennung von deskriptiven Kennzahlen und Qualitätsindikatoren
- Darstellung qualitätsunabhängiger Einflussfaktoren
- Darstellung der Aussagefähigkeit des Indikators

Qualitätsindikatoren wurden methodisch als Managementtolls entwickelt und das sollten dies auch in der Onkologie bleiben.

Disclosure: Jörg Haier: Advisory Role: Onkis (KV-WL); Honoraria: Wyeth, Merck, Serono, Inmedea; Financing of Scientific Research: Roche Pharma

V275

Development of quality management in outpatient oncology

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The progress of oncology in recent decades is characterized by an increasing outpatient long-term health care by specialized doctor´s offices and outpatient clinics. The rapid development was mainly promoted by the “oncologic contract” from 1994 and the implementation of a quality management (QM) according to the ISO-9001 norm in many practices (in 2008 >60%). The combination of the structural quality indicators (QI) of the “oncologic contract” with the ISO-9001 QM has proven very efficient, if a “very high patient satisfaction” and a comparatively “long-term survival” are accepted as valid efficacy QI.
Since Jan. 2004 every practice is obliged to implement a QM, described more precise by the public health authority (GemBA) in Jan. 2006. Whereas in the past structural QI were accepted, now the public quality discussion primarily require procedural QI for measurement of quality, although the value of the already established QIs was not validated before. Procedural QI demand a relevant higher density of documented data. It is reasonable to use procedural QI for all kinds of interactive procedures like combined treatment modalities and interdisciplinary approaches in cancer treatment or the cooperative care giving of clinics and practices. If procedural QI are extensively used to quantify the quality of each single treatment by a single specialized oncologist, the danger of decreasing quality of care is imminent. In that case the focus of the oncologist will shift from optimal medical treatment of the patient to an optimized, complete documentation for the controllers. The differences in structure and action between hospitals, oncologic centers or multi professional teams on one hand and a practice, outpatient clinic or a single oncologist on the other must be taken into consideration when a new set of QI should be introduced. Therefore the WINHO (Wissenschaftliches Institut der Niedergelassenen Hämatologen und Onkologen) in Germany plans to compose a set of validated structural and procedural QI for measurement of quality in outpatient oncology.
In conclusion from the viewpoint of oncologic practices there are the following requirements:
A) The constraint for documentation as low as possible.
B) A compensation for documentation needs.
C) A validation of the new set of QI and their adequacy for measurement of oncologic quality in comparison with the well-established QI in a timely manner.

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Freie Vorträge
CML klinisch

V276

High dose imatinib 800mg induces higher major molecular response (MMR) rates than imatinib 400 mg ± IFN in newly diagnosed BCR/ABL positive chronic phase CML: A randomized comparison of the German CML-Study IV

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Initial imatinib therapy was never optimized. Faster induction of remissions (MMR,complete cytogenetic remission; CCR) in CP by imatinib 800 mg has been reported. The German CML Study Group therefore compared imatinib 800 mg (IM 800) with standard dose imatinib ± IFN (IM 400, IM 400 + IFN) in newly diagnosed CML in a randomized clinical trial. By April 30, 2009, 1022 chronic phase CML patients have been randomized. Comparison was for molecular (MMR rate at 12 months) and cytogenetic remissions, overall (OS) and progression free (PFS) survival and toxicity. 1016 patients were evaluable at baseline, 954 for survival analysis (305 for IM 400, 310 for IM 800, 339 for IM 400+IFN), 845 for cytogenetic and 871 for molecular remission. The three groups were similar regarding median age, sex, median values of Hb, WBC, platelets and EURO score. Median follow-up was 28 months in the imatinib 800 mg arm and 47 (44) months in the imatinib 400 mg ±IFN arms, respectively. The difference is due to the fact that the IM 800 arm started later. The median daily doses of imatinib were 646 mg (209- 800 mg) in the IM 800 arm and 400 mg (184- 720 mg) in the IM 400 ± IFN arms. MMR rate at 12 months was significantly higher with IM 800 than with IM 400 (p=0.0001) or IM400+IFN (p=0.0009). Also CCR was reached faster with IM 800. After 24 months the difference for MMR and CCR was still significant. In an analysis "as treated" patients receiving more than 600 mg/day reached remissions faster than those receiving lower dosages (CCR after a median of 7.8 vs. 8.9 months, MMR after a median of 10.4 vs. 12.9 months). OS (92%) and PFS (88%) at 5 years showed no difference between treatment arms. Type and severity of adverse events (AE) at 12 months did not differ from those expected. Hematologic (thrombocytopenia 7% vs. 4%) and non-hematologic AEs (gastrointestinal 35% vs. 15-24% and edema 29% vs. 16-19%) were more frequent with IM 800, fatigue (14% vs. 7-13%) and neurological problems (15% vs. 6-7%) more frequent with IM 400 + IFN. In conclusion, these data show a faster achievement of MMR and CCR with IM 800 as compared to IM 400 ± IFN up to 24-36 months after start of treatment. The data indicate that the optimal imatinib dose in CP is higher than 400 mg per day. Longer observation is required to determine whether this more rapid achievement of MMR and CCR will translate into better OS or PFS.

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V277

Four-year follow-up of patients with chronic-phase chronic myeloid leukemia (CP-CML) receiving dasatinib 100mg once daily

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Background: Dasatinib, a potent tyrosine kinase inhibitor, is indicated for treating imatinibresistant or -intolerant patients with CML (all phases) or Ph+ acute lymphoblastic leukemia. Based upon results of a phase III dose-optimization study (CA180-034), the approved dosing regimen for patients with CP-CML with resistance, intolerance, or suboptimal response to imatinib was changed to 100mg once daily from the initially approved 70mg twice daily. This study assesses the efficacy and safety of dasatinib 100mg once daily with a minimum follow-up of 48 months.
Methods: Study design and endpoints have been described previously. Patients were randomized using a 2x2 factorial design to 1 of 4 treatment arms: 100mg once daily (n=167), 50mg twice daily (n=168), 140mg once daily (n=167), and 70mg twice daily (n=168).
Results: Similar response rates were achieved in all arms and similar rates of progression-free survival (PFS; defined as no loss of complete hematologic response or major cytogenetic response, development of advanced disease, elevated white blood cells, or death as recorded by site investigators) were observed in resistant patients with or without baseline BCR-ABL mutations. At the 36-month follow-up, the PFS rate with 100mg once daily was highest (Table). PFS data from a minimum follow-up of 48 months will be presented. The long-term safety profile of dasatinib 100mg once daily will also be described. The likelihood of eventually achieving long-term endpoints based on cytogenetic status at 6 and 12 months will be determined.
Conclusions: With a minimum follow-up of 48 months, dasatinib 100mg once daily offers an acceptable benefit-risk profile for patients with CP-CML who are resistant, intolerant, or suboptimally responsive to imatinib. The landmark analyses and the long-term data to be shown will provide useful outcome information to clinicians treating patients with dasatinib according to achieved responses at key intervals, particularly among those with an allogeneic stem cell transplantation option.

Disclosure: Philipp Le Coutre: Honoraria: BMS, Novartis; Financing of Scientific Research: Novartis
Giuseppe Saglio: Advisory Role: BMS, Novartis; Financing of Scientific Research: Novartis; Expert Testimony: BMS, Novartis

Table. PFS/OS (for Abstract V277)

	100mg once daily	70mg twice daily	140mg once daily	50mg twice daily
24-month CCyR (last assessment)	50%	53%	50%	49%
36-month PFS	73%	67%	60%	72%
36-month OS	87%	80%	84%	84%

V278

Significantly higher and more rapid cytogenetic and molecular responses can be achieved in *pre-treated* chronic phase CML patients with high doses of Imatinib as induction therapy (800 mg/day, 6 months) – final results of a Phase III CELSG CML11 "ISTAHIT" TRIAL

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Introduction: Imatinib 400 mg/day represents the current standard treatment for patients with chronic phase (CP) CML. Recently presented randomized phase III trials revealed conflicting results concerning the more potent efficacy of high dose imatinib.

Methods: We present the final results of a multicenter, randomised, 2-arm phase III CELSG "ISTAHIT" trial evaluating imatinib high dose (HD) induction (800 mg/day, 6 months) followed by 400 mg/day as maintenance (experimental arm B) compared to continuous imatinib standard dose (400mg/day; arm A) in pre-treated CP CML patients (*ClinicalTrials.gov Identifier: NCT0032726).*

Results: 113 patients were randomized into arm A and 114 patients into the experimental arm B. No significant differences between treatment groups were observed regarding sex, age and different pre-treatments, which included hydroxyurea (96%), interferon (72%), busulfan (17%) and "others" (26%; mainly AraC). In contrast to complete hematological responses, major cytogenetic responses (MCyR) were significantly higher at 3 and 6 months in the HD arm B (month 3: 25.8% arm A, 48.3% arm B, p=0.002; month 6: 41.9% arm A, 58.8% arm B, p=0.029) and thereafter during the imatinib maintenance phase (month 7 to 24; month 12, i.e. the primary endpoint: 56.8% arm A, 64.4% arm B; month 24: 71.3% arm A, 73.9% arm B), but did not reach statistical significance. Moreover, complete cytogenetic response (CCyR) rates were significantly improved during imatinib HD therapy (month 3: 7.5% arm A, 29.9% arm B, p< 0.001; month 6: 20.4% arm A, 47.4% arm B, p< 0.001) and thereafter (month 12: 31.8% arm A, 52.9% arm B, p=0.006). In line with these findings, major molecular response (MMR^{IS}) rates were also significantly better at 3, 6 and even at 24 months in the HD arm B (month 3: 4.5% arm A, 15.7% arm B, p=0.007; month 6: 10.3% arm A, 34.3% arm B, p< 0.001; month 24: 27.4% arm A, 43.2% arm B, p=0.036). In contrast to comparable non-haematological toxicities during the first 6 months of therapy, grade 3/4 haematological toxicities were significantly more common in the imatinib HD arm B.

Conclusions: Although the primary endpoint (i.e. the achievement of a MCyR at 12 months) was not achieved, this first randomized phase III trial in pre-treated CP-CML patients supports the concept of more rapid and higher rates of cytogenetic and molecular remissions with higher doses of imatinib and confirms the safety and therapeutic efficacy of imatinib in heavily pre-treated CP CML.

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V279

Optimization of imatinib therapy by combination. Final results of the pilot phase of the randomized German CML Study IV

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In a substantial minority of CML patients imatinib fails or shows suboptimal responses. A randomized study was designed to compare standard imatinib vs. imatinib + interferon alpha (IFN) vs. imatinib + low dose araC vs. imatinib after IFN failure (for low- and intermediate-risk patients). Inclusion criteria were newly diagnosed BCR/ABL positive CML in chronic phase (CP). Primary aims are: prolongation of overall (OS) and progression free survival (PFS), rates of hematologic, cytogenetic and molecular remissions and adverse events (AE). The current evaluation represents the final results of the pilot phase of the trial. By the end of 2005, 670 patients were randomized, 13 had to be excluded. 657 patients were evaluable for hematologic (174 with imatinib 400 mg, 196 with imatinib+IFN, 158 with imatinib+araC and 129 with imatinib after IFN-failure), 614 for cytogenetic, and 600 for molecular responses. Patient characteristics of treatment arms were similar for age, sex, median values for Hb, WBC, platelets and for Euro risk score. Median observation time was 62.3 months. 55 patients died, 73 patients were transplanted in 1st CP, 81 patients progressed, 59 patients were switched to other tyrosine kinase inhibitors. 5-year OS of all patients is 92%. 5-year PFS of all patients is 87%. There is no significant survival difference between the treatment arms. At 5 years, the cumulative incidences of achieving complete cytogenetic remission or major molecular remission as determined by competing risks (death, progression) are not different. Type and severity of adverse events (AE) over a 5-years period did not differ from those reported previously. Hematologic AEs grade III/IV were similar in all therapy arms except leukopenia grade III/IV, which was more frequently observed in the imatinib after IFN arm (14%). Non hematologic AEs: Neurologic symptoms and fatigue were more often reported for the therapy arms with IFN. This analysis shows superior survival and durable response rates in all arms. Currently, survival in all treatment arms is equal to, or better than in IRIS. To verify possible differences in survival, e.g. imatinib 400 mg vs. imatinib + IFN, longer observation is planned. Imatinib in combination with, or after IFN, or with low dose araC are feasible and safe treatment modalities. We expect that the study will optimize and improve therapy outcome in CML.

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V280

Improved outcome of transplant in patients with CML

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We have evaluated the outcome of 185 patients who received an allogeneic transplant for CML in our centre since 2002. 124 patients were transplanted in 1.CP of CML from a HLA id. unrelated (URD) (n=70) or sibling donor (SIB) (n=54) who had failed or did not tolerate treatment with a tyrosine kinase inhibitor (TKI). Patients transplanted from a SIB had a 5-yr estimate for overall survival (OS) of 87% (EBMT score at median 2, range 1-4) and pat. transplanted from an URD had a 5-yr estimate for OS of 80% (EBMT score median at 3, range 1-5). All patients received a myeloablative conditioning regimen including in most cases a total body irradiation regimen.
The incidence of acute GVHD grade 2-4 was 70.2% for patient transplanted in 1.CP from URD. Further, 77% of these patients developed a chronic GVHD. Haematological relapse occurred in 11 pat. (18.7%) from which all except one could be successfully treated with DLI, interferon or TKI. The majority of pat. (74.5%) who were transplanted from HLA id. sibling donor received a graft with highly enriched CD34+ cells without any posttransplant immunosuppression and posttransplant adoptive DLI), whereas 25.5% received an unmanipulated graft. Acute GVHD grade 2-4 occurred only in 30% of all patients transplanted from a HLA-identical sibling donor. In 38.2 % of these patients a chronic GVHD occurred, mainly after DLI application. 38 of 42 patients transplanted with CD34+ stem cells received adoptive DLI with or without TKI or/and Interferon alfa due to the occurrence or persistence of moleculare relapse. Only 5 of these patients developed a haematological relapse.
Further, we evaluated 61 pat.with CML in more advanced disease phase with an EBMT score at median of 5 (range 2-8). 55.7% (n=34) were transplanted in 2nd or 3rd CP, 23% (N=14) in acceleration and 21.3% (n=13) in blast crises of CML. The 5-yr estimates for OS declined with increasing EBMT risk score as expected. Pat. with advanced disease phase of CML had an OS of 55%, 45.5% and 15.4 %, respectively. Acute GVHD occurred in 51.8% of all patients, whereas a hematological relapse occurred in 18% 22% and 71.5%, respectively. However, relapse remained the major cause of treatment failure in these patients.
In conclusion, for CML patients the results of allogeneic transplant improved in the recent years and transplant remains especially for pat. with low pretransplant EBMT scores, a highly effective second-line alternative therapy option.

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V281

Evolution of blast crisis (BC) in chronic myeloid leukemia (CML) in the imatinib-era: A rare but early event; need for rapid detection. Results of the German CML Study IV.

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Blast crisis (BC) in CML in the imatinib era is a rare event, but prognosis once it has occurred remains poor. Studies with tyrosine kinase inhibitors (TKI) reported a median survival time of 7-10 months. We aimed to characterize the evolution to BC within the randomized German CML study IV which compares imatinib based strategies in chronic phase CML. By April 2010, BC was observed in 53 patients (pts) out of 1452 randomized pts, with equal distribution amongst the treatment arms. 36 pts (67%) were male. 21 pts (41%) had myeloblastic, 16 pts (30%) lymphatic, and 4 pts (8%) other BC; 11 pts (21%) were not classifiable. At diagnosis of CML, 23 pts (43%) had low, 17 intermediate (32%) and 13 high risk (25%) according to the Euro score. Median age at diagnosis was younger for male pts (41 years; range 18-79) than for female pts (57 years; range 19-77). Median time from diagnosis to onset of BC was 11.5 months (range 0.7-71). Prior to BC, all pts had received imatinib except one who received interferon alpha (IFN) and dasatinib. Two pts had received allogeneic stem cell transplantation (alloSCT) and four other TKIs before BC. Additional chromosomal aberrations (ACA) were detected more frequently in BC pts (18 of 49 or 37%) than in pts without BC (95 of 1,095 pts or 9%) at diagnosis. Cytogenetics at onset of BC were available for 31 pts: 23 pts (76%) had ACAs. 17 (10 different) BCR-ABL mutations were detected in 14 of 33 pts (42%). Median follow-up after BC was 34 months (range 2.3-53). 24 patients were transplanted, 10 pts were treated with other TKI, 4 of these were also transplanted, 16 received other therapies (imatinib in combination with chemotherapy n=7, chemotherapy alone n=9), one no therapy. 32 pts died. Only 19 of the 51 pts (37%) were alive, 16 of them (84%) after alloSCT. 2 pts are alive on second generation TKI and one on busulfan. Median survival after BC was 11.6 months, survival probability at two years was 35%.
BC occurred early after diagnosis in a high proportion of low risk patients and more frequently in pts with ACA at diagnosis. Survival data of BC pts within this study are higher than previous reported. The best chances for survival were by alloSCT. The short median time to BC indicates that evolution to BCR-ABL independence might have occurred already prior to start of imatinib therapy. Early identification of such pts is warranted for an early transplantation.

Disclosure: No conflict of interest disclosed.

Freie Vorträge
Prostata/Urothelkarzinom

V285

Human endogenous retrovirus transcriptional activity in the urothelium is altered in urothelial carcinoma

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Introduction: Human endogenous retroviruses (HERVs) account for up to 9% of the human genome and significantly contribute to the human transcriptome. HERVs have a long history not only as potential pathogens, but also as a source of genetic variation, genome evolution and modulation of gene expression. Moreover, they give rise to disease-associated peptides that can serve as diagnostic markers or targets for T-cell based immune responses. Since HERV activity is often altered in tumors we set out to comparatively investigate transcriptional HERV activity in nonmalignant urothelium and urothelial carcinoma.
Methods: We performed a retrovirus-specific microarray (RetroArray) analysis of overall HERV transcriptional activity in 16 pairs of nonmalignant urothelium (NU) and urothelial carcinoma (UC) samples each derived from the same patient. Selected HERVs were further analyzed by quantitative real-time PCR (QRT-PCR). Active HERV loci were determined by PCR product cloning and sequencing.
Results: Analysis of nonmalignant tissue samples revealed a distinct, urothelium-specific HERV expression profile that consists of six constitutively active HERV taxa. For corresponding tumor samples the general expression profile was confirmed and a trend towards an increased incidence of active HERV taxa was observed, suggesting common regulatory mechanisms. In contrast, QRT-PCR for HERV-T, HERV-E4-1, and HERV-K(HML-6) revealed decreased transcription levels for HERV-E4-1 in tumors (p=0.037) and a similar tendency for HERV-T and HERV-K(HML-6) sequences. HERV locus analysis revealed *de novo* activation of some and increased or decreased transcript levels of several HERV-E and HERV-T proviral elements. Two differentially

active HERV-E loci were found situated in the introns of the genes PLA2G4A and RNGTT in antisense orientation.
Conclusion: We established for the first time a consistent HERV expression profile specific for the human urothelium. Several HERV transcripts identified in urothelium match those observed in other human malignancies. Distinct proviruses are activated in UC and thus, join the list of potential agents that may be related to carcinogenesis or represent novel disease markers. Furthermore, intronic HERV-E proviruses with the potential to contribute to antisense regulation of two cellular genes were identified. Their intronic situation encourages future studies aimed at the relevance of mobile genetic elements in gene expression and carcinogenesis.

Disclosure: No conflict of interest disclosed.

V286

Novel prognostic biomarker signature in the serum of patients with castration resistant prostate cancer (CRPC) based on quantitative analysis of Pten conditional knockout mouse proteome can predict survival with better accuracy than traditional clinical nomograms

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Background: Men with metastatic CRCP have a poor prognosis with a median survival of 16 to 20 months. The course of the disease is heterogeneous. Prognostic information would aid treatment decisions, but nomograms based on clinical are often weak in prognostic accuracy. As rebiopsy is rarely indicated in CRPC, new prognostic serum biomarkers are on high demand. PTEN inactivation has particular relevance to prostate cancer initiation and progression, as is shown by results derived from murine models of prostate cancer by deleting the PTEN tumor suppressor gene specifically in the prostatic epithelium
Methods: 58 patients with CRPC were evaluated retrospectively. Prognostic factors used in clinical nomograms were assessed from the records. New candidate biomarkers were derived from a screen of the murine Pten-dependent glycoproteome and measured by SRM and ELISA in patients' sera. Prognostic and predictive biomarkers for survival were identified based on Kaplan-Meier models. In a second step Random Forest Analysis was performed to identify prognostic and predictive signatures combined from the pooled data of known predictors and newly identified biomarkers.
Results: Univariate analysis showed 15 significant prognostic factors for survival with a Bonferroni-corrected level of significance < 5%. Random forest analysis revealed a five factor prognostic signature, including CRP which has formerly been shown to be a predictive biomarker for survival in CRPC, and four previously unknown biomarkers, predicting survival with only 24% error. This reduces the error in survival prediction by more than 15% compared to known clinical predictors. The known clinical nomograms that were applied to our data as a reference showed accuracies in the exact range as reported in the literature.
Discussion: Large scale targeted measurement of 88 proteins in CRPC patients sera revealed 11 previously undescribed candidate biomarker for survival. The present study is to our knowledge the first attempt to combine novel serum biomarkers in CRPC derived from an experimental model based on a biological rationale with formerly validated biomarkers that are routinely used in prognostic nomograms. Our signature could strongly improve accuracy of prognostic nomograms. The newly identified biomarkers will be assessed in further prospective studies. Doubtlessly the newly identified molecules are interesting candidates as targets for future tumor directed therapies in CRPC.

Disclosure: No conflict of interest disclosed.

V287

Urine from current smokers induces centrosome aberrations and spindle defects *in vitro* in non-malignant human cell lines

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Introduction: Tobacco smoke containing numerous derived chemical carcinogens and causing reactive oxygen species is the main risk factor for urothelial carcinoma (UC). These carcinogens can induce DNA damage leading to chromosomal instability (CIN) which plays a fundamental role in urothelial carcinogenesis. Possible mechanisms leading to CIN could be centrosomal aberrations which cause defective spindles and may be responsible for genetic instability and aneuploidy.
Methods: We have established an *in vitro* model that simulates the effects of smoker urine on bladder epithelium. We evaluated the effect of urine from never smokers (NS) and current smokers (CS) in concentrations of 0 to 50% *in vitro* on cell proliferation, chromosomes, centrosomes and the mitotic spindle of normal human dermal fibroblasts (NHDF) and normal human urothelium cells (UROtsa), both with normal karyotypes (46,XY and 46,XX, respectively). After two weeks of urine treatment, cell cultures were analyzed by centrosome and spindle immunostaining and conventional cytogenetics. Effects were compared to results from untreated controls.
Results: Analysis of NHDF and UROtsa cells revealed that urine from CS induced higher numbers of centrosome aberrations in a dose-dependent and cell line-independent manner when compared to cultures treated with urine from NS and untreated controls (for NHDF cells values are statistically significant $p < 0.025$). Centrosomal alterations correlated with spindle defects, an increase of sporadic chromosomal aberrations and a decline of cell proliferation as measured by Trypan blue staining.
Conclusions: Our observations suggest a causative role of chemical carcinogens in urine from CS in the origin of centrosome and spindle defects *in vitro* leading to CIN and aneuploidy and may significantly contribute to urothelial carcinogenesis.

Disclosure: No conflict of interest disclosed.

V288

MAGE-C2/CT10 protein expression is an independent predictor of recurrence in prostate cancer

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Introduction: The cancer-testis (CT) family of antigens is expressed in a variety of malignant neoplasms and is silent in normal tissues, except germ cells. CT antigen expression is rare in prostate cancer. MAGE-C2/CT-10 is a novel CT antigen. The objective of this study was to analyze extent and prognostic significance of MAGE-C2/CT10 protein expression in prostate cancer.
Methods: 348 prostate carcinomas from consecutive radical prostatectomies, 29 castration-refractory prostate cancer, 46 metastases, and 45 benign hyperplasias were immunhistochemically analyzed for MAGE-C2/CT10 expression using tissue microarrays.
Results: Nuclear MAGE-C2/CT10 expression was identified in only 3.3% primary prostate carcinomas. MAGE-C2/CT10 protein expression was significantly more frequent in metastatic (19.4% positivity) and castration-resistant prostate cancer (21.7% positivity; $p < 0.001$). Nuclear MAGE-C2/CT10 expression was identified as predictor of biochemical recurrence after radical prostatectomy ($p=0.015$), which was independent of preoperative PSA, Gleason score, tumor stage, and surgical margin status in multivariate analysis ($p < 0.05$).
Conclusions: MAGE-C2/CT10 expression in prostate cancer correlates with the degree of malignancy and indicates a higher risk for biochemical recur-

rence after radical prostatectomy. Based on these results MAGE-C2/CT10 is suggested as a potential target for adjuvant and palliative immunotherapy in patients with prostate cancer.

Disclosure: No conflict of interest disclosed.

V289

The role of soluble adenylyl cyclase in proliferation and apoptosis of prostate cancer

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Introduction: Stimulation of apoptosis is a promising strategy for the prevention of tumor growth. cAMP-signaling plays an essential role in modulating apoptosis in different cell types. Till now the role of this pathway was restricted to the membrane-bound adenylyl cyclase. In the present study, the contribution of the alternative source of cAMP, i.e. soluble adenylyl cyclase (sAC), was investigated in prostate carcinoma cell lines, i.e. LNCaP and PC3, which demonstrate a marked sAC-expression.
Methods/Results: For this purpose LNCaP and PC3-cells were treated with KH7 (Cayman), a specific inhibitor of sAC. Apoptosis was evaluated by caspase-3 cleavage (western blot) and by appearance of subG1 population (flow cytometry). KH7 dose-dependently reduced cellular cAMP content with maximal effect at 20 μM. With the similar dose-dependence KH7 suppressed proliferation of both cell lines and induced a rise in LDH-release and apoptosis. In contrast, an inactive analogue of KH7, i.e. KH7.15 (ChemDiv) had no effect on all these parameters. To demonstrate the applicability of the sAC inhibitor in a clinically relevant setup we further combined sAC inhibition with γ-irradiation. Treatment with KH7 at concentration closed to IC_{50} (10 μM) allowed the reduction of the γ-irradiation by 50%, i.e. 5 Gy instead of 10 Gy, to reach the similar anti-proliferative and pro-apoptotic effect. The western blot analysis revealed a pronounced expression of sAC in biopsies from human prostate carcinoma and only a weak expression of this cyclase in benign prostatic hyperplasia.
Conclusion: sAC is overexpressed in human prostate carcinoma and plays a significant role in its proliferation and apoptosis. The inhibition of sAC during irradiation therapy enables reduction of the γ-irradiation doses and, therefore, may be a novel strategy to treat prostate carcinoma.

Disclosure: No conflict of interest disclosed.

V290

Cisplatin-hypersensitivity of NTERA cells is mediated through a CHK2/p53 dependent activation of NOXA

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Cisplatin-based chemotherapy is widely used for cancer therapy. Especially testicular germ cell tumors (TGCT) are cured at high rates, which was linked to a rapid and extensive induction of apoptosis. To identify key players in cisplatin-sensitivity of TGCTs we used a model based on the cell line NTERA. Pulse treatment of these cells with retinoic acid (RA) renders them about 10fold less sensitive to cisplatin allowing comparison of hypersensitive cells and cells with reduced sensitivity within the same cell system.
In a first step, we used a kinase inhibitor library to identify kinases involved in sensitivity of NTERA cells. Out of 160 kinase inhibitors only a CHK2 inhibitor reduced cisplatin sensitivity in NTERA cells. siRNA-mediated silencing of CHK2 confirmed this result. In addition, pre-treatment of the cells with RA significantly reduced CHK2 phosphorylation upon cisplatin. These results indicate a prominent role of CHK2 activation for cisplatin hypersensitivity. Since CHK2 promotes its pro-apoptotic function by phosphorylation of p53, we also silenced p53 using specific siRNAs. Indeed, silencing of p53 led to a complete loss of hypersensitivity. To examine the mechanisms behind this p53 activity, we compared the induction of p53-dependent pro-apoptotic genes BAX, PUMA, NOXA, Fas, and KILLER/DR5 in cells preincubated with or without RA. RA-treated cells showed higher basal levels of the tested mRNAs except for NOXA. Only minor differences in cisplatin-induced gene expression were observed for BAX, PUMA, Fas and KILLER/DR5. In contrast, induction of NOXA was significantly reduced in RA-treated cells suggesting a major role for NOXA in cisplatin-hypersensitivity.
To distinguish between p53-dependent apoptosis through either transcriptional activation of target genes (which should be blocked by Pifithrin-a) or direct cytoplasmic functions (inhibitied by Pifithrin-μ), NTERA cells were incubated with these Pifithrins prior to cisplatin-treatment. Pifithrin-μ prevented cisplatin-induced apoptosis whereas Pifithrin-a did not. Unexpectedly, Pifithrin-μ caused a massive decrease in the mRNA levels of the examined target genes whereas a decrease could not be achieved with Pifithrin-a.
Our results show that cisplatin-hypersensitivity is entirely dependent on p53, which is activated directly or indirectly by CHK2 upon cisplatin. One proapoptotic target of p53, namely NOXA, may have a prominent role for induction of apoptosis in these cells.

Disclosure: No conflict of interest disclosed.

Fortbildung

Evidence-based complementary and alternative medicine (CAM) in oncology

V291

Use of complementary medicine in cancer patients

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Introduction: The frequency with which cancer patients use complementary and alternative medicine (CAM) is investigated in plenty of surveys but its actual extent is a matter of discussion. No comprehensive systematic review has been published since 1998.
Methods: We systematically reviewed surveys from Australia, Canada, Europe, New Zealand and the USA assessing the prevalence of CAM use in cancer patients.
Results: 151 studies from 18 countries with more than 65,000 cancer patients were included. Many surveys had methodological drawbacks and small sample sizes. Heterogeneity of CAM use was high and to some extent explained by differences in survey methods. The combined estimate for the proportion of patients using CAM at the time of the surveys was 40% (95% CI: 33% to 47%). Meta-regression suggested an increase of CAM use over the last 30 years, especially after 2000. Within Europe, CAM use was highest in German-speaking countries.
Conclusions: The overall prevalence of CAM use found in this review was lower than often claimed. However, if on average 40% of cancer patients report to have used CAM at least once, and a certain part of them denotes themselves as committed CAM users the health care systems have to implement clear strategies how to deal with this no more longer “invisible” mainstream.

Disclosure: No conflict of interest disclosed.

V292

CAM-CANCER – A European, evidence-based information platform for health professionals

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The CAM-CANCER Project aims at providing oncologists and other health professionals with evidence-based information on Complementary and Alternative Medicine (CAM) for cancer patients.
CAM-CANCER, or the Concerted Action for Complementary and Alternative Medicine Assessment in the Cancer Field, is a European network for informa-

tion and research on CAM used in cancer treatment. The project was originally funded by the European Commission under the 5th Framework Programme.
Since the completion of the EU-funding period, this project was taken over and further developed by the National Research Center in Complementary and Alternative Medicine (NAFKAM) at the Department of Community Medicine, University of Tromsø, Norway. The CAM-CANCER Consortium involves scientific societies in several countries and bases its review work on scientific and transparent methodologies.
The CAM-CANCER website at www.cam-cancer.org provides oncologists and other health professionals with information on prevalent CAM therapies used by cancer patients. The methodology for assessing the efficacy and safety of CAM therapies is available at the website. CAM-CANCER publishes its results in the form of concise, peer-reviewed, regularly updated and freely accessible reports - called CAM summaries - with the aim of enabling clinicians to make informed decisions.
The next stages of the CAM-CANCER project will include translation of CAM summaries into European and Asian languages and further refinement of the collaborative network.

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V293

Selenium for prevention and treatment of cancer

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Introduction: Selenium is a trace element essential to humans; its role in oncology is being controversially debated.
Higher selenium exposure and supplemental selenium intake have been discussed to protect against several types of cancers, but long-term exposure to low doses has also been suspected to increase the risk of certain diseases, such as skin cancer and diabetes mellitus type II. Selenium supplements are widely used by cancer patients against adverse effects of conventional cancer therapy. Recently, selenium has also been investigated as anti-cancer drug.
This talk will give an overview of the evidence regarding the beneficial and harmful effects of selenium supplementation in cancer patients and hereby inform clinical decision making.
Methods: Two systematic Cochrane reviews on „Selenium for preventing cancer" and „Selenium for alleviating the side effects of chemotherapy, radiotherapy and surgery in cancer patients" and a non-systematic literature review on its use as anti-cancer agent were conducted.
Results: Six randomised controlled trials investigated the preventive efficacy of organic and inorganic selenium supplements against non-melanoma skin cancer, prostate cancer prevention, and liver cancer. Authors of the Cochrane review concluded that there is no convincing evidence that selenium supplements can prevent cancer in men, women or children.
Two randomised controlled trials investigated sodium selenite for the treatment of lymphoedema and the prevention of erysipelas in affected limbs after cancer surgery . Review authors concluded that it was unclear whether the reported results in these trials reflected a clinically relevant benefit of selenium supplementation.
Two trials on the radioprotective efficacy of sodium selenite in patients receiving radiotherapy of the pelvic or head/neck region found a lower rate of diarrhea in the selenium group receiving pelvic radiation, but no radioprotective effect in the ENT trial.
Only limited clinical evidence is available regarding the use of selenium as anti-cancer drug.
Cases of accidental toxic exposure have been reported; there is evidence that long-term supplementation can exhibit adverse effects.
Conclusions: Selenium supplementation in cancer patients remains a field where the widespread use contrasts with the limited clinical evidence supporting it. When counselling cancer patients, physicians should address patients' needs, but also consider safety issues.

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Marco Vinceti: No conflict of interest disclosed.

V294

The role of vitamin D in oncology

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Calcitriol, the biologically active form of vitamin D (1,25(OH)D), exerts its effects mainly through binding to nuclear vitamin D receptor (VDR). Calcitriol has been shown to be an antiproliferative, prodiffentiation, proapoptotic agent and an inhibitor of cell migration. Animal and human in vitro studies strongly indicate that vitamin D may have benefits for many forms of cancer. Inadequate levels of circulating 25-hydroxy vitamin D (25(OH)D) are associated with an increased risk and poor prognosis of several types of cancer. At the same time vitamin D appears to exert other complex effects, which result in better pain control in cancer patients.
Epidemiological data indicate that vitamin D deficiency is relatively common in Europe. Insufficient levels (< 50 nmol/l) may be found in 30-70% of healthy adults. A metaanalysis of randomized trials reported an association of vitamin D supplementation and a significant (7%) reduction in overall mortality in healthy subjects.
There is a strong inverse association between circulating vitamin D concentrations and risk of colorectal cancer in western European populations. Similarly, the risk of pancreatic cancer is associated inversely with vitamin D intake. Ultraviolet radiation exposure is associated with a lower risk of non-hodgkin lymphomas and may be associated with increased survival rates in patients with early-stage melanoma. A significant association between VDR polymorphism and incidence of skin cancer has been reported.
1,25(OH)D has antiproliferative and prodifferentiation effects in human melanoma cells and has been shown to induce apoptosis in these cell lines; it has an inhibitory effect on the spreading of melanoma cells in vitro. A recent and ongoing clinical trial is studying the effect of VDR polymorphism on Breslow thickness in early malignant melanoma. Vitamin D and analogues have antiproliferative effects in human pancreatic carcinoma as well as in hepatoma cells in vitro and in vivo.
Vitamin D supplementation reduces the risks of falling and of bone fractures. In addition, recently, vitamin D levels were shown to be associated with improved pain control and lower requirements for analgesic in cancer patients.
Thus, vitamin D appears to have an important role in cancer prevention, it might contribute to anticancer treatments and it probably has a relevant role in palliative cancer care with respect to preventing falls, fractures and pain.

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V295

Complementary medicine for treatment of menopausal symptoms in breast cancer patients – a review of clinical trials

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Many breast cancer patients suffer from side effects of their endocrine therapy. Climacteric complaints with hot flashes, night sweats, sexual dysfunction, anxiety, depression, and musculoskeletal pain lead to a worsening of therapy adherence in many cases. Concurrent therapy with SSRIs, Gabapentin or Clonidin have been shown to be effective in several RCTs, but many patients refuse to use these medications because they are afraid of additional side effects.
Complementary therapies are popular, but only during the last years quality as well as quantity of clinical research in this field is increasing. Three RCTs

with isolated soy isoflavones did not show a superiority versus placebo. Two of four clinical studies with black cohosh showed a reduction of hot flashes, in the third study there was no effect on hot flashes but sweating was reduced in the treatment group, in the fourth study there was no difference between verum and placebo. In a phase-II-study daily intake of 40g bruised flax seed reduced hot flashes by 50%. Homeopathic treatment was helpful in an observational study but positive effects were not reproducible in two following RCTs. In a recent meta analysis of acupuncture in treating hot flashes in breast cancer patients verum-acupuncture was significantly more effective than sham-acupuncture. Also a complex 8 week treatment group with yoga, meditation and breathing exercises reduced hot flashes in breast cancer patients. Two small pilot studies suggest that stellate ganglion block may decrease number and severity of hot flashes too.
Increasing quality and quantity of clinical research in complementary treatment allow a deeper understanding of optional therapeutic effects on menopausal symptoms in breast cancer patients.

Disclosure: No conflict of interest disclosed.

V296
Evidence of Chinese medicine in oncology

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Several modern drugs have been developed from Chinese decoctions (extractions by boiling of biological or chemical materials). The decoctions are based on case histories and small studies are published. For acupuncture treatment studies for symptom control (nausea & vomiting, pain control) are available. How can we prove the efficacy and the effectiveness of this experience based medical system and its potential use in connection with our standard treatments?
1. The efficacy of chinese decoctions is proven by many drugs developed from this source. Drugs, that induce cell differentiation (ATRA, ATO) and cytotoxic drugs (irinotecan, topotecan) have their roots in chinese medicine. Indirubin, that inhibits the cyclin-depending kinase-1, was developed from an old chinese decoction (Danggui Longhui Wan) and is studied for CML treatment now. From Hydroxycamptotecin widely used Topoisomerase I inhibitors were developed and newer research shows promising effects on apoptosis- inducing factor and angiogenesis.
Therefore Chinese Medicine may be seen as a reservoir for further drug development. For tumor cell destruction the use of an isolated monosubstance allows better dosing than a biological substance. But it may be worth testing for other end-points, comparing Indirubin with the Danggui Longhui Wan - Decoct for quality of life and overall survival.
2. The effectiveness must be proven in the context of established treatment standards, where new strategies hopefully wil improve prognoses. Chinese Medicine in its history was not developed for calculated cell destruction. It is based on a conclusive concept of diagnostic procedures and resulting treatment concepts to harmonise a disturbed balance inside the body. This may sound confusing from the viewpoint of western medicine, but the underlying idea to influence interaction between the healthy body and the malignant disease is in accordance with modern research (Antiangiogeneses, Microenvironment).
Research here is more difficult as Chinese Medicine is established as an individualised treatment and the composition of the decoction can change weekly. This means we will face research problems as with individualised treatments in Western Medicine. Differences occur in the aim for the individualisation (specific tumour characteristics, individual interactions). However for scientific studies the problems (large homogeneous groups) are similar. New research strategies on this treatment concepts may be necessary.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium
Aktuelle Aspekte der Therapie von Ösophagus- und Magenkarzinom

V299
Neoadjuvant and adjuvant therapy of gastric adenocarcinoma

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Background: Gastric cancer represents a major cause of cancer-related morbidity and mortality. Despite optimal surgery localised tumours that extend beyond the submucoa are associated with a 5-year survival around 20-30%. Therefore multimodal treatment may be offered to improve survival.
Methods: The most recent ASCO presentations, original reports, reviews and metaanalyses will be reviewed and the consequences drawn by the national S3 guideline committee will be discussed.
Results: Several trials compare preoperative radiochemotherapy with surgery alone for localized esophageal cancer, including adenocarcinomas of the gastroesophageal (GE) junction. Three single trials show significantly improved survival (Walsh et al. 1990, Tepper et al 2006, van der Gaast et al 2010). Several trials investigated perioperative chemotherapy in adenocarcinomas of the GE-junction and the stomach. Three trials show significantly improved survival rates (Allum et al 2009, Cunningham et al 2006, Boige et al 2007). Recent metaanayses confirm the value of preoperative radiochemotherapy and preoperative chemotherapy for esophageal, GE-junction and gastric adenocarcinomas (Gebski et al. 2007, Ronellenfitsch et al 2010), therefore preoperative radiochemotherapy or perioperative chemotherapy are accepted treatment standards.
Although sole adjuvant chemotherapy can lead to some improvement in overall survival, this approach is not recommended, as only 40 % of patients are postoperatively fit enough to receive chemotherapy. Patients who missed the recommended preoperative treatment may be considered for postoperative radiochemotherapy if they are in good general condition (Macdonald et al 2001).
Conclusion: For adenocarcinoma of the GE-junction (T3 or higher) preoperative radiochemotherapy or pre- and postoperative chemotherapy are recommended. Adenocarcinoma of the gastric body (T3 or higher) should routinely be treated with pre- and postoperative chemotherapy.

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V300
The treatment of inoperable or metastatic stomach cancer

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Stomach cancer is the second most common cancer related death worldwide. It accounts for approximately 700.000 deaths per year. Once inoperable or metastatic, stomach cancer is incurable and median overall survival with conventional chemotherapies rarely exceede 10 months. For decades, 5-fluorouracil and cisplatin represented the only systemic treatment option. However, over the last years, significant advances have been achieved. These include the development of orally administered fluoropyrimidine analogues which can be used in place of intravenous 5-fluorouracil, and the addition of newer agents such as oxaliplatin and docetaxel which have demonstrated efficacy in patients with advanced disease. Most recently, the use of trastuzumab for targeting HER-2 positive stomach cancer resulted in significant improvement of overall survival without relevant increase in toxicity. Further targeted therapies are under investigation, and it is likely that these agents will change the way we diagnose and treat stomach cancer in the future.

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Expertenseminar
Neurotoxicity – long term side effects

V301

Biological mechanismus of neurotoxicity

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Central and peripheral neurotoxicity is a limiting factor of common chemotherapeutic regimens. Beneath others, platinum derivatives, vincristine and taxanes often lead to polyneuropathies. The cumulative dose, age and dispositions like diabetes mellitus or high consume of alcohol influence the individual risk to develop a potentially painful sensory polyneuropathy, which may be accompanied by an affection of the autonomic nervous system, depending on the substance used. Several chemotherapeutic agents can also affect the central nervous system. Recovery often is incomplete. Pathophysiology of neurotoxicity include affections of the neuronal bodies and axons by impaiered mitochoandrial function, ion channel dysfuntion, transport deficits and further mechanisms. Methotrexate inhibits dihydrofolate reductase leading to a depletion of folate derivatives necessary for both nucleic acid synthesis and the methyl group donor S-adenosylmethionine (SAM). A reduction of SAM-synthesis leads to a decreased availability of methyl groups in the CNS, e.g. for neuurotransmitter and myelin synthesis. Manipulation of SAM-metabolism may be a preventive and therapeutic strategy in the case of methotrexate-induced neurotoxicity.

Disclosure: No conflict of interest disclosed.

V302

Neurotoxicity of chemotherapy

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Chemotherapy-induced toxicity might affect the central nervous system (CNS), cranial nerves, the peripheral nervous system (PNS) and the autonomous nervous system. Side effects may occur immediately, early, late or even after completion of therapy. Substances known to harbour a high risk of CNS toxicity are methotrexate (MTX), cytarabin (ara-C), ifosfamide (Ifo), cisplatin, 5-fluorouracil and others; substances with a well known toxicity to the PNS are vinca-alkaloids, platinum-derivates, bortecomib and others. A severe, but infrequent complication is progressive myelopathy with ascending tetraparesis after intrathecal administration of MTX and ara-C, in particular as part of a triple-therapy including steroids.
Therapeutic measures are limited after occurrence of neurotoxicity and prognosis might be dismal. Therefore careful monitoring and prophylaxis is essential, as e.g. thiamine administration to prevent Ifo-induced severe encephalopathy and vitamine E application to minimize the risk of platinum induced peripheral neuropathy. It is to be considered, that patients with preexisting neurological disorders, like e.g. diabetic peripheral neuropathy are especially prone to a high risk of severe neurotoxicity. It is also of note, that single modalities potentially toxic to the CNS, as e.g. whole brain irradiation in combination with high-dose MTX, might be synergistically toxic.

Disclosure: No conflict of interest disclosed.

Expertenseminar
Neues in der Diagnostik und Klassifikation beim Multiplen Myelom

V303

Novel disease classifications in multiple myeloma (MM) as a basis for guiding MM-therapies

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The knowledge, diagnostics and treatment for MM have changed beyond recognition over the past 2 decades. During the early 1980s, MM inevitably resulted in a slow progressive decline in the quality of life until death after about 2 years (y), while today patients (pts) can expect a 50% chance of achieving a complete remission (CR), median overall survival (OS) of 5y and a 20% chance of surviving longer than 10y.
As the MM-management is rapidly changing, guidelines that incorporate strategies for the optimal control of the disease are increasingly important and help us to employ the best available care.
Criteria that differentiate MGUS, asymptomatic (smoldering) MM, symptomatic MM, solitary plasmacytoma and extramedullary MM have been defined by the IMWG. MGUS is defined by the presence of a paraprotein < 30g/l, BM clonal plasma cells (PC) < 10%, but no evidence of MM or light-chain (AL) amyloidosis. In smoldering MM, the paraprotein is ≥30g/l and/or clonal BM PC ≥10%, without related organ or tissue impairment (ROTI). MM exhibits some or all of the pathologic findings and ROTI. To precisely differentiate these distinct entities, MM-specific investigations are required and facilitate appropriately timed intervention. The clinical staging system by Durie and Salmon is based on factors correlating with tumor mass and has largely been replaced by the ISS. Advances in conventional cytogenetics (CG) and FISH have improved the ability to detect prognostically relevant chromosomal abnormalities, including del 17p, t(4;14) and t(14;16) by FISH and del 13 or hypoploidy via CG. A Mayo risk stratification model in the era of novel therapies, has evaluated FISH, CG and PCL-index that segregates pts into high- and standard-risk. Novel classification proposals have analyzed the ISS or other known risk factors in conjunction with novel parameters, such as $eGFR_{MDRD}$, free light chain-, FACS- and molecular-markers, whereby specific gene expression signatures, or tumor cell signalling (e.g. Akt) allow to define distinct MM-classifications.
Present MM-management aims at achieving a normal life with minimization of disease-related symptoms. Despite impressive advances - including an increased understanding of the pathobiology (which has translated into a broadened spectrum of available targeted therapies, giving hope to further improve pt outcome) - we still face important challenges to overcome in individual MM care, the most pending being addressed at this seminar.

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Wissenschaftliches Symposium
Medical treatment of Head and Neck Cancer

V305

Biology of head and neck cancers

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Introduction: Head and neck cancers occur in a variety of anatomical subsites and comprise a multitude of histological tumor types. However, more than 90% of these tumors are head and neck squamous cell carcinomas (HNSCC) of the oral cavity, larynx and pharynx. Although the sequence of tumor formation from preinvasive squamous lesions to metastatic HNSCC is known since decades and key molecular events such as p53 mutations have been discovered many years ago, several novel infectious, epigenetic, genetic and transcriptional alterations have been described which today allow for a better understanding of these tumors.
Results: The most important recent finding concerning the biology of HNSCC is certainly the emerging of an entirely novel subset of tumors in which not the classic risk factors but infection with human papilloma virus (HPV) is the driving force for the initiation and progression of disease. Depending on tumor site, sex, age and geographical region a varying number (between 0% and 90%) of HNSCC cases can be attributed to HPV infections. These tumors are morphologically as well as prognostically distinct and show defined infection dependent molecular alterations such as virus driven p53 and retinoblastoma pathway inactivation. The second group of HNSCC can be attributed to alcohol and tobacco smoke as major risk factors, however, several genetic polymorphisms and tumor syndromes have also been associated with this disease. The pathways suggested to be involved in the biology of conventional HNSCC include p53, the epidermal growth factor receptor (EGFR), insulin-like growth factor receptor (IGFR), phosphatidylinositol-3-kinase (PI3-K/Akt), mammalian target of rapamycin (mTOR) and nuclear factor κB (NF- κB) pathway as well as several others. In addition, modern transcriptomics have found integrin signalling as well as antigen presentation to be highly altered in HNSCC. Epigenetic changes including alterations in the microRNAome are also most prevalent in this cancer type. This talk will give a comprehensive overview on the most important findings of the above mentioned molecular alterations in HNSCC.

Conclusion: Understanding the biology of HNSCC is of utmost importance since it is known that the specific sets of molecular alterations in these tumors directly influence the response to conventional and novel targeted chemotherapeutics as well as to radiotherapy and thereby ultimately define the fate of the HNSCC patient.

Disclosure: No conflict of interest disclosed.

V306

Selected Abstract

Presence of circulating tumor cells in peripheral blood of patients with inoperable squamous cell carcinoma of the head and neck region (SCCHN) depends on nodal status

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Introduction: Lymph node metastasis frequently occurs in SCCHN and is generally associated with increased risk of locoregional relapse and development of distant metastasis. The molecular mechanisms regulating tumor cell dissemination and thus the potential targets for novel treatment strategies are still largely unresolved. In this study, we established a flow cytometric method to detect CTCs in peripheral blood samples from SCCHN patients. We determined their overall frequency and assessed their association with the stage of the primary tumor and the nodal status. In addition, we followed their kinetics during local and systemic treatment.
Methods: Peripheral blood samples from consecutive unselected 64 patients with SCCHN presenting for primary (N=23) or adjuvant first-line treatment (N=30) or for treatment of recurrent disease (N=11) were collected before initiation of treatment. The absolute numbers of CTCs defined as EpCAM+ cytokeratin+ CD45− in 3.75 ml blood were determined by flow cytometry. Multiple logistic regression analysis was performed to assess the association of T stage, N stage and total tumor volume with the presence of CTCs. In a subset of SCCHN patients (N=34) the interference of local or systemic treatment with CTC numbers was determined.
Results: CTCs were detected in 27 of 64 SCCHN patients (42%) with a mean ± standard deviation of 1.8 ± 1.4 CTCs per 3.75ml blood whereas none were found in samples from healthy donors (N=16). In the total SCCHN cohort no significant association of CTCs with clinical parameters could be observed. In patients with inoperable tumors the presence of CTCs did not correlate with T stage or tumor volume but was significantly associated with a nodal stage of N2b or higher (p=.02), which is also the major threshold for development of hematogenous metastases. This association remained significant in the multivariate logistic regression model. In the CTC+ cases sequential analyses in the course of treatment revealed a decrease in CTC numbers below detection limit in 12 patients (71%) while CTC numbers remained stable or even increased during treatment in 5 patients (29%).
Conclusions: Detection of CTCs might represent a novel non-invasive prognostic tool in SCCHN. Their prognostic relevance and potential in monitoring tumor response and predicting treatment outcome needs further evaluation.

Disclosure: No conflict of interest disclosed.

V307

Selected Abstract

Influence of AKT1, AKT2 and FRAP1 Polymorphisms on response and survival in head and neck cancer (SCCHN) patients treated with Docetaxel and Cetuximab

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Purpose: The PI3K/PTEN/AKT/mTOR signaling pathway plays a fundamental role in transmitting signals from membrane receptors to downstream targets that regulate apoptosis, cell growth and angiogenesis and it has been implicated in resistance to several chemotherapeutic agents. The aim of this study was to investigate whether single nucleotide polymorphisms (SNPs) in AKT1, AKT2 and FRAP1 (encoding mTOR) were associated with the tumor response and survival in platinum-pretreated patients (pts) with recurrent and/or metastatic head and neck cancer (SCCHN) who received cetuximab (400 mg/m^2 week 1 then 250 mg/m^2/wk) plus docetaxel (35 mg/m^2 d 1, 8, 15 q 4 wk) for a maximum of 6 cycles in a phase II study (CETAX).
Methods: Six single SNPs in AKT1 (rs3803304, rs2494738), AKT2 (rs892119, rs8100018) and FRAP1 (rs892119, rs2295080) were genotyped by means of Real Time PCR system and analysed for association with response to therapy and survival.
Results: Forty-seven pts (37 male, 10 female) were evaluated (median age: 60 yrs [range: 46-75 yrs]; primary tumor site: hypopharynx 13; oropharynx 12; oral cavity 10, other 7). Twenty-eight pts were evaluable for response. The median follow up was 7 months [0-16 months]. We observed an increased risk of progression with the genetic variation AKT1:rs3803304 (Hazard ratio [HR], 4.33; 95% CI, 1.19 to 15.86, p= 0.027). Pts homozygous for AKT1:rs3803304 experienced a shorter progression free survival (PFS) than those either heterozygous or with a wild-type genotype (p=0.015). In contrast, AKT2, FRAP1 and the SNP AKT1:rs2494738 were not associated with an increased recurrence risk, neither with a shorter PFS. Genetics variation in AKT1, AKT2 and FRAP1 were not associated with overall survival or response.
Conclusions: AKT1:rs3803304 might modulate clinical outcomes in SCCHN pts who received cetuximab plus docetaxel. Within KRAS and BRAF mutation analyses these findings may serve as potential markers for may be used to modelling the treatment strategy for the selection of the optimal treatment regimens.

Disclosure: No conflict of interest disclosed.

Fortbildung

Gerinnung

V309

Implications of current clinical practice guidelines for the prevention and treatment of cancer-associated thrombosis

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Coagulation activation is a characteristic feature of most malignancies and may become clinically apparent as venous thromboembolism (VTE), a potentially life-threatening complication commonly referred to as Trousseau's syndrome. The pathophysiology of cancer-associated VTE comprises all aspects of Virchow's triad (i.e. stasis, endothelial damage and hypercoagulability) and gains additional complexity due to the thrombogenic side effects of novel anti-angiogenic agents such as lenalidomide or bevacizumab. Particularly, tissue factor (TF) circulating in plasma in association with tumor-derived microparticles contributes to intravascular coagulation activation in various types of malignancy. In this regard, evidence emerges that the procoagulant phenotype of cancer cells is, at least in part, controlled by defined genetic events in molecular tumorigenesis. Furthermore, by promoting angiogenesis and hematogenous metastasis, several components of the activated hemostatic and fibrinolytic systems are directly involved in tumor progression. Because hematologists and oncologists increasingly recognize cancer-associated VTE as a major contributor to morbidity and mortality, international societies have recently provided or updated clinical practice guidelines for the prevention and treatment of Trousseau's syndrome: In the surgical cancer patient, pharmacological VTE prophylaxis has proven efficacious, and extended prophylaxis for 3-4 weeks is recommended for patients at very high risk. Based on post-hoc subgroup analyses, primary VTE prophylaxis with low-molecular-weight heparin (LMWH) or fondaparinux is also recommended for hospitalized medical cancer patients, but no randomized controlled trial has been specifically conducted on this patient population. Due to conflicting study results and an overall low incidence of VTE, prophylactic anticoagulation is not routinely recommended for cancer patients receiving ambulatory chemotherapy. However, specific indications such as therapy with lenalidomide may require primary VTE prophylaxis, and various scoring systems using both clinical and

hematological data as well as specific biomarkers (e.g. D-dimer, TF) are currently being developed to more accurately predict a patient's individual risk. Whereas long-term treatment with LMWH is recommended as standard therapy for Trousseau's syndrome, the role of anticoagulants as an adjunct to cancer therapy in the absence of established VTE remains an unresolved issue.

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V311

Antiangiogenic drugs and thromboembolic complications

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Tumor neoangiogenesis is crucial for small tumors to overcome the shortage of oxygen supply while growing.
The monoclonal antibody bevacizumab, the tyrosine kinase inhibitors (TKI) sunitinib and sorafenib and the immunomodulatory drugs thalidomide and lenalidomide all exhibit antiangiogenic properties. Antiangiogenic agents target either soluble growth factors like VEGF or bFGF or can block their receptors by interfering with intracellular domains.
However, these growth factors are also produced by normal cells and currently available antiangiogenic drugs are not specifically targeting unique features of tumors cells.
An increased risk of arterial (ATE) and venous thromboembolism (VTE) has been reported for these drugs, although data are inconsistent.
In thalidomide and lenalidomide, a hypercoagulable state has been reported especially when combining them with chemotherapy or glucocorticoids. Rates up to 30 and 40% have been described for thalidomide and between 5-75% for lenalidomide plus high-dose dexamethasone. Aquired resistance to activated protein C, increased F VIII levels and other abnormalities of the coagulation system have been detected. The use of low molecular weight heparins or ASA seem to abrogate the prothrombotic effects.
Pooled data analysis of more than 1700 patients treated with bevacizumab and chemotherapy showed an increased risk for ATE (3.8% bevacizumab-containing therapy vs 1.7% control arm), but not for VTE. Others have reported a risk of 11 to 23% for VTE. As bevacizumab also has been associated with an increased risk of bleeding, the use of anticoagulants is much more problematic and experience is very limited at the moment.
TKI mostly have multiple targets including VEGF-R isoforms among others. Arterial complications especially cardiac ischemia occurred more frequently with sorafenib than placebo in renal cell cancer patients, but hemorrhages were also reported.
Conclusions: Multiple interactions exist between tumor cells and the coagulation system. Tumor cells may have multiple strategies to ensure successful angiogenesis. Interference with angiogenesis still is poorly understood in cancer patients and antithrombotic strategies need to be carefully introduced into clinical practice.

Disclosure: No conflict of interest disclosed.

Fortbildung

Rolle des Hämato-Onkologen bei Tumoren des Hodens und der Blase

V312

Optimizing treatment in germ-cell tumors. What are the issues?

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International consensus guidelines have facilitated the care of patients with germ-cell tumors. However, fine-tuning of the treatment of is ongoing. In patients with stage I disease limited to the testis, the main goal is the implementation of surveillance strategies for patients unlikely to suffer systemic relapses. If assessed and followed correctly, the majority of patients with stage I disease might be spared the burden of toxicity from adjuvant treatment. Risk factors for relapse might support treatment decisions. In patients with metastatic "good prognosis" disease according to the IGCCCG classification, three cycles of PEB remain the "gold standard" of care. Four cycles of PE should be reserved for patients unable to tolerate bleomycin (Einhorn, ASCO 2009). In patients with more advanced "intermediate prognosis" germ-cell tumors, the addition of paclitaxel to four cycles of PEB has been explored in a randomized phase III trial. With the final results still pending, this trial is unlikely to show conclusive results as accrual has been slow and the trial had to be stopped prematurely. In patients with a "poor prognosis" initial presentation as well as in patients with relapsed disease after first-line treatment, high-dose chemotherapy should be considered. Several controversial issues remain. Patients with extensive or unresectable late relapses as well as patients with malignant transformation of teratoma represent rare, but ongoing clinical dilemmas. The follow-up of patients after successful treatment remains a matter of intensive debate. In view of emerging data on the negative effects from diagnostic radiation exposure, intensive follow-up schedules with CT scans every two to three months should clearly be avoided. The quality of care is a major concern and will have to be addressed. Many patients with germ-cell tumors are still being treated at centers too inexperienced in the often complex treatment decisions. As a result false decisions are being made. A recent analysis in multiply relapsed germ-cell tumors found gross treatment errors in about two thirds of patients (Lorch, Ann Oncol 2010). In conclusion, the treatment of patients with germ-cell tumors is continuously being refined. However, improved patient care will only translate into improved outcomes, if patients are assessed and followed correctly. Long-standing experience in the highly specialized care of germ-cell tumors is required and reference centers should be contacted early.

Disclosure: No conflict of interest disclosed.

V313

High-dose chemotherapy in patients with germ-cell tumors 2010

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High-dose chemotherapy (HDCT) in patients with metastatic germ-cell tumors has been explored in three main clinical scenarios. In patients with intermediate or poor prognosis germ-cell tumors according to the IGCCCG criteria, no unequivocal benefit from upfront treatment intensification could be shown (Motzer, J Clin Oncol 2007). However, patients with primary mediastinal non-seminomas, patients with very advanced disease and extrapulmonary viszeral metastases as well as patients with a slow marker decline do seem to profit from upfront HDCT. More recently, a prospective randomized trial has also shown an improved progression-free survival with the early use of HDCT (Daugaard ASCO 2010). However, due to poor accrual, this trial did not reach its target sample size and failed to show statistical significance. In patients with relapse or progression after first-line chemotherapy and "good prognostic" features, the only prospective randomized IT94 trial failed to show a benefit from intensification of first-salvage treatment by HDCT. However, numerous phase II trials and several carefully performed large scale retrospective analyses clearly showed superiority of HDCT over conventional-dose first salvage treatment (Beyer, Ann Oncol 2002, Lorch, ASCO 2010). Another prospective randomized trial with adequate trial design is scheduled to address this issue in an unselected group of patients. Finally, HDCT is usually considered for second or subsequent salvage treatment. In this rare subgroup of patients with multiply relapsed and often refractory tumors, no randomized data are available. However, stable long-term survival rates of about 20% can be achieved with intensification by HDCT (Lorch, Ann Oncol 2010). The treatment decisions about using HDCT are complex and require longstanding expertise in the treatment of patients in these rare clinical scenarios. In a recent analysis, relevant treatment errors were identified in two thirds of patients, who required second or subsequent salvage treatment (Lorch, Ann Oncol 2010). In conclusion, HDCT remains a relevant treatment option in important clinical scenarios. In patients in whom HDCT is considered, treatment centers with long-standing experience in HDCT in this patient population should be contacted.

Disclosure: No conflict of interest disclosed.

V314

Chemotherapy for bladder cancer. Fit, unfit and elderly: Which treatment for which patient?

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Introduction: Cisplatin-containing combination chemotherapy has been the standard of care in the treatment of urothelial cancer (UC) since the late 1980s. However, up to 50% of patients are unfit for cisplatin-containing chemotherapy, either due to a poor PS and/or impaired renal function, or due to co-morbidity that forbids high-volume hydration. These conditions increase with age. The peak incidence of UC is in patients >60 years. In general, the absolute number of cancer cases in persons aged 65 years and older is expected to double between 2000 and 2030 and the proportion of those aged 75 years and older is projected to increase from 30% in 2000 to 42% in 2050. Therefore, we expect an increasing number of patients >65 years with UC in the near future. So far, no standard chemotherapy has been established for patients ineligible for cisplatin-based standard chemotherapy.
Results: Trials with clearly defined 'unfit' patients or patients with multiple adverse prognostic factors are rare. The first randomised phase II/III trial in this setting was conducted by the EORTC and recently presented (De Santis et al, ASCO annual meeting 2010) and compared carboplatin/vinblastin/methotrexate (M-CAVI) and carboplatin/gemcitabine (GC) in patients unfit for cisplatin. Recently, the phase III data of this trial were presented and for the first time, overall survival (OS) and progression free survival (PFS) data for this patient group was available. The ITT analysis (n=238) of the primary endpoint OS did not show a statistically significant difference between the two treatment arms with a median OS of 9.3 and 8.1 months (mos) for GC and M-CAVI, respectively. Median PFS was 5.8 mos on GC and 4.2 mos on M-CAVI. Both regimens were active with an overall response rate of 41.2% and 30.3% for GC and M-CAVI, respectively. For confirmed responses, the difference was statistically significant in favor of GC (p=0.01). Severe acute toxicity was higher on the M-CAVI arm (9.3% on GC and 21.2% on M-CAVI).
Conclusion: Patients ineligible for cisplatin benefit from carboplatin-based combination chemotherapy. GC was less toxic but about as effective as M-CAVI. New strategies for clinical studies in patients with impaired renal function, PS 2 and/or comorbidities should be designed and prioritized.

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Mark Bachner: No conflict of interest disclosed.

Freie Vorträge
Multiples Myelom klinisch

V316

Treatment of light chain amyloidosis using a combination of lenalidomide and dexamethasone failing melphalan containing chemotherapy

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Introduction: No standard treatment is available for relapsed or refractory amyloid light-chain amyloidosis (AL). The efficacy of lenalidomide has been proven in patients (pts) with multiple myeloma but its role in AL is not yet defined.
Patients: Since 2006 51 pts AL were treated with lenalidomide / dexamethasone (LD) at our center. Median age is 58 years (range 42-74). Twenty-seven pts. had pre-treatment with high-dose melphalan and 24 pts. with M-Dex. Twenty-three pts. had a creatinine clearance below 40 ml/min at start of LD, 10 pts were on chronic hemodialysis. The starting dosage of L was 15 mg and was adapted to renal function (15 mg every 48 hours for creatinine clearance < 40 ml/min, 15 mg 3-times a week for dialysis patients). The starting dosage of D was 20 mg (day 1 - 4). Prophylaxis against infections consisted of ciprofloxacine. Prophylaxis against thrombosis was performed with ASS 100 mg in the majority of pts.
Results: Median follow-up is 24 (range 1-36 months). 23 pts are alive, median overall survival is 25 months. The median number of administered LD cycles is 5 (range 1-15). Nine pts stopped therapy due to side effects after receiving less than 3 cycles; 1 pts is still on therapy with LD. Hematological toxicity > NCI grade 2 required dose reduction of L in 12 pts. The following side effects > NCI grade 2 were observed: fatigue in 36% of pts., worsening of kidney function in 20%, infections in 8% and deep vein thrombosis in 6% of the pts. All pts who developed deep vein thrombosis had prophylaxis with ASS and additional risk factors for thrombosis. No further significant toxicities were reported. Seven and 18 pts achieved complete or partial remission of the gammopathy after a median of 3 LD cycles, respectively. Four of those pts had organ response. Causes of death were progression of amyloid organ disease in 9 pts, infections in 3 pts. and 1 pt. died not related to treatment or amyloidosis.
Conclusion: We report on 51 pts with AL treated uniformly with dose-reduced LD. The hematological remission rate is high (61% of 41 evaluable pts) and survival is encouraging in these heavily pre-treated AL pts. Using prophylaxis against infections and thrombosis the treatment was feasible and not associated with undue toxicities encountered in pts with far advanced AL. Treatment with dose-reduced LD is a good treatment option in pts with relapse or no response after standard melphalan-containing therapy and might prolong survival.

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Stefan Schönland: Financing of Scientific Research: Finanzielle Förderung Center of Excellence von Celgene erhalten

V317

Final results of a comorbidity and risk factor analysis in consecutive multiple myeloma (MM) patients (pts): development of an easily assessable MM-specific risk score (Freiburger Comorbidity Index [FCI]) and comparison with previously established comorbidity indices (CIs), namely Kaplan Feinstein (KF), Charlson-Comorbidity (CCI), Satariano (SI), Hematopoietic cell transplantation-specific comorbidity index (HCT-CI) on progression free survival (PFS) and overall survival (OS)

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Introduction: Comorbidities (CM) and a deteriorated functional status have been demonstrated to affect PFS and OS. Thus, CM analyses seem to be exceedingly needed, especially in MM, as these pts are typical elderly and some are frail. The study aim was to determine CM, to compare previously established CM scores and to define a new, easily scored CI to ascertain CM risks on PFS and OS in MM.
Methods: We determined age, performance status via Karnofsky Index (KI), hypertension, diabetes, secondary malignancies, pain, liver-, heart-, lung-diseases and renal impairment (eGFR) in 127 MM pts who received standard (n=65) or high-dose chemotherapy (n=62) at our institution between 1997 and 2003. Via uni- and multivariate Cox regression analyses, we developed an easily assessable MM-specific risk score (FCI). Furthermore, we investigated established CIs, namely KF, CCI, SI, HCT-CI and the new FCI on PFS and OS in MM. We defined a low- and high-risk-group for each score as pts scoring ≤ median vs. >median CI points.
Results: Via multivariate analysis, the KI ≤ 70%, moderate or severe lung impairment and eGFR ≤ 30ml/min/1.73m^2 were key factors for decreased OS, with hazard ratios (HR) of 2.2, 2.8 and 2.9, respectively. When incorporating these risk factors (RF) within the new FCI, we identified largely different median OS with 0, 1 and 2-3 RF of 118, 53 and 25 months (ms), respectively (p< 0.005). The comparative analysis of the KF, CCI, SI and HCT-CI identified the KF and HCT-CI as useful for MM-pts, revealing strikingly different median OS of 98 vs. 44ms (p=0.007) and 81 vs. 41ms (p=0.002) for 'low-´ vs. 'high-risk-pts'. Furthermore the FCI showed distinct median OS differences of 118 vs. 41ms (p< 0.0001) between 'low-´ vs. 'high-risk-pts'. A confirmatory analysis on an even larger consecutive MM pts cohort (n=466) from our group (De Pasquale et al., 2010) verified the prognostic relevance of the FCI and

suggested also that a weighted CM scoring may be of even greater benefit. Thus, within a combined analysis of this previous and our current MM cohort (n=593 pts) a weighted FCI as well as the inclusion of other prognostic parameters, such as ISS, within a test- and validation-set is being pursued.
Conclusions: Our data underline that CM in MM pts are important prognostic determinants for diminished PFS and OS. Our results indicate that a reduced performance status is clinically valuable as well as an accurate - though easily assessable - CM evaluation in MM pts.

Disclosure: No conflict of interest disclosed.

V318

Prognostic impact of chromosomal abnormalities in elderly patients with multiple myeloma – final analysis of the DSMM II trial

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Introduction: Chromosomal aberrations (CA) have emerged as important outcome predictors in multiple myeloma (MM). However, there is only scarce data on the implication of CA in elderly patients (pts.) receiving high-dose chemotherapy (HD-CTX) followed by autologous stem cell transplantation.
Methods: Between 05/2001 and 08/2006, 549 pts. 60-70 yrs. of age with newly diagnosed symptomatic MM entered the *DSMM II* trial of the *Deutsche Studiengruppe Multiples Myelom* to receive two cycles of HD-CTX (melphalan 140 mg/sqm) followed by ASCT after 3-4 cycles of dexamethason-based induction chemotherapy (IC; arm A1) or no IC (arm A2). cIg-FISH and a comprehensive set of DNA probes were applied to all pts. from whom sufficient bone marrow specimen were obtained (n=305). Clinical database was last updated in 12/2009.
Results: An interim analysis (05/2007) with relatively short follow-up time (mFU 83 weeks) revealed 17p deletion (17p-) and translocation t(4;14) as the only independent markers influencing EFS. 17p- and deletion of chromosome arm 22q were correlated with significantly shorter OS (trend for t[4;14]). Deletion of chromosome arm 13q was not an independent prognostic marker in the interim analysis. Thus, HD-CTX & ASCT appear not to provide long-term disease control in cases with t(4;14) or 17p-.
Conclusions: After completion of molecular cytogenetic analyzes in more than 300 pts., final results of the study will be presented at the meeting.

Disclosure: No conflict of interest disclosed.

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V319

Targeted therapy in Multiple Myeloma: Results of first phase I study with everolimus (RAD001)

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Introduction: The mammalian target of rapamycin (mToR) plays an important role in multiple myeloma (MM). Inhibition of mToR blocked myeloma cell growth in vitro as well as in the INA-6 preclinical xenograft model. The mToR inhibitor everolimus (RAD001) is approved for immunosuppression and recently for the treatment of renal cell cancer.
Methods: In an investigator-initiated phase I/II open label trial, patients ≥ 18 years with relapsed or refractory multiple myeloma (MM) were included after at least two lines of previous treatment. The patients received a fixed dose of oral everolimus for six months following a classical dose-escalation design with three planned dose levels (5 mg, 7.5 mg and 10 mg, cohorts of 3 to 6 patients). Patients benefiting from study drug were allowed to continue on therapy. To obtain insights into the biological activity of everolimus, serum dose levels were monitored and bone marrow evaluation was performed three times. Lymphocyte subtypes were analyzed every four weeks.
Results: Seventeen patients were enrolled (13 men and 4 women, age range 52 to 76 years). The primary endpoint of this trial was safety. Since no DLT were observed the intended final daily dose of 10 mg everolimus was reached. Only 2 out of 7 SAE during treatment were assessed as possibly related to the study drug (pulmonary embolism and atypical pneumonia). Except for 2 severe thrombocytopenias no > grade 3 AE were observed during treatment. Remarkably, few infectious complications were seen despite the known immunosuppressive activity of everolimus. Anti-myeloma activity was documented in 9 out of 15 evaluable patients. One partial response in a heavily pre-treated patient and stable disease in eight additional patients (in one case lasting 9 months) were seen.
Conclusions: Everolimus given orally at doses of 5 mg to 10 mg daily showed an acceptable safety profile in heavily pre-treated multiple myeloma patients. The observed responses are promising and allow to consider further studies including combination strategies.

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Martin Gramatzki: Advisory Role: Novartis Pharma AG; Financing of Scientific Research: Novartis Pharma AG

V320

Comprehensive assessment (CA) of organ function and comorbidities (CM) in a large consecutive multiple myeloma (MM) patient (pt) cohort on progression free survival (PFS) and overall survival (OS)

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Introduction: The prognostic importance of CM is increasingly recognized. In a previous analysis, we identified a decreased Karnofsky-index [KI], moderate/severe lung function and renal impairment (RI, by eGFR) as relevant factors for decreased PFS and OS in MM pts and combined these in an easily assessable CM-score (Freiburger comorbidity index [FCI], Terhorst et al. 2009). Thus, for a significant CA, we aimed to re-evaluate CM factors, the FCI and various CM-scores in a larger pt cohort.
Methods: We retrospectively analysed 466 consecutive MM pts treated in our department between 2003-2009 and performed uni- and multivariate analyses of laboratory and function parameters. We investigated the Kaplan Feinstein index (KF; scoring MM), adjusted KF (not scoring MM), Hematopoietic cell transplantation-specific comorbidity index (HCT-CI) and the new FCI to determine their prognostic value on PFS/OS by assigning pts to a 'low' or 'high risk group' according to ≤ or > median score points.
Results: Pts showed a median age of 62 years (ys). Multivariate analysis of function parameters identified the KI ≤ 50% and age >59 ys as most relevant risk factors with hazard ratios (HR) of 3.8 and 2.0, respectively. Of note, RI constituted a strong risk factor via univariate, but not via multivariate analysis. Furthermore, multivariate analysis of laboratory values revealed ß2-microglobulin (ß2-MG), high-risk cytogenetics, increased LDH, albumin and bone marrow infiltration as most relevant, with elevated HRs between 1 and 2. The CM assessment identified the adjusted KF as a suitable CM-score for MM-pts, as well the HCT-CI and FCI, all showing large median OS differences of 143 vs. 36months (ms), 117 vs. 49ms and 113 vs. 39ms (logrank-test p< 0.0001 each) for 'low-' vs. 'high-risk-pts', respectively.
Conclusions: CMs in MM are frequent and a detailed, preferably weighted CM assessment combined with RF analysis appears of significance for risk evaluation in MM pts. In multivariate analysis, RI failed to show significance, suggesting that incorporation of novel agents may overcome the negative prognostic significance of RI. Our results highlight the debate on CA which seems vastly useful to implement into future clinical trials. In addition, within a combined analysis of our previous and current MM cohort, a weighted FCI,

with inclusion of other prognostic parameters within a test- and validation-set, is being pursued.
1st, 2nd and 3rd authors contributed equally

Disclosure: No conflict of interest disclosed.

V321

Prevalence of monoclonal gammopathy of undetermined significance in a densely populated, highly industrialized area in Germany

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Background: We utilized the biobank of the ongoing population-based, prospective Heinz Nixdorf Recall study to determine the prevalence of monoclonal gammopathy of undetermined significance (MGUS) in the densely populated and highly industrialized Ruhr area in Germany.
Methods: The Heinz Nixdorf Recall study cohort comprises 4814 men and women from 3 large adjacent cities. Subjects were randomly selected from statutory lists of residence and gave informed consent. We screened serum samples from the baseline examination which took place from 2000 until 2003. Standard serum electrophoresis was combined with parallel screening immunofixation electrophoresis (IFE) using pentavalent antisera (Hydragel 12 IF, Penta-Kit, Sebia, Fulda, Germany). Where a M-Protein was visible or suspected, confirmatory IFE followed. All gels were evaluated independently by LE and AH. Definition of MGUS cases was based on common criteria including M-Protein concentration, laboratory results, and disease history.
Results: 165 MGUS cases were identified in a total of 4708 screened samples, translating into a prevalence of 3.5% (95% CI, 3.0 - 4.1). The median age of MGUS cases was 63 years (47 - 75), 103 (62%) were male, and we observed an increase in prevalence with increasing age. The age-standardized prevalence (U.S. 2000) was 3.9% (95% CI 3.2 - 4.5) which was higher than previously reported ($p< 0.05$). We found the following distribution of monoclonal protein isotypes: IgG 59%, IgA 17%, IgM 28%, biclonal 2.4%, κ 55%, and λ 44%. Concentrations of the M-Proteins ranged from unmeasurable - 22.4 g/l with a median of 5.3 g/l. After a median observational time of 5 years, 3 MGUS cases progressed to multiple myeloma and 1 case developed a diffuse large B-cell lymphoma, representing a progression rate of 0.5%/year (95% CI 0.13 - 1.3).
Conclusion: The higher age-standardized prevalence of 3.9% in the Heinz Nixdorf Recall cohort compared to that reported by Kyle et al. and the differences in isotype distribution (IgG 59% vs. 69%, IgA 17% vs. 11%) may be explained by the different screening strategies. To quantify the impact of the screening IFE in detecting monoclonal proteins, we are currently re-evaluating the electrophoresis strips using a mask covering the pentavalent tracks on the gels. A complete analysis of the gel re-evaluation will be presented at the conference. Whether environmental factors might also contribute to the increase in prevalence is the focus of ongoing research.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium
Are age limits no longer important for stem cell transplantation?

V324

How to improve immune reconstitution after SCT

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Post-transplant T cell deficiency after allogeneic bone marrow transplantation is associated with considerable morbidity and mortality from infections (especially viral and fungal) and malignant relapse. Therefore strategies to enhance post-transplant T cell reconstitution could significantly improve the overall outcome of allogeneic bone marrow transplantation. We have developed several approaches in mouse models and have begun to translate these into clinical trials. These approaches include:
a) administration of Interleukin-7 which promotes thymopoiesis and peripheral T cell proliferation and survival,
b) keratinocyte growth factor, which operates predominantly by preserving thymopoiesis through its effects on thymic epithelial stroma,
c) leuprolide, which induces a transient sex steroid inhibition, which has a variety of effects that support lymphopoiesis, and
d) adoptive therapy with ex vivo generated T cell precursors.
We will provide an update of our progress both in the laboratory as well as in the clinic for all four approaches.

Disclosure: No conflict of interest disclosed.

V325

Is there an upper age limit for allogeneic stem cell transplantation in patients with multiple myeloma and OMF?

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The reduction of therapy-related complications and the introduction of reduced-intensity conditioning regimens has increased the upper age limit and encouraging results of allogenic stem cell transplantation in AML and MDS-patients up to the age of 70 years have been reported. The role of allogeneic SCT for Multiple Myeloma and Primary myelofibrosis (PMF) patients is not well defined. PMF is a stem cell-derived clonal myeloproliferative disorder in which the primary disease process is a clonal proliferation of multiple cell elements especially the megakaryocytes. This proliferation is accompanied by an increased secretion of different cytokines with a secondary intramedullary fibrosis, osteosclerosis, angiogenesis, and extramedullary hematopoiesis. Survival of PMF patients may vary widely from several months to many years depending on risk factors such as blasts, WBC and anemia. The fact that PMF affects primarily the elderly group of patients (median age at diagnosis 65years), it is important as well to estimate the accompanying co-morbidities which could influence the therapeutic decisions. Importantly, the pharmaco-medical treatment options for this disease such as growth factors, androgens, interferon-α and conventional cytotoxic medications lead only to symptomatic palliation without altering the natural history of the disease. Currently, the only available curative therapy for myelofibrosis is allogeneic hematopoetic stem cell transplantation (AHSCT) which is still associated with a substantial treatment-related morbidity and mortality, resulting in an overall survival of only 14% for patients >45years after standard myeloablative conditioning. Using a dose reduced conditioning (RIC) followed by allografting PMF patients >55years with intermediate and high risk achieved an estimated 5 year survival of 48%. Because no effective conventional treatment is available and AHSCT can cure patients with PMF, AHSCT is a clear indication for intermediate and high risk PMF patients with low cormorbidities up to the age of 70 years. Also in multiple myeloma patients AHSCT has been performed successfully up to the age of 65years. RIC resulted in a lower treatment related mortality, but the relapse rate is rather high and the curative potential, if any, is only modest. Therefore, it remains unclear as to how much of an additional benefit elderly patients with myeloma would obtain from AHSCT as opposed to non-intensive novel therapies, which are currently available.

Disclosure: No conflict of interest disclosed.

V326

Influence of age on outcome of allogeneic SCT in patients with CLL and low grade lymphoma

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Introduction: Allogeneic hematopoietic cell transplantation (HCT) offers the chance to cure patients with chronic lymphocytic leukemia (CLL) or follicular

lymphoma (FL). It is the best treatment option for patients with chemotherapy-refractory stages of CLL or FL. In advanced CLL 4-year progression-free survival (PFS) is between 34% and 58%. In FL 5-year PFS ranges across different clinical trials from 52% in advanced disease to 83% in chemo-sensitive disease. The majority of patients surviving without signs of progression beyond these landmarks are cured from their disease. Non-relapse mortality (NRM) for both indications ranges from 15% to 30%.
For CLL widely accepted indications for allogeneic HCT are: (1) 17p-CLL requiring treatment, (2) refractory disease after purine-analogue therapy and (3) relapse within two years after intensive prior chemotherapy. For FL early relapse after high-dose therapy, refractory disease and marrow failure are widely accepted indications. If any of these criteria is fulfilled, the life expectancy is 2 years or less. Taking into consideration that the median age at diagnosis is 70 years in CLL and 60 years in FL, the majority of patients with an indication for allogeneic HCT are in their seventies. Life expectancy of healthy people at that age is 12 to 15 years. While early regimen-related toxicities of reduced-intensity conditioning (RIC) are fairly acceptable, graft-versus-host disease and infections represent a major challenge for elderly patients. Extensive experience exists for allogeneic HCT up to the age of 70 years. However, still only the fittest 70 years old patients get an allogeneic HCT. The outcome of these rare patients is hardly representative for the general population. Accordingly, in retrospective analyses age has not been shown uniformly to be an adverse risk factor. The effect of age across various series of elderly patients will be reviewed and case reports of transplantation in elderly patients with CLL and FL will be discussed at the meeting.
Conclusion: Advanced age per se should not be considered a contraindication against allogeneic HCT. Individually, the risk of death related to the underlying malignant disease, concomitant diseases and the age-dependent life expectancy have to be weighed carefully against each other by experienced transplant physicians. Desirably, the current practice to transplant selected patients above the age of 70 years should be evaluated in clinical trials.

Disclosure: Johannes Schetelig: Employment or Leadership Position: Oberarzt Medizinische Klinik und Poliklinik I
Gerhard Ehninger: Employment or Leadership Position: Klinik Direktor Medizinische Klinik und Poliklinik I; Advisory Role: Verwaltungsrat der DKMS; Stock Ownership: Rhön AG

Freie Vorträge
Immuntherapie 1

V328

Reinforcement of cancer immunotherapy by adoptive transfer of *cblb*-deficient Cytotoxic T Lymphocytes combined with a Dendritic Cell Vaccine

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Introduction: Various approaches to induce immunological rejection of tumors including transfer of autologous tumor infiltrating lymhocytes (TIL) after *ex vivo* clonal expansion or application of *ex vivo* transduced antigen specific T cell (TCR) transgenic T cells have been elaborated. In general, ATC has been combined with lympho-depleting agents (e.g. cyclophosphamide). However, the therapeutic efficacy of these cancer immunotherapy approaches is limited due to insufficient *in vivo* activation, expansion and survival of transferred effector immune cells, which is mainly due to suppressive mileu signals and immune evasion mechanisms induced by TGF-β. The E3 ubiquitin ligase Cbl-b is a key regulator of T cell activation and is assumed to confer TGF-β resistance. Thus we performed a proof-of-concept study evaluating Cbl-b targeting as "intracellular adjuvant" strategy to improve adoptive T cell transfer (ATC) for cancer immunotherapy.
Methods: We first tested the *in vitro* sensitivity of CTL towards TGF-β mediated immuno-suppressive cues and then *in vivo* evaluated the anti-tumor reactivity of *cblb*-deficient CTL in murine tumor models alone or in combination with a dendritic cell (DC) vaccine.
Results: *Cblb*-deficient CTL are hyper-responsive to TCR/CD28-stimulation *in vitro* and protected from the negative cues induced by TGF-β. Unexpectedly, adoptive transfer of polyclonal, non TCR-transgenic *cblb*-deficient CTL is not sufficient to reject B16ova or EG7 tumors *in vivo*. Thus, *cblb*-deficient ATC is *in vivo* re-activated by a DC vaccine (i.e. SIINFEKL-pulsed DC). In strict contrast to ATC monotherapy, this approach markedly delays tumor outgrowth and significantly increase survival rates, which is paralleled by an increased CTL infiltration rate to the tumor site and enrichment of ova-specific and IFN-g-secreting CTL in the draining lymphnode. Moreover, compared to wild-type CTL, *cblb*-deficient mice vaccinated with the DC vaccine show an increased cytolytic activity *in vivo*.
Conclusions: In summary, we provide experimental evidence that genetic inactivation of *cblb* in polyclonal, non-TCR transgenic adoptively transferred CTL serves as a novel "adjuvant approach", suitable to augment the effectiveness of established anti-cancer immunotherapy in immune-competent recipients.

Disclosure: No conflict of interest disclosed.

V329

Multivirus-specific T cell immunotherapy to prevent or treat infections of allogeneic stem cell transplant recipients

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Introduction: Viral infections cause morbidity and mortality in allogeneic HSCT recipients. We and others have successfully generated and infused adoptive T-cell lines specific for EBV, CMV and Adv using adenovector-modified monocytes and EBV-transformed lymphoblastoid cell lines (EBV-LCL) as antigen presenting cells (APCs). We have shown that as few as $2x10^5$/kg trivirus-specific cytotoxic T lymphocytes (CTL) proliferated by several logs post-infusion and appeared to protect the recipients against all three viruses. Despite the encouraging clinical results, broader implementation of this "trispecific" CTL approach is limited by high production costs, complexity of manufacture and the prolonged generation time (4-6 wks EBV-LCL and 6-8 wks CTL).
Methods: To overcome these limitations we have developed new, GMP-compliant CTL generation strategies. As APCs we now use DCs nucleofected with non-viral DNA plasmids to stimulate T-cells. These minimized, antibiotic-resistance marker free plasmids encode the viral antigens EBNA1, LMP2 and BZLF1 (EBV), Hexon and Penton (Adv) and IE1 and pp65 (CMV). Secondly, we culture the activated T-cells in IL-4 (1,000 U/ml) and IL-7 (10 ng/ml) for 12 days which promotes the survival of both high and low frequency antigen-specific CTL and sustains the breadth of reactivity in our lines. Finally we introduce a new, gas permeable cell culture device (G-Rex) which promotes the expansion and survival of large cell numbers in a closed system.
Results: Using nucleofected DCs as APCs, we can reproducibly generate multivirus-specific CTL lines as tested by IFN-γ ELIspot Assay (EBV: EBNA1 272, LMP2 187, BZLF1 251, Adv: Hex 315, Pen 96, CMV: IE1 272, pp65 767 mean SFC/$1x10^5$ CTL; n=7). Generated CTLs are polyclonal comprising CD4+ and CD8+ T cells. CTLs produce multiple cytokines (IL2, IFN-γ, TNFα) after antigen stimulation and show cytolytic function against pepmix-pulsed as well EBV-infected targets (LCL), with no alloreactivity assessed by Cr^{51} release and H3 proliferation assays. By using the G-Rex device, virus-specific CTLs expand multiple logs enabling just one round of stimulation to reach sufficient cell numbers for infusion.
Conclusions: By implementing these changes we can now produce multivirus specific CTL in just 10 days rather than 10 weeks reducing costs >90%. Our approach, extendable to additional viruses, should be of value for prophylactic and treatment applications for high risk allogeneic HSCT recipients.

Disclosure: No conflict of interest disclosed.

V330

Effector mechanisms of affinity maturated and Fc-engineered mini-antibodies directed against the AML stem cell antigen CD96

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Introduction: Despite novel treatment options relapse occurs in the majority of AML patients. This might be attributable to resistant leukemic stem cells (LSC) escaping conventional treatment regimes. Targeted therapies against AML-LSC may represent potent therapeutic approaches for AML therapy. Here, the generation and characterization of engineered chimeric mini-antibodies derived from the murine antibody TH-111 and targeting CD96 - a target antigen recently identified on LSC - is described.
Methods: The V-regions of TH-111 were isolated by phage display and the derived scFv fragment was affinity maturated by a combined strategy of random mutagenesis and phage display. Variants of the scFv were fused to human IgG1-Fc wildtype or a variant with enhanced effector functions. The recombinant molecules were expressed in 293T cells and purified. Specific binding was analyzed by flow cytometry. Antibody-mediated direct (antiproliferative) and indirect effector mechanisms (CDC and ADCC) were analyzed by MTT and in a classical ^{51}Cr-release assay, respectively.
Results: A functional scFv fragment was generated from the murine antibody TH-111. The scFv retained the specificity of the parental TH-111 antibody as evidenced by competition binding assays. After in vitro affinity maturation improved scFv variants with 4-5 fold enhanced antigen binding capacity were isolated. Mini-antibodies with wildtype and affinity maturated scFv variants were generated. The recombinant molecules did neither show direct anti-proliferative effects nor complement mediated lysis. In contrast, the mini-antibodies were effective in mediating ADCC of CD96-positive KG1a and HSB-2 cells via recruitment of mononuclear effector cells. The mini-antibody containing the affinity-maturated scFv and the engineered Fc-variants demonstrated the highest lytic capacity, suggesting that affinity to CD96 as well as efficient Fc receptor binding contribute to the observed effects.
Conclusions: In the current study, novel immunoconstructs targeting CD96, a target antigen on AML stem cells were generated. Analysis of effector mechanisms mediated by these molecules revealed that ADCC, an important effector mechanism of clinically approved therapeutic antibodies, was triggered. In summary these antibody derivatives can serve as starting points for the development of novel treatment strategies for AML patients; these may include direct in vivo application or ex vivo engineering of stem cell grafts.

Disclosure: No conflict of interest disclosed.

V331

Effector mechanisms of a novel [CD16x(CD20)$_2$]-directed bispecific antibody *in vitro* and *in vivo*

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Introduction: Analysis of Fc receptor (FcR) polymorphisms in rituximab-treated patients as well as studies in transgenic mice lacking FcR activation demonstrated the crucial role for FcR and effector cell recruitment in antibody therapy. Therefore, enhancing antibody dependent cellular cytotoxicity (ADCC) using bispecific antibodies (bsab) may represent a promising strategy to optimize antibody-based therapy. In the current study the cytotoxic potential of a novel recombinant CD20-directed bsab [CD16x(CD20)$_2$] in the tribody format was analyzed *in vitro* and *in vivo*.
Methods: The bsab was expressed in HEK cells and purified using affinity chromatography. ^{51}Cr release assays using CD16$^+$ effector cells and different CD20$^+$ tumor cell lines or primary tumor cells were performed. Depletion of autologous B-cells in whole blood was examined *in vitro.* Furthermore, the bsab was tested in humanized mice transplanted with CD34$^+$ cord blood cells for its ability to deplete B-cells *in vivo*.
Results: [CD16x(CD20)$_2$] bound to both CD20 and FcγRIIIa (CD16a) on target and effector cells, respectively. In ADCC assays the bsab mediated lysis of two CD20$^+$ human burkitt's lymphoma cell lines in a dose-dependent manner. Lysis rates obtained with the bsab were significantly higher compared to rituximab irrespective of the CD16a polymorphism at position 158. The bsab efficiently triggered lysis of primary tumor cells from ten patients with B-cell lymphomas (B-CLL; MCL). Lysis rates ranged from 20-50% and were significantly higher compared to rituximab. Importantly, specific lysis was also observed when autologous NK-cells were used as effector cells. To investigate this autologous killing capacity in more detail, B-cell depletion in whole blood was examined. [CD16x(CD20)$_2$] efficiently reduced B-cell numbers accompanied by activation of NK-cells. Finally, the bsab significantly reduced B-cell numbers *in vivo* in a humanized mouse model.
Conclusions: The novel bsab [CD16x(CD20)$_2$] more efficiently triggered ADCC than rituximab *in vitro* irrespective of the CD16a polymorphism. Importantly, lysis of primary tumor cells in an autologous setting demonstrated that the patients' effector cells can be efficiently trigged by the novel tribody molecule. Additionally, the [CD16x(CD20)$_2$] bsab demonstrated B-cell depletion *in vivo*. In conclusion, [CD16x(CD20)$_2$] may represent a promising treatment strategy particularly for patients expressing the unfavourable CD16a-F158 variant on immune effector cells.

Disclosure: No conflict of interest disclosed.

V332

Characterization of allorestricted T cell receptors (TCR) with specificity for FMNL1 and HER2/neu for potential clinical application

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Adoptive T cell therapy has demonstrated effectivity in the treatment of selected malignant diseases. However, this approach is often limited by the difficulty to obtain autologous tumor specific T lymphocytes. Allorestricted peptide-specific T cells with specificity for a defined tumor associated antigen (TAA) might be a preferential source for effector cells with high anti-tumor reactivity.
We have generated several HLA-A2-allorestricted T cell lines and clones with specificity for the TAA FMNL1 and HER2/neu. TCR-encoding genes from selected cell lines and clones were retrovirally transduced into healthy peripheral blood mononuclear cells (PBMC). TCR-transduced PBMC were functionally investigated regarding functional avidity, peptide-specificity and tumor-reactivity in vitro and in vivo. Furthermore, we adopted single photon emission computed tomography (SPECT) 3D imaging to monitor ^{111}In-labelled TCR-transduced human PBMC in immunodeficient (NOD-SCID) mice bearing tumors derived from inoculation with human breast cancer cell lines.
TCR-transduced PBMC demonstrated dose-dependent specificity for peptides derived from FMNL1 and HER2 and revealed tumor-reactivity against diverse tumor cell lines expressing naturally FMNL1 or HER2/neu. Expression, peptide-specific function and anti-tumor reactivity of transduced TCR were enhanced after diverse modifications including murinization of TCR αβ constant regions and codon optimization. Interestingly we identified a dominant HER2$_{369}$-recognizing TCR α-chain with specific peptide-recognition in com-

bination with varying β-chains of the same Vβ family derived from TCR with different specificities. Moreover, one chimeric TCR composed of this dominant α-chain and one β-chain derived from another $HER2_{369}$-specific TCR showed enhanced functional avidity, CD8 independency and tumor reactivity. Our primary SPECT imaging data in vivo showed that PBMC transduced with the specific TCR showed a strong accumulation signal whereas this was not the case in non-transduced PBMC. Moreover, preliminary data showed preferential survival and reduced tumor manifestations in mice treated with TCR-transduced T cells suggesting that PBMC transduced with the selected allorestricted TCR might recognize the tumor specifically in vivo.
In conclusions, our results suggest a potential for selected TCR for clinical application and provide important information for the development of TCR-transfer strategies targeting overexpressed self antigens.

Disclosure: No conflict of interest disclosed.

V333

Reprogramming T cells of CMV-negative donors with CMV-specific T cell receptor RNA

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Cytomegalovirus (CMV)-associated disease is a life-threatening complication in patients after allogeneic hematopoietic stem cell transplantation (HSCT). Although antiviral drug therapy is successfully used to reduce the risk of CMV disease, long-term virus control requires the re-establishment of protective antiviral T cell immunity in the host. The latter is challenging, particularly if the donor is CMV-negative and thus, no CMV-reactive T cells are being transferred from donor to recipient during HSCT. Grafting nonreactive T cells of CMV-negative donors by virus-antigen specific T cell receptors (TCR) may be an efficient means to transfer CMV specific T cell function into allogeneic HSCT recipients. In this study, we have reprogrammed T cells of CMV-negative donors with human TCR recognizing the immunodominant HLA-A*0201-binding CMVpp65 epitope 495-503. To overcome the limitations of retroviral TCR gene transduction that hamper clinical translation, we used *in vitro* transcribed RNA encoding CMV-specific TCR for electroporation of non-reactive human T cells. This procedure resulted in transient surface expression of the introduced TCR for at least 3 days as demonstrated on both $CD4^+$ and $CD8^+$ T cells. TCR expression levels were sufficient to trigger IFNγ secretion and cytolytic activity against pp65 peptide-pulsed target cells and moreover against human fibroblasts upon CMV infection. We also observed that TCR RNA transfection of $CD4^+$ T cells turned them into potent CMVpp65/HLA-A*0201-specific T helper cells. This was demonstrated by co-incubating them with immature dendritic cells (DC), which resulted in maturation of DC only in the presence of the CMVpp65 epitope.
We also transfected pure naive and memory $CD8^+$ T cell subsets isolated from peripheral blood of CMV-negative donors. Although 90% of naive $CD8^+$ T cells were CMVpp65/HLA-A*0201 tetramer positive after electroporation, they mediated only marginal lysis toward CMV-infected fibroblasts. In contrast, memory $CD8^+$ T cells showed strong TCR expression and cytotoxicity against CMV-infected fibroblast up to one week. In summary, our data demonstrate that non-reactive human T cells can be easily redirected with CMVpp65 TCR RNA, thereby gaining CMV-specific T cell effector function for a considerable time period. We believe that CMVpp65 TCR RNA has the potential to be further developed as a therapeutic 'off-the-shelf' reagent for CMV-positive patients who undergo allogeneic HSCT from CMV-negative donors.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium
Controversies in the therapy of Primary CNS Lymphoma (PCNSL)

V334

High-dose methotrexate and beyond: Which is the optimal chemotherapy in PCNSL?

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The current therapeutic knowledge in PCNSL comes from large retrospective series, meta-analyses of published trials, several single-arm phase-II trials, a single randomized phase III trial, which was prematurely terminated due to inadequate accrual, and a single randomized phase II trial. The use of high-dose methotrexate (HD-MTX)-based chemotherapy, followed or not by whole-brain radiotherapy, is the commonest treatment in these studies. Methodological pitfalls in these studies, scarse biological and molecular knowledge and lacking of randomized trials are the main limitations for therapeutic progress. Importantly, the first worldwide randomized trial with completed accrual was recently reported [*Ferreri AJM, et al. The Lancet 2009*]. This trial demonstrated that, in patients ≤75 years old with PCNSL, the addition of HD-cytarabine to HD-MTX results in consistently better outcome and acceptable toxicity over HD-MTX alone. Thus, MTX+cytarabine combination should be considered as the standard chemotherapy combination for PCNSL patients and as the control arm for future randomized trials since it is supported by the best level of evidence available in PCNSL. Despite this benefit, current results in PCNSL patients remain unsatisfactory. In line with therapeutic strategies for aggressive lymphomas, it is unthinkable to treat PCNSL exclusively with antimetabolites and the assessment of other drugs active against other phases of the tumour cell cycle should be considered for future trials. Some alkylating agents (i.e., temozolomide, ifosfamide, thiotepa, nitrosoureas) are interesting candidates since they are able to cross the BBB, exhibit anti-lymphoma activity, are active against phase-G0 cells, and increase cytotoxicity of antimetabolites. Rituximab could be another candidate, especially considering its safe profile. Its combination with HD-MTX-based chemotherapy is feasible, but several doubts on its capability to cross the BBB exist. HD-chemotherapy supported by ASCT has produced encouraging results in PCNSL. However, this strategy seems feasible in young and fit patients, which excludes one third of PCNSL patients. All these preliminary contributions deserve to be assessed in future randomized trials, whcih will require a more effective international, multidisciplinary cooperation. Prospective trials assessing new potentially active drugs in failed patients are strongly encouraged.

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V335

Do PCNSL patients need high-dose chemotherapy? Pro

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Primary central nervous system lymphoma (PCNSL) has posed a challenge since it was first described. It represents approximately 4% of intracranial neoplasms and 4- 6% of extranodal Non-Hodgkin's Lymphomas. The prognosis of PCNSL patients is poor: median survival of untreated patients is 1.5-3.3 months. Historically, whole brain radiotherapy (WBRT) has been the standard treatment for PCNSL, producing a response rate of 60-97%, a median survival of 14 months, and a 5-year survival of 3-26%, however, almost all patients relapse after a few months. The addition of chemotherapy to WBRT has been recommended to improve survival, and three large retrospective multicenter surveys with over 1000 patients showed that high-dose methotrexate (HD-MTX) is the most efficient known cytostatic, while any regimen without HD-MTX correlates with outcomes no better than with RT alone. The combination of cytarabine with HD-MTX has been shown to improve remission and overall survival rates. Nevertheless, most patients eventually relapse. Dividing therapy into "induction" and "consolidation" seems obvious when experiences of treating high-risk systemic lymphoma and other hematologic malignancies

into PCNSL therapy strategies are considered. A further challenge is to overcome the intact blood-brain-barrier in mind after a remission has occurred. The common standard of consolidating these patients is whole brain radiotherapy (WBRT). The Freiburg group has introduced the replacement of WBRT with first-line high-dose chemotherapy treatment including carmustine and thiotepa, followed by autologous stem cell transplantation (ASCT) as consolidation in phase-II trials. This approach's efficacy has been demonstrated in patients relapsing with PCNSL in a multicenter French trial. These promising results have inspired international collaboration between the "IELSG" and the "Kooperative Studiengruppe PCNSL Freiburg", who are currently performing a multinational randomized phase-II trial evaluating MTX/AraC combinations with/without thiotepa and rituximab as induction therapy and high-dose-chemotherapy and ASCT versus dose-reduced WBRT for consolidation therapy in patients < 70 years.

Disclosure: No conflict of interest disclosed.

V336

Do PCNSL patients need high-dose chemotherapy? Contra

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High dose chemotherapy achieves therapeutic drug levels in brain, CSF and throughout the neuraxis. Phase I and phase II studies have been patterned upon the successful implementation of marrow-depleting high dose chemotherapy regimens utilized to treat systemic lymphoma. Autologous stem cells are provided to rescue the patients from drug-induced leukopenia or thrombocytopenia. Treatment has been provided to recurrent or newly diagnosed PCNSL. "Induction therapy" to achieve a remission is provided with MTX and/or ARA-C and followed by thiotepa based regimens or by ARA-C, melphalan, carmustine and etoposide. For several reasons, this approach should still be considered experimental:

- Response rates after high-dose in newly diagnosed PCNSL are not better than with conventional therapy despite a younger median age of the study populations.
- With the exception of one trial treatment has been combined with mandatory radiotherapy or with irradiation in all other situations than complete response (CR) to high-dose, such that long-term tumor control as a result of high-dose alone cannot be evaluated.
- The only high-dose trial without radiotherapy has failed to achieve results comparable to the ones achieved with conventional chemotherapy alone.
- A long-term follow-up of combined high-dose and radiotherapy showed no better results than long-term follow-up of a comparable population having been treated with conventional chemotherapy alone.

Disclosure: Uwe Schlegel: Honoraria: Vortragshonorare von mundipharma

V337

Selected Abstract
The role of whole brain radiotherapy in primary management of patients with primary central nervous system lymphoma (G-PCNSL-SG1 trial)

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Background: No standard therapy has been established for primary central nervous system lymphoma (PCNSL) thus far. With high-dose methotrexate (HDMTX) based chemotherapy followed by whole brain radiotherapy (WBRT) prolonged survival can be achieved, however, with an increased risk of late neurotoxicity, especially in the elderly. In this randomized phase IV trial the role of WBRT after HDMTX was evaluated.
Methods: Immunocompetent adult patients with newly diagnosed PCNSL and adequate renal function were included and randomized to chemotherapy followed by WBRT (45 Gy in 1.5 Gy fractions) or chemotherapy alone. All patients were to receive 6 cycles HDMTX 4g/m2 d1 from 1999-2007 and HDMTX plus ifosfamide 1.5 g/m2 d3-5 thereafter. After chemotherapy patients randomized to WBRT received consolidating WBRT in case of complete remission (CR) (arm A1) or rescue WBRT when CR was not achieved (arm B1); patients randomized to chemotherapy alone received no further therapy in case of CR (arm A2) and HD-cytarabine in case of no CR (arm B2).
Results: Of 551 patients enrolled (median age 63 years) 526 fulfilled the eligibility criteria and received HDMTX-based chemotherapy. CR rate was 34.6% (182/526 patients). 66 patients (12.5%) died on therapy and 49 dropped-out prematurely. Thus, a total of 411 patients entered the post-HDMTX phase with a known response status, and 318 were treated as randomized (*per protocol* (PP) population). In the total PP population median progression-free survival (PFS) was 18.3 in the chemotherapy + WBRT arms (A1+B1, n=154) and 12.0 months in the chemotherapy alone arms (A2+B2, n=164) (p=0.13). For patients with CR after HDMTX-based chemotherapy, the median PFS in arm A1 (n=56) was 36.3 months *versus* 21.5 months in arm A2 (n=96) (p=0.038). For patients without CR after HDMTX -based chemotherapy the median PFS in arm B1 (n=98) was 5.6 months *versus* 3.0 months in arm B2 (n=68) (p=0.003). No significant difference in overall survival (OS) was found between all these patients groups.
Conclusions: The PFS prolongation by the addition of WBRT in all patient groups analysed confirms the important role of radiotherapy for disease control. However, the lack of significant OS benefit with WBRT, most probably due to the efficacy of salvage treatments administered at relapse, justifies its omission from first-line treatment in PCNSL.

Disclosure: No conflict of interest disclosed.

V338

Future studies in PCNSL: What are the goals?

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Treatment of PCNSL has evolved over the past 3 decades from whole brain radiotherapy (WBRT) to include chemotherapy plus cranial irradiation and most recently, chemotherapy alone. Despite the lack of randomized phase III data, there is widespread consensus that the addition of chemotherapy has improved response, remission duration and survival over WBRT alone. Recent work has focused on trying to achieve balance between improving disease control without causing treatment-related toxicity of the brain that can lead to permanent disability. High-dose methotrexate (HD-MTX) is the single most effective agent to date even though it plays a minimal role in the treatment of comparable systemic diffuse large B-cell lymphomas. Its efficacy, even as a single agent, has been well-established, but it is a potent neurotoxin when combined with full-dose WBRT. HD-MTX-based regimens alone appear to achieve comparable survival when similar regimens are combined with WBRT, with less neurotoxicity. However, most patients continue to relapse and die of tumor progression. Therefore, there is a need to identify novel, effective agents against PCNSL and more active regimens to reduce relapse. A variety of approaches are under study including high-dose chemotherapy with stem cell rescue and low-dose WBRT in combination with chemotherapy. Further study is needed to determine which approaches are best and potentially which subgroups, clinical or biologic, may benefit from these approaches.

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Expertenseminar
Magenkarzinom

V340

Palliative therapy in gastric cancer

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Background: Gastric cancer including cancer of the esophago-gastric junction is the 4th most common malignant tumor and the 2nd-most common cause of cancer-related death worldwide. In Western countries, most gastric cancers are diagnosed in advanced stages and lack curative treatment options.
Methods: A review of the literature, of recent congress contributions and of currently conducted studies illustrates the standard of care and new approaches in the palliative treatment of gastric cancer.
Results: Chemotherapy (Ctx) has shown to prolong survival, to improve symptoms and to maintain a better quality of life. Combination Ctx including a platinum compound (cis- or oxaliplatin) plus a fluoropyrimidine (5-FU or capecitabine or S-1, the latter is available only in Japan) is regarded as superior to monotherapy. With the addition of docetaxel to a platinum compound plus 5-FU, the efficacy of treatment was increased at the cost of more toxicity. The classic 3-weekly "DCF" regimen is no more recommendable in the palliative setting and should be replaced by less toxic but equally effective modified schedules like "Gastro-Tax" and "FLOT". Second-line Ctx, preferably on the basis of irinotecan (+/- 5-FU), can be recommended in patients who progress following first-line treatment and are still eligible for systemic treatment. About 20% of gastric cancers exhibit overexpression of the growth factor receptor Her2. Trastuzumab is a monoclonal antibody directed against Her2 and has shown to prolong survival and improve response rate and progression-free survival when combined with cisplatin and 5-FU or capecitabine (ToGA study). The anti-VEGF-directed monoclonal antibody bevacizumab was also studied in combination with Ctx but did not lead to an improvement in overall survival in the global AVAGAST study. Cetuximab, a monoclonal antibody directed against EGFR, is currently studied in the global EXPAND study.
Conclusion: Systemic Ctx should be considered in patients presenting with advanced unresectable gastric cancer. Personalization of treatment has started on the basis of the tumor Her2 expression status allowing for an anti-Her2-directed therapy in patients with Her2-overexpressing tumors.

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Expertenseminar
Lehrstücke aus der pädiatrischen Hämatologie

V341

Myelodysplastic syndromes in childhood: Is there a difference?

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Myelodysplastic Syndromes (MDS) in childhood are rare with an estimated incidence of 1.8 children per million per year accounting for less than 5% of pediatric hematological malignancies. The 2008 revision of the WHO classification introduced the provisional entity of refractory cytopenia of childhood (RCC) reflecting the fact that ~50% of children with MDS present with neutropenia and/or thrombocytopenia and less than 5% blasts in a frequently hypocellular bone marrow. Due to the lack of data confirming the prognostic value it is controversial if MDS in children with an increase of blasts should be classified using the same categories as in adults. The EWOG-MDS proposed to retain the category of refractory anemia with excess blast in transformation (RAEB-T) for patients with 20-29% bone marrow blasts until sufficient data are available. A decision that is supported by the fact that children with RAEB and RAEB-T have a comparable outcome, if treated by hematopoietic stem cell transplantation (HSCT).
In the pediatric population MDS is often associated with congenital disorders that are involved in essential pathways such as DNA damage response pathways (Fanconi Anemia), telomere maintenance (dyskeratosis congenita), ribosome biogenesis (Diamond Blackfan anemia) or control of apoptosis (sever congenital neutropenia). MDS arising in this context as well as after chemo+/- radiotherapy is defined as secondary MDS. However, it is to be recognized that children with primary MDS may have an underlying yet unknown defect predisposing them to develop MDS early in life. Supportive evidence for this hypothesis may be derived from data demonstrating that children with MDS receiving HSCT suffer from an unexpected high rate of transplant related mortality.
Most importantly, therapy in childhood MDS aims for cure and not palliation. Therefore HSCT remains the treatment of choice in the majority of children with MDS. In RCC, there the risk of relapse is negligible, the reduction of intensity of the conditioning regimen is crucial in order to reduce the risk of long term toxicities and preserve fertility. A proportion of patients with RCC responds to immunosuppressive therapy. However, it is unknown how many of these patients will develop more advanced disease later in life. Although there is no doubt that all patients with advanced MDS need HSCT, the optimal approach, including the role of intensive chemotherapy or epigenetic agents prior to HSCT, remains controversial.

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V342

Genetic and acquired hemophagocytic syndromes: Extending the spectrum from an acute childhood disease to a chronic condition in adults

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Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition of immune- dysregulation characterized by hypercytokinemia and T cell and macrophage proliferation.
Methods: Clinical, immunological and genetic data will be reported and the relevance for differential diagnosis in inflammatory or immunological diseases in adults will be discussed.
Results: Acquired HLH can occur at any age and is associated with infections, malignancies and autoimmune diseases. Moreover, HLH is the predominant feature of a group of autosomal recessively inherited disorders called familial hemophagocytic lymphohistiocytosis (FHL) which mainly affect infants. HLH diagnosis is based on clinical symptoms, typical alterations of laboratory values and immunological analyses. In FHL, transient improvement can be achieved by immune-modulating treatment, but hematopoietic stem cell transplantation is required for definite cure. So far, mutations in four underlying genes (*PRF1, UNC13D, STX11, STXBP2*) have been identified which cause an impairment of the granule-secretion dependent cytotoxic function of T cells and NK cells. Increasing awareness of the disease and the availability of genetic testing has led to the identification of numerous late-onset cases up to 60 years of age. Recently, atypical presentations resembling chronic variable immunodeficiency or chronic active EBV infection have been observed in patients carrying hypomorphic mutations in *UNC13D* and *STXBP2*. Interestingly, these cases can be distinguished from typical, early onset cases by functional analyses of the cytotoxic cells.
Conclusion: Identification of FHL related genes has improved our understanding of the function of cytotoxic cells. Genetic forms can occur at any age with presentations that overlap with other immunological disorders. Functional analysis and genetic testing should also be considered in late-onset or atypical cases in order to establish the diagnosis and initiate adequate treatment.

Disclosure: No conflict of interest disclosed.

Expertenseminar
Maligne Lymphome und PET

V345

PET and the role of antibodies in the treatment of Hodgkin Lymphoma

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Introduction: To date, most patients with Hodgkin Lymphoma (HL) can be cured with chemotherapy, radiotherapy or combined modality treatment. However, current treatment is associated with severe side effects and late toxicities such as infertility, cardiovascular damage and secondary malignancies. Moreover, there is still no curative treatment for patients who relapse after high dose chemotherapy and autologous stem cell support (HD-CT).
Methods and results: To date, the biggest challenge in the treatment HL is the reduction of treatment related toxicity without loss of efficacy. The use of interim PET very early during first line treatment has been shown to reliably predict poor outcome for patients. Ongoing clinical trials will answer the question, whether the treatment can be reduced safely for responding patients and whether treatment intensification can salvage non-responders. However, standardized criteria for the evaluation of PET have yet to be established and international efforts are under way.
Another approach to achieve reduction of toxicity could be the use of antibodies that specifically target either HL-specific antigens as CD30, or antigens expressed on cells of the microenviroment as CD 20, CD 40 and CD 80. Although early clinical trials testing monoclonal anti CD30 antibodies have been disappointing, current studies testing highly immunogenic antibodies and sophisticated immunotoxins are ongoing and preliminary results show high remission rates.
Conclusions: Due to advances over the past decades, treatment of HL is highly efficient. Current efforts aim to reduce toxicity and maintain or even improve efficacy by using PET-based response assessment and by the evaluation of novel, less toxic drugs including recombinant antibodies.

Disclosure: No conflict of interest disclosed.

V346

PET-based treatment strategies in non-Hodgkin's lymphomas

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The effectiveness of antilymphoma therapy is judged on the basis of imaging techniques which have become more and more refined in recent years. In pre- and post-treatment staging, positron emission tomography using the tracer 18-fluor-deoxyglucose is more accurate than computed tomography. In addition, PET performed after a few cycles of therapy (mid-treatment / interim PET) has been shown to correlate with long-term outcome in aggressive non-Hodgkin's lymphomas: patients with a negative interim PET scan have a much lower likelihood of progression or relapse than patients with a positive scan. The positive and negative predictive values vary from study to study. The variability between studies may be explained by differences in the timing of interim PET scanning in relation to the previous cycle of chemotherapy, the use of hematopoietic growth factors and, most importantly, the method used for the evaluation of PET. Criteria developed for end-of-treatment PET evaluation may not be suitable for mid-treatment assessment. The therapeutic consequences to be drawn from mid- or post-treatment PET scans have not been defined. Randomized trials are required to resolve the question whether patients with an insufficient PET response may benefit from alternative treatment strategies. Outside such trials, interim and end-of-treatment PET scans cannot be used to guide treatment decisions in non-Hodgkin´s lymphomas.

Disclosure: No conflict of interest disclosed.

Wissenschaftliches Symposium
Treatment optimization in Multiple Myeloma

V347

Selected Abstract

Zoledronic acid therapy versus control in patients with Multiple Myeloma in stage I (Durie & Salmon): Results of a phase III study of the "Deutsche Studiengruppe Multiples Myelom (DSMM)" and "Ostdeutsche Studiengruppe Haematologie und Onkologie (OSHO)"

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Introduction: Bone disease is a hallmark of multiple myeloma. It is associated with bone pain, fractures, hypercalcemia and has major impacts on quality of life. Before lytic lesions become apparent, a high rate of bone resorption is already existent in the majority of the patients. The standard in asymptomatic multiple myeloma is "wait and see". Due to their inhibitory effect on bone resorption, bisphosphonates prevent skeletal-related events in myeloma and might be beneficial by interrupting the vicious cycle between osteoclast activation and myeloma progression thus exhibiting anti-tumor activity. Zoledronic acid is a third generation bisphosphonate which induces a strong inhibition of bone resorption. The present phase III study investigated the effect of treatment with zoledronic acid on progression-free survival (PFS) in patients with stage I multiple myeloma. Secondary objectives were time to develop skeletal-related events, as well as tolerability/safety of zoledronic acid.
Methods: This prospective, randomized, open multicenter study started in 2000. PFS is calculated from start of the treatment to disease progression or death. Progression was defined as progression in stage II or III (Durie & Salmon), progression of osteolytic lesions or occurrence of skeletal-related events. 140 patients were available for analysis (71 zoledronic acid, 69 control). Patients aged > 18 years with a diagnosis of multiple myeloma according to the criteria of the British Columbia Cancer Agency Stage I were enrolled in this clinical trial. Zoledronic acid (4 mg i.v.) was administered every 4 weeks.
Results: For the incidence of skeletal-related events, a trend favoring zoledronic acid was detected (p=0.056). No patient in the zoledronic acid group experienced skeletal related events. Progression according to the definition of the protocol occurred in 19 patients treated with zoledronic acid and 26 patients in the control group, respectively (26.8% vs. 37.7%). Kaplan-Meier plots for progression-free survival showed a trend favoring zoledronic acid, but difference was not statistically significant (log-rank: p=0.34).
Conclusions: This study comparing zoledronic acid with no treatment in multiple myeloma patients stage I according to Durie & Salmon showed a trend favoring zoledronic acid in regard of both skeletal-related events and progression of multiple myeloma, although a statistical significance was not reached, possibly since the planned sample size was not recruited.

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V348

Role of new drugs

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The median overall survival of patients with multiple myeloma (MM) treated with conventional chemotherapy was about 3 years. A significant survival improvement as a result of the incorporation of thalidomide, its new analog lenalidomide, and the proteasome inhibitor bortezomib has been observed for patients diagnosed in the more recent years.
Autologous stem cell transplantation (ASCT) is the gold standard in the front-line therapy of younger patients with MM. The greatest benefit from ASCT in terms of survival is obtained in patients achieving CR (complete remission). However, the benefit of achieving CR seems to vary with the treatment regimen. There is evidence that the incorporation of novel drugs not only results in higher pre- and post-transplant CR-rates, but may also improve the depth of response and/or prolong CR. Especially the results of post-transplant consolidation/maintenance with new drugs are encouraging. For instance, a meta-analysis of studies of thalidomide maintenance after ASCT gave evidence that this substance improves the overall survival.
In the era of novel drugs, ASCT should be optimized instead of replaced. CR-rates of over 50% and a CR-rate ten years post high-dose therapy of more than 10% open the door for cure in MM.
About 50% of the MM-patients are not eligible for transplantation due to high age or comorbidity. For these patients, a combination of melphalan/prednisone resp. dexamethasone with one of the new drugs is considered as the treatment of choice. In this setting, the CR-rate of 5% could be improved to 20-30%. Dependent on a patient´s individual risk factors (e.g. thrombosis or renal insufficiency) the appropriate substance and dose should be chosen. Further options including combinations of new substances are currently in clinical studies examined. Future aim is to find predictive factors for the efficacy of a drug or drug combination for a single patient.
Another treatment option for MM-patients is an allogeneic stem cell transplantation (allo SCT). At present, the reduced-intensity conditioning (RIC) transplantation replaced the formerly usual myeloablative allografting because of the high mortality risk of the latter. Nevertheless, the risk of allo SCT is higher compared with ASCT. There is still need for further investigation how to improve outcome with allo SCT. Eventually the new drugs are candidates for this purpose, but further studies are necessary to assess their possible role in allo SCT regimen.

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V349

Treatment intensification and allogeneic transplantation

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The survival of patients with multiple myeloma has improved over the last decade as a result of melphalan-based high-dose therapy followed by autologous stem cell transplantation (Auto-SCT), the introduction of novel anti-myeloma agents with remarkable efficacy in relapsed and refractory myeloma, and improvements in supportive care. Indeed patients with standard risk factors (absence of t(4;14),(14;16),17p-) may live for 7-10 years with good quality of life. Up to now only about 10 - 15% of patients undergoing a tandem autograft procedure will be in remission 10 years after the transplant. For in most of the reports none of the patients in CR 10 years after autografting relapsed - these patients might be cured. After the introduction of the novel agents in the induction therapy prior and in the consolidation and maintenance therapy post-transplant the rate of CR and the progression-free survival have been markedly improved. Thus the group from Little Rock chaired by Prof. Barlogie have from their new TT3-protocol including the novel agents prior and after their tandem auto-SCT programme now projected a 10 yera survival of 50% and for the standard risk patients achieving a CR a rate of continous CR at 10 years of 60%.

Allogeneic stem cell transplantation (Allo-SCT) is up to now the only treatment with a proven curative potential for myeloma. This is in part due to the graft-versus-myeloma effect (GVM), mediated by immune competent donor lymphocytes, at best illustrated by the induction of sustained (molecular) remissions following donor lymphocyte infusions (DLI) and may also be due in part to absence of contaminating myeloma cells in the donor graft. But upfront comparisons between tandem auto SCT and auto/RIC-allografting revealed conflicting results. Whereas the Italian Study Group showed a significant advantage of the allo-arm for PFS and OS, the French IFM study group showed no advantage, even a slight disadvantage in OS for the allo-group.
The role of Allo-SCT in myeloma however is debated due to the high mortality and morbidity associated with conventional myeloablative regimens with this procedure while convincing evidence for a survival benefit is lacking.
But for patients with an early and chemosensitive relapse after an autograft current European recommendations suggest to go ahead with an allogeneic SCT. Long-term disease control could be demonstrated in several trials for these patients who otherwise have a very poor prognosis.

Disclosure: No conflict of interest disclosed.

Fortbildung

Aktuelle Entwicklungen in der Diagnostik und Therapie der CLL

V352

Molecular monitoring for treatment decision

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Over the recent years, many prognostic factors have been identified in CLL. Based on assessment of BCR structure and function, a subdivision is possible into subtypes (IGHV unmutated and mutated, V3-21 usage) with distinct biological and clinical characteristics. Recurrent genomic aberrations (i.e. 11q23 and 17p13 deletion) and gene mutations (*TP53*, *ATM*) help to define biological and clinical subgroups. In addition, serum markers (e.g. TK, ß2-MG), cellular markers (e.g. CD38, ZAP70) and clinical staging impacts outcome in CLL. The biological characterisation of CLL has not only led to progress in outcome prediction but also has begun to be translated into novel treatment strategies. Nonetheless most factors associated with prognosis have not been thoroughly interrogated for their predictive value in the light of different therapeutic approaches. Emerging data from the use of these factors within prospective trials identifies subgroups of CLL patients with early disease progression, refractoriness to treatment and short survival after specific therapeutic approaches. In particular, patients with deletion 17p13 and/or TP53 mutation are candidates for clinical trials investigating alternative (non-chemotherapeutic) treatments. The 17p13 abnormality is the first biological marker to become incorporated into risk-stratified, first-line treatment approaches in CLL, and is recommended for testing also outside clinical trials. With a growing number of agents acting on specific biological targets and used in different clinical situations, the future is likely to bring the identification of predictive factors in CLL.

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Wissenschaftliches Symposium

Nicht kleinzelliges Bronchialkarzinom - welche Therapie ist evidence-based?

V355

Neoadjuvant therapy in stage III

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Introduction: Treatment of stage III has curative potential. Definitive chemoradiotherapy (CTx/RTx) is standard of care in substages (IIIA3, IIIA4 - "Robinson"-Classification). induction therapy followed by surgery (S) remains an important option for selected patients (pts) (esp. IIIA3). This review will focus on evidence-based descision making.

Methods: For the German S3-Guideline a literature research was generated for treatment of stage III. The existing literature (2008/updated 2009) was screened and evaluated with typical criteria. We focus on these findings and an update with current literature.
Results: 1) Stage III represents a heterogeneous group. The current IASLC classification has regrouped pts based on prognosis. We will have to adopt this new IASLC classification. Further subdivision comes from pragmatically orientated "Robinson"- defining IIIA1, IIIA2, IIIA3, IIIA4 and IIIB. 2) Definitive CTx/RTx is a typical approach for the majority of pts in IIIA3, IIIA4 and IIIB. 3) S is still accepted a standard for IIIA1/IIIA2. Moreover, in IIIA3, the large North American Intergroup trial (Albain, Lancet) favours induction therapy (CTx/RTx) followed by S - especially following organ sparing S (lobectomy). Within this large randomized trial significant benefit was shown for PFS and in pts with lobectomy following induction CTx/RTx. This multicenter trial demonstrated significant treatment-related mortality following extensive S (pneumonectomy). Joint databases in Zürich/Essen have demonstrated that in experienced centers, pneumonectomy can be safely performed following induction CTx/RTx (Weder, J Thorac Cardiovasc Surg). For IIIA4 and IIIB, induction CTx followed by S and postop RTx has shown comparable results to induction CTx followed by CTx/RTx and S (Thomas, Lancet Oncology). Further Groups have focussed on induction CTx followed by S in IIIA3 (Laurent, Ann Oncol 2003). It is not clear, what selection factors might guide descision for either induction CTx or induction CTx/RTx. For Pancoast tumors (T3-4Nx) induction CTx/RTx followed by S remains treatment of choice - based on higher complete resection rates (Rush Ann Thoracic Surg; Marra, Eur Resp J). 4) Toxicity management of S in this setting has to be implemented for these strategies. Experience of multidisciplinary treatment groups is important when evaluating the benefit/risk ratio for an individual pt.
Conclusions: Both induction CTx and CTx/RTx remain important treatment options for stage III

Disclosure: No conflict of interest disclosed.

V357

Selected Abstract
The gefitinib Long-Term Survivor (LTS) – a species on its own? Molecular and clinico-pathological characteristics of German Long-Term Survivors treated in the Iressa Expanded Access Program (EAP)

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Lung cancer is the leading cause of cancer-related death world-wide and has a poor prognosis. In selected patients with advanced non-small cell lung cancer (NSCLC) the *epidermal growth factor receptor* (*EGFR*) tyrosine kinase inhibitor (TKI) gefitinib (Iressa) shows response rates ≥70% and a significant prolongation of progression free survival (PFS). Clinico-pathological and molecular characteristics such as gender, smoking status, histology, *EGFR* or *k-ras* mutations are considered to be predictive for response or resistance to *EGFR*-TKIs. In this study, pretherapeutic tissue specimens of German patients with advanced NSCLC or head and neck cancer (HNC), undergoing long-term treatment (≥3 years) with gefitinib in the International Iressa EAP, were analyzed. Of 1925 patients enrolled, who had progressive disease after at least one course of chemotherapy or radiation or were ineligible for both, 20 (1.0%) LTS were identified; 13 with appropriate tissue specimens available. These were analyzed for *EGFR* and *k-ras* mutations, *EGFR* and *c-met* amplification, and protein expression of *EGFR*, *E-cadherin*, *CD133* and *breast cancer resistance protein* (*BCRP1*). The findings were compared to those of primary resistant patients (RP) matched for gender, histology and smoking status. All patients - 8 women and 5 men - had received 1-2 prior therapies. 2 patients had squamous cell lung cancer (SCC), 10 patients pulmonary adenocarcinoma and 1 patient adenocystoid HNC. 7/13 patients were never smokers. Except for SCC all LTS showed *EGFR* mutations. In turn 5/12 RP showed *k-ras*, but no *EGFR* mutations. 1 LTS had an *EGFR*, and 1 RP a *c-met* amplification. Surprisingly, 1 LTS with SCC had a *k-ras* mutation. *E-cadherin* and *EGFR* expression was not different between LTS and RP, whereas *CD133* was exclusively (5/12 *vs.* 0/12) and *BCRP1* predominantly (7/12 *vs.* 2/12) expressed in LTS. These molecular characteristics were associated with a significantly longer mean PFS (61.3 *vs.* 1.1 mo.) and mean survival time (95.1 *vs.* 16.1 mo.) of the LTS and moreover, with a significantly longer mean PFS on previous therapies (13.6 *vs.* 7.8 mo.) suggesting also a prognostic impact. These data demonstrate that pretherapeutic tissue specimens and established biomarkers predict response to gefitinib in pretreated adenocarcinoma patients. Moreover, they suggest that markers indicating multidrug resistance may characterize a subgroup of favorable LTS and thus matter of interest for further evaluation.

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V358

Non-small cell lung cancer – what treatment is evidence-based? Non-curative treatment strategies

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First-line chemotherapy of advanced NSCLC consists of platinum-based doublets containing third generation anticancer drugs. Chemotherapy in addition to best supportive care improves survival with an absolute gain of approximately 10% at 1 year (NSCLC Collaborative Group JCO 2008, 26, 4617). Chemotherapy also relieves cancer-related symptoms. Cisplatin-containing protocols are slightly superior to carboplatin-based protocols (Ardizzoni A et al. JNCI 2007, 99, 847). Cisplatin plus pemetrexed is superior to cisplatin plus gemcitabine in patients with non-squamous NSCLC (Scagliotti G et al. JCO 2008, 26, 3543). Elderly patients and patients with reduced performance status also benefit from palliative chemotherapy but require well tolerated protocols and enhanced supportive care measures. Maintenance therapy usually prolongs progression-free survival but prolongation of survival has only recently been shown for pemetrexed (Ciuleanu T et al. Lancet 2009, 374, 1432). In patients previously treated with chemotherapy, docetaxel, pemetrexed and erlotinib are established as standard of care. Strategies to improve the outcome of chemotherapy in patients with NSCLC include customized chemotherapy and integration of targeted therapies. While customized chemotherapy remains experimental, targeted therapies have already demonstrated efficacy in phase III trials. Cetuximab added to cisplatin plus vinorelbine increased survival in patients with advanced EGFR-positive NSCLC (Pirker R et al. Lancet 2009, 373, 1225), while cetuximab added to carboplatin plus paclitaxel did not improve progression-free survival (Lynch TL et al. JCO 2010, 28, 911). A meta-analysis confirmed the benefit of cetuximab when added to platinum-based chemotherapy (Thatcher N et al. WCLC 2009). Bevacizumab added to chemotherapy improved outcome in selected patients with advanced non-squamous cell NSCLC (Sandler A et al. NEJM 2006, 355, 2542; Reck M et al. JCO 2009, 27, 1227). Gefitinib improved progression-free survival compared to carboplatin plus paclitaxel in patients with EGFR-activating mutations in their tumors (Mok T et al. NEJM 2009, 361, 947). In the second-line setting, gefitinib had efficacy similar to docetaxel (Kim ES et al. Lancet 2008, 372, 1809).

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V359

Different *FLT3*-ITD integration sites are associated with differential sensitivity to midostaurin *in vitro*

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Introduction: In AML, the recently described tyrosine kinase domain-1 (TKD1)-ITDs of *FLT3* show insertion sites within the beta1-sheet, nucleotide binding loop and beta2-sheet, respectively. Multivariate clinical analysis revealed that TKD1-ITDs within the beta1-sheet are unfavorable prognostic factors. Recently, we uncovered rewired signaling and differential responsiveness to tyrosine kinase inhibitors (TKIs) of a beta2-sheet-ITD (A627E). Here, we characterized TKD1-ITDs of the beta1-sheet and nucleotide binding loop in a cellular reconstitution model.
Methods: TKD1-ITDs isolated from patient material, were sequenced, subcloned and stably transfected into growth-factor dependent hematopoietic Ba/F3 cells. Constitutive FLT3 phosphorylation and activation of downstream signaling was analyzed by Western-blotting. Transformation potential was analyzed by colony formation in methylcellulose medium and by withdrawal of IL-3. Induction of apoptosis in response to midostaurin (PKC412) was measured by PI-staining.
Results: Biological characteristics of *FLT3*-ITDs from two structural domains of FLT3-TKD1 were characterized: (1) beta1-sheet-ITDs E611V (96nt) and Q613E (99nt) and (2) nucleotide binding loop-ITD A620V (84nt). Ba/F3 cells expressing these ITDs revealed colony formation in methylcellulose assays and growth-factor independent proliferation. Western-blotting showed constitutive phosphorylation of FLT3 and of downstream signaling nodes (STAT5/AKT/ERK). Compared to a juxtamembrane domain (JMD) ITD (36nt), we observed less induction of apoptosis in TKD1-ITDs investigated at 24h of incubation across all concentrations of PKC412 used. However, the difference in sensitivity gradually decreased when incubating for 36h and 48h. Currently, additional FLT3-TKIs are being investigated and results will be presented.
Conclusion: Our results employing three different TKD1-ITDs from beta1-sheet and nucleotide binding loop revealed that TKD1-ITDs mediate constitutive activation of FLT3 receptors leading to transformation of hematopoietic cells. Compared to a JMD-ITD, TKD1-ITDs analyzed revealed differential responsiveness in induction of apoptosis to midostaurin. These *in vitro* data suggest that different ITD integration sites may be associated with differential sensitivity to midostaurin *in vivo* and provides a rationale to prospectively analyze not only the *FLT3*-ITD mutation status but also the ITD integration site in ongoing/future clinical trials using FLT3-TKIs.

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V360

The Vent-like homeobox gene *VENTX* promotes human myeloid development and is highly expressed in acute myeloid leukemia

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Background: Recent studies suggest that a variety of regulatory molecules active in embryonic development such as clustered and non-clustered homeobox genes play an important role in normal and malignant hematopoiesis. Since it was shown that the Xvent-2 homeobox gene is part of the BMP-4 signalling pathway in Xenopus, it is of particular interest to analyze the function of the human homologue VENTX in normal hematopoiesis and leukemogenesis.
Aim: To identify the role of VENTX in normal and malignant hematopoiesis.
Methods: Expression of the VENTX gene was analyzed in normal human hematopoiesis and AML by microarray and qPCR. To test the impact of the constitutive expression of VENTX on human progenitor cells, $CD34^+$ cord blood (CB) cells were retrovirally transduced with VENTX or the empty control vector and analyzed using *in vitro* and *in vivo* assays.
Results: qRT-PCR documented expression of the gene in lineage positive hematopoietic subpopulations, with the highest expression in $CD33^+$ myeloid cells. Of note, expression of *VENTX* was negligible in normal $CD34^+/CD38^-$ but detectable in $CD34^+$ normal BM human progenitors. In contrast to this, leukemic $CD34^+/CD38^-$ from AML patients (n=3) with translocation t(8,21) showed significantly elevated expression levels compared to normal $CD34^+$ BM cells (50-fold; $p \leq 0.0001$). Gene expression and pathway analysis demonstrated that in normal $CD34^+$ cells enforced expression of *VENTX* initiates genes associated with myelopoiesis and downregulates genes involved in early lymphopoiesis. The constitutive expression of *VENTX* in normal CD34+ human progenitor induced a significant increase in the number of myeloid colonies (48 ± 6.5 compared to 28.9 ± 4.8 CFU-G per initially plated 1000 CD34+ cells; n=11; p=0.03) and a complete block in erythroid colony formation compared to the control (15.5 ± 3.9 and 81.9 ± 17.9 for *VENTX* and GFP control; n=11; $p < 0.003$). In the NOD/SCID mouse xenograft model, *VENTX* expression in $CD34^+$ CB cells promoted generation of myeloid cells with an over 5-fold and 2.5-fold increase in the proportion of human $CD15^+$ and $CD33^+$ primitive myeloid cells as compared to the GFP control; n=5, p=0.01) resulting in an inversion of the lympho-myeloid ratio from 25.1 in the control to 2.7 in the *VENTX* arm (p=0.003). In this study we could show for the first time that the constitutive expression of *VENTX* perturbs normal hematopoietic development and indicate a role of *VENTX* in normal and malignant myelopoiesis.

Disclosure: No conflict of interest disclosed.

V361

Overexpression of the homeobox gene *Cdx4* induces erythroid leukemia in the murine bone marrow transplantation model

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Background: Aberrant expression of developmental factors such as homeobox genes has been shown to contribute to development of leukemia. The caudal-like Cdx members are important upstream regulators of *Hox* genes during embryogenesis and as such have the potential to act as potential oncogenes.
Methods: To test the impact of aberrant Cdx4 expression on murine hematopoietic progenitors, 5-FU enriched BM was retrovirally transduced with Cdx4 and analyzed by *in vitro* and *in vivo* assays. Expression of *Cdx4* in different hematopoietic subpopulations was determined by qPCR and microarray experiments were performed to identify possible target genes.
Results: qPCR analyses revealed high *Cdx4* expression in early murine hematopoietic progenitors and significant downregulation towards the more differentiated hematopoietic stages (p=0.005). Among different lineage positive hematopoietic subpopulations, *Cdx4* was lowest expressed in $Ter119^+$ erythroid precursors. *In vitro*, overexpression of *Cdx4* in murine BM progenitors enhanced the proliferative potential in liquid expansion assay and conferred serial replating capacity (CFU total after 2^{nd} replating: $2.6x10^7 \pm 3.2x10^6$ SEM/ 500 input cells in 1^{st} CFC, n=8). Immunophenotyping of the colonies revealed a 4.1-fold increase of erythroid $Ter119^+$ cells in 1° and 72.9-fold increase in 2° CFC (n=4, p=0.02 and 0.05, resp.). In contrast to data previously published by Bansal *et al.* where Cdx4 was shown to induce AML with myelomonocytic features in BALB/c mice, all our Cdx4-transplanted mice died with a median latency of 309 days which by Ter119-staining was histopathologically diagnosed as erythroid leukemia (n=10). Furthermore, immunophenotyping revealed the majority of the leukemic cells to be positive for CD71 expression. At time of death, Cdx4-transplanted mice displayed splenomegaly with massive erythroid infiltration, a severely decreased lymphoid:myeloid ratio < 1:5 and presence of erythroid blasts in PB, BM and

spleen. Gene expression profiling of BM progenitor cells transduced with Cdx4 showed deregulation of genes involved in signal transduction processes as well as leukemogenic *Hox* genes compared to empty vector control.
Conclusion: Overexpression of Cdx4 confers self-renewal property to transduced murine BM progenitors *in vitro* and *in vivo* induces erythroid leukemia. This suggests Cdx4 to be a novel factor in the development of erythroid leukemia.

Disclosure: No conflict of interest disclosed.

V362

CBL deletion mutants found in patients with AML predominantly cooperate with class III receptor tyrosine kinases to induce transformation of IL-3 dependent cells

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Introduction: Aberrant Function of Receptor Tyrosine Kinases (RTKs) is found in many human hematologic malignancies and solid tumours. Besides overexpression and activating mutations receptors can be aberrant activated by impaired downregulation. The CBL protein is a negative regulator of many receptors by causing their ubiquitination. Alterations of CBL have been found in hematopoietic malignancies, e.g. AML and CML but also in lung cancer.
We analyzed the oncogenic potential of Cbl deletion mutants in cytokine receptors and RTKs expressing Ba/F3 cells. It was the aim of this study to investigate if the malignant transformation by CBL is a potentially general mechanism in human cancer.
Methods: The cDNA of wildtype receptors (FLT3, c-KIT, PDGFRA, PDGFRB, EGFR, c-MPL, EPOR) was transduced in Ba/F3 cells via a retroviral expression vector. Stable receptor expression after transduction and fluorescence-activated cell sorting (FACS) was confirmed by western blotting and cellsurface-marker expression by flow cytometry. Proliferation and apoptosis assays were done in presence and absence of IL-3 or receptor-ligands and selective PTK inhibitors.
Results: Coexpression of RTK class III wildtype receptors and CBL deletion mutants causes IL-3 independent and ligand dependent growth of Ba/F3 cells. Selective PTK inhibitors abrogate this proliferation. RTK class III-WT/CBLΔexon8 cells show a more than 10 fold hyperproliferation (FLT3: 12,24x; c-KIT: 11,96x; PDGFRα: 11,6x; PDGFRβ: 10,39x) compared to RTK class III-WT/CBL-WT cells in presence of 100ng/ml ligand. Ba/F3 cells expressing EGFR or coexpressing EGFR and CBL-WT or CBL mutants show EGF dependent and weak IL-3 independent growth. EGFR-WT/CBLΔexon8 cells show a 1,6 fold proliferation compared to EGFR-WT/CBL-WT cells in presence of 100ng EGF. Coexpression of cytokine receptors EPOR-WT or c-MPL-WT and CBLΔexon8 causes weak IL-3 independent growth and ligand dependent growth. Ba/F3 cells coexpressing EPOR-WT or c-MPL-WT and CBLΔexon8 have a 1,1 fold respectively 1,3 fold hyperproliferation rate compared to cells expressing EPOR-WT or c-MPL-WT/CBL-WT in presence of 0,25U/ml EPO respectively 100ng/ml TPO.
Conclusion: An alternative mechanism for the constitutive activation of RTKs in tumors occurs through inactivation of a negative regulator. CBL seems to be a selective negative regulator of the RTK class III family and shows only weak interaction with other RTKs and class I cytokine receptors.

Disclosure: No conflict of interest disclosed.

V363

Leukemia-initiating and maintaining cell populations in mouse models of AML and CML

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Stem cells play an important role in the pathogenesis and maintenance of malignant tumors. Consequently, the major target of new therapeutic strategies has to be the tumor stem cell. Acute and chronic myeloid leukemia (AML and CML) are stem cell diseases. Most therapy regimens target the blast population unknowingly whether it contains the leukemia maintaining cells (L-MC). Inefficient targeting of LMC is considered responsible for the relapse after the induction of complete remission in AML. Aim of the study was to determine the leukemia initiating cell (L-IC) in mouse models of high risk t(6;9)(DEK/CAN)- as well as low risk t(15;17)(PML/RAR)- and t(8;21)(AML1/ETO)-positive AML. We also studied the L-IC and L-MC in a murine BCR/ABL-positive CML. To select and amplify cells with L-IC potential, we used a novel approach in order to select for "stem cell fitness". The oncogenes were expressed in Sca1+/lin- cells which were enriched for "long term" (LT)-HSC (lin-/Sca1+/c-Kit+/Flk2-) and "short term" (ST)-HSC (lin-/Sca1+/c-Kit+/Flk2+) by cell sorting. After a passage in semi-solid medium (10 days) and inoculation into lethally irradiated mice cells harvested after 12 days from the spleen colonies were then inoculated into sublethally irradiated mice for the analysis of leukemia development. Subpopulations (LT-HSC, ST-HSC, CMP) of resulting leukemias were then analyzed for their potential to propagate/maintain the leukemia in 2° recipients. We found that DEK/CAN and PML/RAR initiated leukemia only from the LT-HSC with a high penetrance, whereas AML1/ETO-L-IC was able to gave origin from both LT- and ST-HSC population with a very low penetrance. BCR/ABL only sporadically originated CML from LT-HSC whereas from the the more mature Sca1+ population penetrance was close to 100%. Interestingly neither AML1/ETO-AML or BCR/ABL-CML were transplanted into secondary recipients whereas DEK/CAN- and PML/RAR-positive AML were efficiently propagated in serial transplantations. The propagation of established DEK/CAN- or PML/RAR-positive AML was not restricted to the LT-HSC population, but occurred even from more mature and heterogeneous cell populations. These findings indicate that in DEK/CAN- and PML/RAR-induced AML there is a difference between L-IC and L-MC. In contrast to the L-IC cells represented by a very rare subpopulation of LT-HSC, the L-MC seem to be represented by a larger and phenotypically heterogeneous cell population.

Disclosure: No conflict of interest disclosed.

V364

The hedgehog signalling pathway represents a new target in AML patients with normal karyotype

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Introduction: The hedgehog signaling is an embryonic pathway like the Wnt or Notch pathway and propagates disease development and oncogenic transformation in certain cancers. In previous studies we identified the hedgehog signaling pathway as essential for the maintenance of leukemic stem cells in CML, while regular hematopoetic stem cells are independent of hedgehog signaling. Furthermore other groups reported that the hedgehog signaling pathway is activated in certain AML cell lines (Kobune et al., 2009). Therefore the aim of the presented study was to investigate the role of hedgehog signaling in distinct AML subtypes.
Results: The transcription factor Gli1 represents a direct downstream target of the hedgehog pathway and high expression levels indicate activation of hedgehog signaling. Therefore immunohistochemistry staining for Gli1 was performed on 44 bone marrow samples from AML patients, which represent all different FAB subtypes (n = 4 per subtype and AML from MDS). 37 patients (84%) demonstrated high expression levels for Gli1, while Gli1 expression was not detectable in bone marrow of healthy donors (n=5). Also other pathway members like Smo (55%) and the activating Hh ligands Shh/Ihh (36%) were upregulated in certain AML samples. Interestingly, patients with high Smo expression showed reduced survival time compared to patients with absent Smo expression.
To validate if abrogation of Hedgehog signaling by blocking the activating receptor Smo can affect growth, survival and colony formation of primary AML cells *in vitro*, we used 2 different Smo inhibitors, Cyclopamine and LDE225 (Novartis). Pharmacological inhibition of Smo in AML samples (n=20) induced apoptosis and reduced proliferation in 45% of the examined samples. The same AML samples also showed reduced colony forming ability after Smo inhibiton, indicating a loss of the leukemic progenitor population. There was no correlation of response with Flt3 status, presence of MLL-fusion

oncogenes or certain chromosomal aberrations. In contrast, all patients that were responsive to Smo inhibition had a normal karyotype. Furthermore, AML patients that showed the strongest response to Smo-inhibition in vitro had a dramatically shorter survival time than non-responders.
Conclusion: Thus we conclude that the Hh pathway is activated in subtypes of human AML and represents an interesting target for treatment of certain patient populations, especially patients with normal karyotype.

Disclosure: No conflict of interest disclosed.

Freie Vorträge
Sarkom

V365

Functional expression of CysLT1 in pediatric and adult type soft tissue sarcomas: A potential new therapeutic target

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Introduction: CysLT1, a G protein-coupled receptor for inflammatory mediators of the cysteinyl-leukotriene family, is expressed on mesenchymal cells such as smooth muscle cells, and may contribute to migration/metastasis and growth of malignant cells. We therefore analyzed expression and function of S1P receptors in pediatric and adult type soft tissue sarcoma (STS) cell lines and primary STS.
Methods: The cell lines RD (embryonal rhabdomyosarcoma=RMS), A-673, RD-ES, TC71 (three Ewing sarcoma cell lines), HT-1080 (Fibrosarcoma) and U-2197 (pleomorphic sarcoma/NOS) were cultured in RPMI 1640 medium supplemented with 10 % FBS. Primary sarcoma cells were isolated by collagenase digestion. Expression of CysLT1 was analyzed by real-time RT-PCR (TaqMan). For functional analysis, actin polymerization (as a first step in cell migration) was measured by fluorescence microscopy and flow cytometry. Phosphorylation of the MAP-kinase/Erk1/2 was assessed by Western blot.
Results: mRNA of CysLT1 was consistently found in all cell lines and all primary STS analyzed (pleomorphic sarcoma/NOS n=10, leiomyosarcoma n= 9, synovialsarcoma n=8, liposarcoma n=8). The cysteinyl-leukotriene LTD4 induced significant actin polymerization particularly in rhabdomyosarcoma and Ewing sarcoma cells, while phophorylation of the proliferation-related MAPK/Erk1/2 was observed in all cell lines with the exception of RD. Also in primary STS cells (pleomorphic sarcoma/NOS and chondrosarcoma), Erk/MAPK phosphorylation was detected in response to LTD4. Preincubation with pertussis toxin, which blocks G(i) protein-coupled signaling, abrogated this effect.
Conclusions: CysLT1 is expressed and functionally active in pediatric and adult type soft tissue sarcoma cells. The availability of CysLT1 antagonists already used in asthma therapy strongly suggests to further evaluate CysLT1 as a potential new therapeutic target.

Disclosure: No conflict of interest disclosed.

V366

Activation of the hedgehog pathway confers a poor prognosis in embryonal and fusion gene negative alveolar rhabdomyosarcoma

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Introduction: Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children and comprises two major histological subtypes: alveolar rhabdomyosarcoma (ARMS) and embryonal rhabdomyosarcoma (ERMS). 75% of ARMS harbor reciprocal chromosomal translocations leading to fusion genes of the forkhead transcription factor FOXO1 and PAX3 or PAX7. The hedgehog (Hh) pathway has been implied in tumor formation and progression of various cancers including RMS. However, whether Hh pathway activation presents a general feature of RMS or whether it is restricted to specific subgroups has not yet been addressed.
Methods: We analyzed parametern of Hh pathway activation and muscle differentiation by gene expression profiles in two distinct cohorts of RMS patients, assessed marker genes as class predictors for any subgroup of RMS and correlated gene expression profiles with patients survival.
Results: Marker genes of active Hh signaling, i.e. Patched1 (Ptch1), Gli1, Gli3 and Myf5, are expressed at significantly higher levels in ERMS and fusion gene negative ARMS compared to fusion gene positive ARMS in two distinct cohorts of RMS patients. Consistently, Gli1 expression correlates with Ptch1 expression in ERMS and fusion gene negative ARMS, but not in fusion gene positive ARMS. In addition, expression levels of MyoD1 are significantly lower in ERMS and fusion gene negative ARMS, pointing to an inverse association of Hh activation and muscle differentiation. Moreover, Myf5 is identified as a novel excellent class predictor for RMS by receiver operating characteristic (ROC) analysis. Importantly, high expression of Ptch1 or low MyoD1 expression significantly correlate with reduced cumulative survival in fusion gene negative RMS underscoring the clinical relevance of these findings.
Conclusions: By demonstrating that Hh signaling is preferentially activated in specific subgroups of RMS, our study has important implications for molecular targeted therapies, such as small molecule Hh inhibitors, in RMS.

Disclosure: No conflict of interest disclosed.

V367

Outcomes of Patients (pts) with advanced soft-tissue sarcomas (STS) treated in clinical trials (CTs) vs expanded access programs (EAPs): a decade of experience with single-agent trabectedin (Tr)

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Background: Pts who do not qualify for CTs may enter EAPs when available, allowing treatment with new agents prior to regulatory approval when no other options are left. Extensive data collected with single-agent Tr for more than a decade allow us to compare outcomes from this unselected population with pts rigorously selected for CTs.
Methods: Data on 879 STS pts included in CTs and EAPs globally were retrospectively analyzed. 620 pts were included in phase II CTs (1999-2008) and 259 were in EAPs (1998-2002). Most patients had undergone prior surgery (96% CTs and 93% EAPs) and about 50% had received prior radiotherapy (52% CTs and 55% EAPs). The following Tr dose and schedule regimens were used: every 3 weeks 1.5mg/m^2 24h IV, 1.3mg/m^2 3h IV and weekly 0.58mg/m^2 3h IV.
Results: See Table on next page.
Conclusions: Available data offer an oppportunity to compare CT data with clinical practice in EAPs. As expected, the EAP pts had a worse ECOG PS, a wider variety of rare subtypes, increased likelihood of bone and brain metastases and were more heavily pretreated. Nonetheless, clinical activity was noted in both CT and EAP groups. EAPs are potentially useful for patient care as well as for evaluating the comparative effectiveness of new agents that can be expected in clinical practice following regulatory approval.

Disclosure: Peter Reichardt: Advisory Role: Mitglied internationaler Advisory Boards; Honoraria: Honorare fuer Vortraege; Financing of Scientific Research: Teilnahme an Trabectedinstudien
Sebastian Bauer: Honoraria: Honorare fuer Vortraege; Financing of Scientific Research: Teilnahme an Trabectedinstudien

Table. Baseline characteristics (for Abstract V367)

	CT (n=620)	EAP (n=259)
Median age (range)	52 (14–81)	47 (14–80)
ECOG PS 0-1 / 2-4	99% / 1%	80% / 18%
Histology (most common)	Leimyosarcoma 49%; Liposarcoma 24%; Synovial 7%, MFH 3%; Fibrosarcoma 2%; Rhabdomyosarcoma 2%; Others 12%	Leimyosarcoma 26%; Lipo 17%; Synovial 13%; MFH 8%; Fibrosarcoma 7%; Rhabdomyosarcoma 5%; Others 25%
Histology G1-2/3-4	30% / 50%	27% / 41%
Metastasis (most common)	Lung 65%; Liver 25%; Bone 7%, Brain 0%	Lung 64%; Liver 22%; Bone 19%; Brain 2%
No prior chemotherapy 1-2 / ≥3	81% / 14%	57% / 43%
Prior chemotherapy	95%:Antracycline+Ifosfamide 78%; Antracycline 14%; Gemcitabine+Docetaxel 11%; Gemcitabine 7%; Ifosfamide 2%	100%: Antracycline+Ifosfamide 92%; Antracycline 6%; Gemcitabine+Docetaxel 2%; Gemcitabine 10%; Ifosfamide 0%
Prior chemotherapy setting	Advanced 68%; Adjuvant 8%; Both 19%	Advanced 79%; Adjuvant 4%; Both 17%

Table. Results

	CT (n=620)	EAP (n=259)
Trabectedin Response	CR 1%; PR 6%; *SD 42%	CR 0%; PR 5%; **SD 32%
Trabectedin median cycles (range)	3 (1-59)	2 (1-22)
Median PFS, months	2.3 [95% CI(2.0-2.8)]	1.6 [95% CI(1.5-2.0)]
Median OS, months	13.0 [95% CI(11.7-14.3)]	9.1 [95% CI(6.5-11.2)]
	(* median of 6 Tr cycles received)	***(** median of 4 Tr cycles received)***

V368

Topoisomerase-based chemotherapy in adults with relapsed or refractory pediatric-type sarcoma

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Introduction: To assess the efficacy and safety of topoisomerase-based (TOPO) regimens in adult patients (pts) with pediatric-type sarcoma who had failed induction chemotherapy.
Patients and methods: Pts with Ewing sarcoma/PNET, osteosarcoma, embryonal and alveolar rhabdomyosarcoma, synovial sarcoma or desmoplastic small round cell tumors, refractory or relapsed after at least one prior induction chemotherapy, inoperable, locally advanced or metastatic extent, ECOG 0-2, measurable and progressive disease, adequate organ functions treated with TOPO-inhibitor based regimens, consisted of irinotecan, topotecan or etoposide (combined either to carboplatin or cyclophosphamide) were retrospectively analysed. Tumor response was assessed every second cycle as defined by RECIST.
Results: 19 pts, median age 36 yrs (21-60), 6 females, 13 males, have been identified. All pts had been received previous induction treatment according to (inter)national study protocols (EURAMOS, CWS, EUROEWING, EUROBOSS). Regimens consisted of topotecan + cyclophosphamide (n=14), single-agent irinotecan (2), etoposide + carboplatin (2) and topotecan + carboplatin (1). Second-line TOPO-based treatment was applied in 15 pts (≥ third-line, 4 pts). 10 pts had refractory disease (evidence of tumor progression during induction chemotherapy); 5 pts had early relapses within 6 months and in addition 4 pts after more than 24 mos (late relapse). Pts received a median of 2 cycles (range, 1-6). CTC toxicity consisted mainly of hematologic toxicity (all pts experienced grade 3 or 4 granulocytopenia) as well as nausea/vomiting and elevation of ASAT/ALAT. No toxic death was seen. Summary of anti-tumor activity: 1 confirmed partial response (5%) and 7 pts attained disease stabilisation (SD) (37%). PR lasted 381 days and median duration in pts with SD was 195 days (range, 95-468). Pts with refractory disease had a lower chance to attain a response (PR/SD) to treatment (p=0.055). The 3/6-mos PFR were 47% and 35% for all pts. Differences were seen in exploratory subanalyses regarding type of relase (refractory- vs. early/late relapse, p=0.016) and line of treatment (second- vs. higher, p=0.05), respectively.
Conclusions: Only limited activity was seen in adult pts with refractory or relapsed pediatric-type sarcomas with a regimen which has proven activity in pediatric pts. Adults with refractory small cell sarcoma appear to have a similar dismal outcome as seen in pts with common adult-type histologies.

Disclosure: No conflict of interest disclosed.

V369

Sunitinib malate in metastatic alveolar soft part sarcoma

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Introduction: Alveolar soft part sarcoma are very rare tumors with an incidence of 0.5/100,000/year, the tumor origin is still unknown. Main tumor localization are upper or lower limb with high metastatic potential to the lung, brain, bone and other soft tissues. Systemic treatment with chemotherapy or local therapy with e.g. radiotherapy exhibits no effect on ASPS due to minor chemosensitivity. The prognosis of metastatic ASPS remains poor. In a small study on five patients 37.5mg Sunitinib malate orally applicated once daily in a compassionate use program showed antitumor activity in metastatic ASPS. The tumor cells exhibit a translocation of t(X;17) (p11.2;q25) resulting in the ASPACR1-TFE3 fusion gene with downstream receptor tyrosine kinase activation.
Methods: Two patients with locally advanced ASPS (one primary tumor site located at the lower limb, the other one in the abdominal cavity) with distant metastases to the lung were previously treated with palliative chemotherapy with three cycles of epirubicine and ifosfamide, one patient was switched after tumor progression to a doxorubicine / dacarbazine containing regime and application of three cycles. Due to further tumor progression sunitinib malate 50mg e.g. 37.5mg once daily was started.
Results: During the treatment no WHO grade III / IV toxicitiy was noted, the tolerance to the therapy was good, in one patient a regular therapy for milde arterial hypertension WHO grad II was initiated. CT scan of the lung and abdominal cavity was performed every three month past therapy induction and showed a minor response according RECIST criteria of the lung metastases and the primary tumor site. Both patients are still on therapy after 6 month of treatment.

Conclusion: Alveolar soft part sarcomas are rare tumors with limited therapeutic options and early tumor spread (lung, brain). Sunitinib malate showes antitumor activity in those patients with reduction of tumor related symptoms and radiological response in the CT scan. Further studies for other tyrosine kinase inhibitors in the treatment of ASPS have to be evaluated.

Disclosure: No conflict of interest disclosed.

V370

Metastasectomy in patients with GIST in the era of imatinib – improved survival?

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Background: Imatinib (IM) treatment of patients with GIST rarely induces complete remissions and most patients eventually progress. The value of metastasectomy has not been prospectively validated and data from an ongoing trial will take years to mature. Therefore, identification of patients who might benefit from metastasectomy remains a challenge in clinical practice.
Methods: We analyzed our GIST data base (n=215) for overall survival (OS) in patients with metastatic disease (n=117) who underwent metastasectomy (n=65). Covariates included perioperative treatment with IM, resection status (R0, R1, R2), location of metastases and PDGFR/KIT mutational status.
Results: Median follow-up (FU) from time to diagnosis and time from first IM doses was 3.2 years. 65 patients underwent metastasectomy, with 48 pts (74%) receiving perioperative IM with a median FU of 4.5 years. Median OS for all patients undergoing metastastectomy was 8 years, as compared to 3.4 years in pts with metastatic disease not undergoing metastasectomy (p=0.003). Median OS was not reached in 23 pts with macroscopically complete resection (R0 and R1, n=23), and 69% of pts are alive after 8.2 years.
In comparison, OS of pts with incomplete resections (R2, n=13) was 3.9 years (p=0.007). Median OS for patients with KIT exon 11 mutation undergoing metastasectomy (n=24) was 8 years.
Patients with hepatic (+/- peritoneal) metastases showed a better survival than those with peritoneal metastases only (p=0.0036).
Conclusions: This large long-term follow-up analysis implicates a possible long-term benefit from R0/R1 metastasectomy in patients with metastatic GIST. In contrast, incomplete resection, including debulking surgery, appears not to be beneficial with respect to overall survival. However, confounding by selection bias cannot be excluded in this hypothesis-generating, retrospective analysis.

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Sebastian Bauer: Honoraria: Vortragshonorare von der Firma Novartis

Fortbildung
Tumorspezifische Therapien bis zum Lebensende?

V375

The patient´s desire – an independent ethical factor contributing to therapeutic decision making?

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Therapeutic decision making generally relies on a given underlying medical indication and the patient's informed consent. So far, the concept of medical indication has been analyzed and operationalized for clinical purposes by medical ethics, and the concept of the patient's informed consent is broadly secured by legislation and clinical and ethical guidelines. Informed consent implies thorough and appropriate delivery of information and an according treatment option communicated to the patient, who can accept or refuse this offer.
Within this concept of medical decision making, it is under debate in medical ethics, to what extend the patient's (or the relatives') desires for certain treatment options should play a role, if at all.
This congress contribution summarizes the actual discussion towards the incorporation of the patient's desire into therapeutic decision making, besides ascertaining the underlying medical indication and the patient's informed consent. It systematically reviews the given literature concerning the patient's desires with regard to anticancer therapies, palliative care, role of relatives, care during final phase, and place of death, and tries to encompass these facts into the existing theoretical concepts of medical (and ethical) decision making.

Disclosure: No conflict of interest disclosed.

V376

Ethical analysis of decisions to limit tumorspecific therapies

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Introduction: There is ample evidence that disputes about withdrawing, withholding and forgoing tumorspecific therapies occur frequently and carry the risk of causing conflict and being a burden for patient as well as clinicians. In addition the spiraling costs of cancer therapeutics that achieve only marginal benefits is under increasing scrutiny.
Methods: Using the four principles of medical ethics (beneficence, non-maleficence, patient autonomy and justice) four criteria are proposed that should be factored in the decision and the communication about limiting tumor-specific treatments: that is marginal benefit of the intervention, patient's capability for autonomous decision-making based on coping behaviour and level of information, benefit-harm-ratio of the treatment as perceived by the patient and the relevance of treatment costs need to be discussed. These criteria are built into a stepwise ethical decision model.
Results: The decision model helps analysing whether it is justifiable for the physician to limit care without consent of the patient. It also helps to identify cases where continuing tumorspecific therapy on the request of the patient is justifiable even if physicians find it inappropriate.
Conclusion: The goal of the ethical analysis is to show that a principled approach to requests for "inappropriate" treatment is better suited to solve conflicts about limiting treatments than the futility argument which basically forestalls the debate about value disagreements.

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Treatment algorithms in drug therapy

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Drug therapy is the mainstay in patients with advanced prostate cancer. More recently, a multitude of agents have become available. This leads the way to personalized treatment and care. The following topics will discussed

Endocrine therapy
- continuous or intermittent
- treatment of patients with heart failure
- combined endocrine and chemotherapy
- osteoprotection

Chemotherapy
- therapy of asymptomatic patients
- alternatives to docetaxel

Bone metastases
- bisphosphonates or denosumab

Immunotherapy
- data and approval

Treatment algorithms for different stages of disease can be derived on the basis of published data.

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