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ORIGINAL ARTICLE

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Risk for cytomegalovirus infection following reduced intensity allogeneic stem cell transplantation

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Abstract Preliminary data suggest a faster immune recovery following non-myeloablative stem cell transplantation because of the persistence of recipient T cells, but the real impact on post-transplant infectious complications remains unknown. We retrospectively analysed the incidence of cytomegalovirus (CMV) infection in twenty patients following reduced intensity conditioning with busulfan/fludarabine±thiotepa and post-transplant immunosuppression with cyclosporine A/mycophenolate mofetil. Results were compared with 20 patients receiving myeloablative transplants during the same time period and who were matched for CMV risk group and for donor origin. The cumulative incidence of CMV infection following reduced intensity vs. myeloablative transplants was 60.4% vs. 40.0%, respectively (p value 0.1, log rank test). The risk for CMV infection in both cohorts was increased after in vivo T cell depletion with antithymocyte globulin (75% and 60%, respectively). Acute GVHD preceded the diagnosis of CMV infection by a median of 25 (range, 9–61) days following reduced intensity transplants and a median of 14 (range, 10–34) days in myeloablative transplants. Recurrent CMV infections were observed only in patients receiving reduced intensity transplants. Using multivariate analysis only reduced intensity transplantation and in vivo T cell depletion had a significant impact on the risk of CMV infection. In our series the incidence for CMV infection following reduced intensity transplants seems to be increased as compared with risk-matched myeloablative transplants. When adding anti-T cell antibodies to the conditioning regimen, the risk for CMV infection increases by up to 75%. Thorough studies of the risk of post-transplant viral infection are necessary to optimize surveillance as well as pre-emptive and/or prophylactic treatment strategies in the non-myeloablative transplantation setting.

Keywords Cytomegalovirus (CMV) infection · Reduced intensity conditioning · Non-myeloablative stem · Cell transplantation

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Introduction

The major goal for introducing non-myeloablative conditioning regimens was to reduce transplant-related mortality [2, 5, 18, 27]. If so this would lead to a wider use of allogeneic stem cell transplantation, especially in elderly patients or younger patients with significant comorbidity who are therefore not eligible for conventional myeloablative allografting. Different reduced intensity conditioning regimens have been developed for this purpose during recent years, resulting in long-lasting donor lympho-hematopoietic chimerism and substantial graft-versus-malignancy activity [9, 13, 16, 20]. Regarding transplant-related complications such as infections, it was hypothesised that surviving host immune cells following non-myeloablative conditioning might put the patient at a lower risk for post-transplant infectious complications. Preliminary data on immune reconstitution following non-myeloablative transplants show reconsti-

tution patterns similar to or even faster than those for conventional myeloablative transplants, especially in patients with mixed chimerism [7, 22, 24]. Moreover, the incidence of severe and life-threatening infections seems to be diminished following non-myeloablative stem cell transplantation (SCT), although larger randomized trials are not available thus far [14, 19]. Intensification of pretransplant immunosuppression by adding anti-T cell antibodies with either broad (antithymocyte globulin) or narrow specificity (e.g. Alemtuzumab) to non-myeloablative conditioning regimens in an effort to increase post-transplant donor chimerism might result in a high incidence of complicated viral infections due to prolonged immune paresis [4, 21].

To better define the risk of CMV infection we retrospectively analysed patients undergoing dose-reduced allogeneic SCT at our institution. Results were compared with concurrently treated patients who underwent myeloablative allogeneic SCT.

Patients and methods

Patients

Between June 1999 and 2002, 20 patients received non-myeloablative transplants from either HLA-identical sibling donors (n=11) or from HLA-matched (n=4) or HLA-mismatched (n=5) unrelated donors for advanced hematological malignancies. Detailed patient characteristics are listed in Table 1.

Patients were eligible for reduced intensity SCT if they were >50 and ≤75 years of age with: either diagnosis of acute leukemia in complete remission, partial remission, or untested relapse (<30% bone marrow blasts); chronic myelogenous leukemia in chronic or accelerated phase (<30% bone marrow blasts); poor-risk myelodysplastic syndrome identified by the international prognostic scoring system (IPSS); non-Hodgkin's lymphoma (patients who were not eligible for autologous SCT and/or failed prior therapy with an alkylating agent and/or fludarabine); or any of these diseases following relapse after autologous stem cell transplantation. Patients with refractory acute leukemia, chronic myelogeneous leukemia blast crisis, or low-risk myelodysplastic syndrome were generally not recommended for non-myeloablative transplants but could be treated at the discretion of the investigators.

Patients <50 years of age were eligible for non-myeloablative SCT only in the case of medical contraindications for standard allogeneic stem cell transplantation.

The controls were patients who received transplants at our institution from October 1999 until June 2002 using myeloablative conditioning. Patients and controls received comparable antiviral and antifungal prophylactic regimens and supportive care mea-

Table 1 Patient characteristics

	Reduced intensity transplant (n=20)	Myeloablative transplant (n=20)
Diagnosis		
Acute leukemia		
CR1, CR2	4 (20%)	7 (35%)
>CR2, refractory, post autologous SCT	8 (40%)	6 (30%)
Chronic myelogenous leukemia		
Chronic phase	0	3 (15%)
Advanced phase	3 (15%)	1 (5%)
Lymphoma, advanced phase	1 (5%)	3 (15%)
Myelodysplastic syndrome	4 (20%)	0
Median patient age (years, range)	57 (26–66)	36 (26–50)
Median Karnovsky Score	70 (20–100)	100 (50–100)
Median donor age (years, range)	47 (24–71)	38 (22–58)
Median time from diagnosis to SCT (months, range)	23 (2–158)	9 (3–71)
Sex match (recipient/donor)		
Male/female	5 (25%)	3 (15%)
Others	15 (75%)	17 (85%)
CMV serostatus (recipient/donor)		
Negative/negative	1 (5%)	1 (5%)
Negative/positive	2 (10%)	2 (10%)
Positive/negative	6 (30%)	6 (30%)
Positive/positive	11 (55%)	11 (55%)
Conditioning		
Cyclophosphamide/TBI (12 Gy)	10 (50%)	0
Chemotherapy alone (myeloablative)	10 (50%)	0
Busulfan/fludarabine±thiotepa (reduced intensity)	0	20 (100%)
Donor		
HLA-matched related	11 (55%)	12 (60%)
HLA-matched unrelated	4 (20%)	2 (10%)
HLA-mismatched unrelated	5 (25%)	6 (30%)

surements. All patients gave written informed consent. Controls were matched for CMV risk group as defined by CMV serostatus of the recipient and the donor and by donor type (related or unrelated).

Preparative regimens

For reduced intensity transplants, intravenous busulfan (3.2 mg/kg/d) was administered on days –6 and –5, followed by fludarabine 30 mg/m^2/d for 3 consecutive days (day –4 to –2). Unmanipulated allogeneic peripheral blood or bone marrow stem cells were infused on day 0 (at least 48 h after the last dose of fludarabine). For patients not being in remission/chronic phase thiotepa (250 mg/m^2) was added on day –7 to intravenous busulfan/fludarabine. Patients receiving unrelated stem cell grafts additionally received rabbit antithymocyte globulin (Thymoglobulin, IMTIX SangStat, Germany) 5.0–7.5 mg/kg total dose given in two or three divided doses on days (–3), –2 and –1.

Myeloablative conditioning regimens consisted of either cyclophosphamide (120 mg/kg) plus fractionated total body irradiation (12 Gy) or other myeloablative chemotherapy regimens according to the underlying disease. In the case of unrelated stem cell transplants, patients additionally received low-dose thymoglobulin, as recently published [23].

Prophylaxis, diagnosis, and treatment of graft-versus-host disease (GVHD)

Cyclosporine A (CsA) and mycophenolate mofetil (MMF) were administered according to the Seattle protocol for reduced intensity transplants [20]. MMF was discontinued on day +28 without tapering except for patients with acute GVHD. In patients receiving myeloablative transplants, CsA was combined with methotrexate according to the standard Seattle regimen [26].

Acute and chronic GVHD were diagnosed from clinical symptoms and/or biopsies from skin, oral mucosa, liver, and gut and classified according to the previously published standard Seattle criteria [10, 25]. Acute GVHD >II° was treated with steroids (2 mg/kg/d).

Supportive care

No prophylactic antibiotics were administered during neutropenia. If leukocytes dropped below 1.0 G/L, patients received G-CSF (5 µg/kg/d) to accelerate hematopoietic recovery. All patients received *Pneumocystis carinii* pneumonia prophylaxis with trimethoprim-sulfamethoxazole, one DS tablet three times weekly until day 180 after transplantation. For Herpes simplex and Varicella-zoster virus prophylaxis patients received either valacyclovir 500 mg orally twice daily or low-dose acyclovir 250 mg/m^2 intravenously three times daily from the beginning of conditioning. Antifungal prophylaxis consisted of fluconazole 400 mg/d from the beginning of conditioning until day +73.

Irradiated (25 Gy) leukocyte-depleted random platelet units from single donors and red cells were given when hemoglobin levels dropped to <8.0 g/dL and platelet counts dropped to <20 G/L.

Chimerism analyses

The degree of hematopoietic chimerism in the peripheral blood and/or bone marrow was evaluated on days +14, +28, +60, +90, and at 6 months after transplantation and then every 6 months by means of fluorescent in situ hybridisation to detect X and Y chromosomes for sex-mismatched transplants and/or variable nuclear tandem repeat (VNTR) analysis according to previously published standard techniques [8]. The sensitivity of our polymerase chain reaction method allowed the detection of 5–10% of donor cells in the presence of recipient cells, and vice versa. Full donor chimerism was defined as $\geq$90% donor cells in peripheral blood or BM, mixed chimerism as $\geq$10 and <90% donor cells.

CMV screening, definition and treatment of CMV infection

Surveillance for CMV (pp65 antigenemia) was performed using peripheral blood samples on a weekly basis until day +100. CMV infection was defined according to published standard criteria [17]. Pre-emptive ganciclovir (5–10 mg/kg/d) was administered at the time of first detection of CMV antigenemia (pp65) in peripheral blood for at least 3 weeks followed by maintenance therapy three times weekly for an additional 2 weeks.

Statistical analysis

The data were analysed as of 15 September 2002. Overall survival was calculated from the date of SCT to the date of death from any cause or date of last follow-up. Probabilities of overall survival were estimated using the Kaplan-Meier method and compared using the log-rank test [15]. Cumulative incidence estimates were calculated for CMV infection, relapse, non-relapse mortality and acute GVHD using the NCSS statistical software package (Kaysville Utah, USA) [11]. Relapse incidence was calculated from the date of SCT to the date of documented disease relapse/progression, and non-relapse mortality was defined as the probability of death without relapse or disease progression. Multivariate Cox regression model was used to analyse the influence of selected variables (donor age, recipient age, CD34+ cell dose, acute GVHD, recipient CMV serostatus, donor CMV serostatus, donor type, and conditioning) on the risks for CMV infection/disease. Median times to the onset of events were compared using the Wilcoxon rank sum test.

Results

Engraftment and chimerism

Following reduced intensity transplantation two patients died of multiorgan failure before engraftment on days +5 and +7, respectively. Another patient with treatment-related acute myelogenous leukemia died on day +11 because of refractory disease. Only one patient rejected his HLA class I mismatched stem cell graft and died of septic multiorgan failure on day +35. All other patients had primary leukocyte engraftment (defined as the first of 2 consecutive days with neutrophils >0.5 G/L) after a median of 11 (range, 8–14) days. Donor chimerism to various degrees was demonstrated in all engrafted patients as early as day +14 after SCT. None of the patients received donor lymphocyte infusion either for relapse or for conversion of mixed to full donor chimerism.

All control patients receiving conventional myeloablative transplants had primary leukocyte engraftment after a median of 11 (range, 8–22) days and full donor chimerism in peripheral blood and/or bone marrow at any time point tested after transplantation.

Survival, non-relapse mortality, and relapse

At 2 years overall survival was 37.9% (95% confidence interval, CI, 14.2–61.6%) reduced intensity transplants and 36.6% (95% CI, 3.4–69.8%) following myeloablative transplantation. The cumulative incidence of non-relapse mortality was 40.6% (95% CI, 22.6–73.1%) for reduced intensity transplants and 57.8% (95% CI, 32.4–100%) for myeloablative transplants. During the observation period 6/20 patients relapsed following reduced intensity conditioning (cumulative incidence 32.6%; 95% CI, 16.9–63.1%) and 2/20 patients relapsed following conventional allografting (cumulative incidence 12.5%; 95% CI, 3.4–45.9%) (p value 0.0977, log-rank test).

Acute GVHD

Following reduced intensity transplants acute GVHD II-IV° was diagnosed in 8/20 patients after a median of 29 (range, 9–90) days (cumulative incidence 47.0%, 95% CI, 29.2–75.8%). Following conventional allografting, acute GVHD II-IV° was diagnosed in 10/20 patients after a median of 17 days (range, 5–42 days) (cumulative incidence 56.5; 95% CI, 38.1–83.7%). Median time to the onset of acute GVHD was statistically significantly shorter following myeloablative allografting (p=0.046, Wilcoxon rank sum test).

CMV infection

The cumulative incidence of CMV infection following reduced intensity transplants was 47.3% (95% CI, 29.4–76.0%) at day 100 and 60.4% (95% CI, 41.4–87.9%) at day 200 after transplantation. In controls the cumulative incidence of CMV infection was 40.0% (95% CI, 23.4–68.4%) at day 100 with no late CMV infection beyond day 100 (Fig. 1). None of the patients in either cohort developed or died of CMV disease. Following reduced intensity transplants, the cumulative incidence of CMV infection was 45.5% (95% CI, 23.8–86.8%) for recipients of sibling allografts and 75.0% (95% CI, 50.1–100%) for patients receiving unrelated stem cell grafts. The corresponding incidences for control patients were 33.3% (95% CI, 15.0–74.2%) and 50.0% (95% CI, 25.0–100%) (Fig. 2a, b).

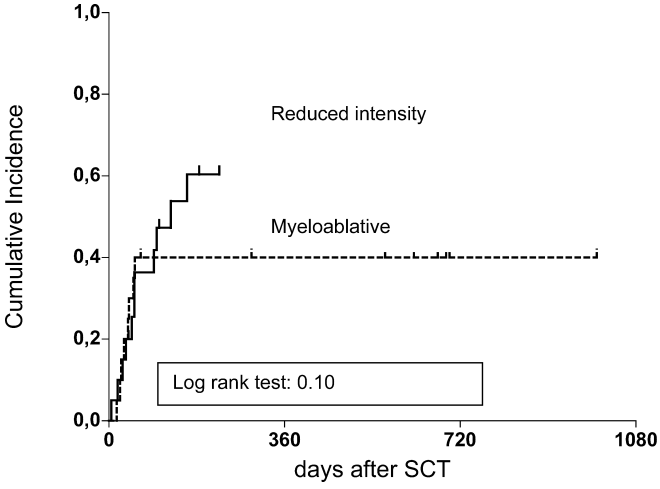

Fig. 1 Cumulative incidence of CMV infection following reduced intensity and myeloablative allogeneic stem cell transplantation

In eight of eleven patients (73%) with CMV infection following reduced intensity transplantation, acute GVHD was diagnosed a median of 25 (range, 9–61) days prior to infection. Following conventional allografting acute GVHD was diagnosed a median of 14 (range, 10–34) days before CMV infection in 5/8 (63%) patients (differences n.s., Wilcoxon rank sum test).

Following reduced intensity transplantation 4/11 (40%) patients had recurrent CMV infection and all had signs of ongoing GVHD requiring prolonged immunosuppression. None of the patients following myeloablative allografting had recurrent CMV infection.

Multivariate analysis of risk factors for CMV infection

The only two factors associated with a significantly increased risk for CMV infection were reduced intensity transplants and the use of in vivo T cell depletion with antithymocyte globulin (Table 2).

Table 2 Multivariate analysis of risk factors for CMV infection

Variable	Relative risk (95% confidence interval)	p value
Age donor (continuous)	0.91 (0.80–1.04)	n.s.
Age recipient (continuous)	1.09 (0.97–1.22)	n.s.
CD34+ x10^6/kg (continuous)	0.96 (0.67–1.37)	n.s.
Acute GVHD II-IV° (absent vs. present)	0.96 (0.06–15.99)	n.s.
CMV serostatus donor (+ve vs. –ve)	4.26 (0.39–46.17)	0.2
CMV serostatus recipient (+ve vs. –ve)	23.73 (0.63–887.86)	0.08
Type of transplant		
Reduced intensity vs. myeloablative	23.62 (1.80–312.51)	**0.02**
In vivo T cell depletion	9.40 (1.1–82.02)	**0.04**

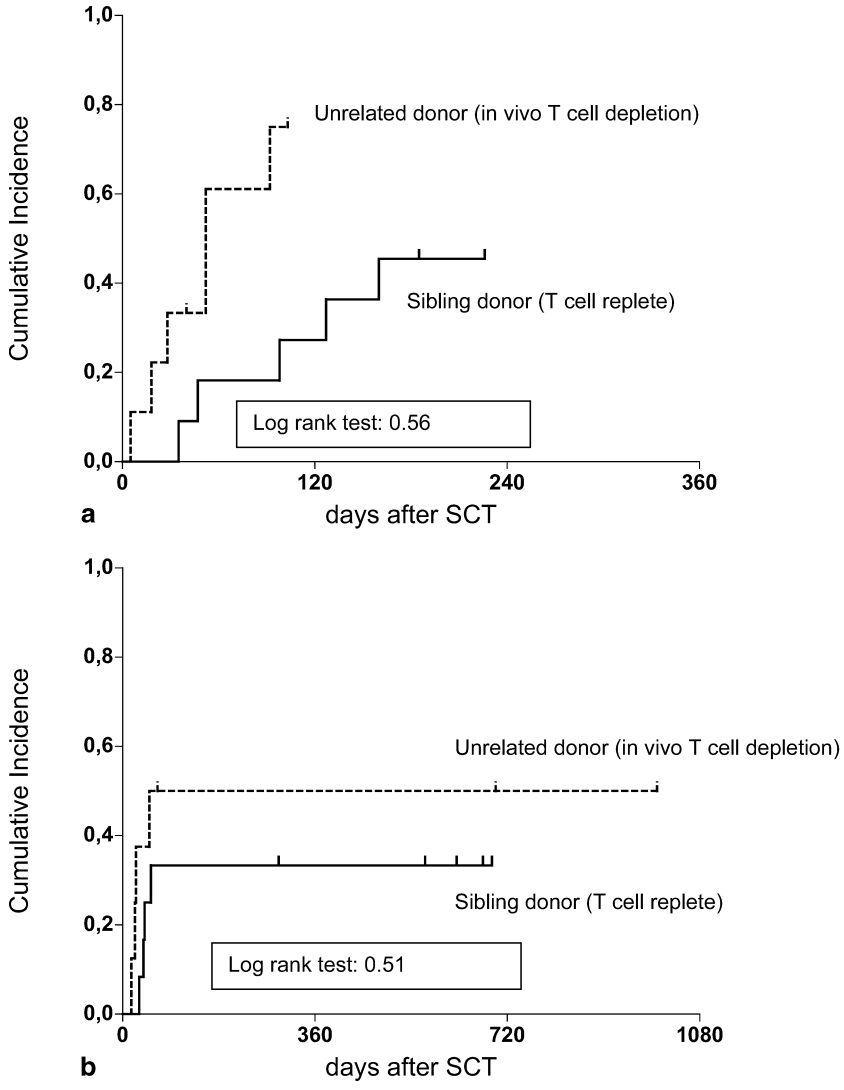

Fig. 2a, b Cumulative incidence of CMV infection following reduced intensity (**a**) and myeloablative (**b**) allogeneic stem cell transplantation. Patients with unrelated donor transplants received in vivo T cell depletion with antithymocyte globulin

Discussion

This small retrospective single-centre analysis clearly demonstrates a trend towards an increased incidence of CMV infection following dose-reduced non-myeloablative stem cell transplantation, although none of the patients died of CMV disease. It was recently suggested that the use of anti-T cell antibodies as part of the dose-reduced conditioning regimen might have a detrimental influence on immune reconstitution, thereby increasing the probability of CMV infection by up to 85% in patients at risk (i.e. CMV +ve recipients receiving grafts from either CMV +ve or –ve donors, and CMV –ve recipients receiving grafts from CMV +ve donors) [4, 21]. Similarly, the cumulative risk of CMV infection in our cohort receiving unrelated stem cell grafts after in vivo T cell depletion with Thymoglobulin following reduced intensity conditioning was 75%. However, since the incidence of CMV infection does not exceed 50–60% even in patients at risk receiving in vivo/ex vivo T cell depletion in the context of myeloablative transplants as shown by us and by the results of other investigators, additional factors might account for this observation [6, 13, 23].

One reason might be that dose-reduced transplants are primarily considered for elderly patients and age is a well-known risk factor for CMV disease. The median age of patients receiving non-myeloablative transplants is at least 10 to 20 years older than that of patients receiving conventional myeloablative allografts. Consequently, CMV risk groups are more frequent in these elderly patients and account for up to 95% in our patient cohort. However, matching for CMV risk groups between patient and controls should account for this bias.

It is more likely that the immunosuppressive potential of the non-myeloablative conditioning regimen and the strategy of post-transplant immunosuppression significantly contribute to the risk of infection. So far, no comparative data on the effects of more or less intensive non-myeloablative regimen on toxicity, post-transplant GVHD incidence, and immune reconstitution are available, and different post-transplant immunosuppressive regimens make it difficult to definitively compare all the

published results with regard to these aspects. More recently, the use of MMF has been discussed as an independent risk factor for (complicated) CMV infection following myeloablative allografting and it is noteworthy that we and others observed recurrent and/or late CMV infections only in patients receiving post-transplant immunosuppression with MMF but not in patients receiving the classical CsA/methotrexate regimen following myeloablative transplantation [12, 14].

Since acute GVHD is an additional risk factor for the development of CMV infection/disease, it is not surprising that 63–73% of our patients with CMV antigenemia were diagnosed with acute GVHD prior to infection, requiring additional immunosuppression with steroids. Although not achieving statistical significance due to the low patient number, the time from onset of acute GVHD to CMV infection was delayed in non-myeloablative transplantation (25 vs. 14 days). Another important finding of our study, and this has also been described by the Seattle group, was that the onset of acute GVHD following non-myeloablative transplantation was significantly delayed when compared with myeloablative transplants, although the overall incidence of acute GVHD did not differ between the two groups [14]. This suggests that, by using CsA/MMF in the context of dose-reduced transplantation, T cell-mediated alloreactions such as GVHD are delayed and, on the other hand, this more immunosuppressive rather than myeloablative approach renders the patient at a higher and prolonged risk at least for CMV infection.

In conclusion, we found a substantial, if not increased, risk for CMV infection following reduced intensity stem cell transplantation. Patient and/or donor age and consequently CMV risk group and, on the other hand, acute GVHD seem not to be the main reasons for this observation. The role of post-transplant immunosuppression (e.g. the use of CsA/MMF) and its effect on B, T, and/or dendritic cells, as well as the role of the degree of post-transplant donor chimerism on transplant-related complications such as GVHD and infections, remains to be determined. For the present, at least the same surveillance and pre-emptive anti-CMV strategies as following conventional myeloablative allografting are recommended for patients receiving non-myeloablative transplants. Whether patients receiving additional in vivo T cell depletion are candidates for prophylactic rather than pre-emptive ganciclovir warrants further investigation.

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