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LETTER TO THE EDITOR

Getting the Whole Picture: Adding Patient-reported Outcomes to Adjuvant Endocrine Treatment Evaluation in Premenopausal Breast Cancer Patients

To the Editor:

The integration of Patient-Reported Outcomes (PROs) has gained relevance recently within treatment toxicity evaluation. Patient reports have been identified to provide complementary information on treatment toxicity (1,2) compared to proxy-rate based assessments (e.g., CTCAEs) in various cancer populations. This led the FDA and others (3,4) to recommend the utilization of PROs for cancer outcome research and in clinical routine.

Looking at the well established, gold standard tamoxifen treatment (TT) for premenopausal, early breast cancer (BC), data on the so called excellent risk-benefit ratio (5) derived from the original admission trials at most lack PROs. At least, some more recent studies indicate a distinct prevalence of side effects originating from treatment induced estrogen suppression such as hot flushes or sexual problems. Understanding risks and benefits of TT from a patient perspective might thereafter be of vital importance for capturing a more precise picture of symptom burden in this patient population.

Additionally, symptom burden is known to modulate adherence behavior particularly in patients who consider themselves as cured while experiencing iatrogenic harm. Regarding the considerable nonadherence rates reported in BC patients receiving tamoxifen (6,7) a detailed understanding of the association with TT toxicity might, thus, be essential for health the optimization of care efforts.

The objective of our study was first to determine prevalence and severity of patient-reported physical side effects and psychosocial burden in premenopausal, early BC patients receiving upfront TT. Second, the degree of subjectively experienced symptoms compared with data derived from current pivotal trials was investigated. Additionally, the association between patient's symptom burden and treatment adherence was determined.

We conducted a computer-based, cross-sectional PRO-assessment (June 2009–February 2011) including the following instruments: FACT-B/+ES, HADS and the Self-reported measure of medication adherence questionnaire (SMAQ). Symptom frequencies were presented as percentages (95% confidence intervals) and compared with data from the ABCSG-12 trial (5). Ethical approval was provided for the study.

The final study sample comprised 156 patients with a median age of 47 years (range 26–59) and a median TT duration of 18.3 months. 58.9% of all patients were fully adherent with regard to accuracy of medication intake according to the SMAQ.

Most frequent symptoms were hot flushes (82.8%), sleep disorders (86.0%), and weight gain (39.7; please find details in Table 1). Overall, PROs indicated higher prevalence rates for all symptoms but depression as compared to data derived from the ABCSG-12 trial. Significantly higher PRO-prevalence rates were found for hot flushes, sleeping disorders, breast sensitivity, and fatigue. Symptoms significantly associated with TT adherence were vaginal itching/irritation (RR 1.54; 1.01–2.3), vaginal dryness (RR 1.51; 1.01–2.2), and weight gain (RR 1.78; 1.2–2.6). Vaginal itching or dryness, hence, seemed to increase the probability for nonadherence by about 50%, while weight gain was identified as the strongest associated factor with nonadherence. All other items did not show statistical significance.

Our PRO study confirms a notably high level of psychosocial burden and physical side effects in premenopausal BC patients undergoing adjuvant TT. Evidence published only recently seems to support these findings claiming higher frequencies of several

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Table 1. PRO-side Effects Compared to the ABC SG-12 Data

	PRO, % (95% CI)	ABCSG-12
Vasomotor symptoms		
Hot flushes*	82.8 (77–89)	3%
Cold sweats	40.5 (33–48)	
Night sweats	61.9 (54–70)	
Sleep disorder*	86.0 (81–91)	10%
Gynecologic symptoms		
Vaginal discharge	25.8 (19–33)	
Vaginal itching/irritation	14.2 (9–20)	
Vaginal bleeding/ spotting	3.2 (0–6)	1%
Vaginal dryness	24.4 (18–31)	
Pain or discomfort with intercourse	16.6 (11–23)	
Lost interest in sex	26.1 (19–33)	
Breast sensitivity	22.9 (16–30)	3%
Gastrointestinal symptoms		
Weight gain	39.7 (32–47)	
Having vomited	1.9 (0–4)	
Diarrhea	3.8 (1–7)	2%
Feeling bloated	17.2 (11–23)	
Nausea	5.8 (2–10)	5%
Psychological symptoms		
Dizziness	8.9 (4–13)	2%
Mood swings	39.2 (31–47)	
Being irritable	35.9 (28–43)	
Being nervous	27.4 (20–34)	
Lack of energy	35.3 (28–43)	16%
Depression	3.3 (0–6)	5%
Anxiety	7.8 (4–12)	
Pain		
Pain	16.1 (10–22)	
Headache	17.2 (11–23)	14
Joint Pain	35.7 (28–43)	8

*The 95% CI does not contain the ABCSG-12 reference value.

symptoms when subjectively reported, e.g., hot flushes/sweats or weight gain than known from previous pivotal studies (8). The frequencies of several symptoms herein distinctively exceed the reported frequencies for adverse events for premenopausal women in the ABCSG-12 study. Additionally, we were able to demonstrate that the subjectively highly burdensome symptoms of vaginal itching/irritation, dryness, and weight gain can impact on adherence behavior.

Basch (3) also claimed PROs to more accurately capture side effects, to be more sensitive to underlying changes in patients' functional status and questioning the methodological appropriateness of proxy-rated toxicity profiles. Accordingly, evaluation methods based on clinician-rates—as generally used in clinical trials—tend to underestimate or miss symptoms potentially even leading to preventable disease. Similar findings were also obtained by Fellowes (LIT), who found the frequency of physician-recorded side effects of endocrine agents to significantly differ from the frequency reported by patients.

At this point, we have to note that the indirect comparison of symptom frequencies of this study with prevalence rates reported in the literature limits the interpretation of results and cannot replace direct comparisons of PROs and proxy-rates in the same patient population. However, we were able to demonstrate that established prevalence rates of tamoxifen side effects do not represent the whole picture of premenopausal BC patients' symptom burden. Hence, monitoring a patient's subjective perception of her side effects might present valuable complementary information to proxy-rated symptom burden contributing to increased knowledge and a more comprehensive illustration of treatment impact. This seems to be crucial also regarding adherence behavior. We therefore highly recommend the integration of PROs as standard evaluation method in daily clinical practice to obtain more accurate and individualized estimates of TT toxicity. This might increase adherence and in conjunction treatment outcome.

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REFERENCES

1. Basch E, Abernethy AP. Supporting clinical practice decisions with real-time patient-reported outcomes. *J Clin Oncol [Comment Editorial]* 2011;29:954–6.

2. Brettschneider C, Luhmann D, Raspe H. Informative value of Patient Reported Outcomes (PRO) in Health Technology Assessment (HTA). *GMS Health Technol Assess* 2011;7:Doc01.

3. Basch E. The missing voice of patients in drug-safety reporting. *N Engl J Med* 2010;362:865–9.

4. FDA. *Patient-reported Outcome Measures. Use in Medical Product Developement to Support Labeling Claims*. US Department of Health and Human Services Food and Drug Administration Guidance for Industry, 2009.

5. Gnant M, Mlineritsch B, Stoeger H, *et al.* Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. *Lancet Oncol* 2011;12:631–41.

6. Cella D, Fallowfield LJ. Recognition and management of treatment-related side effects for breast cancer patients receiving adjuvant endocrine therapy. *Breast Cancer Res Treat* 2008; 107:167–80.

7. Hershman DL, Shao T, Kushi LH, *et al.* Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Cancer Res Treat* 2011;126:529–37.

8. Ruhstaller T, von Moos R, Rufibach K, *et al.* Breast cancer patients on endocrine therapy reveal more symptoms when self-reporting than in pivotal trials: an outcome research study. *Oncology* 2009;76:142–8.