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Breast Cancer Patients on Endocrine Therapy Reveal More Symptoms when Self-Reporting than in Pivotal Trials: An Outcome Research Study

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Key Words
Breast cancer · C-PET · Endocrine therapy · Menopausal symptoms · Self-reporting

Abstract
Objectives: The purpose of this investigation was firstly to assess the overall frequency of subjectively experienced symptoms self-reported by patients receiving endocrine therapy and secondly to compare these symptoms with side effects assessed by clinicians in pivotal trials. ***Methods:*** Unselected patients with early and advanced breast cancer receiving endocrine therapy were approached consecutively during a routine outpatient visit. They received a questionnaire called *Checklist for Patients with Endocrine Therapy* (C-PET), a validated self-assessment tool to determine prespecified symptoms associated with endocrine therapy. Data on toxicity were also obtained from previously published trials. ***Results:*** 405 patients were approached and 373 agreed to participate in this study. Some symptoms were significantly more often recorded by the women in the adjuvant setting completing the C-PET than by physicians' reports in pivotal trials: hot flushes/sweats (C-PET 70%, ATAC 40% and BIG1-98 38%), low energy (C-PET 45%, ATAC 15% and BIG1-98 9%), fluid retention (C-PET 22% and BIG1-98 7%) and vaginal dryness (C-PET 30% and BIG1-98 3%). Similar differences were observed in the metastatic and adjuvant setting. ***Conclusions:*** A simple tool like the C-PET questionnaire is able to reflect the treatment burden of endocrine therapies and may be helpful to improve communication between patients and care providers. Some symptoms were significantly more often reported by the women in the C-PET than by physicians in pivotal trials.

Introduction

Hormonal therapy has become the therapy of choice for women with breast cancer who are considered likely to respond to endocrine therapy, aiming to improve survival and quality of life. In patients with breast cancer, health care professionals rank side effects and distress caused by hormonal treatment frequently lower than

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those associated with chemotherapy [1], suggesting that the side effects do not significantly affect quality of life [2], although hormonal therapy is prescribed for a longer time period than chemotherapy. This perception is supported by a previously published study demonstrating that health care professionals underreport side effects related to hormonal treatment [3]. However, side effects of hormonal therapy play a greater role in the interpretation of major adjuvant trials as previously, because the toxicity profile of the different treatment options is important for the optimal choice of treatment, which has to be balanced against a minimal survival advantage. Usually, toxicity and tolerability profiles of a treatment have been inferred from physician-recorded adverse events, but controversy exists regarding the accurate assessment of symptoms.

The primary objective of this investigation was to assess the overall frequency of subjectively experienced symptoms by breast cancer patients receiving endocrine therapy, and the secondary objective was to compare it with frequencies reported in pivotal trials. Whereas breast cancer patients in the former setting received endocrine therapy in a very informal manner outside of a study setting and were therefore self-reporting their symptoms, side effects in the latter were assessed by clinicians and not by the patients.

Patients and Methods

This prospective, cross-sectional investigation was conducted in women with both early and advanced breast cancer. The women were approached during a routine outpatient visit. The study forms containing the self-explanatory leaflet regarding this study, an informed consent form and the study questionnaires were given to all women receiving endocrine therapy in a participating center. The questionnaire was completed prior to their consultation with the doctor. Upon completion of the questionnaire, the women were offered the opportunity to discuss their side effects with their doctor.

All women with breast cancer who were receiving any form and any line of hormonal therapy were included; only patients concomitantly receiving chemo- and immunotherapy were excluded from the study. During the consultation the doctor received the completed questionnaire and provided the information pertaining to the type and indication for the hormonal therapy (early or advanced stage), and previous treatment with ovarian ablation and/or chemotherapy. The menopausal status was not required as it was retrospectively determined by age (</>50 years) and/or the type of treatment.

The women completed the *Checklist for Patients with Endocrine Therapy* (C-PET) [4, 5], an interactive self-assessment tool which was developed and tested by a European Task Force and is also available in a validated German version. It records the frequency of 13 prespecified symptoms associated with endocrine therapy. It only focuses on the incidence of an event without grading its severity. In addition to the C-PET, International Breast Cancer Study Group (IBCSG)/Linear Analogue Self-Assessment Scales were utilized to address the side effects of hormonal therapy and treatment burden, the results being discussed elsewhere [6].

For comparison, we selected some pivotal trials representing key trials in the field of endocrine therapy in our opinion. The toxicity data of the pivotal trials were retrieved from the publications and, in the case of BIG1-98 [7], additional information on side effects, e.g. nausea, fatigue/lethargy, edema and vaginal irritation, was obtained from an unpublished report prepared for health authorities.

This multi-institutional study was conducted in oncology outpatient departments of four regional teaching hospitals and by four affiliated oncologists working in private practice in Eastern Switzerland. Ethical approval was provided by the local ethical committees.

Exact confidence intervals for proportions were calculated using Sterne's method [8] and comparisons between groups were made using Fisher's exact test. For comparisons between early and advanced breast cancer (table 1), $p < 0.05$ was considered to be statistically significant. When comparing symptom frequency between different trial data, Bonferroni-corrected (per symptom) confidence intervals were employed for the number of trials under consideration to maintain a global significant level of 0.05. More specifically, in table 2 confidence intervals were computed using a significance level of $0.05/2 = 0.025$ and in table 3 using $0.05/3 = 0.016$.

Results

Patient Characteristics

Of the 405 patients approached, 373 agreed to participate in this study (92%). The reasons for declining varied: 17 patients gave no reason, 5 did not understand due to language difficulties, 6 gave their clinical condition as a reason, 2 had no time, 1 had forgotten her glasses and 1 was apparently psychotic.

At the time of study entry, the median age of the 373 study patients was 61 years (range 29–88 years) and the 20th percentile was 51 years; 302 and 71 patients were treated in adjuvant and metastatic setting, respectively, and 213 patients had received chemotherapy before endocrine therapy. The types of hormonal therapies used are listed in figure 1. The largest group receiving one form of endocrine therapy comprised the 200 postmenopausal women who received tamoxifen: 31 patients were in blinded studies comparing tamoxifen with an aromatase inhibitor.

Frequency of Symptoms

Table 1 lists the frequencies of symptoms reported by the women. Only the reporting of *weight gain* and *hot flushes/sweats* was significantly greater for those receiv-

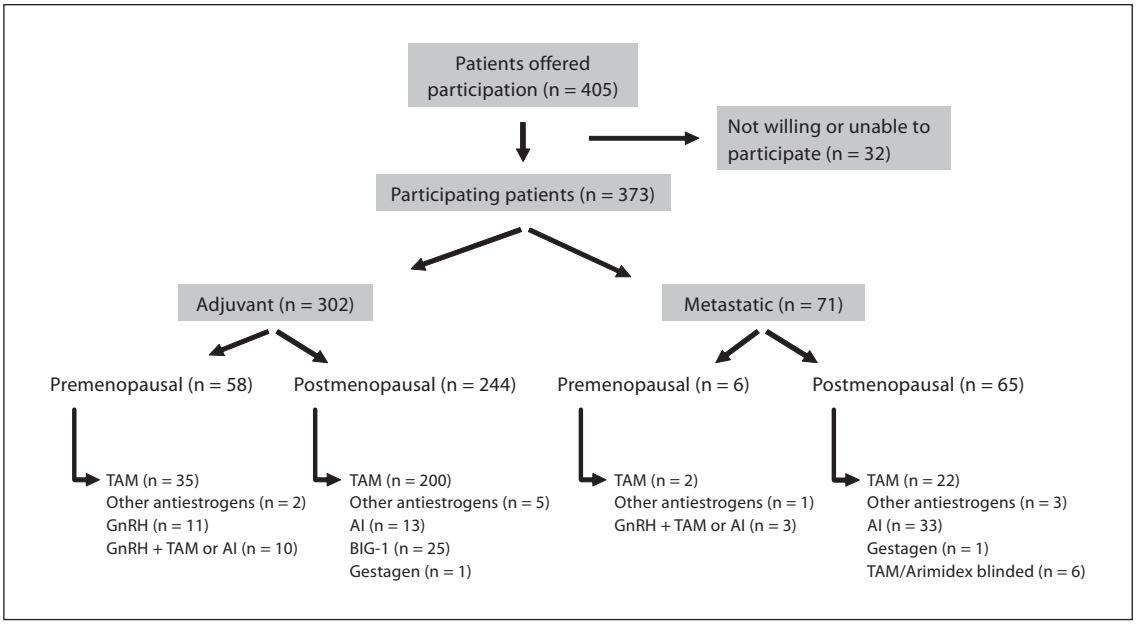

Fig. 1. Patient characteristics. TAM = Tamoxifen; AI = aromatase inhibitor.

Table 1. Frequencies of side effects reported by breast cancer patients in the C-PET

Side effects C-PET	Early stage (n = 302)			Advanced stage (n = 71)			All patients (n = 373)			p value Fisher's exact test[1]
	n	%	CI	n	%	CI	n	%	CI	
Vaginal dryness	106	35	29–42	20	28	17–41	126	34	28–40	0.33
Vaginal bleeding	7	3	1–5	2	3	0–11	9	2	1–5	0.68
Breathlessness	50	17	11–22	14	20	11–32	64	17	13–22	0.60
Skin rash	34	11	8–16	3	4	1–13	37	10	7–14	0.08
Decreased sex drive	89	29	24–36	20	28	17–41	109	29	24–35	0.89
Irritability	53	18	13–23	13	18	10–31	66	18	14–23	0.86
Fluid retention	61	20	15–26	12	17	9–29	73	20	15–25	0.62
Low energy	138	46	39–52	35	49	36–63	173	46	41–52	0.60
Nausea	28	9	6–14	9	13	6–24	37	10	7–14	0.38
Weight gain	147	49	42–55	20	28	17–41	167	45	39–51	0.002
Hot flushes/sweats	220	73	67–78	40	56	43–69	260	70	64–75	0.009

CI = Exact confidence interval for the proportion of patients indicating the symptom.
[1] Adjuvant vs. metastatic, unadjusted for multiple comparisons.

ing adjuvant therapies compared to those with metastatic disease. No significant difference in the frequency of reports was evident regarding the other symptoms. Likewise, we found no significant difference in the frequencies of C-PET-reported adverse events between postmenopausal patients taking antiestrogens and those taking aromatase inhibitors.

Comparisons with Pivotal Trials

We compared the frequencies of adverse events found in our study with those reported in several pivotal studies.

Firstly, we compared the data from our largest homogenous group of patients, i.e. postmenopausal women in the adjuvant setting receiving tamoxifen, with the con-

Table 2. Frequencies of side effects following tamoxifen treatment mentioned in C-PET compared to pivotal trials in postmenopausal patients with early breast cancer

Side effects	0	50	100%	n/total n	%	CI, %
Hot flushes/sweats						
C-PET				139/200	70	61–77
BIG1-98				1,516/3,988	38	36–40
ATAC				1,229/3,094	40	38–42
Low energy/lethargy						
C-PET				90/200	45	37–54
BIG1-98				345/3,988	9	8–10
ATAC				466/3,094	15	14–17
Vaginal discharge						
C-PET				25/200	12	8–19
BIG1-98						
ATAC				354/3,094	11	10–13
Irritability/mood/depression						
C-PET				33/200	16	11–24
BIG1-98						
ATAC				469/3,094	15	14–17
Nausea						
C-PET				18/200	9	5–15
BIG1-98				418/3,988	10	9–12
ATAC				315/3,094	10	9–12
Vaginal dryness/irritation						
C-PET				60/200	30	23–38
BIG1-98				122/3,988	3	2–4
ATAC						
Vaginal bleeding						
C-PET				4/200	2	0–6
BIG1-98				413/3,988	10	9–12
ATAC				253/3,094	8	7–9
Fluid retention/edema						
C-PET				43/200	22	15–29
BIG1-98				288/3,988	7	6–8
ATAC						

Table 3. Frequencies of side effects following treatment with tamoxifen or aromatase inhibitors mentioned in C-PET compared to pivotal trials in postmenopausal patients with metastatic breast cancer

Side effects	0	50	100%	n/total n	%	CI, %
Hot flushes						
C-PET				32/61	52	37–68
Nabholtz et al. [11]				115/352	33	27–39
Bonneterre et al. [10]				137/665	21	17–25
Mouridsen et al. [12]				151/910	17	14–20
Nausea						
C-PET				6/61	19	3–23
Nabholtz et al. [11]				114/352	32	26–39
Bonneterre et al. [10]				86/665	13	10–16
Mouridsen et al. [12]				138/910	15	12–18
Vaginal dryness/irritation						
C-PET				15/61	25	13–41
Nabholtz et al. [11]				15/352	4	2–8
Bonneterre et al. [10]				13/665	2	1–4
Mouridsen et al. [12]						
Breathlessness						
C-PET				10/61	16	7–31
Nabholtz et al. [11]						
Bonneterre et al. [10]						
Mouridsen et al. [12]				128/910	14	11–17
Weight gain						
C-PET				15/61	25	13–41
Nabholtz et al. [11]				7/352	2	1–5
Bonneterre et al. [10]				12/665	2	1–4
Mouridsen et al. [12]						
Low energy/lethargy						
C-PET				30/61	49	33–65
Nabholtz et al. [11]				7/352	2	1–5
Bonneterre et al. [10]				13/665	2	1–4
Mouridsen et al. [12]				99/910	11	9–14
Vaginal bleeding						
C-PET				0/61	0	0–8
Nabholtz et al. [11]				9/352	3	1–6
Bonneterre et al. [10]				12/665	2	1–4
Mouridsen et al. [12]						
Irritability/mood/depression						
C-PET				10/61	16	7–31
Nabholtz et al. [11]				23/352	7	4–11
Bonneterre et al. [10]				32/665	5	3–7
Mouridsen et al. [12]						

trol arms of two of the most important and largest studies comparing an aromatase inhibitor with tamoxifen [7, 9]. Not all of the symptoms recorded by the C-PET were published in these two studies; however, we received unpublished data from the BIG1-98 trial. Table 2 demonstrates that *hot flushes/sweats* were significantly more often reported by our patients compared with the pivotal studies: 70% using C-PET versus 40 and 38% reported in the ATAC and BIG1-98, respectively. *Low energy* was reported by 45 (C-PET) versus 15 and 9% (ATAC and BIG1-98, respectively), *fluid retention* by 22 (C-PET) versus 7% (BIG1-98) and *vaginal dryness* by 30 (C-PET) versus 3% (BIG1-98). In contrast, *vaginal bleeding* was reported significantly less in our group of patients (2% with C-PET vs. 8 and 10% in the ATAC and BIG1-98 trial, respective-

ly). The other side effects were comparable between the two groups. Of note, in the pivotal studies, toxicity data were collected cumulatively whereas in our cross-sectional investigation only the question 'are you suffering from one of these symptoms…' was asked.

Secondly, we compared the responses of our group of postmenopausal women with metastatic disease who received either tamoxifen or an aromatase inhibitor to those of three pivotal studies investigating tamoxifen versus anastrozole or letrozole as first-line therapy for postmenopausal women with advanced breast cancer [10–12]. To ensure a fair comparison, we pooled the control and the investigational arm from the pivotal studies and did likewise in our patient group including patients from a blinded trial. Again, not all symptoms recorded with C-PET were recorded in all the pivotal studies. As shown in table 3, *hot flushes/sweats, low energy, weight gain* and *vaginal dryness* were significantly more frequently reported in our cross-sectional study.

Discussion

The self-reported frequency of symptoms experienced by our study patients was considerably increased, amounting to 70% for *hot flushes/sweats*, 45% for *low energy* and 30% for *vaginal dryness*, for example. Surprisingly, we did not find a significant difference in reported side effects between early and advanced stage of the disease apart from *weight gain* and *hot flushes/sweats*, suggesting that patients with advanced disease do not care so much about these symptoms or rather have problems to maintain their weight in a more advanced stage. Our study cohort was too small to reveal a significant difference between different treatment options.

The strength of our study was certainly the ease of access to possible participants, the user-friendly questionnaire and the collection of data from all women receiving endocrine therapy during the observation period of this study. Furthermore, women participating in this study were derived from different care settings, including private oncologists, non-academic institutions and a regional cancer center. Another advantage was the ease to complete and validate the findings due to the data collection tool utilized. Finally, complete data were also obtained from the small non-participating group. The C-PET is a tool which enables to assess adverse events without the patient being influenced by caregivers, as it was completed by the patient without the help of nurses and before consulting the doctor, whereas adverse events in clinical trials are usually collected by doctors, nurses and/or the study coordinators.

A weakness of our study was the lack of definition regarding the patient group for practical reasons which resulted in missing prospective data concerning menopausal status, extent of disease and receptor status. However, receptor status was probably irrelevant for endocrine side effects. There was some difficulty regarding the wording caused by the translation into German when making a comparison between pivotal studies and ours; for instance, *low energy* in our investigations was compared with *lethargy* (Nabholtz et al. [11] and Bonneterre et al. [10]) and *fatigue* (BIG1-98 and ATAC), *vaginal dryness* with *vaginal irritation* (BIG1-98) and *fluid retention* with *edema* (BIG1-98).

Of course, the comparison between results of our cross-sectional study and those observed in pivotal trials has some limitations and cannot replace a direct comparison between self-reported symptoms by patients and symptoms assessed by physicians in a specifically designed study to investigate this question. In our cross-sectional survey, women were asked at different time points and at different stages of disease compared to the selected patients entered into the trials. Furthermore, as mentioned above, in the pivotal studies toxicity data were collected cumulatively whereas our trial was a cross-sectional investigation. Also, the comparison with pivotal trials is in some way arbitrary. However, the significantly different incidences in some symptoms observed between our study and the pivotal studies cannot solely be explained by the above-mentioned two features. Even the results of the comparisons between the adjuvant and metastatic setting in our study and the pivotal trials showed little variation.

Some symptoms like *breathlessness, nausea* and *mood changes* are less clearly attributable to endocrine therapy and were reported with low frequency (<20%) in both our study and the pivotal trials.

Vaginal bleeding was the only symptom with a significantly lower incidence in our study group than in pivotal studies. It is reasonable that a medically clearly defined symptom characterized by being more an incident than a chronic symptom is reported with lower frequency in our cross-sectional study than in the collection of cumulative toxicities in the pivotal trials.

In our opinion, the most important finding was the much higher frequency of symptoms like *hot flushes/sweats, weight gain, vaginal dryness, low energy* and *fluid retention* reported by women in our study compared with those reported by physicians in the pivotal randomized

studies. These differences are striking. Some of these symptoms such as *hot flushes/sweats, weight gain* and *vaginal dryness* are subjective symptoms clearly assigned to endocrine therapy and postmenopausal status, with others, e.g. *low energy* and *fluid retention*, being more difficult to assign.

The obvious explanation for the differences in the frequency of reported events between the pivotal studies and ours could be that professionals do not document all the symptoms experienced by the patients. Many symptoms are also highly subjective, non-life-threatening and difficult to grade. As we know from several other publications, physician-guided symptom assessment is not sufficient to give an overall picture of the real side effects of endocrine treatments and is underestimating the real treatment burden [3, 13]. Usually, investigators are certainly more interested in severe side effects like bone fractures, or coronary or cerebral thrombosis, than in ill-defined, uncomplicated and difficult-to-treat symptoms such as hot flushes, weight gain or low energy. However, especially these symptoms may significantly affect the patients' quality of life. Since the authors, editors and regulatory agencies of previous studies were more interested in safety and survival than in quality-of-life data, not all of the endocrine therapy-related symptoms addressed in our study could be found in published pivotal studies. The frequency of weight gain, a disturbing, subjective symptom, can be easily compared to the objective weight changes in a future trial to address treatment burden of symptoms versus objective adverse events for example.

Patients do not always discuss their symptoms with the doctor, possibly because they have already mentioned them during their previous consultation, or they perceive the doctor may not be interested in them or does not have enough time for less serious symptoms affecting well-being rather than safety. They may attribute the cause of their symptoms to menopause, the symptoms may not constantly disturb them, or it is a taboo to speak about particular symptoms, for example vaginal dryness and problems regarding intercourse [14]. Other reasons include the patient's feeling that the investigator is not the appropriate person to address these symptoms, e.g. a medical oncologist or surgeon instead of a gynecologist, and finally patients may be convinced that the doctor will not be able to improve specific symptoms or may even stop their treatment.

Due to the many possible explanations for the findings, questionnaires could be perceived to be an ideal screening tool for obtaining a more accurate picture of the true frequency of symptoms and their effect on the patient. However, then the same frequencies of symptoms should be reported in quality-of-life subdata obtained from studies. In fact, the ATAC study analyzed quality of life in a substudy [15]. Here the symptom hot flushes/sweats was subdivided into hot flushes (32%), cold sweats (11%) and night sweats (24%), thus rendering a comparison difficult, since several women were assessed repeatedly. However, vaginal dryness was reported only by 8% of the women, lack of energy by 20% and weight gain by 23%, compared to 30, 45 and 49%, respectively, in our study. Only approximately one third of the women participated in the quality-of-life subgroup of the ATAC study, implying that the participating women were selected twice, first for the general trial and second for the substudy. Additionally, the aim of the ATAC trial was to compare the two drugs rather than to assess the impact of their adverse effects.

Studies comparing existing tools, e.g. C-PET, EORTC QLQ 30 and BC module or IBCSG standard QOL questionnaires used in different settings (completed by patients alone before the consultation or with help of the care providers), will help to achieve a better understanding of apparent or truly different results.

In conclusion, we were able to demonstrate that higher frequencies of symptoms, e.g. *hot flushes/sweats, vaginal dryness, weight gain, low energy* and *fluid retention*, were reported by women receiving endocrine therapy in the C-PET tool than in previous pivotal studies. To accurately describe subjective, non-life-threatening symptoms, a tool like this questionnaire (C-PET) is helpful, particularly to highlight potentially treatable symptoms before the consultation with the doctor. C-PET is a very simple and cost-effective questionnaire, short and feasible, not requiring intensive instruction. It could improve communication between patients and care providers regarding possible side effects. Such a simple instrument might therefore improve the quality of life of women on endocrine therapy.

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