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Long-Term Side Effects of Adjuvant Therapy in Primary Breast Cancer Patients: Results of a Web-Based Survey

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Keywords

Adjuvant treatment · Aromatase inhibitors · Breast cancer · Chemotherapy · Endocrine therapy · Quality of life · Side effects · Toxicity

Abstract

Background: Chronic treatment sequelae may substantially reduce the long-term quality of life in breast cancer survivors. ***Methods:*** We report a comprehensive Web-based survey on the presence of long-term side effects of adjuvant anti-breast cancer therapy in 1,506 patients who had been diagnosed with primary breast cancer at least 1 year before. ***Results:*** Fatigue, depression, depressive mood, concentration deficit, pain, changes of mucosa and skin appendages, as well as symptoms of peripheral neuropathy were the most prevalent reported complaints. Chemotherapies – taxane-based regimens in particular – were associated with increased rates of long-term symptoms, including persistent peripheral neuropathy. Overall, the data show a substantial prevalence of a wide variety of potentially treatment-associated symptoms over a protracted time frame after the diagnosis of breast cancer. The burden of symptoms was high for fatigue, depression, sleep disturbances, pain, and peripheral neuropathic symptoms. ***Conclusion:*** Estimating the burden of chronic toxicities should contribute to enhance rational decision-making on treatments including chemotherapy in patients with low versus high risk of recurrence.

Introduction

Almost all patients with primary breast cancer receive adjuvant cancer therapies to reduce the risk of local recurrence and metastases. While these antihormonal and chemotherapeutic treatments help to improve long-term disease-free survival and/or overall survival in a significant proportion of patients, these therapies are associated with significant acute and chronic toxicities [1–3]. Chronic treatment sequelae may substantially reduce the long-term quality of life in large numbers of breast cancer survivors. Estimating the burden of these chronic toxicities is an important component of a comprehensive evaluation of patient-reported outcomes. It may thus contribute to enhance rational decision-making on the use of chemotherapies in patients with low- versus high-risk breast cancer.

Methods

We performed a comprehensive survey on long-term side effects of adjuvant therapy in patients who had previously been diagnosed with primary breast cancer at least 1 year before taking the survey. An electronic questionnaire was provided during May and June 2016 on the Facebook social network page [4] and the website of Brustkrebs Deutschland e.V. [5], a German breast cancer organization.

Data gathered included demographic characteristics, time interval since diagnosis, histological type, size and spread of breast cancer, receptor and lymph node status, type of adjuvant therapies and the specific drugs used, metastasis status, and secondary malignancies. Patients provided information on the presence of long-term side effects by checking listings of potential side effect plus optional free-text entry. They also rated the side effects by their

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Table 1. Demographic, disease, and anticancer treatment characteristics

Parameter	Value (N = 1,506)
Age	
Median, years (range)	49 (20–81)
<35 years, %	7
>35–45 years, %	24
>45–55 years, %	43
>55–65 years, %	20
>65 years, %	6
Time since primary diagnosis of breast cancer, %	
1–2 years	39
3–5 years	30
6–10 years	21
≥11 years	10
Breast cancer characteristics, %	
HR(ER and/or PR)-positive	56
HER2 0, 1+, or 2+	19
HER2-positive 3+	15
Triple-negative	17
Sentinel lymph node involvement	31
Additional lymph node involvement	27
Tumor stage, %	
T1	45
T2	45
T3	9
T4	2
Metastatic disease, %	
Metachronous metastases	4
Anticancer therapy, %	
Radiotherapy	82
Antihormonal therapy	78
Chemotherapy	75
HER2-targeted therapies[a]	26

[a]Patients could have received 1 or more HER2-targeted monoclonal antibodies.

HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Table 2. Drugs used for anticancer treatment

Parameter	Value (N = 1,506)
Chemotherapies, %	
Epirubicin	44
Cyclophosphamide	37
Paclitaxel	32
Docetaxel	26
Carboplatin	8
Fluorouracil	8
Doxorubicin	7
nab-Paclitaxel	3
Liposomal doxorubicin	1
No data	8
No chemotherapy	26
Antihormonal drugs, %	
Tamoxifen	80
Aromatase inhibitor	32
Aromatase inhibitor and tamoxifen	12
GnRH analogs	5
Antibodies, %	
Trastuzumab	18
Pertuzumab	1
Others, %	
Trastuzumab-emtasine	0.2
Lapatinib	1

GnRH, gonatropin-releasing hormone.

respective frequency, and thus the periods with perceived severe burden, in five categories.

Data from patients who completed all relevant questions were compiled using spreadsheet software and analyzed using descriptive statistics from Survey Monkey (Web-based survey tool).

Results

Demographic Data

A total of 1,506 patients fully participated in the survey. Their median age was 49 years (range 20–81 years); 43% of the patients were 45–55 years old and 99% were female. The median time since breast cancer diagnosis was in the range of 3–5 years; 31% of the patients had received their diagnosis more than 5 years before taking the survey (table 1).

Disease Characteristics

In terms of the receptor status, 56% of the patients reported a hormone receptor-positive breast cancer, 15% indicated a human epidermal growth factor receptor 2(HER2)-positive (3+) status, and 17%, a triple-negative tumor (defined as negative for estrogen and progesterone receptors AND not HER2 3+; any reallocations of HER2 2+ patients by in situ hybridization were not accounted for). The others did not report on their receptor status.

A positive sentinel lymph node was reported by 31% of the patients, and 27% indicated further involved lymph nodes. Tumor size was <2 cm (T1) in 45%, 2–5 cm (T2) in 45%, and >5 cm (T3/T4) in 9% of the patients. Since the primary breast cancer diagnosis, metastatic disease had been detected in 4% of the patients, mostly affecting bones, lymph nodes, and lungs; 10% did not report their metastatic status.

Adjuvant Breast Cancer Treatments

Radiotherapy (82%), antihormonal treatment (78%), and chemotherapy (75%) were the most common modalities of adjuvant anticancer therapy. There were some inconsistencies in the reports on antihormonal therapies: 16% of the patients reported an antihormonal therapy despite having stated an absence of hormone receptor positivity; 6% received an antihormonal drug despite having

reported no antihormonal treatment. Therefore, a total of 78% probably had a hormone receptor-positive breast cancer.

Taxanes (61%), anthracyclines (52%), and cyclophosphamide (37%) were the most commonly used chemotherapeutics.

A total of 18% of all patients reported to have received HER2-directed therapies; this includes 80% of the patients with HER2 3+ positive status and 24% of those with HER2 0–2+ status.

In the subgroup of patients treated with antihormonal drugs, tamoxifen (80%) and aromatase inhibitors (32%) were the most commonly used substances (table 2).

Information on Potential Side Effects

Patients received information on potential side effects of adjuvant cancer therapy predominantly from their treating physician (81%), the Internet (32%), information brochures (27%), and nursing staff (27%).

Long-Term Side Effects of Adjuvant Therapies

Regardless of the type of adjuvant therapy, hot flashes, fatigue, and sleep disturbances were the most common symptoms, each reported by more than two-thirds of the patients. Pain in bones, muscles, or joints was also highly prevalent, each reported by at least half of the overall patient cohort. A similar proportion of patients experienced cognitive and mood disturbances (concentration deficit, symptoms of depression). Peripheral neuropathic symptoms including numbness and/or tingling of feet or hands was documented by a quarter of the cohort. Hair and nails were affected in more than one-third of the patients.

Association of Chemotherapy with Long-Term Side Effects

Overall, chemotherapy was associated with increased prevalence of all reported symptoms. Specifically, concentration deficits (+22%), nail changes (+31%), hair loss (+33%), tingling of hands (+20%), numbness (+26%) and tingling of feet (+22%) were increased by ≥20% versus adjuvant therapy without the use of antineoplastic chemotherapeutics (table 3, fig. 1).

Among all patients who reported taxane-containing therapies, the prevalences of neuropathic long-term effects such as numbness, tingling, and pain of hands or feet were substantially higher than in those who received no taxanes.

Association of Taxane Chemotherapy with Long-Term Side Effects

Compared to non-taxane-based adjuvant therapies, the use of taxanes was associated with a strongly increased prevalence of nail changes (+26%), hair loss (+22%), and

Table 3. Long-term side effects in patients without and with chemotherapy

	Without chemotherapy, % (*N* = 384)	With chemotherapy, % (*N* = 1,122)	Difference, %
Hair loss	16	49	33
Nail changes	19	50	31
Numbness, feet	4	30	26
Tingling, feet	6	28	22
Concentration deficit	46	68	22
Tingling, hands	11	31	20
Tingling and pain, feet	8	24	16
Numbness, hands	13	29	16
Bone pain	50	63	13
Tingling and pain, hands	9	20	11
Dry oral mucosa	19	30	11
Dry genital mucosa	36	47	11
Muscular pain	41	52	11
Loss of libido	43	54	11
Exhaustion	61	72	11
Vertigo	17	25	8
Joint pain	58	65	7
Dry eyes	27	33	6
Visual disturbances	26	31	5
Fatigue	66	71	5
Depressed mood	43	46	3
Depression	14	16	2
Sleep disturbances	68	69	1
Hot flashes	71	72	1

Table 4. Long-term side effects in patients who received adjuvant therapies without or with taxanes

	Adjuvant therapy without taxanes, % (*N* = 652)	Adjuvant therapy including taxanes, % (*N* = 854)	Difference, %
Nail changes	27	53	26
Numbness, feet	10	34	24
Tingling, feet	11	31	20
Concentration deficit	52	71	19
Tingling, hands	16	34	18
Numbness, hands	16	31	15
Tingling and pain, feet	12	26	14
Muscular pain	42	54	12
Dry genital mucosa	39	49	10
Tingling and pain, hands	12	22	10
Exhaustion	64	73	9
Bone pain	54	63	9
Loss of libido	46	55	9
Hot flashes	67	75	8
Joint pain	59	66	7
Visual disturbances	25	32	7
Dry oral mucosa	23	30	7
Fatigue	67	72	5
Dry eyes	29	34	5
Vertigo	20	25	5
Sleep disturbances	66	70	4
Hair loss/partial hair loss	28	50	2
Depression/depressed mood	52	52	0

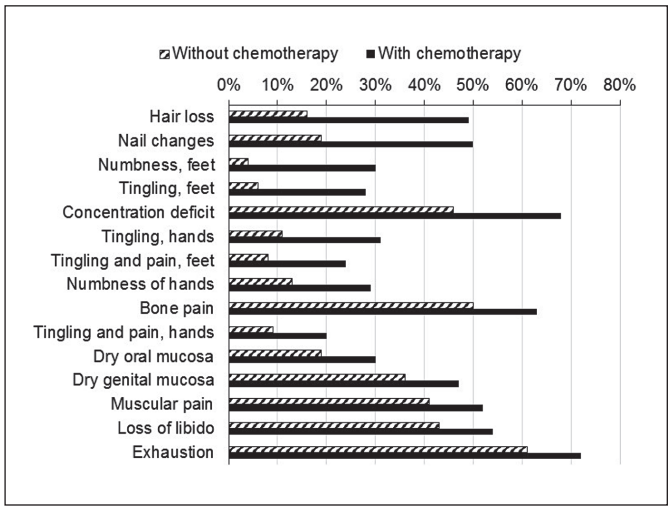

Fig. 1. Long-term prevalence (%) of side effects in patients who received adjuvant therapies with or without the use of chemotherapeutic drugs (items with ≥10% difference in prevalence in both groups are shown in the order of decreasing difference).

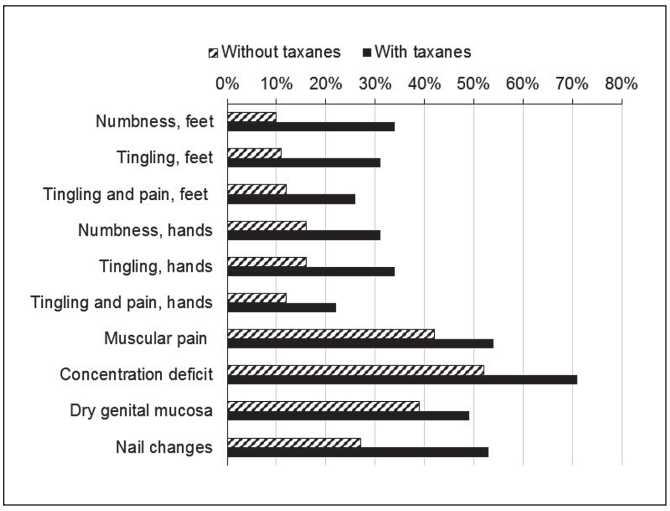

Fig. 2. Long-term prevalence (%) of side effects in patients who received adjuvant therapies with or without the use of taxanes (items with ≥10% difference in prevalence in both groups).

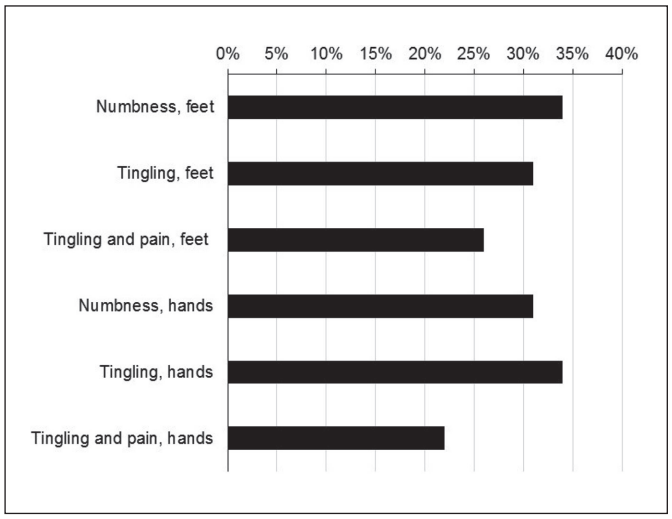

Fig. 3. Long-term prevalence (%) of neuropathic side effects in patients who received adjuvant therapies with taxanes.

neuropathic symptoms: numbness (+24%) and tingling (+20%) of feet, numbness (+15%) and tingling (+18%) of hands, as well as tingling plus pain in feet (+14%) and hands (+10%) (table 4, fig. 2). The neuropathic symptoms in taxane recipients (fig. 3) tended to be more prevalent in those with triple-negative versus receptor-positive tumors (fig. 4).

Association of Antihormonal Therapy with Long-Term Side Effects

Compared to patients who did not receive endocrine therapy, those who used antihormonal drugs more often reported hot flashes (+19%) and vaginal dryness (+11%), while hair loss was less common (–19%). Dry eyes and visual disturbances were experienced by roughly one-third of patients taking these drugs.

Among the subclasses of antihormonal drugs, aromatase inhibitors were associated with a relatively high prevalence (73%) of joint pain, whereas loss of libido was prevalent with gonadotropin-releasing hormone (GnRH) analogs (69%).

Long-Term Side Effects in Patients with Exclusive Taxane Chemotherapy versus Exclusive Antihormonal Therapy

When comparing these two modalities, side effects were generally more prevalent in the taxane-treated patients. The association of certain symptoms, including concentration deficit (+22%), nail changes (+31%), hair loss (+44%), and various peripheral neuropathy symptoms (+12 to +25%, particularly tingling and numbness of feet), with taxane therapy was apparent.

Association of the Time Interval since Breast Cancer Diagnosis with Side Effects

The distribution of side effects was similar in patient groups with different time intervals since diagnosis. The side effects with ≥10% of difference of prevalence between two of these time frames were numbness of feet (17% at >5 years vs. 28% at 1–2 years) and tingling of feet (17% at >5 years vs. 27% at 3–5 years after diagnosis).

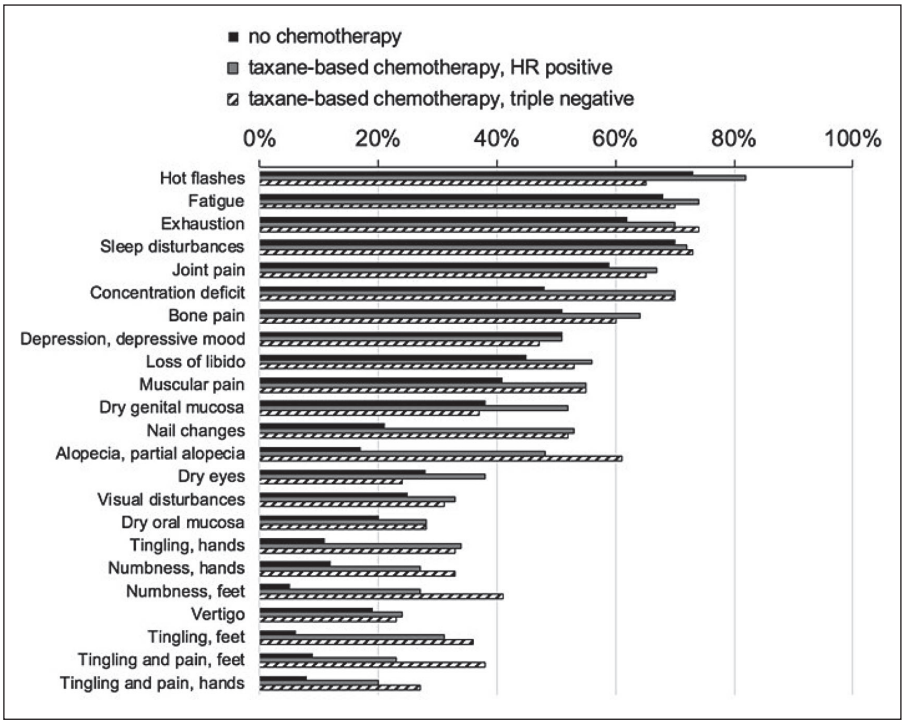

Fig. 4. Long-term prevalence (%) of side effects in patients who received adjuvant therapies without chemotherapeutics versus those treated with taxanes, shown by receptor status.

Perceived Burden Associated with Side Effects

The most severe burden of symptoms (categories always/often severely burdened) was reported for fatigue (79%) and depression (79%), sleep disturbances (77%) and tiredness (76%). Pain in various localizations (72–75%) caused an important burden as well. Peripheral neuropathic symptoms (numbness, tingling and pain in hands and feet) was reported as causing always/often a severe burden by 65–69% of the affected patients.

Discussion

We conducted a large Web-based survey in breast cancer patients with a broad range of characteristics and intervals after primary diagnosis. To our knowledge, this is the largest dataset on long-term sequelae of adjuvant breast cancer drug therapy in Germany.

Taxanes were the more frequently used antineoplastic drugs reflecting current treatment practice, while tamoxifen was used in most patients with antihormonal therapy.

Fatigue, depression/depressive mood, concentration deficit, pain, changes of mucosa and skin appendages, as well as symptoms of peripheral neuropathy were the most prevalent complaints. Overall, the data show a substantial prevalence of a wide variety of potentially therapy-associated symptoms over a protracted time frame after the diagnosis of breast cancer. The burden of symptoms, a measure of their severity and subjective effect, was high for many symptoms including fatigue, depression, sleep disturbances, and peripheral neuropathy. Of note, painful symptoms at various localizations were reported by a large proportion of the patients and showed higher long-term prevalence in the participants who received chemotherapy.

A striking result was the pronounced burden of persisting symptoms even in patients with a time since diagnosis of more than 5 years. In patients who received both antihormonal therapy and chemotherapy, the long-term persistent effects of chemotherapy may be superimposed with adverse effects of ongoing use of antihormonal drugs. It would therefore be of interest to analyze the time course of symptoms in patients who did not receive any antihormonal therapy (e.g., those with triple-negative breast cancer) to determine the prevalence of true lasting effects of chemotherapy in patients who have long since completed their adjuvant treatments. However, for certain symptoms that are characteristic of taxanes, such as peripheral neuropathy, the time course may well be deduced from the data: These symptoms show a somewhat declining but still substantial prevalence in patients with long time intervals of 5 years since diagnosis.

Our study is associated with several limitations. The use of an online questionnaire, particularly via Facebook, likely selected for younger patients, thus reducing the representativeness for the overall breast cancer population in Germany. Asking which (long-term) side effects occur without a clear specification of a time frame (e.g., the last 3 months) may have resulted in the inclusion of

symptoms that had abated some time ago, thus blurring the distinction between slowly reversible and truly long-term symptoms for the patients with a short interval since diagnosis. However, the shortest interval since diagnosis included was 1 year, which makes it likely that symptoms present at this stage are actually chronic. In addition, the different intensities and durations of symptoms may result in recall biases. In the patients who developed metastases, the relapsed disease and its antineoplastic treatment might have caused symptoms unrelated to the initial adjuvant therapy.

Rating the burden of symptoms by the proportion of particularly burdensome episodes may result in an enhanced emphasis on rarely occurring severe symptoms versus permanently present but less intense symptoms. The true burden of symptoms may be more precisely described by measuring their frequency, duration, and intensity separately. A fraction of the patients did not report their hormone receptor status. We do not expect this to influence the reported side effect frequencies.

A number of symptoms, e.g., fatigue, depression, pain, and menopausal symptoms, may occur independently of any cancer therapy in the context of malignancies and ageing. In our cohort, roughly one-third of the patients were older than the mean age at menopause in the western countries (51.4 years) [6]. These factors, which are unrelated to treatment, may have biased the estimates of frequencies and intensities of side effects.

Conclusions

Patient-reported outcomes have an increasingly important role in the assessment of quality of care in oncology. This analysis of a survey dataset acquired in a large population of breast cancer patients spans a broad range of follow-up durations. It indicates a high burden of long-term side effects of adjuvant anticancer therapy, particularly in patients who received taxane chemotherapeutics.

Assays that identify patients who are expected to have a long-term benefit from chemotherapy versus those who may not benefit may help to spare the use of toxic drugs in a significant percentage of patients, thus reducing the burden of long-term sequelae of chemotherapy. The ultimate effect may be improved quality of life in breast cancer survivors.

Disclosure Statement

Both authors have no conflict of interest to declare.

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