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Brief Report

Fatigue in patients with metastatic breast cancer undergoing single-agent taxane-based chemotherapy: a real-world data global network

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Alessandra Fabi, Elizabeth M. Gavioli, Renuka Wakade, Maria C. Spera, Santiago Miracle, Neus Valveny, Elizabeth Butler, Maria DePizzol, Pier Adelchi Ruffini and Marcello Allegretti

Abstract

Background: Cancer-related fatigue (CRF) occurs in nearly all patients with metastatic breast cancer (MBC).

Objectives: This real-world analysis aimed to describe the prevalence and importance of fatigue in patients with MBC within 3 months of treatment with single-agent taxane-based chemotherapy during the timeframe of 2020–2022 in the United States and Europe. It was also conducted to assess whether there was a difference in relapsed patients compared to patients diagnosed *de novo*.

Design: Electronic health records were analyzed from approximately 150 million patients to identify patients with MBC who underwent taxane treatment.

Results: In 2021, 50,490 patients had MBC, of whom 16,170 were diagnosed *de novo* and 34,330 experienced relapse. The proportion of patients undergoing taxane-based chemotherapy was 7.5% ($n = 1220$) and 13.4% ($n = 4590$), respectively, and the prevalence of any fatigue and CRF was similar between the groups (24.6% *versus* 25.7% and 6.6% *versus* 5.4%, respectively).

Conclusion: At least one in four patients with MBC undergoing taxane-based treatment will experience fatigue. This highlights the importance of validating screening tools to identify CRF, which is necessary to advance clinical trials aimed at investigating treatment strategies to improve patient-centered outcomes for fatigue.

Keywords: breast cancer, cancer-related fatigue, metastatic breast cancer, taxane

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Correspondence to:
Alessandra Fabi
Precision Medicine Unit in Senology, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, P.le A. Gemelli n. 8, Rome 00168, Italy
alessandra.fabi@policlinicogemelli.it

Elizabeth M. Gavioli
Renuka Wakade
Elizabeth Butler
Dompé US, San Mateo, CA, USA

Maria C. Spera
Dompé Farmaceutici S.p.A., L'Aquila, Italy

Santiago Miracle
Neus Valveny
Regulatory & Start-up, TFS HealthScience, Solna, Sweden

Maria DePizzol
Pier Adelchi Ruffini
Marcello Allegretti
Dompé Farmaceutici S.p.A., Milan, Italy

Background

Breast cancer (BC) is a major cause of morbidity and mortality among adults worldwide.[1] While the majority of patients with BC are diagnosed at an early stage of disease; unfortunately, an estimated 20–30% of patients will eventually develop recurrent metastatic disease.[2] Taxane-based chemotherapy remains the standard of care for certain patients with BC, especially for patients whose tumors are negative for hormone receptor expression (ER) (HER)2.[3] However, treatment with taxane-based regimens is strongly associated with side effects such as febrile neutropenia, neuropathy, and fatigue.[4]

Fatigue is a debilitating and persistent condition of exhaustion that interferes with usual daily life activities and functioning.[5] It is the most reported symptom across all cancer patients, and when related to the malignancy itself or the neoplastic treatment, it is referred to as cancer-related fatigue (CRF).[5,6] Fatigue occurs in nearly all patients with metastatic BC (MBC), and typically peaks during treatment, most commonly

chemotherapy or radiotherapy. CRF may have a potential impact on worse quality of life, and poor clinical outcomes observed by chemotherapy interruptions and dose delays as well as decreased recurrence-free survival.[7–9]

CRF is multifactorial and can involve mental, physical, and physiological factors that may change depending on the treatment stage.[10] CRF is subjective and can be assessed from patient self-reports, such as the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale or Brief Fatigue Inventory, with no current gold standard, which may lead to under-reporting and lack of treatment intervention.[11] Only since 2016, fatigue has been considered a syndrome, acknowledged as a multifactorial phenomenon in oncological patients, and included in the International Statistical Classification of Diseases, 10th edition, Clinical Modification (ICD-10-CM) based on specific criteria. This real-world data analysis aimed to analyze the prevalence of fatigue in patients with locally advanced (LA) or MBC undergoing single-agent taxane-based chemotherapy, and to assess whether there was a difference in fatigue in relapsed patients compared to patients diagnosed *de novo*.

Methods

Data source

A real-world evaluation of patients with LA or MBC was conducted using electronic health records from TriNetX LLC (Cambridge, MA, USA), a global research network, that contains de-identified real-world data from approximately 150 million patients in 115 Health Care Organizations (72 in the United States and 42 in Europe which included Spain, United Kingdom, Germany, Belgium, Estonia, Poland, Lithuania, Bulgaria, and Italy). These data were taken from 117 clinical sites of which 76% were academic-based and 24% were community institutions. There was an exception granted to the Institutional Review Board for this study since all data were de-identified.

Study design

To identify patients with MBC, International Classification of Diseases (ICD)-10 codes were extracted using both structured information and natural language processing. Subjects were identified with a diagnosis of MBC who underwent chemotherapy with single-agent taxane (paclitaxel, docetaxel) in 2020, 2021, and 2022 (first quarter). HER2 negative was considered if there were no references to HER2-positive status in the clinical history or if the patients had not received any medication targeting the HER2 receptor (trastuzumab, pertuzumab, and margetuximab). After splitting the cohort based on '*de novo*' (first-line treatment) *versus* 'relapsed' (second- or further-line treatment), we assessed the prevalence of fatigue (any type, R53.x) and CRF (R53.0) within the first 3 months after initiation of taxane.

The objective of this study was to describe the prevalence of fatigue, as reported by clinicians using ICD-10-CM codes, in patients with MBC undergoing single-agent taxane-based chemotherapy. A second objective was to assess whether relapsed subjects had a higher prevalence *versus* those diagnosed *de novo* at an advanced stage. Descriptive analysis using proportions was reported.

Results

The database search was conducted in 2022 and analyzed 43,796,640 patients within the TriNetX LLC network in 2020, 45,559,040 patients in 2021, and 19,431,220 patients in the first quarter of 2022. Of these, 423,530 patients had BC in 2020, 379,880 in 2021, and 142,140 patients had BC diagnosis in the first 3 months of 2022. Advanced MBC was 13% ($n=55,210$) in 2020, 13.3% ($n=50,490$) in 2021, and 12.6% ($n=17,890$) in 2022 from the BC cohort. In 2021, among the 115 sites, 32% ($n=16,170$) were diagnosed *de novo*, and 68% ($n=34,330$) experienced relapse. Further patient distribution according to BC characteristics is depicted in Table 1. Within the BC cohort, HER2-negative distribution was as follows: 12.8% ($n=54,070$) in 2020, 13.1% ($n=49,580$) in 2021, and 11.8% ($n=16,730$) in 2020.

Within the MBC cohort, taxane therapy was used by 25.1% ($n=13,880$) in 2020, 26.1% ($n=13,200$) in 2021, and 27.4% ($n=4910$) in 2021 (Table 1). Furthermore, within the *de novo* group, the proportion of patients undergoing single-agent taxane-based chemotherapy was 8.0% ($n=1470$), while the relapsed group had 13.1% ($n=4800$) for 2020, and was 7.5% ($n=1220$) and 13.4% ($n=4590$) for 2021, respectively (Figure 1). Almost one-third of relapsed patients had

Table 1. Patients distribution by years and according to BC characteristics in TriNetX.

Patient distribution	2020		2021		2022*	
All patients	43,796,640		45,559,040		19,431,220	
BC	423,530		379,880		142,140	
Setting population	55,210	13.0%	50,490	13.3%	17,890	12.6%
+ Diagnosed *de novo* metastatic BC	18,480	4.4%	16,170	4.3%	2890	2.0%
+ Relapsed BC	36,740	8.7%	34,330	9.0%	14,820	10.4%
+ *De novo*, with BC in the prior year	20,520	4.8%	19,170	5.0%	9910	7.0%
+ Relapsed	16,220	3.8%	15,160	4.0%	4910	3.5%
+ Any taxane – at any time	13,880	3.3%	13,200	3.5%	4910	3.5%
HER2 negative or unknown	54,070	12.8%	49,580	13.1%	16,730	11.8%
+ Single-agent taxane – at any time	6550	1.5%	6040	1.6%	2480	1.7%
+ Fatigue R53.0 or R53.83 1 month before taxane	790	0.2%	710	0.2%	710	0.5%
+ HER2 negative or unknown	6340	1.5%	5860	1.5%	2370	1.7%

BC, breast cancer; HER2, hormone receptor expression.

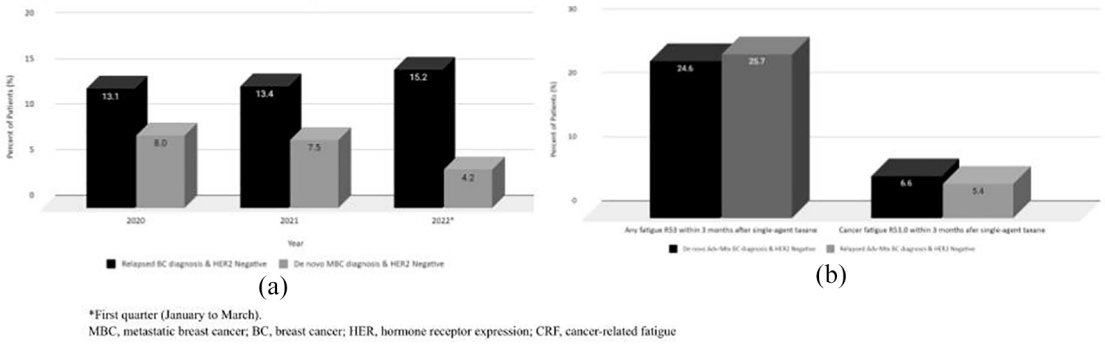


Figure 1. (a) Proportion of patients undergoing single-agent taxane-based chemotherapy among patients with *de novo* advanced BC and relapsed advanced BC. (b) Prevalence of CRF in 2021 among patients with *de novo* advanced BC and relapsed advanced BC.
BC, breast cancer; CRF, cancer-related fatigue.

previously received taxane therapy: 27%, 28%, and 29% in 2020, 2021, and 2022, respectively.

For 2021, the prevalence of fatigue within 3 months after single-agent taxane, of any type, was similar between the *de novo* and relapsed groups (24.6% *versus* 25.7%) as well as CRF (6.6% *versus* 5.4%), respectively (Figure 1). This was similar to 2020, in which no notable differences were noted among the *de novo* and relapsed

groups for any type of fatigue (22.4% *versus* 25.6%) and CRF (4.8% *versus* 5.6%), respectively. Overall, 26.7% and 21.2% of all fatigue was coded as CRF in the *de novo* and relapsed groups, respectively.

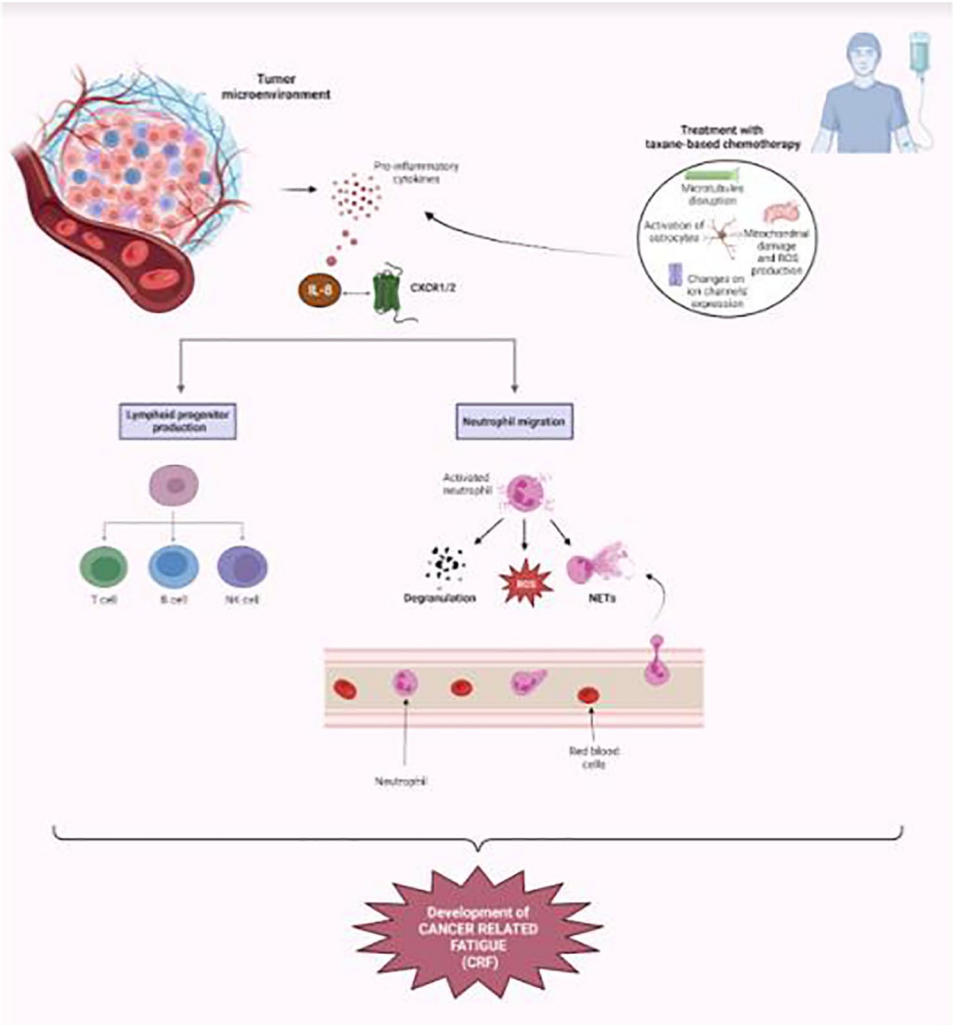
Discussion

In this study, we used real-world data and highlighted that at least one in four patients with MBC undergoing taxane-based chemotherapy suffer from fatigue, independent of disease history and other factors. Fatigue remains an unmet medical need in patients BC particularly in patients receiving taxanes.

From our data, the numbers remain high for diagnosis of fatigue, even though CRF is frequently underreported or untreated either because of lack of assessment or use of ineffective interventions.[7,12,13] This is much less than previous reports that have described 87% of patients with BC experiencing frequent fatigue while receiving taxane therapy.[13] The FiX study surveyed 2508 patients living with cancer to better understand the patients' knowledge and perception of CRF.[12] Of these, 58% of patients did not feel well informed about fatigue, and 41% were never asked about fatigue from their provider. Only 13% of patients received a fatigue assessment to complete as recommended by current guidelines.[5,12] Current guidance is to regularly screen for fatigue throughout the care of patients and their cancer journey including at diagnosis, at regular intervals during treatment, end of treatment, and if clinically indicated.[5] Once identified, fatigue intensity levels should be assessed from patient self-reports, such as the FACIT-Fatigue scale. Yet, there remains no gold standard to date for assessment tools, and national guidelines have recommended several tools based on consistency.[5] Several studies are underway to validate these assessment tools such as a recently completed multinational, prospective study that aims to determine the minimum clinically important difference in the FACIT-Fatigue score in patients with MBC receiving treatment with taxane-based chemotherapy.[14]

A complex pathophysiology and dysregulation of biochemical and psychological systems each can contribute to the development of CRF.[10,15,16] Interventions with the highest level of evidence and consensus recommendation are physical activity, yoga, massage therapy, cognitive/behavioral therapy, and psychotherapy.[5,13] Overall, these interventions focus on indirect factors and lack specific targeting of the physiological causes of CRF, such as hyperinflammation. Dysregulated signaling of the proinflammatory chemokine interleukin-8 (CXCL8; IL-8) pathway has been associated with inflammatory diseases and fatigue syndrome (Appendix). In patients with BC, significant increases in cytokines, including IL-8, were shown to increase during taxane-based chemotherapy and were associated with the worst fatigue symptoms expressed by patients.[16] Even with the introduction of biologicals and targeted therapy for BC treatment, taxane therapy is common as demonstrated by our data and continues to be the preferred systemic therapy for recurrent unresectable MBC.[3]

Limitations of this study include the lack of demographic data including racial and ethnic descriptions, as these groups are commonly underrepresented in clinical trials and may benefit from real-world analysis.[17] Likewise, this real-world analysis may not reflect all patients in the United States and Europe affected by BC. The range of any form of BC from the TriNetX LLC database was 7.3% to 9.6% from 2020 to early 2022 when it was reported that in 2020, there were 3,886,830 (11.8%) women living with female BC in the United States.[18] This analysis may also be underreporting CRF since the data were drawn from ICD codes which are physician-dependent reporting and the prevalence of fatigue may actually be higher in these patients. Therefore, this study contains the risk of missing data bias which may lead to underrepresentation of fatigue. As mentioned above, there is a lack of validated screening tools for CRF, and therefore it is unknown whether the patients experienced mild, moderate, or severe symptoms related to fatigue and the impact on their quality of life. The analysis was conducted during 2020, the year of the COVID-19 pandemic, and the following years and months of the pandemic. It is known that the pandemic and the lockdowns in various countries led to delays in cancer treatment care due to the postponement of screening, medical visits, or surgeries. There are differences in the side effect profiles and administration schedules of different taxanes including therapies. The two most commonly used taxanes are paclitaxel and docetaxel with some data supporting an increased risk of fatigue with docetaxel.[19] Moreover, biological information was not able to be obtained to determine whether patients with certain tumor characteristics such as



Appendix. Upregulation of IL-8 and the inflammatory response in CRF IL-8 (CXCL8) is a proinflammatory chemokine expressed in immune, endothelial, and tumor cells that activate a signaling cascade after binding its receptors, CXCR1/CXCR2. Dysregulated signaling at the IL-8–CXCR1/CXCR2 axis has been associated with increased levels of proinflammatory cytokines during chemotherapy treatment which occurs along with fatigue symptoms in patients with breast cancer.

triple-negative BC (ER-/PGR-/Her2-) or other subtypes have an increased risk of fatigue. Lastly, taxane chemotherapy is commonly used in combination with MBC, and concomitant treatment regimens including hormonal therapy or targeted therapies were not evaluated in this data set. This will be of future importance as research continues to explore new combination strategies such as the use of immunotherapy and CDK4/6 inhibitors which also have a known safety concern of fatigue.[20]

Conclusion

This real-world analysis demonstrated that at least one in four patients with MBC undergoing taxane-based treatment suffer from fatigue. Fatigue remains a challenge in patients with BC, highlighting the need for validation of screening tools to identify CRF. Validation of a screening tool will enable clinical trials to focus on investigating treatment approaches to improve patient-centered outcomes.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have approved this manuscript and consent for publication.

Author contributions

Alessandra Fabi: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – review & editing.

Elizabeth M. Gavioli: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing.

Renuka Wakade: Conceptualization; Investigation; Methodology; Resources; Validation; Writing – review & editing.

Maria C. Spera: Data curation; Formal analysis; Investigation; Resources; Writing – review & editing.

Santiago Miracle: Data curation; Formal analysis; Investigation; Writing – review & editing.

Neus Valveny: Data curation; Formal analysis; Investigation; Resources; Writing – review & editing.

Elizabeth Butler: Methodology; Resources; Validation; Writing – review & editing.

Maria DePizzol: Conceptualization; Investigation; Methodology; Resources; Validation; Writing – review & editing.

Pier Adelchi Ruffini: Formal analysis; Investigation; Writing – review & editing.

Marcello Allegretti: Conceptualization; Investigation; Methodology; Resources; Validation; Writing – review & editing.

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Competing interests

AF is a consultant for Dompé Farmaceutici S.p.A, participant on advisory boards for Roche, Novartis, Lilly, Pfizer, MSD, Pierre Fabre, Eisai, Epionpharma, Gilead, Seagen, Astra Zeneca, and Exact Science. EMG, RW, MCS, EB, MD, PAR, and MA are employees of Dompé Farmaceutici S.p.A. The other authors have no conflicts of interest to declare.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID iD

Elizabeth M. Gavioli https://orcid.org/0000-0002-6436-0748

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