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Original Article

Incidence of patient-reported fatigue developing on palbociclib and endocrine therapy for advanced HR+ HER2– breast cancer

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Abstract

Objectives: Fatigue is a common nonhematologic toxicity of the CDK4/6 inhibitor palbociclib in metastatic breast cancer (MBC) patients with prevalence rates of clinician-rated all-grade and grade 3/4 fatigue of 39.2% and 2.5%, respectively. We prospectively assessed the incidence of fatigue emerging on palbociclib using patient-reported measures and explored potential predictors.

Methods: Eighty-eight patients with HR+ HER2– MBC without fatigue initiating palbociclib with endocrine therapy were assessed before and monthly across the initial 6 cycles. Clinically meaningful levels of patient-reported fatigue (Functional Assessment of Chronic Illness Therapy Fatigue Scale, FACIT-F < 34), severity of, and functional interference due to fatigue (NCI Patient-Reported Outcomes for CTCAE, PRO-CTCAE) were assessed. Hematologic and nonhematologic predictors were examined pretreatment and concurrent with fatigue assessments.

Results: Patient-reported fatigue emerged in 21/88 patients [incidence rate 23.9% (95%CI, 15.4%-34.1%)] within 2.8 ± 1.7 treatment cycles. PRO-CTCAE-rated incidence rate of severe fatigue and fatigue interference was 14.8% (95%CI, 8.1%-23.9%) and 10.2% (95%CI, 4.8%-18.5%), respectively. Lower pretreatment absolute neutrophil count (ANC) levels predicted treatment-emergent fatigue ($P = .01$), but ANC levels on treatment did not ($P = .78$). Other pretreatment predictors were long sleep duration ($P = .02$) and low physical activity (trend, $P = .07$). Treatment-emergent fatigue was associated with objectively measured long sleep duration on treatment ($P = .02$), but not other measures ($P \geq .35$).

Conclusions: One-quarter of patients with HR+ HER2– MBC initiating palbociclib report rapidly emergent clinically meaningful fatigue, often with severe symptoms and functional interference. Treatment-emergent fatigue is associated with both pretreatment (lower ANC levels, longer sleep duration) and on-treatment (long sleep duration) hematologic and nonhematologic profiles.

Key words: metastatic breast cancer; fatigue; sleep; activity; cyclin-dependent kinase inhibitors.

Implications for practice

Our results indicate that therapeutic advances in the metastatic breast cancer setting such as palbociclib and endocrine therapy that can increase life expectancy can also lead to increased fatigue and possibly reduce the quality of life; however, biological markers and behavioral factors may help to identify at-risk populations that may ultimately help optimize treatment plans.

Introduction

Cancer-related fatigue (CRF) is characterized by a subjective sense of physical, emotional, and/or cognitive tiredness.[1] Resulting from cancer or cancer treatment, CRF is unlike typical fatigue as it is out of proportion to recent physical activity.[2,3] Across studies, prevalence estimates range widely (25%-99%) for patient-reported CRF during treatment depending on the patient population and tools used to assess fatigue. In addition to the adverse impact on functioning and quality of life, CRF can lead to discontinuation of fatigue-inducing cancer

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therapies and may persist after treatment cessation.[4] CRF occurs in more than 75% of cancer patients with metastatic disease.[5-8]

Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) are used with endocrine therapy in HR+ HER2− metastatic breast cancer (MBC). Trials using the CDK4/6i palbociclib with endocrine therapy estimate the occurrence of fatigue at any level amongst 40% of patients, significantly higher than fatigue estimates of 29% in endocrine therapy alone.[9] Pooled data from clinical trials of palbociclib estimate the prevalence of the clinician-rated (CTCAE) severe (grade 3/4) fatigue around 2.5%.[9] Similar rates of all-grade and severe fatigue have been seen in randomized trials using the other commercially available CKD4/6 inhibitors, ribociclib, and abemaciclib.[10-14] Notably, these adverse events utilize clinician assessment. Unlike other common adverse events, fatigue is a subjective symptom, requiring the patient's report, which was the focus of the current investigation.

Beyond the need to understand the incidence of patient-reported fatigue on palbociclib therapy, the potential associations of treatment-emergent fatigue with neutropenia and behavioral factors are unknown. In general, the pathogenesis of fatigue with CDK4/6i remains unclear despite significant efforts to understand the underlying mechanisms.

To address these gaps, we conducted a prospective cohort study to estimate the incidence and course of patient-reported fatigue during the first 6 cycles of palbociclib combined with endocrine therapy in women with HR+ HER2− MBC using patient-reported assessments of fatigue. We also examined the associations of fatigue with neutropenia, sleep disturbance, and physical activity.

Methods

We enrolled patients with HR+ HER2− MBC initiating standard-dose palbociclib with endocrine therapy (aromatase inhibitor letrozole or fulvestrant) who did not report fatigue before initiation of palbociclib (ie, Functional Assessment of Chronic Illness Therapy Fatigue Scale [FACIT-F] score < 34). Patients were followed approximately monthly across the first 6 palbociclib treatment cycles or until palbociclib was discontinued (eg, due to disease progression or tolerability concerns), or if study participation was withdrawn (eg, due to study/time burden) (Figure 1A). The study was approved by the Dana Farber/Harvard Cancer Center Office for Human Research Studies guided by the ethical principles in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research prepared by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. All participants provided written informed consent.

Participant selection

Participants were recruited at the Dana Farber/Harvard Cancer Center from 5/2018 to 1/2021 (n = 115, Figure 1B). Potential participants were identified using a clinical alert in the electronic medical record when the initial palbociclib prescription was issued. Participants were scheduled to start palbociclib at the standard initial dose of 125 mg daily, 3 weeks on followed by 1 week off, in combination with letrozole or fulvestrant as part of routine clinical treatment.

Data collection

Data were collected at 7 timepoints in all participants, once at baseline (before palbociclib initiation or within the first 14 days of the first treatment cycle) and once during the third week of each of the first 6 treatment cycles. Diary-based and objective sleep/activity data were collected over a continuous 7-day interval at each of these timepoints. Hematologic data were obtained from clinical records as per routine palbociclib monitoring and were therefore not time-synched to other research assessments.

Patient-reported fatigue assessments

Patient-reported fatigue was assessed using the Functional Assessment of Chronic Illness Therapy Fatigue Scale (PROMIS FACIT-fatigue), a 13-item self-report measure integrating fatigue severity and interference.[15] Grading of both patient-reported fatigue severity and fatigue interference was assessed using the Patient-Reported Outcome Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).[16]

Oncologic and hematologic factors potentially associated with fatigue

Data on concurrent endocrine therapy and any prior radiation therapy or chemotherapy used in the metastatic setting were collected during screening. Dose adjustments and reasons for adjustments were extracted from medical records and verified with the patients. Hematologic assessments were obtained as part of clinical monitoring during palbociclib therapy at baseline and across the 6 cycles.

Subjective and objectives measures of behavioral factors potentially associated with fatigue

Sleep was assessed subjectively using a week-long daily sleep diary and objectively using an actigraph (Actiwatch Spectrum Plus, Philips Respironics, Murrysville, PA). The primary sleep measures of interest in the diary and actigraphy were sleep duration and efficiency.

Physical activity was assessed subjectively using the International Physical Activity Questionnaire (IPAQ) and objectively using a commercially available activity tracker (FitBit, Alta, or Inspire, San Francisco, CA). The IPAQ is a 7-item self-report measure that quantifies time spent performing physical activity in the previous 7 days as Metabolic Equivalent of Task (MET)-minutes per week, reflecting the ratio of the rate of energy expended during an activity to the rate of energy expended at rest.[17] Daily activity counts on the FitBit were averaged across 7 days using standard settings provided with the FitBit proprietary algorithm.

Mood was assessed using the 9-item Patient Health Questionnaire (PHQ-9).[18] Pain was assessed using the item #10 score on the Patient-Reported Outcomes Measurement Information System—Global Health questionnaire.[19]

Statistical analysis

The primary endpoint was new-onset fatigue after palbociclib treatment initiation, defined as a FACIT-F score ≥34 or discontinuation of palbociclib specifically because of fatigue emergence. Secondary endpoints were the PRO-CTCAE fatigue severity and interference items. Incident rates were estimated based on dichotomized FACIT-F scores (<34 vs ≥34) and PRO-CTCAE fatigue severity item and fatigue interference item grades (3 or 4 vs <3). The rate of fatigue incidence on the FACIT-F in the presence

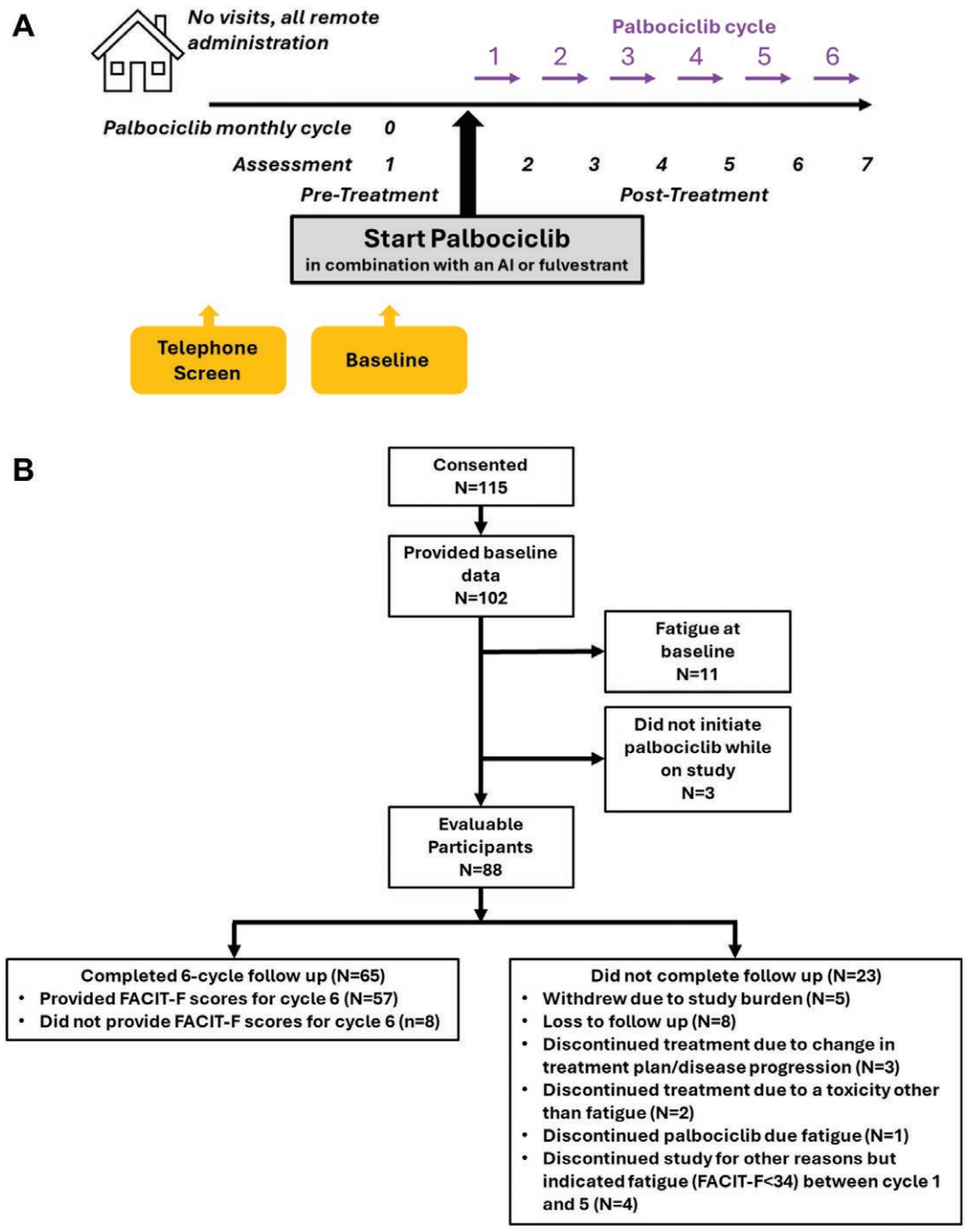

Figure 1. Study design and recruitment.

of competing risks (eg, disease progression or study burden) was estimated using the cumulative incidence function. Concordance between FACIT-F and PRO-CTCAE severity scales was assessed by comparing FACIT-F scores between PRO-CTCAE categories, or agreement between dichotomized FACIT-F and PRO-CTCAE scores (Cohen's κ) or between rescaled FACIT-F scores and PRO-CTCAE scores (Kendall Tau-b)[20] (see Supplementary Section for additional details).

On-treatment associations of FACIT-F fatigue scores with treatment-related factors were tested by comparing FACIT-F fatigue scores with absolute neutrophil count (ANC) values as a continuous outcome or between categories of sleep- and activity-related outcomes. Sleep duration was categorized as long (>9 h), normative (7-9 h), and short (<7 h) weekly averages based on recommended durations for adults.[21,22] Sleep efficiency and patient-reported physical activity (total MET minutes per week) were categorized into tertiles based on the distribution. The objectively measured activity was dichotomized as a low weekly average (≤4000 steps per day) versus normative and high activity.[23]

Baseline levels of each treatment factor predicting treatment-emergent fatigue were tested using generalized estimating equations with a binomial distribution after adjusting for palbociclib cycle number, age (dichotomized on median age), concurrent endocrine therapy (letrozole vs fulvestrant), depression (dichotomized PHQ-9 score ≥ 10), pain, baseline FACIT-F fatigue score, and prior treatment with radiation or

chemotherapy in the metastatic setting. On-treatment associations of each variable with FACIT-F fatigue scores were tested using generalized linear mixed models adjusting for the same covariates listed above. Prediction of treatment-emergent fatigue by baseline objectively measured physical activity was not estimated due to missing data in the majority (57%) of the women (data available only in 38 women). Proportions were compared using Fisher's exact tests. All statistical tests were 2-sided. A significance threshold was set at $P < .05$. Analyses were conducted using statistical software (SAS version 9.4; Cary, NC).

Results

Of 115 patients consented, 13 did not provide baseline fatigue assessment data, leaving 102 eligible patients, of whom 14 additional participants were excluded because their baseline FACIT-F fatigue score indicated fatigue ($n = 11$) or they did not initiate palbociclib treatment as planned ($n = 3$). Therefore, a total of 88 participants who provided data for the primary outcome of patient-reported fatigue were included in the analysis (Figure 1B).

The median age of study participants in the final analytic sample was 59 years (range 29-82 years); the majority were White (92.0%), naturally postmenopausal (86.3%). A total of 71.6% received palbociclib with letrozole and 28.4% with fulvestrant (Table 1). Prior treatments received in the metastatic setting included chemotherapy (20.5%) and radiation (26.1%). As shown in Table 1, baseline measures show the absence of fatigue and ANC, sleep, and physical activity in the normative range.

Incidence and time-to-onset of fatigue

New-onset fatigue was observed in 21 participants (23.9% [95% CI, 15.4%-34.1%]). One participant discontinued palbociclib due to fatigue.

Fifty-eight (65.9%) patients provided FACIT-F data through the entire 6-cycle follow-up. The remaining 30 contributed data for only a portion of the 6-cycle follow-up, of whom 5 withdrew after indicating treatment-emergent fatigue on the FACIT-F; the remaining withdrew due to loss-to-follow-up, study burden, or other reasons (Figure 1B). FACIT-F scores were available from 323 treatment cycles, and the majority (72.3%) were from patients who provided data for at least 4 treatment cycles. Amongst those who withdrew early without indicating fatigue, the mean duration of data collection was 2.8 ± 1.7 treatment cycles. Using this interval, the cumulative incidence of fatigue was 17.0% (95% CI, 10.2-25.3), calculated after the first 3 treatment cycles and accounting for attrition as a competing risk (Figure 2A).

Based on the PRO-CTCAE, 13 women reported that their fatigue was severe and 9 women reported that their fatigue caused significant interference with their functioning translating to incidence rates of 14.8% (95% CI, 8.1%-23.9%) and 10.2% (95% CI, 4.8%-18.5%), respectively. Moderate to high levels of congruence were observed between the FACIT-F and the PRO-CTCAE fatigue severity and interference scales (see Supplementary Section).

Time course of treatment-emergent fatigue and treatment modifications

The mean time to treatment-emergent fatigue was 1.8 ± 1.7 treatment cycles, with treatment-emergent fatigue presenting most frequently ($n = 11$, 52% of the fatigued population) in the second treatment cycle (Figure 2B). After excluding 7 (33%) patients who lacked fatigue data from subsequent treatment cycles after incident fatigue emerged, fatigue presented more commonly as a persistent or recurrent course ($n = 9$, 64%) than a transient, rapidly rebounding course ($n = 5$, 36%), although the difference was not statistically significant (binomial test $P = .21$, Figure 2C).

Data on palbociclib treatment modifications (Figure 2D) were available for 380 palbociclib cycles. Approximately one-quarter of cycles involved a cycle delay, dose reduction, or both, occurring at least once in a total of 47 participants.

Pre- and early-treatment factors related to fatigue

Hematologic predictors

ANC was measured 4.5 ± 1.5 times per participant, with an ANC available for 83% of corresponding treatment cycles. At the time of palbociclib initiation, 97% of ANC values were >1.5 K/μL, whereas 57% of ANC values were subsequently ≤1.5 K/μL during palbociclib therapy ($P < .01$, Fisher's exact), as expected. Lower baseline ANC values significantly predicted treatment-emergent fatigue ($P = .01$). Baseline ANC levels did not differ between those who did versus did not have prior chemotherapy in the metastatic setting (3.9 ± 1.6 vs 3.8 ± 1.5, $P = .84$). The odds of developing treatment-emergent fatigue were 89% higher for each K/μL of lower baseline ANC values (OR: 1.89 [95%CI, 1.09-3.30], Figure 3A). ANC values during palbociclib therapy were not associated with the emergence of fatigue ($P = .47$, Figure 3B). The presence of neutropenia with palbociclib exposure was notably not temporally associated with fatigue ($P = .18$, Fisher's exact); 55% and 50% of the ANC values were >1.5 K/μL at the incident and preincident palbociclib cycle when fatigue was detected, respectively.

Sleep duration and sleep efficiency

Self-reported sleep duration at baseline significantly predicted the emergence of fatigue; longer sleep duration predicted more fatigue ($P = .03$). When dichotomized, treatment-emergent fatigue was observed more commonly in long sleepers at baseline versus the short and normative sleep duration groups together (42% of 26 vs 16% of 50, respectively, $P = .02$, Figure 3C). Self-reported sleep efficiency at baseline did neither predict treatment-emergent fatigue ($P = .16$, Supplementary Figure S1A) nor was treatment-emergent fatigue associated with on-treatment measures of sleep duration or sleep efficiency (both $P > .18$, Supplementary Figure S1B and C).

Fatigue emerging on treatment with palbociclib was not associated with objectively assessed sleep duration or sleep efficiency at baseline (both $P > .35$) (Supplementary Figure S1D and E). During palbociclib therapy, those with the longest objectively measured sleep duration had significantly more fatigue ($P = .02$, Figure 3D), but treatment-emergent fatigue was not associated with objectively quantified sleep efficiency on palbociclib therapy ($P = .62$, Supplementary Figure S1F).

Physical activity

There was a statistical trend for lower levels of patient-reported physical activity at baseline predicting the emergence of fatigue ($P = .09$, Supplementary Figure S1G); treatment-emergent fatigue was observed more commonly in patients

Table 1. Patient and Disease Baseline Characteristics.

No. of patients	88
Median age, years (range)	59 (29–82)
Race [*n* (%)]	
White	81 (92.0%)
Black	2 (2.3%)
Other	5 (5.7%)
Ethnicity [*n* (%)]	
Non-Hispanic/Non-Latina	66 (75.0%)
Other	22 (25.0%)
Menopause Status [*n* (%)]	
Postmenopausal	76 (86.3%)
Ovarian suppression	12 (13.6%)
Chemotherapy in metastatic setting [*n* (%)]	18 (20.5%)
Radiation in metastatic setting [*n* (%)]	23 (26.1%)
Concurrent Endocrine Treatment [*n* (%)]	
Fulvestrant	25 (28.4%)
Letrozole	63 (71.6%)
Fatigue (mean ± SD)	
FACIT-fatigue	44.3 ± 5.1
PRO-CTCAE—fatigue severity	0.9 ± 0.7
PRO-CTCAE—fatigue interference	0.6 ± 0.6
Absolute neutrophil count (mean ± SD)	3.9 ± 1.6
Sleep (mean ± SD)	
Subjective duration (hours)*	7.2 ± 1.5
Subjective efficiency (%)*	81.2 ± 11.1
Objective duration (hours)**	7.2 ± 0.8
Objective efficiency (%)**	84.0 ± 6.6
Physical activity (mean ± SD)	
METs	2161.6 ± 2326.8
Steps	5217.2 ± 3458.1
Depression (PHQ-9 total score ≥ 10) [*n* (%)]	4 ± 4.9
Pain—POMIS-GH Item #10 (mean ± SD)	1.6 ± 1.9

reporting the lowest tertile of physical activity versus those in the higher 2 tertiles combined (50% of 14 vs 20% of 61, respectively, P =.07). However, patient-reported physical activity levels on treatment were neither associated with the emergence of fatigue (P =.35, Supplementary Figure S1H) nor was treatment-emergent fatigue associated with objectively measured levels of physical activity while on treatment (P =.45, Supplementary Figure S1I).

Discussion

This prospective, single-arm cohort study evaluated the incidence of CRF in patients with HR+/HER2− MBC initiating a combined palbociclib and endocrine therapy regimen. Approximately one-quarter reported the development of clinically significant CRF within the first 6 cycles of therapy, with roughly 15% reporting serious or severe symptoms. Phase III trials of palbociclib and endocrine therapy for HR+/HER2− MBC report rates of provider-assessed all-grade fatigue occurring cumulatively during a much longer, extended course of treatment than our study, in approximately 38%, with severe rates of approximately 2.0%, in the first line[24] and pretreated settings.[25] Fatigue is a shared toxicity among all CDK4/6 inhibitors, with similar rates of fatigue reported in trials of the other available CDK4/6 inhibitors. For example, rates of clinician-rated all-grade fatigue and severe fatigue were 36.5% and 2.0% with ribociclib,[26] and 40% and 1.8% with abemaciclib[27] in the first-line phase III studies. Therefore, we expect that rates of patient-reported fatigue may be similar across CDK4/6 inhibitors. It is well established that provider-assessed toxicity can diverge from patient-reported,[28] and it is not unusual to see discordance, with higher reported rates of symptoms from patient reports. Results of the current study highlight the value of integrating PROs when assessing CRF in future clinical trials.

Understanding risk factors for fatigue, and the expected timing of fatigue onset and severity, may provide guidance for clinicians starting this regimen. Knowing that patients with specific pretreatment risk factors—lower ANC and longer sleep duration—may be more likely to subsequently experience fatigue and that clinically relevant fatigue is most likely to present by the second cycle of therapy, which provides valuable clinical information. Clinicians can counsel patients about expectations on therapy and emphasize the need for communication about potential side effects: the vast majority of patients did not develop fatigue, with those who did experience fatigue having onset early in the treatment course and with identifiable risk factors. While this study did not specifically evaluate if dose modification improved symptoms, modification was common, occurring in one-quarter of cycles at least once in over half of patients. Notably, a persistent or recurrent course of fatigue in those with fatigue emergence whose treatment was modified suggests that modification might not influence the fatigue course, although the sample size for this observation was small. Nonetheless, it has been demonstrated that dose modifications do not impact efficacy with palbociclib and are generally encouraged as an acute toxicity management strategy.[29] Similarly, although higher levels of physical activity on treatment did not correlate with less fatigue in this study, exercise interventions in patients with MBC are feasible and have been associated with improvements in quality of life and physical function.[30]

It is notable that fatigue emergence was not related to neutropenia developing on palbociclib. Neutropenia with CDK4/6i is short-lasting, recovers with treatment holds, and is not associated with infectious sequelae such as febrile neutropenia.[31] Palbociclib induces a reversible cellular quiescence of early hematopoietic progenitor cells rather than the irreversible cellular death seen with cytotoxic chemotherapy,[32] and this on-target toxicity is thought to be mediated specifically through inhibition of CDK6.[33] Our observation that the emergence of neutropenia on treatment was not associated with treatment-emergent fatigue is aligned with this known difference in mechanisms of action of CDK4/6-induced versus traditional chemotherapy-induced fatigue. In contrast, lower baseline ANC was associated with the development of fatigue on treatment. It is possible that women with MBC with lower baseline ANC, possibly due to prior cytotoxic chemotherapy, radiation, or other inherent factors, are more susceptible to developing fatigue on CDK4/6 inhibitors.

Our finding that long sleep duration and possibly low physical activity at baseline, before treatment initiation, predict treatment-emergent fatigue might identify a group of patients with pre-existing behavioral patterns before initiating palbociclib therapy that put them at higher risk for developing fatigue on treatment. These associations were seen

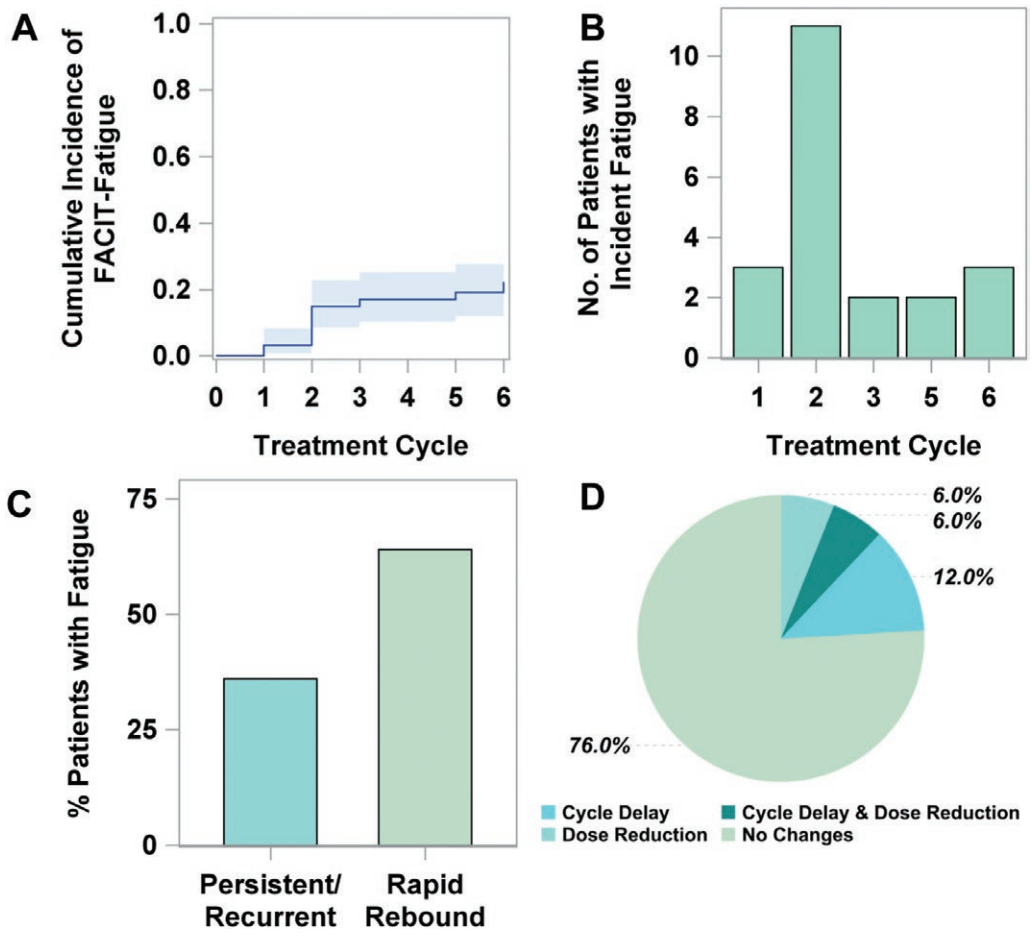

Figure 2. Cumulative incidence and time course of patient-reported clinically meaningful treatment-emergent fatigue on palbociclib with endocrine therapy and treatment modifications. The rate of treatment-emergent clinically meaningful fatigue incidence on the patient-reported FACIT-F for 21 of 88 evaluable participants who developed fatigue in the presence of competing risks ($n = 25$) including early withdrawal from study and early discontinuation of palbociclib, both without indication of fatigue on FACIT-F, was estimated using the cumulative incidence function (A). Frequency of patients reporting clinically meaningful levels of treatment-emergent fatigue on the FACIT-F by treatment cycle (B). Clinical pattern of presentation of treatment-emergent fatigue in the subset of patients with fatigue ($n = 14$) who provided time course data from subsequent treatment cycles after incident fatigue emerged (C). Proportion of 380 palbociclib cycles with data across the 6-cycle follow-up period in 88 patients that had a treatment modification (D).

with subjectively assessed sleep and physical activity, but the relationships were not observed when assessed objectively, potentially due to inadequate statistical power given missing data for objective assessments. Longer objectively measured sleep while on treatment was significantly associated with more fatigue, possibly indicating a compensatory prolonging of sleep related to treatment-emergent fatigue, although the directionality and causal relationship cannot be established given the concurrence of these measurements on treatment. Nonetheless, these observations point to the value of focusing efforts supporting behavioral modification for those most at-risk for treatment-emergent fatigue; trials of interventions targeting sleep duration and improving physical activity may help identify the therapeutic value of such strategies.

Reports of poor sleep and CRF are well documented, although causality is not well established. CRF-associated sleep disruptions reported poor sleep quality, increased nighttime awakenings, difficulty maintaining and falling asleep, and increased daytime napping.[34,35] The commonly occurring coincidental report of poor sleep with fatigue suggests shared etiology, potentially changes in circulating cytokines.[36] While objective assessment of sleep using actigraphy and polysomnography are limited, results are mixed and include the association of fatigue with a small increase in objectively measured sleep duration over the course of treatment,[37] consistent with our findings.

Strengths of this study are the longitudinal measurement of fatigue directly from patient's self-report. The repeated-measures approach allows a greater understanding of the kinetics of fatigue, especially in the initial months of palbociclib administration. Other important strengths of this study include the concurrent administration of both the more comprehensive FACIT-F fatigue measure and the shorter and easier-to-administer PRO-CTCAE fatigue, enabling further evaluation of its validity.

Study limitations

There are several limitations to this analysis. Baseline measures were not collected until the first 14 days of the first palbociclib cycle in several participants due to delays in identifying potential participants. Additionally, a subset of patients invited to the study declined participation for unknown reasons, some of which may have been related to the development of fatigue; consequently, our estimate of treatment-emergent fatigue may be an underestimate instead

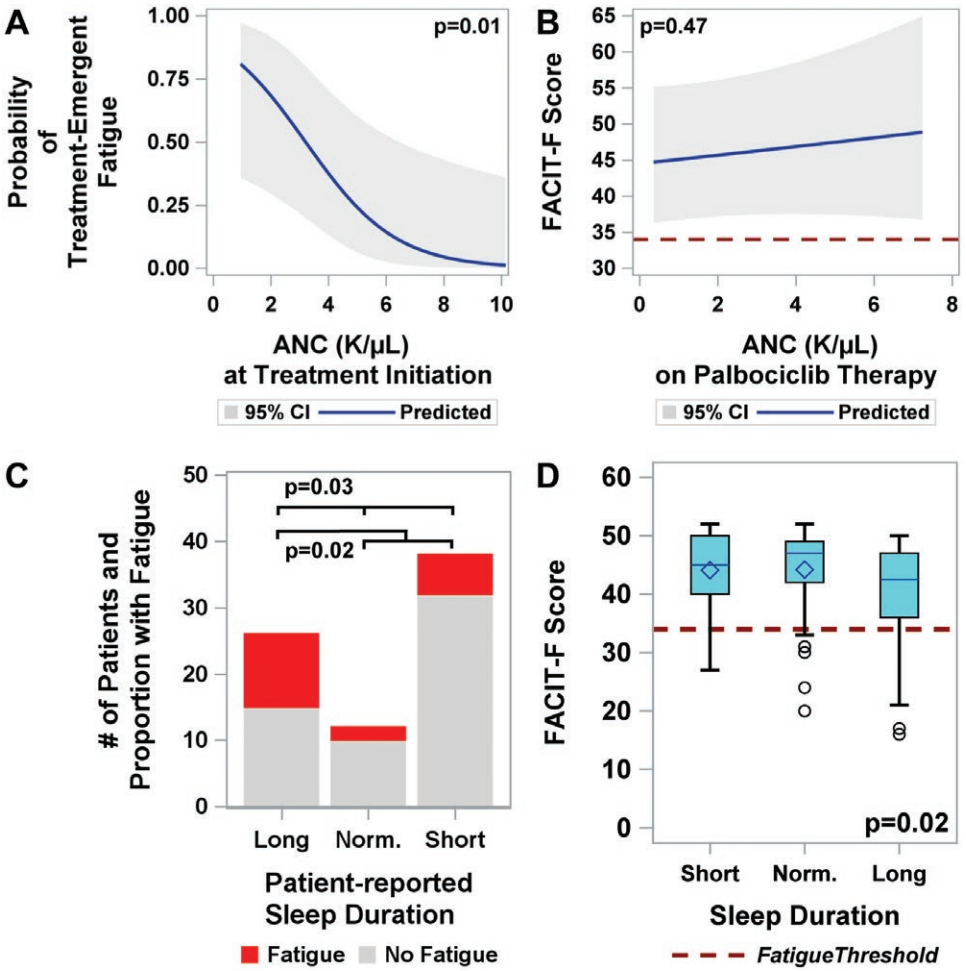

Figure 3. Pre- (before treatment initiation) and early- (within ~1 week of treatment initiation) treatment patient characteristics associated with patient-reported clinically meaningful levels of treatment-emergent fatigue on palbociclib with endocrine therapy. Probability of reporting clinically meaningful level of treatment-emergent fatigue based on ANC levels at palbociclib treatment initiation (A). Association between ANC levels on palbociclib therapy and FACIT-F scores on treatment (B). Frequency of patients and corresponding proportion of patients reporting clinically meaningful levels of fatigue by patient-reported sleep duration category—long (>9 h), normative (7-9 h), and short (<7 h) weekly averages calculated from daily diaries (C). Distribution of on-treatment fatigue scores by objectively measured sleep duration category—long (>9 h), normative (7-9 h), and short (<7 h) weekly averages calculated from actigraphy (D). For (A) and (B), model-adjusted predicted values and 95% CI around prediction are shown as solid line and shaded area, respectively. For (B), horizontal dashed line indicates FACIT-F threshold below which clinically meaningful fatigue is present.

of being an overestimate. No control group was used in this single-arm study; therefore, it is not known how different the incidence of fatigue would be in an MBC population not taking CDK4/6i in combination with endocrine therapy. We also do not know how patient-reported fatigue incidence on palbociclib directly compares with other CDK4/6i treatments. Finally, recently reported long-term follow-up from the major CDK4/6i trials have suggested improved overall survival with agents other than palbociclib,[11,38] and future CDK4/6i prescribing patterns may be in flux.

Conclusions

Therapeutic advances in the MBC setting have translated to longer life spans, but achieving this requires prolonged exposure to therapies that have toxicity and potential for detrimental effects on quality of life. Identifying the subset of patients at risk for treatment-emergent fatigue by detecting lower pretreatment ANC and longer sleep duration, as well as the development of longer sleep duration on treatment, may provide a valuable screening strategy. Determining the etiology of such toxicities, as well as predictors and therapeutic interventions, may help improve a patient's ability to remain on palbociclib in order to receive an optimal therapeutic benefit and maintain a good quality of life.

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Author contributions

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Conflict of interest

A.W., L.B.F., E.E., M.N., S.M.B., J.W.W., and S.C.T. do not have any nonfinancial interests to report. S.A.R.: No financial arrangements or connections that are pertinent to the submitted manuscript. Nonfinancial interests that could be relevant to the submitted manuscript are declared as the following S.A.R. holds patents for (1) Method and device for preventing alterations in circadian rhythm (U.S. patent application Ser. No. 10/525,958), and (2) Methods and devices for improving sleep performance in subject exposed to light at night (U.S. Application No. 61/810,985); S.A.R. owns equity in Melcort Inc.; has provided paid consulting services to Sultan & Knight Limited, Bambu Vault LLC, Lucidity Lighting Inc.; and has received honoraria as an invited speaker and travel funds from Starry Skies Lake Superior, University of Minnesota Medical School, PennWell Corp., and Seoul Semiconductor Co. Ltd., FALK FOUNDATION E.V.; S.A.R. has received grant/research support from Seoul Semiconductor Co. Ltd., Biological Innovation and Optimization Systems, LLC, Merck & Co., Inc., Pfizer Inc., Vanda Pharmaceuticals Inc., Lighting Science Group, National Institutes of Health, and NASA. These interests were reviewed and managed by Brigham and Women's Hospital and MassGeneralBrigham in accordance with their conflict-of-interest policies. H.J.: Consultant/advisory board member for Bayer, Merck, and Hello Therapeutics, and has grant/research support from National Institutes of Health, Merck, and Pfizer. Her spouse is an employee at Arsenal Biosciences, and has equity in Merck Research Lab. E.L.M.: Consultant/advisory board member for Lilly, AstraZeneca, Gilead, and Novartis. H.P.: Funding from National Comprehensive Cancer Network/AstraZeneca. D.S.: Funding from National Cancer Institute, American Association for Cancer Research, and Capability Maturity Model Integration. Personal fees from the *Journal of the American Medical Association* for editorial services. Research funding to institution from Grail. No other disclosures. E.Z.: Grant/research support from Jazz Pharmaceuticals and Harmony Biosciences; received consultant fees from MindUP and Samsung; and received honoraria as an invited speaker for the National Comprehensive Cancer Network and the Young Survival Coalition.

Data availability

Individual-level data are not publicly available due to containing information that could compromise the privacy of research participants. These data are available on request from the corresponding author (H.J.) after necessary institutional agreements are established.

Supplementary material

Supplementary material is available at *The Oncologist* online.

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