ORIGINAL RESEARCH

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Sleep Quality Analysis in Metastatic Breast Cancer Patients Receiving Cyclin-Dependent Kinase 4-6 Inhibitor

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ABSTRACT Objective: Sleep quality (SQ) may decrease in breast cancer patients following the treatment. The aim of this study was to assess the SQ of breast cancer patients treated with Cyclin-dependent kinase(CDK) 4–6 inhibitor plus endocrine therapy(ET). **Metarial and Methods:** The data were collected from three different cancer centers. Eighty consecutive patients were included in this study. The Pittsburg Sleep Quality Index(PSQI) was employed for the assessment of the SQ in metastatic breast cancer patients after receiving treatment with CDK4–6 inhibitors plus ET for at least three months. **Results:** The PSQI scores revealed that 68.8% of patients treated with CDK4–6 plus ET have poor SQ. The mean score of the PSQI was 8 (ranging from 1-17). Univariate analysis was employed, revealing a significantly higher sleep latency (p= 0.024), sleep disturbance (p= 0.011), and daytime dysfunction (p= 0.012) in patients receiving letrozole as compared to patients treated with Fulvestrant. Similarly, the mean score of the PSQI was also higher in letrozole-treated patients in comparison with Fulvestrant-treated patients (p= 0.042). The multivariate analysis revealed a significantly higher rate of daytime dysfunction in letrozole-treated patients as compared to Fulvestrant-treated patients (The odds ratio was 0.51, 95% confidence interval, 0.30 to 0.86; p=0.008). In addition, no significant difference was observed in the sleep quality of patients receiving either Ribociclib or Palbociclib. **Conclusion:** The study evidently shows worsening of SQ in patients receiving letrozole in comparison with patients receiving Fulvestrant. CDK4–6 inhibitors have a similar effect on SQ.

Keywords: Quality of life; sleep quality; cyclin-dependent kinase 4-6 inhibitor; breast cancer; treatments

Hormone receptor-positive (HR+), human epidermal growth factor 2 (HER-2)- negative breast cancer can be categorized as the most common subtype, which accounts for two-thirds of all breast cancers.[1] Numerous innovations have been made in the development of therapeutic interventions for the management of hormone-positive metastatic breast cancer (mBC).[2] The introduction of novel therapies such as cyclin-dependent kinase (CDK) 4-6 inhibitors and endocrine therapy (ET) have been successfully employed in the treatment of mBC, either as monotherapy or combination therapy to prevent endocrine resistance.[2] The combination oncotherapy comprising of CDK 4-6 inhibitors with ET has also been useful in the treatment of luminal subgroups of mBC. However, these novel treatments often have certain advantages as well as disadvantages. In addition, recent advances in the treatment modalities for mBC have improved overall survival time and with efforts directed toward enhancing the quality of life (QoL). Moreover, sleep is an important component of the QoL and is measured globally using the Pittsburg Sleep Quality Index (PSQI). A patient's QoL is critically affected by disease symptoms as well as treatment-related factors. Numerous case studies and clinical observations have indicated the negative ef-

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fects of chemotherapy and ET, thereby altering patient's QoL and often leading to early treatment discontinuation. However, patients with mBC need continuity of treatment, and therefore it is vital to improve the patient's QoL in such cases. In addition, the disease symptoms and progression in mBC cases also cause alterations in the patient's QoL. The prevalence of insomnia in mBC patients can range from 23 to 61%.[3] Moreover, data from the Young-Pearl trial displayed that the patient's receiving palbociclib, ET, and capecitabine, showed delayed diarrhea, nausea, vomiting, and time of physical deterioration. However, worsening of insomnia in mBC was highly significant in patients receiving palbociclib and ET.[4] Furthermore, data from Paloma 3 trial exhibited a high incidence of insomnia in patients receiving palbociclib (12.5%) as compared to the placebo group (9.9%).[5] Thus, the aim of this study was to compare the sleep quality of patients receiving CDK 4-6 inhibitors and ET as a treatment for HR+ mBC.

MATERIAL AND METHODS

STUDY DESIGN

A multicenter, retrospective trial was conducted by collecting data from three cancer centers. The trial was designed to assess as well as compare the sleep quality in patients receiving treatments for estrogen receptor-positive or progesterone receptor-positive mBC or both. Predesigned questionnaires for the assessment of sleep quality were obtained and interpreted by a clinical neurophysiologist. The study was approved as a multicenter trial on October 26th, 2021, by the KSU Non-Invasive Clinical Research Ethics Committee (no: 2021/34-02). Furthermore, the study was conducted in accordance with the Declaration of Helsinki. Additionally, informed consent was also obtained from all patients included in the survey.

PATIENTS

The study obtained extensive data from three cancer centers. The inclusion criteria were HER-2 negative and HR+ patients receiving CDK 4-6 inhibitors and ET as treatment. Data from 80 consecutive patients with HER-2 negative and HR+ were obtained and included in the study. The sleep quality assessment was performed using PSQI in patients who received the said treatment for at least 3 months. Histological and pathological diagnosis of all patients was made to confirm estrogen and/or progesterone receptor-positive HER-2 negative breast cancer. A retrospective record was obtained for variables such as histologic type, patients' age, menopausal status, clinical stage at diagnosis, type of treatments, initiation date of CDK 4-6 inhibitors, prior adjuvant chemotherapies, or endocrine therapies, and progression time.

The widely popular and efficient PSQI analysis was performed to assess the sleep quality and sleep dysfunction in patients. Furthermore, the PSQI was improved by Buysse et al. and validated for the Turkish population by Ağargün et al.[6,7] The PSQI score comprises of a nineteen-item questionnaire with a self-report scale employed for evaluation of sleep quality and discomfort in the past month. Moreover, the PSQI scale comprises of 7 components, viz., the efficiency of sleep, duration of sleep, sleep onset latency, need for medications to sleep, sleep disturbance, daytime dysfunction, and overall sleep quality. The sum of the score obtained from 7 components ranges between 0 and 21. A PSQI score of more than 5 points is indicative of poor sleep quality.[8]

STATISTICAL ANALYSIS

Statistical analysis of the obtained data was performed using IBM SPSS Statistics (version 20.0 IBM Corp., Armonk, NY). The continuous variables were expressed as the median and interquartile ranges, whereas categorical variables were expressed as the number of patients. The Shapiro-Wilk test was employed to test the normal distribution of the continuous variables. Furthermore, the chi-squared test was employed for comparison between groups from categorical variables. Moreover, the Mann-Whitney U test was performed to evaluate sleep quality and its association with treatments. The significance of the predictive value of each variable used in the assessment of sleep quality was calculated using a binary logistic regression test in multivariate analyses. The variables with statistical significance in univariate analysis ($p \leq 0.05$) were selected as a predictor of sleep quality in the logistic regression model. All statistical tests were evaluated using a 2-tailed signifi-

cance test. Furthermore, the threshold value for statistical significance was $p \leq 0.05$.

RESULTS

The current work comprised extensive clinical data from 80 patients diagnosed with mBC who received CDK 4-6 inhibitors and ET as treatment.

Patients with a median age of 55 years (28-89 years) during initial diagnosis were selected. Moreover, around 56 patients (70%) received no previous treatment, 10 patients (12.5%) were previously treated with chemotherapy, 14 patients (17.5%) received ET, and 33 patients (41.3%) had visceral metastasis (also see Table 1).

Fifty-four (67.5%) patients received CDK 4-6 inhibitors as treatment in combination with letrozole [28 patients (35%) received palbociclib and letrozole whereas 26 patients (32.5%) received ribociclib and letrozole]. Furthermore, 26 patients (32.5%) received letrozole in combination with fulvestrant for mBC. In patients receiving the first-line treatment, five (19.2%) patients were treated with palbociclib and fulvestrant, whereas two patients (7.6%) were treated with ribociclib and fulvestrant. Approximately 85.2% of patients received CDK 4-6 inhibitors with letrozole as the first-line treatment [24 (44.4%) patients received palbociclib and letrozole, whereas 22 (40.7%) patients received ribociclib and letrozole].

Poor sleep quality was observed in 55 (68.8%) patients indicated from the PSQI score (global score was <5). The mean score of the PSQI was 8 (1-17). Furthermore, no statistical significant difference was observed between PSQI indicators of patients treated with either palbociclib or ribociclib. Additionally, the patients treated with letrozole had significantly higher sleep latency ($p=0.024$), sleep disturbance ($p=0.011$), and daytime dysfunction ($p=0.012$) as compared to patients treated with fulvestrant. The mean score of the PSQI was also higher in patients receiving letrozole as compared to patients receiving fulvestrant ($p=0.042$). Table 2 summarizes the univariate and multivariate analyses of the components of PSQI of the patients. Furthermore, the multivariate analysis also revealed a significantly higher rate of daytime dysfunction in patients receiving letrozole as com-

TABLE 1: Characteristic of patients.

Characteristic	Number PSQI≤5 (percentage)	Number PSQI>5
Median age at diagnosis (range)	51 (28-75)	55 (36-89)
Sex no of patients		
Female	25 (100%)	54 (98.2%)
Male	0	1 (1.8%)
Clinical stage at diagnosis		
Non-metastatic	7 (18%)	24 (43.6%)
Metastatic	18 (72%)	31 (56.4%)
Menopause status		
Premenopausal	7 (18%)	11 (20%)
Postmenopausal	18 (72%)	44 (80%)
Median Ki-67 (range)	20 (10-40)	25 (5-60)
Hormone receptor status		
ER+/PR+	24 (96%)	49 (89.1%)
ER+/PR-	1 (4%)	5 (9.1%)
ER-/PR+	0	1 (1.8%)
Sites of metastasis		
Bone only	15 (60%)	32 (58.2%)
Bone+Visceral	8 (32%)	16 (29.1%)
Visceral only	2 (8%)	7 (12.7%)
Combination of therapy		
Palbociclib+Letrozole	7 (28%)	21 (38.2%)
Ribociclib+Letrozole	7 (28%)	19 (34.5%)
Palbociclib+Fulvestrant	7 (28%)	9 (16.4%)
Ribociclib+Fulvestrant	4 (16%)	6 (10.9%)
Prior systemic therapy		
None	19 (76%)	42 (76.4%)
Chemotherapy	0	2 (3.6%)
Anti-hormonal therapy	1 (4%)	4 (7.2%)
Chemotherapy+anti-hormonal therapy	5 (20%)	7 (12.8%)
Response to CDK 4-6 inhibitors		
Complete response	10 (40%)	13 (23.6%)
Partial response	15 (60%)	35 (63.6%)
Stable disease	0	7 (12.7%)
Progression after CDK 4-6 inhibitors		
No	24 (96%)	44 (80%)
Yes	1 (4%)	11 (20%)
Sleep quality, median (range)	1 (0-1)	2 (1-3)
Sleep latency, median	1 (0-3)	2 (1-3)
Sleep duration, median	0 (0-1)	1 (0-3)
Normal sleep efficiency, median	0 (0-1)	0 (0-3)
Sleep disturbance, median	1 (0-2)	2 (1-3)
Sleep medication use	0 (0-1)	0 (0-3)
Daytime dysfunction, median	0 (0-1)	2 (0-3)
PSQI score	3 (1-5)	10 (6-17)

PSQI: Pittsburgh Sleep Quality Index; ER: Estrogen receptor; PR: Progesteron receptor; CDK 4-6: Cyclin-dependent kinase 4-6.

TABLE 2: PSQI of patients.

			Univariate analysis	Multivariate analysis			
PSQI indicators	**Letrozole**	**Fulvestrant**	**p value**	**p value**	**Palbociclib**	**Ribociclib**	**p value**
Sleep quality, median (range)	2 (0-3)	1.5 (0-3)	0.58	-	2 (0-3)	2 (0-3)	0.632
Sleep latency, median (range)	2 (0-3)	1 (0-3)	0.024	0.212	1.50 (0-3)	2 (0-3)	0.366
Sleep duration, median (range)	0 (0-3)	0 (0-3)	0.419	-	0 (0-3)	0.0 (0-3)	0.50
Normal sleep efficiency, median (range)	0 (0-3)	0 (0-3)	0.888	-	0 (0-3)	0 (0-3)	0.54
Sleep disturbance, median (range)	2 (0-3)	1 (1-3)	0.011	0.445	1 (0-3)	2 (1-3)	0.095
Sleep medication use, median (range)	0 (0-3)	0 (0-3)	0.416	-	0 (0-3)	0 (0-3)	0.087
Daytime dysfunction, median (range)	2 (0-3)	1 (0-3)	0.012	0.013	1 (0-3)	1 (0-3)	0.67
Score of PSQI, median (range)	9 (1-17)	6.5 (1-15)	0.042	0.895	8 (1-15)	7.5 (1-17)	0.85

PSQI: Pittsburgh Sleep Quality Index.

pared to patients receiving fulvestrant (The odds ratio was 0.51, 95% confidence interval, 0.30 to 0.86; p=0.008).

The sleep quality was associated with the best objective response with CDK 4-6 inhibitors (p=0.038). Complete response and partial response rates were more common in the group with good sleep quality, while the stable disease revealed a high incidence of poor sleep quality group. The best objective response according to the PSQI score is given in Table 3.

Additionally, the median follow-up time from the initial diagnosis of breast cancer was 31.5 months (8-1440 months). Whereas the median follow-up time after initiation of CDK 4-6 inhibitor treatment was 12.5 months (3-41 months). Furthermore, during a median follow-up time, the incidence of recurrence was observed in 11 patients treated with CDK 4-6 inhibitors. Evidently, all the patients with recurrent disease conditions depicted poor sleep quality with PSQI scores above 5.

DISCUSSION

The current study revealed that the sleep quality of patients receiving CDK 4-6 inhibitors in combination with fulvestrant was significantly better in comparison to CDK 4-6 inhibitors in combination with letrozole (p=0.042). Moreover, sleep disturbance, sleep latency, and daytime dysfunction were evidently higher in patients receiving letrozole as compared to in patients receiving fulvestrant. The study showed that around 68.8% of patients treated with CDK 4-6 inhibitor and

TABLE 3: Objective response of patients according to sleep quality.

	PSQI score ≤5	**PSQI score >5**		
Best objective response with CDK 4-6 inh	**Number**	**Number**	**Total**	**p value**
Complete response	10 (43.5%)	13 (56.5%)	23	0.038
Partial response	15 (30.0%)	35 (70.0%)	50	
Stable disease	0	7 (100.0%)	7	

CDK: Cyclin-dependent kinase; PSQI: Pittsburgh Sleep Quality Index.

ET had poor sleep quality. Therefore, both ET and CDK 4-6 inhibitors may affect overall patients' quality of sleep and QoL independent of clinical efficacy.

Fulvestrant is an estrogen receptor down-regulator that blocks estrogen-receptor function.[9] The data from the FALCON trial compared the efficacy of fulvestrant and anastrozole in patients with mBC as a first-line treatment demonstrating significantly prolonged progression-free survival.[10] Moreover, Arthralgia was higher in patients receiving fulvestrant as compared to patients receiving anastrozole. Incidences of hot flushes were similar with fulvestrant and anastrozole treatment. Additionally, the FALCON trial also showed that QoL of the patient treated with fulvestrant was numerically favored, and deterioration was sustained for a longer time as compared to anastrozole treatment.[11] The current study also showed that the patients receiving letrozole treatment have worse sleep quality as compared to fulvestrant treatment. However, the underlying mechanism exhibiting such action yet remains unclear.

ET causes aggravation of menopausal symptoms as well as muscle and joint pain.[11] Additionally, treatment with CDK 4-6 inhibitors causes fatigue, diarrhea, nausea, and vomiting. Furthermore, the impact on the sleep quality of patients receiving these drugs is not well documented. The outcomes of the PEARL trial were assessed for comparative analysis of the QoL in postmenopausal patients with mBC receiving capecitabine and palbociclib in combination with ET. The study indicated a marked improvement in insomnia from baseline in patients receiving capecitabine after 5 cycles. However, patients receiving palbociclib and ET did not reveal any improvement until 16 cycles.[12] Additionally, the Young-Pearl study also reported similar results in patients receiving capecitabine versus palbociclib and ET in premenopausal mBC patients. No significant improvement in insomnia was observed and was further worsened with palbociclib and ET treatments.[4] Similarly, the MONALEESA-7 trial also revealed worsening insomnia in premenopausal mBC patients receiving ribociclib and ET treatments.[13]

The current study revealed that the sleep quality was similar in mBC patients treated with both ribociclib and palbociclib. Although fulvestrant is generally preferred as second-line treatment, sleep quality in patients receiving fulvestrant was better than letrozole treatment. Moreover, the daytime dysfunction was also markedly impaired in letrozole treated patients as compared to fulvestrant treated patients. Furthermore, no significant difference was observed in the sleep quality of patients treated with either ribociclib or palbociclib. Complete response and the partial response rate were more common in the patients with good sleep quality, while the stable disease condition depicted poor sleep quality. All of the patients with recurrent disease had poor sleep quality depicting PSQI scores above 5. A previous study had shown that QoL scores are associated with subsequent survival time in patients with mBC; however, no reports were published on the early stages of breast cancer.[14] In the current study, mBC outcome and sleep quality are associated; however, the worsening of sleep quality in patients with poor prognosis cannot be ascribed as a cause or an effect. Evidently, numerous reports have been published on the association of sleep with immunity, and studies have also suggested a strong regulatory effect of sleep on immune functions.[15] Moreover, sleep disturbance can lead to immuno-suppression and augment the release of cancer-stimulatory cytokines.[16] Furthermore, a strong regulatory effect may augment metastatic stages in cancer along with sleep deprivation. In the current work, the overall response rate (ORR) (including either complete or partial response) was higher as compared to patient data from the MONALEESA-2 trial.

Therefore, the conclusion from the current small cohort is that patients treated with fulvestrant as first-line treatment causes higher rates of ORR. Moreover, CDK 4-6 inhibitors combined with ET have greater benefits in cancer remission with consecutive treatment cycles. However, it is difficult to assess and ascribe the effects of either CDK 4-6 inhibitors or ET on sleep quality, which is a limitation of the current study. Additionally, the other limitations of the study include a short follow-up period and the lack of evaluation of other

QoL indices. A larger cohort with a greater number of patients and multicentric trials involving mBC patients may help draw a better conclusion.

CONCLUSION

In conclusion, the current study is the first trial to investigate the sleep quality of breast cancer treated with ET plus CDK 4-6 inhibitor. Patients receiving letrozole treatment depicted worse sleep quality in comparison to patients treated with fulvestrant. Additionally, the CDK 4-6 inhibitors also have a similar deteriorative impact on sleep quality.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** Özgecan Dülgar; **Design:** Özgecan Dülgar, Sevgi Ferik; **Control/Supervision:** Özgecan Dülgar; **Data Collection and/or Processing:** Özgecan Dülgar, Teoman Şakalar, Seval Ay, Ertuğrul Bayram; **Analysis and/or Interpretation:** Özgecan Dülgar; **Literature Review:** Özgecan Dülgar; **Writing the Article:** Özgecan Dülgar; **Critical Review:** Özgecan Dülgar; **References and Fundings:** Özgecan Dülgar.*

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