RESEARCH ARTICLE

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Impact of Treatment Related Neutropenia on Response to Palbociclib in Metastatic Hormone Positive, her2neu Negative Breast Cancer

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Abstract

Cyclin-dependent kinases (CDK4/6) inhibitors play an important role in the management of metastatic hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-) breast cancer. They act by inhibiting the proteins CDK4 and CDK6, which are implicated in the advancement of the cell cycle and unchecked cell proliferation- the primary causes of the development of cancer. The blocking of these proteins can slow or stop the growth of cancer cells. Palbociclib is a highly active substance in the management of hormone positive, her2neu negative metastatic breast cancer [1]. **Methods:** A retrospective study was conducted at King Fahad Hospital (Al Jaber Oncology Centre). Sixty-four metastatic, hormone-positive, HER2neu-negative breast cancer cases who received. Palbociclib were included in the study and followed up for a median time of 30 months. **Results:** Our study indicated that 58 patients were treated with Palbociclib combined with letrozole (90.6%), whereas 6 patients (9.4%) were treated with Palbociclib along with fulvestrant. Neutropenia induced by Palbociclib occurred in 87.5% of cases, whereas 12.5% of cases did not experience neutropenia (8 cases). Regarding neutropenia, our study showed that 32.1% of the participants experienced grade I neutropenia, while 58.9% had grades II, and 8.9% had grade III neutropenia. A dose reduction of Palbociclib was implemented in 19 cases (29.7%) throughout the entire treatment duration. With the adjustment of the dose of Palbociclib, there was no statistically significant difference between the different doses. The 30-month PFS rate was 75% with the dose of 100 mg, 90.9% with 75 mg, and 97.2% with the dose of 125 mg. Median PFS was not reached. A total of 5 deaths were noted in the entire study group. There was no statistically significant difference in overall survival based on neutropenia grades. **Conclusion:** Neutropenia induced by palbociclib and subsequent dose reduction did not impact the disease outcome.

Keywords: Breast cancer- CDK4/6 inhibitors- Palbociclib- grades of neutropenia- Disease outcome

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Introduction

Breast cancer is the most prevalent cancer among women globally, with about 60–65% of cases being hormone receptor-positive and HER2-negative. Endocrine therapy is a standard treatment for hormone receptor–positive metastatic breast cancer, but most patients usually develop acquired resistance. As a result, the introduction of CDK4/6 inhibitors has become a significant turning point in treating metastatic hormone-positive HER2-negative breast cancer. The use of CDK4/6 inhibitors alongside endocrine therapy has become the standard treatment approach for individuals with hormone receptor-positive (HR +)/HER2-negative (HER2-) advanced breast cancer [2].

Cyclin-dependent kinases (CDKs) represent a group of serine/threonine kinases that are crucial in regulating cell cycle advancement and cancer progression. CDK4/6 inhibitors consist of palbociclib, ribociclib, and abemaciclib. They are compounds that inhibit CDK 4 and 6, preventing the phosphorylation of retinoblastoma and cell growth, thereby hindering the transition from G1 to S phase in the cell cycle [1].

Palbociclib was the first CDK4/6 inhibitor used for individuals with HR+/HER2 metastatic breast cancer. v Palbociclib became the initial authorized CDK4/6 inhibitor for individuals with HR+/HER2 metastatic breast cancer. The earlier phase III clinical trials, PALOMA-2 and PALOMA-3, demonstrated that Palbociclib extended PFS and OS when used alongside endocrine therapy. The

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most frequent adverse events associated with Palbociclib were myelosuppression, especially neutropenia. The occurrence rate of neutropenia across all grades was noted in 80% of instances, with grades 3/4 making up 66%. Although neutropenia is common, it was noted that only a small number of patients experienced febrile neutropenia .Both trials demonstrated that Palbociclib extended PFS and OS when used alongside endocrine therapy. Tfhe most frequent adverse events associated with Palbociclib were myelosuppression, especially neutropenia. The occurrence rate of neutropenia across all grades was noted in 80% of instances, with grades 3/4 making up 66%. Although neutropenia is common, it was noted that only a small number of patients experienced febrile neutropenia.The mechanism of neutropenia associated with Palbociclib involves the differentiation of precursor cells in the bone marrow through cell cycle arrest without DNA damage or apoptosis. Palbociclib-induced neutropenia is rapidly reversible when Palbociclib is discontinued. Palbociclib is well tolerated and its neutropenia is manageable through dose reduction or treatment adjustment without affecting efficacy [3].

Our study aims at evaluating if palbociclib related neutropenia has an impact on disease outcome in patients with HR+/HER2 metastatic breast cancer

Materials and Methods

A retrospective study was conducted at King Fahad Hospital (Al Jaber Oncology Centre) on Sixty-four metastatic, hormone positive, her2neu negative breast cancer patients who received Palbociclib between January 2020 till December 2024

Eligibility criteria include patients with age 18years with metastatic hormone positive her2neu negative breast cancer received Palbociclib. Patients with double malignancy ,pregnant , lactating or with serious comorbidities were excluded from our study .This study was approved by the Institutional Review Board (IRB) of king fahad hospital . Patients were treated with Palbociclib plus endocrine therapy either aromatase inhibitors or fulvestrant. Patients received Palbociclib with starting dose 125mg once daily on a schedule of 3 weeks followed by 1 week off, administered orally. Regarding endocrine partner, either letrozole 2.5 mg or exemestane 25 mg was administered orally once a day. Fulvestrant was given with a dose of 500 mg intramuscularly every 2 weeks for the first 3 doses and then every 4 weeks. Premenopausal patients received LHRH agonists during Palbociclib treatment. All patient data were obtained from medical records including patient demographics, clinical and pathologic details disease status, metastatic disease sites, laboratory studies including complete blood count before and after treatment .

Statistical analysis

Statistical analyses were conducted using the IBM SPSS Statistics for Windows, version 22.0. The unadjusted odds ratio (OR) and adjusted OR, with the 95% confidence interval (CI), were calculated from univariate and multivariate analyses, PFS was estimated with Kaplan–Meier methods and compared with the log-rank test. p-value less than 0.05 was considered statistically significant.

Results

Sixty-four metastatic, hormone positive, her2neu negative breast cancer cases included in the study and followed up for a median time of 30 months. Demographic and clinical characteristics of the study group are demonstrated in Table 1. Mean age among studied participants was 53.9 ± 11.8 years. Out of the 64 patients, there were 2 males and 62 females. Most of the cases were postmenopausal (51.6%), having right sided disease (56.3%) .We found that most of cases has negative family history of malignancy (81%) .

Regarding pathologic data of the studied group , our study showed that most cases has tumor size >2 and less than 5cm . Most of cases are infiltrating duct carcinoma (71.6%) with N1 disease. All studied participants are hormone positive, her2neu negative. The majority of cases are metastasized to bone (48 cases) followed by lung metastasis

Palbociclib dosing

Our study indicated that 58 patients were treated with Palbociclib combined with letrozole (90.6%), whereas 6 patients (9.4%) were treated with Palbociclib along with fulvestrant. Neutropenia induced by Palbociclib occurred in 87.5% of cases, whereas 12.5% of cases did not experience neutropenia (8 cases).

Regarding neutropenia, our study showed that 32.1% of the participants experienced grade I neutropenia, while 58.9% had grade II, and 8.9% had grade III neutropenia.

Dose modification

A dose reduction of Palbociclib was implemented in 19 cases (29.7%) throughout the entire treatment duration. Table 2 displays the Palbociclib dosage reduction across the entire study and among various levels of neutropenia. In patients with grade, I neutropenia, one patient (5.6%) had a dose reduction to 100mg, while for grade II, 7 patients (21.2%) received a dose of 100mg, and another 7 patients (21.2%) received 75mg. Most cases of grade III neutropenia (80%) were reduced to 75mg. A statistically significant difference in dose reduction was noted (p value 0.001) (Figure 1).

Concerning the leucocytic count, there was a notable reduction in the WBC count following Palbociclib treatment compared to baseline values in the entire study cohort, exhibiting grade I neutropenia, along with grade II and grade III neutropenia (p values <0.001, <0.001, <0.001, and 0.003, respectively). A notable difference was observed in the leucocytic count after Palbociclib treatment between patients with no neutropenia and those with varying degrees of neutropenia (p value <0.001) Table 3.

Table 1. Demographic and Clinico- Pathological Characteristics of the Study Group

Variables	Number (percentage)
Age, year	
Mean ± SD	53.9 ± 11.8
Gender	
Female	62 (96.9%)
Male	2 (3.1%)
Menopausal status	
Premenopausal	20 (32.3%)
Perimenopausal	10 (16.1%)
Postmenopausal	32 (51.6%)
BMI	
Underweight (< 18.5)	8 (12.5%)
Normal weight (18.5-24.9)	22 (34.4%)
Overweight (25-29.9)	24 (37.5%)
Obesity (≥ 30)	10 (15.6%)
Family history of Malignancy	
Negative	52 (81.3%)
Positive	12 (18.8%)
laterality	
Right	36 (56.3%)
Left	25 (39.1%)
Bilateral	3 (4.7%)
Pathology	
IDC	58 (71.6%)
ILC	6 (7.4%)
Tumor size	
T1	2 (3.1%)
T2	26 (40.6%)
T3	18 (28.1%)
T4	18 (28.1%)
Nodal involvment	
N0	3 (4.7%)
N1	39 (60.9%)
N2	20 (31.3%)
N3	2 (3.1%)
Distant metastasis	
M0	0
M1	64 (100%)
DCIS	
Yes	22 (34.4%)
No	42 (65.6%)
Lymphoplasmocytic infilteration	
Yes	19 (29.7%)
No	45 (70.3%)
Perineural invasion	
Yes	22 (34.4%)
No	42 (65.6%)
Uni/Multicentric	
No	5 (7.8%)
Unicentric	48 (75%)
Multicentric	11 (17.2%)
ER	
Negative	0
Mild positivity	1 (1.6%)
Moderate positivity	31 (48.4%)
Strong positivity	32 (50%)
PR	
Negative	7 (10.9%)
Mild positivity	2 (3.1%)
Moderate positivity	28 (43.8%)
Strong positivity	27 (42.2%)
Ki 67	
Low expression	35 (54.7%)
High expression	29 (45.3%)
BRCA1/2	
Negative	58 (90.6%)
Positive	4 (6.3%)
Not detected	2 (3.1%)
Metastatic disease site	
Bone	48 (75%)
Brain	1 (1.6%)
Liver	13 (20.3%)
Lymph nodes	8 (12.5%)
Lung	24 (37.5%)
Local	1 (1.6%)
Number of metastatic sites	
1	38 (59.4%)
2	17 (26.6%)
33	7 (10.9%)
4	2 (3.1%)
Concomitant hormonal treatment	
Letrozole	58 (90.6%)
Fulvestrant	6 (9.4%)

SD, standard deviation; BMI, body mass index; DCIS, ductal carcinoma insitu; ER, estrogen receptor; PR, progesterone receptor; *BRCA*, breast cancer gene.

Correlation between grades of neutropenia ,Demographic and clinico-pathological characteristics of the studied participants

The characteristics were categorized according to the groups regarding tumor laterality and pathology type (p value= 0.045 and 0.019, respectively). A significant statistical difference was found between the groups for bone metastasis (p value 0.009), with grade 2 neutropenia being the most common. Within the study group, one metastatic site per patient was the most common across all levels of neutropenia, although no statistically significant difference was observed Table 4.

Table 2. Dose Reduction of Palbociclib

Dose of palbociclib	125mg	Dose reduction to 100mg	Dose reduction to 75mg	P value
Total (N = 64)	45 (70.3%)	8 (12.5%)	11 (17.2%)	0.001*
No neutropenia (n = 8)	8 (100%)	0	0	
Grade 1 (n = 18)	17 (94.4%)	1 (5.6%)	0	
Grade 2 (n = 33)	19 (57.6%)	7 (21.2%)	7 (21.2%)	
Grade 3 (n = 5)	1 (20%)	0	4 (80%)	

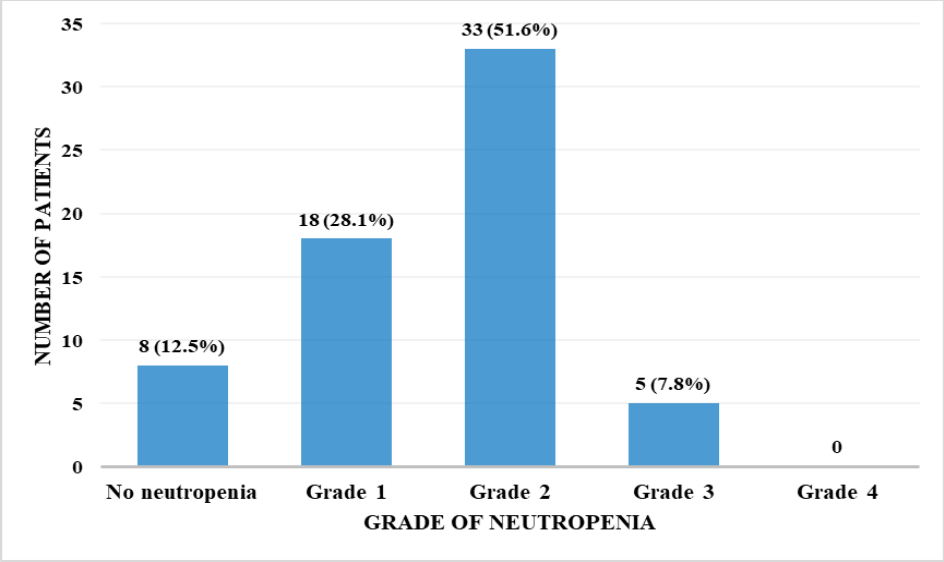

Figure 1. Grades of Palbociclib Induced Neutropenia

Disease outcome and survival

Figure (2) illustrates the Kaplan Meier survival curves for patients treated with Palbociclib, highlighting progression-free survival across various grades of neutropenia. No statistically significant difference was found based on neutropenia grades (p = 0.166, log rank). With the adjustment of the dose of Palbociclib, there was no statistically significant difference between the different doses (p value = 0.159).The 30 months PFS rate was 75% with the dose of 100mg, 90.9% with 75mg and 97.2% with the dose of 125mg. Median PFS has not reached Figure 3.

Regarding overall survival , A total of 5 deaths were noted in the entire study group. Two of them were had grade I neutropenia, while three deaths had grade II neutropenia. There is no statistically significant difference in overall survival based on neutropenia grades (p value=0.719, log rank) (Figure 4).

Table 5 shows the results of the univariate and multivariate logistic regression analysis regarding the risk factors of developing neutropenia after Palbociclib treatment. The predictors were entered the model according to the level of significance in the univariate analysis, stepwise selection and the previous knowledge. There was no statistically significant association between any of the variables and the occurrence of neutropenia in the multivariate regression. Table 6 shows the cox proportional hazards model of the progression free survival. There is a statistically positive association with the presence of lymph node metastasis (HR: 12.13, 95% CI: 1.303-112.921, p value: 0.028) and with higher Ki 67 (HR: 1.053, 95% CI: 1.001-1.108), (p value: 0.045).

Discussion

Palbociclib, a CDK4/6 inhibitor used to treat hormone receptor-positive, HER2-negative metastatic breast cancer,

Table 3. Leucocytic Count at the Baseline and after Palbociclib Treatment

Leucocyte count/mm^3 Mean ± SD	Baseline	After Palbociclib treatment	P value
Total (N = 64)	6.9 ± 2.5	2.8 ± 1.5	<0.001*
No neutropenia (n = 8)	6.4 ± 1.7	5.9 ± 1.2	0.468
Grade 1 (n = 18)	7.7 ± 3.5	3.04 ± 0.7	<0.001*
Grade 2 (n = 33)	6.6 ± 2.1	2.2 ± 0.6	<0.001*
Grade 3 (n = 5)	6.9 ± 2.02	0.9 ± 0.3	0.003*
P value	0.648	<0.001*	

*Significant p value <0.05.

Table 4. Demographic and Clinico-Pathological Characteristics of the Cases According to the Grades of Palbociclib Induced Neutropenia

Variables	No neutropenia (n= 8)	Grade 1 neutropenia (n=18)	Grade 2 neutropenia (n=33)	Grade 3 neutropenia (n=5)	P value
Age, y					
Mean ± SD	50.4 ± 9.4	51.2 ± 12.4	55.1 ± 12.2	61.2 ± 6.3	0.274
Gender					
Female	8 (100%)	17 (94.4%)	32 (97%)	5 (100%)	1
Male	0	1 (5.6%)	1 (3%)	0	
Menopausal status					
Premenopausal	3 (37.5%)	5 (29.4%)	12 (37.5%)	0	0.264
Perimenopausal	0	5 (29.4%)	5 (15.6%)	0	
postmenopausal	5 (62.5%)	7 (41.2%)	15 (46.9%)	5 (100%)	
BMI					
Underweight	1 (12.5%)	2 (11.1%)	3 (9.1%)	2 (40%)	0.312
Normal weight	1 (12.5%)	6 (33.3%)	14 (42.4%)	1 (20%)	
Overweight	6 (75%)	6 (33.3%)	10 (30.3%)	2 (40%)	
Obesity	0	4 (22.2%)	6 (18.2%)	0	
Family history					
Negative	5 (62.5%)	14 (77.8%)	28 (84.8%)	5 (100%)	0.365
Positive	3 (37.5%)	4 (22.2%)	5 (15.2%)	0	
Laterality					
Right	2 (25%)	11 (61.1%)	21 (63.6%)	2 (40%)	0.045*
Left	4 (50%)	7 (38.9%)	12 (36.4%)	2 (40%)	
Bilateral	2 (25%)	0	0	1 (20%)	
Pathology					
IDC	6 (75%)	18 (100%)	31 (93.9%)	3 (60%)	0.019*
ILC	2 (25%)	0	2 (6.1%)	2 (40%)	
Tumor size					
T1	0	0	2 (6.1%)	0	0.729
T2	5 (62.5%)	6 (33.3%)	14 (42.4%)	1 (20%)	
T3	1 (12.5%)	5 (27.8%)	9 (27.3%)	3 (60%)	
T4	2 (25%)	7 (38.9%)	8 (24.2%)	1 (20%)	
Nodal involvement					
N0	0	0	3 (9.1%)	0	0.882
N1	6 (75%)	12 (66.7%)	17 (51.5%)	4 (80%)	
N2	2 (25%)	5 (27.8%)	12 (36.4%)	1 (20%)	
N3	0	1 (5.6%)	1 (3%)	0	
Distant metastasis					
M1	8 (100%)	18 (100%)	33 (100%)	5 (100%)	
DCIS					
Yes	4 (50%)	4 (22.2%)	13 (39.4%)	1 (20%)	0.456
No	4 (50%)	14 (77.8%)	20 (60.6%)	4 (80%)	
Lymphoplasmocytic infilteration					
Yes	2 (25%)	9 (50%)	8 (24.2%)	0	0.122
No	6 (75%)	9 (50%)	25 (75.8%)	5 (100%)	
Perineural invasion					
Yes	1 (12.5%)	6 (33.3%)	12 (36.4%)	3 (60%)	0.404
No	7 (87.5%)	12 (66.7%)	21 (63.6%)	2 (40%)	
Uni/Multicentric					
No	0	0	5 (15.2%)	0	0.008
Unicentric	7 (87.5%)	11 (61.1%)	27 (81.8%)	3 (60%)	
Multicentric	1 (12.5%)	7 (38.9%)	1 (3%)	2 (40%)	

SD, standard deviationL BMI, body mass index; DCIS, ductal carcinoma insitu; ER, estrogen receptor; PR, progesterone receptor; BRCA, breast cancer gene. *Significant p value <0.05.

Table 4. Continued

Variables	No neutropenia (n= 8)	Grade 1 neutropenia (n=18)	Grade 2 neutropenia (n=33)	Grade 3 neutropenia (n=5)	P value
ER					
Mild positivity	0	0	1 (3%)	0	0.609
Moderate positivity	5 (62.5%)	6 (33.3%)	17 (51.5%)	3 (60%)	
Strong positivity	3 (37.5%)	12 (66.7%)	15 (45.5%)	2 (40%)	
PR					
Negative	0	0	7 (21.2%)	0	0.077
Mild positivity	0	1 (5.6%)	1 (3%)	0	
Moderate positivity	7 (87.5%)	6 (33.3%)	12 (36.4%)	3 (60%)	
Strong positivity	1 (12.5%)	11 (61.1%)	13 (39.4%)	2 (40%)	
Ki 67					
Low expression	3 (37.5%)	13 (72.2%)	17 (51.5%)	2 (40%)	0.3
High expression	5 (62.5%)	5 (27.8%)	16 (48.5%)	3 (60%)	
BRCA12					
Negative	7 (87.5%)	17 (94.8%)	30 (90.9%)	4 (80%)	0.193
Positive	0	1 (5.6%)	3 (9.1%)	0	
Not detected	1 (12.5%)	0	0	1 (20%)	
Metastatic disease site					
Bone	7 (14.9%)	11 (23.4%)	28 (59.6%)	1 (2.1%)	0.009*
Brain	0	0	1 (100%)	0	1
Liver	1 (7.7%)	5 (38.5%)	7 (53.8%)	0	0.723
Lymph nodes	1 (12.5%)	2 (25%)	4 (50%)	1 (12.5%)	0.874
Lung	1 (4.2%)	5 (20.8%)	15 (62.5%)	3 (12.5%)	0.197
Local	0	1 (100%)	0	0	0.484
Number of metastatic sites					
1	6 (75%)	10 (55.6%)	18 (54.5%)	4 (80%)	0.949
2	2 (25%)	6 (33.3%)	8 (24.2%)	1 (20%)	
3	0	2 (11.1%)	5 (15.2%)	0	
4	0	0	2 (6.1%)	0	
Concomitant hormonal treatment					
Letrozole	8 (100%)	17 (94.4%)	30 (90.9%)	3 (60%)	0.144
Fulvestrant	0	1 (5.6%)	3 (9.1%)	2 (40%)	0.144

SD, standard deviationL BMI, body mass index; DCIS, ductal carcinoma insitu; ER, estrogen receptor; PR, progesterone receptor; BRCA, breast cancer gene. *Significant p value <0.05.

commonly causes neutropenia, a decrease in white blood cells that can increase the risk of infection. Neutropenia is the most frequent adverse event associated with Palbociclib and is often managed with dose reductions or treatment interruptions [1].

This study aims at identifying risk factors for Palbociclib induced neutropenia and detecting if Palbociclib induced neutropenia affects disease outcome and progression free survival. Sixty-four metastatic, hormone positive, her2neu negative breast cancer cases were included in the study and followed up for a median time of 30 months. Mean age among studied participants was 53.9 ± 11.8 years. Out of the 64 patients, there were 2 males and 62 females. Most of the cases were postmenopausal (51.6%), having right sided disease (56.3%). We found that most of cases has negative family history of malignancy (81%) . Our study showed that most cases has tumor size >2 and less than 5cm (T2 disease) . Most of cases are infiltrating duct carcinoma (71.6%) with N1 disease. The majority of cases are metastasized to bone (48 cases) followed by lung metastasis

In agreement with our finding, a study by Palmieri et al. [4] demonstrated that the median age was 57.0 years (range 24.3–90.9 years), 32% had visceral involvement and 66% had non-visceral involvement with 67% of those having bone-only metastasis. Another study by Lee et al. [5] showed that all patients were female, and the median age was 55 years (range 29–90 years), most patients had ECOG PS 0–1, visceral metastasis were seen in 58.7% of patients and non-visceral in 41.3%. Kim et al. [6] found that the median age was 54 years (range 28 - 87 years), and all the patients were women. There was 58.1% of patients with visceral metastasis while 23% with bone-only disease. These differences may be explained by

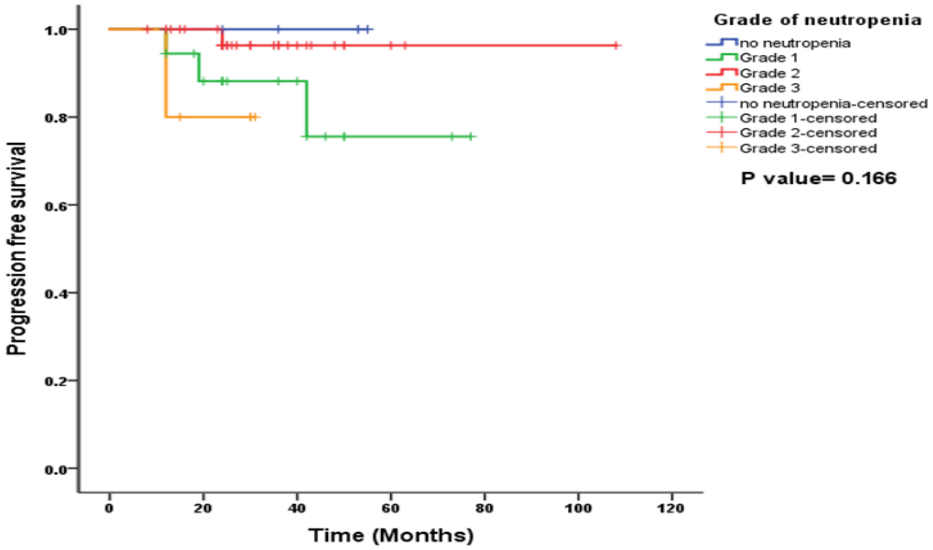

Figure 2. Kaplan Meier Curve of PFS Associated with Grade of Palbociclib Induced Neutropenia

different samplesize and different ethnicity

Our study found that 58 patients were treated with Palbociclib combined with letrozole (90.6%), whereas 6 patients (9.4%) were treated with Palbociclib along with fulvestrant. Neutropenia induced by Palbociclib occurred in 87.5% of cases, whereas 12.5% of cases did not experience neutropenia (8 cases).

Our study showed that 32.1% of the participants experienced grade I neutropenia, while 58.9% had grade II, and 8.9% had grade III neutropenia. A dose reduction of Palbociclib was implemented in 19 cases (29.7%) throughout the entire treatment duration. In patients with grade, I neutropenia, one patient (5.6%) had a dose reduction to 100mg, while for grade II, 7 patients (21.2%) received a dose of 100mg and another 7 patients (21.2%) received 75mg. Most cases of grade III neutropenia (80%) were reduced to 75mg. A significant statistical difference was found between the groups for bone metastasis (p value 0.009), with grade 2 neutropenia being the most common. Within the study group, one metastatic site per patient was the most common across all levels of neutropenia, although of no statistical significance. We found that there is a notable reduction in the WBC count following Palbociclib treatment compared to baseline values exhibiting grade I neutropenia, along with grade II and grade III neutropenia (p values <0.001, <0.001, <0.001, and 0.003, respectively).

Lee et al. [5] found that the initial dose of Palbociclib was 125 mg in 87.1% of patients, and the majority of patients (79.5%) used aromatase inhibitors as a part of their combined endocrine therapy, and 20.5% used fulvestrant. lee et al. [5] found that BSA and baseline myelosuppression, including WBC, ANC, and PLT, were associated with Palbociclib-induced early grade 3/4 NP

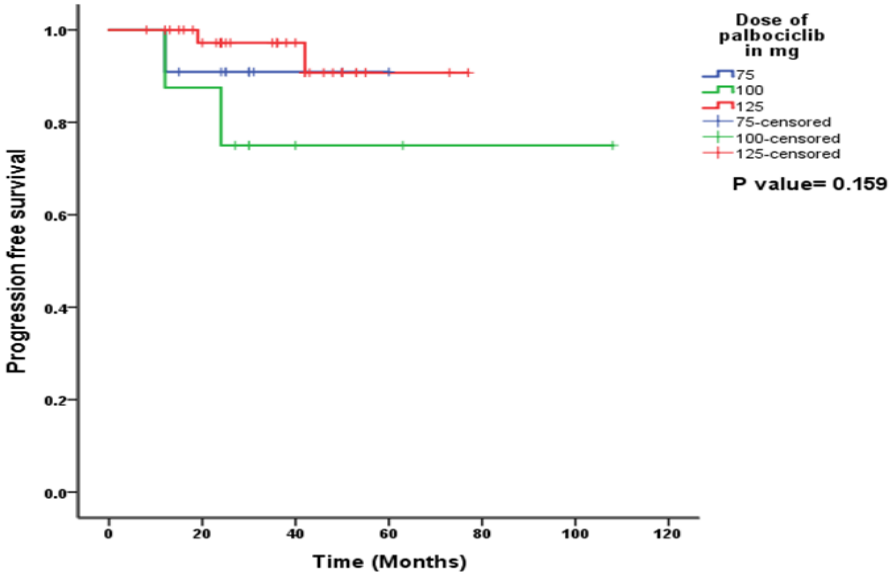

Figure 3. Kaplan Meier Curve of PFS Associated with Dose Adjustment of Palbociclib

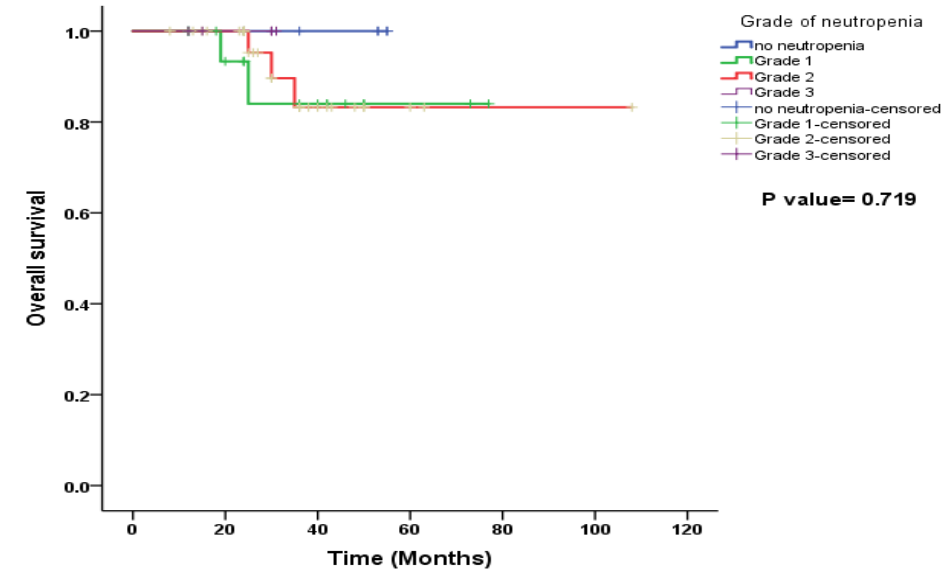

Figure 4. Kaplan Meier Curve of Overall Survival Associated with Grade of Palbociclib Induced Neutropenia

in patients with HR+/HER2− to metastatic breast cancer.

Rugo et al. [7] concluded that neutropenia was the most frequently reported any-grade adverse event with Palbociclib-letrozole (81.8% vs 6.3% with placebo-letrozole) .Most events in the palbociclib-letrozole arm were of grade 3 severity (57.4%); however, neutropenia rarely led to permanent study discontinuation. and febrile neutropenia was rare. Cristofanilli et al. [8] showed that grade 3 or 4 adverse events occurred in 73% in the fulvestrant plus palbociclib group .The most common grade 3 or 4 adverse events were neutropenia in the fulvestrant plus palbociclib , anaemia (ten and three), and leucopenia

As for survival and disease outcome , we concluded that no statistically significant difference was found based on neutropenia grades (p = 0.166, log rank). With the adjustment of the dose of Palbociclib, there was no statistically significant difference between the different doses (p value = 0.159).The 30 months PFS rate was 75% with the dose of 100mg, 90.9% with 75mg and 97.2% with the dose of 125mg. Median PFS has not reached.

Lee et al . [5] showed that the median PFS was 29.0 months (95% CI 22.00–35.99). There was no difference in median PFS between patients with and without early

Table 5. Univariate and Multivariate Logistic Regression for the Predictors of Palbociclib Induced Neutropenia

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.031 (0.965-1.101)	0.365		
Laterality				
Bilateral	Reference		Reference	
Left	10.5 (0.8-145.4)	0.079	6.966 (0.452-107.28)	0.164
Right	34 (2.1-554.7)	0.013*	17.769 (0.938-336.457)	0.055
Type of pathology				
ILC	Reference		Reference	
IDC	4.3 (0.7-28.9)	0.13	3.213 (0.309-33.451)	0.329
Bone only metastasis				
No	Reference			
Yes	0.357 (0.041-3.141)	0.353		
Perineural invasion				
No	Reference		Reference	
Yes	4.2 (0.482-36.565)	0.194	3.55 (0.346-36.414)	0.286
Lymphoblasmocytic infiltration				
No	Reference			
Yes	1.308 (0.239-7.149)	0.757		

OR, odds ratio; CI, confidence interval; ILC, infilterating lobular carcinoma; IDC, infilterating duct carcinoma; *Significant p value <0.05

Table 6. Univariate and Multivariate Cox Proportional Hazards Model of Progression Free Survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	0.967 (0.894-1.046)	0.405		
Number of metastatic sites	1.676 (0.685-4.102)	0.258		
Bone metastasis	0.248 (0.041-1.487)	0.127		
Lymph node metastasis	4.925 (0.822-29.514)	0.081	9.274 (1.153-74.593)	0.036*
Lung metastasis	7.073 (0.781-64.075)	0.082	5.108 (0.433-60.281)	0.195
Lymphoblasmocytic infilteration	2.890 (0.476-17.550)	0.249		
Perineural invasion	3.053 (0.507-18.378)	0.223		
Multicentric tumor	3.710 (0.668-20.621)	0.134		
Positive ER	4.663 (0.518-41.928)	0.169		
Positive PR	4.802 (0.591-39.019)	0.142		
Ki 67	1.070 (1.015-1.128)	0.012*	1.051 (1.001-1.103)	0.046*
BRCA12	3.982 (0.471-33.627)	0.204		
Dose of palbociclib	0.980 (0.942-1.019)	0.316		

OR, odds ratio; CI, confidence interval; ILC, infilterating lobular carcinoma; IDC, infilterating duct carcinoma; *Significant p value <0.05

grade 3/4 NP (p = 0.710). The PFS rates at 6 months and 12 months of the early grade 3/4 neutropenia group and non-early grade 3/4 group were 90.5% and 84.2%, and 73.7% and 73.3%, respectively. Elnaghi KAEA et al. [9] demonstrated that the median progression-free survival (PFS) of the study group was 22 months. No significant difference was observed in PFS according to the 1st cycle of neutropenia or grade of neutropenia. Similarly, no difference in PFS according to palbociclib dose reduction and HER2 low status was observed. Kim SG et al. [6] found a significant improvement in PFS in patients who were managed with palbociclib dose maintenance for a febrile grade 3 neutropenia within the first five cycles compared to that in patients with dose delay or reduction, suggesting that increasing the palbociclib dose using an aggressive dosing schedule can improve clinical outcomes. McAndrew et al. [10] reported a strong association between the early onset of neutropenia and PFS ; however, there was no difference in PFS among patients who experienced grade 3/4 neutropenia versus grade 2 or less in the PALOMA-3 study Finn et al. [11].

In conclusion, palbociclib induced neutropenia was significantly and independently associated with disease outcome , suggesting that neutropenia may be a useful guide in individualized Palbociclib dosing.

Study limitations

Several limitations can be considered in this study. It was a retrospective study, so some data were missing or underestimated. Also sufficient data could not be obtained about risk factors, comorbidities and concomitant drugs. Further studies with larger sample size are required to confirm these findings.

Author Contribution Statement

All authors were involved in planning the research and study design. Material preparation and data collection were performed by M.A and S.Y. Data analysis and interpretation of results were done by A.A& L.N . Statistical analysis was conducted by A.N . The paper draft was written by A.M.A and M.A. All authors reviewed and approved the final manuscript.

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Ethical approval statement

Concerning ethical considerations, an individual written consent was obtained from each patient participating in our study. This study was approved by the King Fahad Hospital-Hofuf . ; and its Institutional Review Board (IRB) approval number is number (H-05-HS-065), on May 14th, 2024. The drugs were supplied either by treatment decisions at state expense, or by health insurance.

Availability of data

All data generated and analyzed during this study can be accessed through direct communication with the corresponding author and the agreement of all research team members. Consent for publication Informed consent for publication was obtained from all participants in the study.

Consent for publication

Informed consent for publication was obtained from all participants in the study

Conflict of interest

the authors declare no conflicts of interest to disclose

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