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INCIDENCE OF PALBOCICLIB INDUCED NEUTROPENIA IN PATIENTS WITH ADVANCED OR METASTATIC BREAST CARCINOMA

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ABSTRACT **Background** Endocrine therapy is commonly used as the standard therapy for HR+/HER2− breast cancer. But due to acquired resistance, the combination of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors and endocrine therapy has led to change in the treatment guidelines for these patients. Haematological toxicity in the form of neutropenia is commonly associated with palbociclib treatment. **Materials and Methods** This study is retrospective observational hospital based study which includes total 88 HR+/HER2− advanced or metastatic breast cancer who were treated with palbociclib and endocrine therapy. We analyzed these patients data with respect to their age, menopausal status, co-morbid condition, ECOG PS and other disease and treatment related factors like disease status, metastatic sites, prior treatment details like chemotherapy/radiotherapy/endocrine therapy, blood test details, palbociclib cycles details including dose, dose reduction if done, start and end of treatment, details of occurrence of neutropenia.**Results** The median age at palbociclib treatment initiation was 59 years (range 39-76years). Most of the patients were postmenopausal (84.08%). Majority of the patients had good ECOG PS 0-1(68.17%) and only 9 patients showed ECOG PS 2-3. Most of the patients presented were in metastatic status at the time of treatment initiation (89.77%).The concomitant hormonal treatment was tab.letrozole 54.54%,Inj.Fulvestrant 29.54% and tab.tamoxifen 15.90%. Total 59 patients showed the decreased in neutrophil count from baseline on the day 15 from initiation treatment (grade I-23.86%, grade II-26.13%, grade III-17.04% and grade IV-1.1%) while 28 patients had normal neutrophil count(31.81%).39 patients had been advised for 1st reduction in the dose with neutropenia seen in 87.41% of these (grade I-40.9%, grade II-25%, grade III-19.31% and grade IV-2.2%).From these patients, 18 patients underwent further dose reduction to 75mg with neutropenia was seen in 88.63%(grade I-45.45%, grade II-30.68%, grade III-12.5%).**Conclusion** Palbociclib treatment, it is effective and safe treatment option for patients with hormone receptor–positive and human epidermal growth factor receptor 2–negative in advanced or metastatic breast cancer (HR+/HER2-).

KEYWORDS : Palbociclib, Neutropenia, Breast Cancer.

INTRODUCTION

Breast cancer remains one of the most commonly diagnosed cancers worldwide (1). In India, breast cancer tops the female-centric cancers, representing nearly 27% of all cancers India reports over 1.4 million cancer cases and 0.9 million cancer-related deaths annually. The available treatment options in metastatic breast carcinoma are highly depend in the molecular subtype (2).Approximately 60–65% of breast cancer cases are hormone receptor-positive (HR+) and human epidermal growth factor 2-negative (HER2−) (3). Endocrine therapy which acts on the estrogen signaling pathway is commonly used as the standard therapy for HR+/HER2− breast cancer. But sometimes acquired resistance is seen in most of the patients with hormonal therapy, hence newer treatment approach is needed (4,5).

The combination of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors and endocrine therapy has led to change in the treatment guidelines for the patients with hormone receptor–positive and human epidermal growth factor receptor 2–negative advanced or metastatic breast cancer (HR+/HER2-) (6,7). This treatment option has significantly increased progression-free survival (PFS) and overall survival (OS) in above mentioned patients (8). Palbociclib, ribociclib, and abemaciclib are the reversible small molecular inhibitors of CDK 4 and 6. They act by blocking the cyclin D and CDK4/6 which inhibit the phosphorylation of retinoblastoma and cell proliferation and thus preventing cell cycle progression from G1 to S phase (9). Palbociclib is a first CDK4/6 inhibitor which is approved in combination with endocrine therapy for patients with HR+/HER2–(10). In PALOMA-2 and PALOMA-3 clinical trials, the efficacy and safety of palbociclib in combination with an aromatase inhibitor as first-line treatment or with fulvestrant in patients with disease progression following endocrine therapy was demonstrated respectively (9,11).

The most common side effect of palbociclib is myelosuppression specifically neutropenia. In studies, the incidence rate of neutropenia was observed in 80% of cases with grade 3/4 observed in 66% (9,11). It was reported to occur most frequently within the first 2 months of palbociclib treatment (12). Though the incidence of neutropenia was high, the incidence of febrile neutropenia was low and also the rate of permanent treatment discontinuation due to neutropenia was low as Palbociclib-induced neutropenia was rapidly reversible when discontinued. An increased incidence of neutropenia may have negative effects on quality of life of patients. The objective of this study to find out the incidence of palbociclib induced neutropenia in patients with hormone receptor–positive and human epidermal growth factor receptor 2–negative in advanced or metastatic breast cancer (HR+/HER2-).

Material and Methods

We retrospectively analysed total 807 breast cancer patients who were registered and treated at our institute from January 2021 to March 2026. This study was approved by the institutional review board. All female patients who were diagnosed with advanced or metastatic breast cancer with confirmation of hormone receptor–positive and human epidermal growth factor receptor 2–negative (HR+/HER2-) histology and treated with Palbociclib for atleast 3 cycles or discontinued treatment within 3 cycles due to haematological toxicity were included in the study. The patient's demographic characteristics including age, menopausal status, co-morbid condition, eastern cooperative oncology group performance status (ECOG PS) were collected. Other information about disease and treatment related factors like disease status, metastatic sites,prior treatment details like chemotherapy/radiotherapy/endocrine therapy, blood test details, palbociclib cycles details including dose, dose reduction if done, start and end of treatment, details of occurrence of neutropenia also collected.

Patients were treated with Tab.Palbociclib with combination with either aromatase inhibitor (Tab.Letrozole 2.5mg OD) or Inj.Fulvestrant (500 mg was administered intramuscularly on 1st,15th,29th day and then monthly for subsequent cycles) or LHRH agonist (Tab.Tamoxifen 20mg OD). Tab.Palbociclib 125mg was given once daily on a schedule of 3 weeks followed by 1 week off, administered orally. To asses the haematological toxicity the presence of neutropenia was identified. The dose modification in Palbociclib was done according to grading of neutropenia. According to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 6.0. Grades 1 and 2 neutropenia were defined as absolute neutrophil counts <1500 to1000/m3 and <1000 to 500/m3, respectively while Grades 3 and 4 neutropenia were defined as absolute neutrophil counts <500 to1000/m3 and <100/m3, respectively. Patients who developed grade 2 neutropenia (without fever/infection), the next cycle of palbociclib treatment was advised to start with same dose when ANC recovered to ≥1000/m3 and in patients with grade 3 neutropenia or grade 2 with fever and/or infection,

palbociclib was withheld until ANC recovered to ≥1000/m3 and then the next cycle of palbociclib treatment was advised to resume with next lower dose. Patients who developed grade 4 neutropenia were advised to discontinued the treatment.

RESULT

A total 88 patients with advanced or metastatic breast cancer with confirmation of hormone receptor–positive and human epidermal growth factor receptor 2–negative (HR+/HER2-) histology and treated with Palbociclib were included in the study. The median age at palbociclib treatment initiation was 59 years (range 39-76years). Maximum patients were in the range of 61-70 years (42.04%). The patients demographic profile is shown in table1.

Table 1: Patients demographic profile

Sr.no	Characteristics	No of patients	Percentage
1	Age at palbociclib initiation		
	<40-50	23	26.13%
	51-60	27	30.68%
	61-70	31	42.04%
	>70	07	7.95%
2	Menopausal status		
	Premenopausal	14	15.90%
	postmenopausal	74	84.08%
3	Co-morbidity		
	Yes	51	57.95%
	No	37	42.04%
4	Ecog PS		
	0	24	27.27%
	1	36	40.90%
	2	19	21.59%
	>3	09	1.02%

Most of the patients were postmenopausal (84.08%) while only 14 patients were premenopausal. Majority of the patients had good ECOG PS 0-1(68.17%) and only 9 patients showed ECOG PS 2-3. Most of the patients presented with metastatic status at the time if treatment initiation (89.77%) while only 9 patients were with advanced but non metastatic status.Total 62 patients were with visceral metastasis and 17 patients were with non visceral metastasis. In prior treatment history, 52.27% patients received chemotherapy and only 6.81% received radiation.The concomitant hormonal treatment was tab.letrozole 54.54%,Inj.Fulvestrant 29.54% and tab.tamoxifen 15.90%. The disease and treatment characteristics are shown in table 2.

Table 2: The disease and treatment characteristics

Sr.no	Characteristics	No of patients	Percentage
1	Disease status		
	Advanced but non metastatic	09	10.22%
	metastatic	79	89.77%
2	Metastatic sites		
	Visceral	62	70.45%
	Non visceral	17	19.31%
3	Prior treatment		
	Chemotherapy	46	52.27%
	Radiation	06	6.81%
	Both	20	22.72%
	No treatment	16	18.18%
4	Concomitant hormonal treatment		
	Letrozole	48	54.54%
	Tamoxifen	26	29.54%
	fulvestrant	14	15.90%

Tab.Palbociclib was started with dose of 125mg for all 88 patients. From these patients 1st dose reduction to 100mg was done in total 39 patients (44.31%) because of high grade neutropenia during their palbociclib treatment. With continuing this dose some patients developed further high grade neutropenia resulting in 2nd dose reduction to 75mg in next 18 patients(20.45%).The dose reduction details are shown in table 3.

Table 3: palbociclib dose reduction

Dose	No of patients	Percentage
Started 125mg	88	100%
1st reduction to 100mg	39	44.31%
2nd reduction to 75mg	18	20.45%

Total 59 patients showed the decreased in neutrophil count from baseline on the day 15 from initiation treatment (grade I-23.86%, grade II-26.13%, grade III-17.04% and grade IV-1.1%) while 28 patients had normal neutrophil count(31.81%).39 patients had been advised for 1st reduction in the dose with neutropenia seen in 87.41% of these (grade I-40.9%, grade II-25%, grade III-19.31% and grade IV-2.2%).From these patients, 18 patients underwent further dose reduction to 75mg with neutropenia was seen in 88.63%(grade I-45.45%, grade II-30.68%, grade III-12.5%).The hematological toxicity is showed in table 4.

Table 4: Haematological toxicity

Dose	125mg	100mg	75mg
Cycle day	C1D15	C1D1	C1D1
No neutropenia	28(31.81%)	11(12.5%)	10(11.36%)
Grade I	21(23.86%)	36(40.9%)	40(45.45%)
Grade II	23(26.13%)	22(25%)	27(30.68%)
Grade III	15 (17.04%)	17(19.31%)	11(12.5%)
Grade IV	1(1.1%)	02(2.2%)	0

After starting the palbociclib, the median progression free survival was 21.4months while 38% patients showed progression during the treatment.

DISCUSSION

This study showed the incidence of neutropenia during the palbociclib treatment in patients with hormone receptor–positive and human epidermal growth factor receptor 2–negative in advanced or metastatic breast cancer (HR+/HER2-).Haematological toxicity specifically neutropenia is very common from the first cycle of palbociclib. Total 59 patients (68.13%) showed the decreased in neutrophil count from baseline on the day 15 from initiation treatment. One study done previously showed the similar (69%) decreased in neutropenia (13).Though the incidence of neutropenia was significant, there was no any incidence of febrile neutropenia in the patients. So no any patients underwent treatment discontinuation due to same. In previous one study, they also showed no treatment discontinuation because of febrile neutropenia(14). Almost 44.31% patients underwent 1st dose reduction because of high grade neutropenia during their palbociclib treatment and further 20.45% patients underwent subsequent dose reduction. But PFS findings from two studies found that dose modifications due to neutropenia do not appear to negatively impact the efficacy of palbociclib.In PALOMA-2 study showed that PFS was similar in patients treated with palbociclib with letrozole who experienced dose reductions and those who did not(15). In PALOMA-3, PFS of patients receiving palbociclib with fulvestrant was same for those who had one or more dose reductions due to neutropenia and those without any dose reduction (16). In this study, the median progression free survival was 21.4months while 38% patients showed progression during the treatment.

In conclusion, though the haematological toxicity in the form of neutropenia is major side effect of palbociclib treatment, it is effective and safe treatment option for patients with hormone receptor–positive and human epidermal growth factor receptor 2–negative in advanced or metastatic breast cancer (HR+/HER2-).

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