



SAFETY PROFILE OF PALBOCICLIB IN ELDERLY PATIENTS WITH HORMONE RECEPTOR-POSITIVE/HER2 NEGATIVE METASTATIC BREAST CANCER: REGIONAL CANCER CENTER EXPERIENCE IN SOUTH INDIA

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Abstract:

Aim: Palbociclib plus endocrine therapy recommended for metastatic hormone receptor positive/human epidermal growth factor receptor 2-negative (HER2 -) breast cancer regardless of age. Prevalence of advanced cancer is more in elderly population, patients age > 65 years usually treated with conservative approach considering the toxicity of aggressive curative intent. These patients are rarely included in clinical trials. This study evaluated the safety profile of palbociclib in elderly patients treated in regional cancer centre in south india.

Materials and methods: Retrospective analysis of elderly patients age > 65 years treated with palbociclib plus letrozole for metastatic hormone receptor positive/ human epidermal growth factor receptor 2-negative (HER2 -) breast cancer treated in regional cancer institute, Madras medical college, Chennai. Safety profile analysed with CTCAE version 4 criteria.

Results: 43 patients details analysed between January 2021 to December 2023. Median age of 68 years. 90% patients had adverse events any grade, 81.3 % had any grade neutropenia, 58.1% had grade 3-4 neutropenia. These adverse events well managed with supportive care measures, dose delays and dose reductions.

Conclusion: Patients aged more than 65 years tolerated palbociclib well in patients with the metastatic hormone receptor-positive/Her2 negative subtype. Addition of palbociclib to endocrine therapy should be evaluated in elderly and frailer patients individually

Keywords: Metastatic breast cancer, elderly patients, palbociclib ,toxicity profile

Introduction:

According to the Global Cancer Observatory India 2022, breast cancer is the most common cancer, with 192 020 cases (13.6%). The mortality rate is 10.7%. Breast cancer is a major public health issue.

There are multiple causes of breast cancer, such as estrogen hormone exposure, lifestyle, and molecular and genetic factors. Because of disease heterogeneity and various subtypes, such as luminal A, B, and HER2 enriched, triple-negative, treatment options and prognoses differ (1-3).

The WHO predicted that 1.5 billion people are aged more than 65 years by the year 2050. India has experienced an exponential increase in the elderly population (8.6% in 2011 to 19.5% in 2050). The majority of elderly cancer patients are not evaluated with a validated systemic assessment tool. Advanced age over 65 years is a risk factor for cancer. 60% new cancer incidence and 70% cancer mortality. The relative risk of breast cancer increases by 5.8 times in women aged 65 years and above (2). The incidence of hormone receptor-positive and Her2neu-negative breast cancer also increases with increasing age (4). The geriatric population with good performance status and fewer comorbid should be treated identically to their young counterparts. Geriatric patients with multiple comorbidities and frailty statuses should not be treated with aggressive intent because it may affect quality of life and the survival rate of patients. Other factors, such as social and cognitive function, affect treatment options and patient compliance. Because of this worrying concern, patients aged more than 65 years are not treated with aggressive intent, resulting in a negative survival rate (5,6). The rationale for a more conservative approach is that older breast cancer patients are more hormone receptor positive and are usually managed with hormonal therapy alone.

Palbociclib, an oral CDK4/6 inhibitor (a cyclin-dependent kinase 4/6 inhibitor), inhibits the G1–S phase. A randomized phase III trial (PALOMA 1-3) demonstrated that palbociclib plus endocrine therapy was associated with good progression-free survival compared with endocrine therapy alone in hormone receptor-positive/HER2-negative metastatic breast cancer patients (7-9). Geriatric populations are usually underrepresented in clinical trials because of advanced age and comorbidities. The percentage of patients aged > 65 years in the PALOMA trials was approximately 45%, suggesting that palbociclib is well tolerated in older patients with manageable toxicities. Palbociclib plus letrozole did not show overall survival benefit in phase III trial. Based on trial results palbociclib approved in all age group (10). Rugo et al, pooled analysis of PALOMA trials 1-3 showed that palbociclib is well tolerated in elderly patients (11-12).

The objective of this study was to evaluate the safety profile of palbociclib in elderly patients with hormone receptor-positive/ human epidermal growth factor receptor 2-negative (HER2 -) metastatic breast cancer treated in our regional cancer centre, Madras Medical college, Chennai from January 2021 to December 2023.

Methods:

A retrospective study analysed at our institute, Madras Medical College Chennai, Department of Medical Oncology, from January 2022 to December 2023. The objective of this study was to evaluate the safety profile of palbociclib in elderly patients older than 65 years. No proper age definition for elderly population in literatures, different study used age cut off over 65 years (13). In this study, we used an age cut-off of more than 65 years as the elderly population. Eligibility criteria included were elderly patients with hormone receptor-positive/ human epidermal growth factor receptor 2-negative (HER2 -) metastatic breast cancer treated endocrine therapy (letrozole 2.5mg) daily plus the recommended tablet palbociclib dose of 125 mg once daily for 3 weeks and then 1 week off. The palbociclib dose was reduced to 100 mg or 75 mg on the basis of adverse event grade. Cycles continued until disease progression or unacceptable toxicity. Geriatric assessment data and performance status data retrieved from patient medical records. G8 score based on questionnaire scale (score 0–17) on the basis of age, poly pharmacy, body mass index, neuropsychological problems, mobility, weight loss, decline in food intake, indigestion or swallowing difficulties, and patient functional status compared with their age groups. A comprehensive geriatric assessment done in patients if the G8 score was less than or equal to 14. The safety profiles of palbociclib and drug-related adverse events were collected and graded according to the CTCAE version 4.0 National Cancer Institute Common Terminology criteria for adverse events.

Results:

During the 24 -month study period from January 2022 --December 2023, 43 patients were analysed. Patient characteristics are listed in Table 1. The median age of the patients was approximately 68 years, and 65% were > 65 years to 70 years. Compared with de novo metastatic disease, recurrent disease contributes the majority of cases (67.44% and 32.5%, respectively). The previously administered endocrine therapy regimens included letrozole (60%), tamoxifen (28%) and exemestane (12%). The previously administered chemotherapy regimens included taxanes (55%), eribulin (20%), capecitabine (15%) and others, such as vinorelbine and anthracycline, which were administered to 10% of the patients. The most common adverse event was neutropenia (any grade 81.3%, grade 3--4 58.1%), and one patient developed febrile neutropenia. These adverse events are well manageable with supportive care measures. The recommended protocols for the management of haematological toxicities are dose delays and dose reduction strategies in geriatric groups. Majority of the patient 83% started with standard dose of 125 mg. Seven patients started with reduced dose 100 mg. Twenty patients (46.5%) received reduced doses due to adverse events. Dose reductions mainly due to haematological toxicity 75% .

Patient Characteristics Table 1

S.NO	CHARACTERSTICS (n= 43)	NUMBER (%)
AGE	MEDIAN	68 years (65.2 – 78.8)
	> 65 – 70 YEARS	28 (65.11%)
	> 70	15 (34.88%)
Metastatic disease	De novo metastatic disease	14 (32.55%)
	Recurrent Disease	29 (67.44%)
ECOG Score	0-1	35 (81.3%)
	>2	8 (18%)
G8 Score	>14	32 (74.4%)

Adverse events during palbociclib plus letrozole treatment. Table 2

Adverse events	Any Grade	Grade 3-4 (%)
All	39 (90%)	30 (69.7 %)
Neutropenia	35 (81.3%)	25 (58.1%)
Febrile Neutropenia	2 (4.6%)	2 (4.6%)
Anemia	12(27.9%)	2 (4.6%)
Thrombocytopenia	9 (20%)	2 (4.6%)
Asthenia	6 (13.9%)	0
Nausea	5 (11.6%)	0
Anorexia	5 (11.6%)	0
Diarrhea	4 (9.3%)	0
Skin rash	2 (4.6%)	0
Alopecia	2 (4.6%)	0

Discussion:

With promising results in the PALOMA trial, palbociclib plus endocrine therapy in hormone receptor-positive/HER2-negative metastatic breast cancer patients improved outcomes with manageable adverse events. CDK 4/6 inhibitors (palbociclib, abemaciclib, and ribociclib) have become the standard of care for first- and second-line patients who are hormone receptor

positive/HER2 negative. There are limited data concerning toxicity in the elderly population. The incidence of Grade 3-4 adverse events in the PALOMA trial ranged from 73%-75%, with neutropenia most commonly reported. An elderly patient in the PALOMA pooled analysis by Rugo et al reported 90% all-grade adverse events and 73% grade 3-4 adverse events. Another pooled analysis by the FDA revealed that 88% of grade 3-4 adverse events occurred at more than 75 years of age, which led to palbociclib dose reduction/interruption in 81% and permanent discontinuation in 32% of the patients. A meta-analysis also revealed an increased frequency of neutropenia in elderly patients, and other adverse events were leukopenia, anaemia, asthenia and infections (14). The safety analysis results of PALOMAGE revealed at least one adverse event in 70% of patients and 43% of grade 3-4 adverse events. The most frequent toxicity was neutropenia (43.2%). The study included patients older than 70 years, and the median age was approximately 79 years. A total of 68.3% of patients had G8 scores less than 14 and Eastern Cooperative Oncology Group (ECOG) performance scores greater than 2 in 17.9% of the patients (15).

The geriatric population with good performance status and fewer comorbid is more likely to benefit from the addition of palbociclib. In contrast, frail elderly patients are likely to suffer from more toxicity; thus, customized treatment strategies are needed for this group because quality of life is more important than survival. There is a higher incidence of neutropenia in this frail subset. Even though it has manageable toxicity, it may worsen the general condition of elderly patients. Finally, functional age is more important than chronological age (16). Palbociclib should be considered in fit patients who need treatment benefits (17).

The limitation of this study are, retrospective design which might have bias in selection or patient information. Prospective geriatric and larger study population define safety of CDK4/6 in elderly and frail population. Other study limitations were the small study sample (n=43). Prospective geriatric and larger study population define safety of CDK4/6 in elderly and frail population. The safety profiles of palbociclib were not compared with those of younger age subgroups that received palbociclib. Autonomy evaluation and health-related quality-of-life events were not evaluated.

Conclusion:

Patients aged more than 65 years tolerated palbociclib well in patients with the metastatic hormone receptor-positive/ human epidermal growth factor receptor 2-negative (HER2 -) subtype. The most common adverse events were neutropenia, which was well managed with dose reduction/interruption, and symptomatic supportive care. The frail population group needed to receive customized treatment options from a treating physician with close monitoring of adverse events. With careful geriatric assessments and good performance status, palbociclib plus endocrine treatment is recommended for patients with the metastatic hormone receptor-positive/HER2 negative subtype.

Declarations:

Funding: None

Conflict of Interest: Nil

Ethical approval: The study was approved by the Institutional Ethics Committee

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