Journal of Geriatric Oncology 14 (2023) 101604

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

journal homepage: www.elsevier.com/locate/jgo

Research Paper

PROPSEA, safety evaluation of palbociclib and ribociclib in older patients with breast cancer: A prospective real-world TOG study

Okan Avcı [a,*], Yakup İriağaç [a], Eyyüp Çavdar [a], Kubilay Karaboyun [a], Murat Araz [b], Teoman Şakalar [c], Ezgi Değerli [d], Özlem Özdemir [e], Ali İnal [f], Birol Ocak [g], Müslih Ürün [h], Abdullah Sakin [i], Seher Yıldız Tacar [j], Mehmet Zahid Koçak [b], Hacer Demir [k], Özden Özer [l], Eda Tanrıkulu Şimşek [m], Mustafa Ersoy [n], Yusuf Karakaş [o], Rukiye Arıkan [p], Onur Eşbah [q], Sercan Ön [r], Elif Şenocak Taşçı [s], Nil Molinas Mandel [t], Sema Türker [u], Turgut Kaçan [v], Hasan Çağrı Yıldırım [w], Özkan Alan [x], Sinem Akbaş [y], Gülhan İpek Deniz [z], Özlem Aydın İsak [aa], Halil Taşkaynatan [ab], Erdoğan Selçuk Şeber [a]

[a] *Tekirdağ Namık Kemal University, Faculty of Medicine, Department of Medical Oncology, Tekirdağ, Türkiye*
[b] *Necmettin Erbakan University, Faculty of Medicine, Department of Medical Oncology, Konya, Turkiye*
[c] *Kahramanmaraş Necip Fazıl City Hospital, Kahramanmaraş, Türkiye*
[d] *İstanbul University, Cerrahpaşa Faculty of Medicine, Department of Medical Oncology, İstanbul, Türkiye*
[e] *İzmir Bozyaka Training and Research Hospital, Department of Medical Oncology, İzmir, Türkiye*
[f] *Mersin City Hospital, Mersin, Türkiye*
[g] *Bursa Uludağ University, Faculty of Medicine, Department of Medical Oncology, Bursa, Türkiye*
[h] *Eskişehir City Hospital, Department of Medical Oncology, Eskişehir, Türkiye*
[i] *Van Yüzüncü Yıl University, Faculty of Medicine, Deparment of Medical Oncology, Van, Türkiye*
[j] *Dr. Sadi Konuk Training and Research Hospital, Department of Medical Oncology, İstanbul, Türkiye*
[k] *Afyon Health Sciences University, Department of Medical Oncology, Afyon, Türkiye*
[l] *Dokuz Eylül University, Faculty of Medicine, Department of Medical Oncology, İzmir, Türkiye*
[m] *Haydarpaşa Numune Training and Research Hospital, Department of Medical Oncology, İstanbul, Türkiye*
[n] *Eskişehir Osmangazi University, Faculty of Medicine, Department of Medical Oncology, Eskişehir, Türkiye*
[o] *Mehmet Ali Aydınlar Acıbadem University, Bodrum Hospital, Department of Medical Oncology, Muğla, Türkiye*
[p] *Marmara University, Faculty of Medicine, Department of Medical Oncology, İstanbul, Türkiye*
[q] *Düzce University, Faculty of Medicine, Department of Medical Oncology, Düzce, Türkiye*
[r] *Ege University, Faculty of Medicine, Department of Medical Oncology, İzmir, Türkiye*
[s] *Mehmet Ali Aydınlar Acıbadem University, Faculty of Medicine, Department of Medical Oncology, İstanbul, Türkiye*
[t] *Koç University, American Hospital, Department of Medical Oncology, İstanbul, Türkiye*
[u] *Zonguldak Atatürk State Hospital, Department of Medical Oncology, Zonguldak, Türkiye*
[v] *Bursa Yüksek İhtisas Training and Research Hospital, Department of Medical Oncology, Bursa, Türkiye*
[x] *Tekirdağ Dr. Fehmi Cumalıoğlu City Hospital, Department of Medical Oncology, Tekirdağ, Türkiye*
[w] *Hacettepe University, Faculty of Medicine, Department of Medical Oncology, Ankara, Türkiye*
[y] *Koç University, Faculty of Medicine, Department of Medical Oncology, İstanbul, Türkiye*
[z] *Private Tansan Outpatient Clinic, Department of Medical Oncology, İstanbul, Türkiye*
[aa] *Dışkapı Yıldırım Beyazıd Training and Research Hospital, Department of Medical Oncology, Ankara, Türkiye*
[ab] *İzmir Private Ege City Hospital, Department of Medical Oncology, İzmir, Türkiye*

ARTICLE INFO

Keywords:
Geriatrics
CDK 4/6 inhibitors
Breast cancer
Adverse events

ABSTRACT

Introduction: In this study, the toxicities and management of palbociclib and ribociclib in older patients (≥65 years) with metastatic breast cancer patients were investigated.
Materials and Methods: Among older patients receiving palbociclib and ribociclib, Geriatric 8 (G8) and Groningen Frailty Index were used to evaluate frailty status. Dose modifications, drug withdrawal and other serious adverse events (SAEs) were recorded and analyzed according to baseline patient characteristics.

* Corresponding author.
E-mail address: drokanavci@gmail.com (O. Avcı).

https://doi.org/10.1016/j.jgo.2023.101604
Received 19 December 2022; Received in revised form 21 March 2023; Accepted 14 August 2023
Available online 6 September 2023

Results: A total of 160 patients from 28 centers in Turkey were included (palbociclib = 76, ribociclib = 84). Forty-three patients were ≥ 75 years of age. The most common cause of first dose modification was neutropenia for both drugs (97% palbociclib, 69% ribociclib). Liver function tests elevation (10%) and renal function impairment (6%) were also causes for ribociclib dose modification. Drug withdrawal rate was 3.9% for palbociclib and 6% for ribociclib. SAEs were seen in 11.8% of those taking palbociclib and 15.5% of those on riboclib. An ECOG performance status of ≥2 and being older than 75 years were associated with dose reductions. Severe neutropenia was more common in patients with non-bone-only metastatic disease, those receiving treatment third-line therapy or higher, coexistance of non-neutropenic hematological side effects (for ribociclib). Neutropenia was less common among patients with obesity.
Discussion: Our results show that it can be reasonable to start palbociclib and ribociclib at reduced dose in patients aged ≥75 years and/or with an ECOG performance status ≥2.

1. Introduction

Advanced age is a major risk factor for breast cancer (BC), and its incidence and prevalence will increase in the next years due to the increasing lifespan of the population. Although significant progress has been made in the diagnosis and treatment of BC, older women still account for the majority of deaths. Older adults are historically underrepresented in clinical trials. Furthermore, older patients in clinical trials may be fitter and not necessarily representative of the real population. Because of these differences, physicians in the oncology field also need "real-world" data when deciding how to treat BC in older patients.

Cyclin-dependent kinase-4 and 6 (CDK4/6) play key roles in cell proliferation. The cyclin D1–CDK4/6–RB1 complex is the major mediator of cellular proliferation mediated by estrogen signaling. Dysregulation of D-CDK4/6-retinoblastoma pathway has been implicated in BC biology [1,2]. Selectively inhibiting CDK4/6 causes cell cycle arrest in the G1 phase, resulting in reduced cell viability and tumor response. Pivotal studies [3–5] of the approved CDK4/6 inhibitors, palbociclib (Pb), ribociclib (Rb), and abemaciclib established the combinatorial strategy of endocrine therapy plus targeted therapy as the preferred treatment approach for most patients with HR-positive and HER2-negative metastatic BC. For many years, those patients were destined to receive chemotherapy with a considerable toxicity burden and minimal activity.

Treatment for older patients with BC should not be based on age alone. The Comprehensive Geriatric Assessment (CGA) is recommended by the International Society of Geriatric Oncology (SIOG) to improve the detection of problems and guide the oncologist in treatment decision-making [6]. However, completing a full CGA may be time-consuming for the patient and the health care professional and this limits its use in everyday practice. Geriatric 8 (G8) and Groningen Frailty Indicator (GFI) stand out as two scales that are easy to apply and have high sensitivity and specificity (respectively) when compared to CGA. Both tests have been previously studied in older patients with breast cancer and have shown their accuracy [7,8].

In this prospective cohort study, the side effects and dosage of CDK 4/6 inhibitors palbociclib and ribociclib, which are increasingly used in older patients with BC, were investigated. The effects of frailty on adverse events, drug tolerability, and treatment compliance were also evaluated using both the G8 and the GFI.

2. Methods

2.1. Study Design and Population

The study was designed as prospective observational and multicenter cohort. Patients with metastatic HR-positive HER2-negative BC who were started on CDK 4/6 inhibitor drugs palbociclib or ribociclib were included. Abemaciclib, which is not reimbursed in Turkey, was excluded. The study was conducted between August 2021 and September 2022. It was approved by a central institutional review board and registered in ClinicalTrials.gov (identifier: NCT05051956). The study was performed in accordance with good clinical practice guidelines and following the recommendations of the Declaration of Helsinki. Patients were enrolled at 28 sites within Turkey, balanced for practice volume and geographic location. All patients were ≥ 65 years old and signed informed consent to participate in the study.

2.2. Data Collection and Assesments

Patients were followed during the first six months of treatment or earlier if the drug was discontinued because of disease progression or drug-related toxicity. Side effect management was left to the physician's preference. G8 and GFI scales were completed by the patient or a first-degree relative at the beginning of the study. Baseline information including whether it was a recurrent or de novo disease when starting the study drug, body surface area (BSA), Eastern Cooperative Oncology Group Performance Status (ECOG-PS), other medications used, comorbid diseases, and metastatic sites were obtained. Patients taking five drugs or more were considered to have polypharmacy. Considering the myelosuppressive effects, the patients were questioned whether they had received chemotherapy in the last six months. The preferred CDK 4/6 inhibitor, starting dose, and combination endocrine therapy were recorded. The first side effect that caused a dose modification was recorded, as weill as side effect management (dose reduction vs. interruption). The same data was obtained for side effects causing a second dose modification. Among the general side effects, anemia, thrombocytopenia, diarrhea, liver function test (LFT)'s elevation, renal function impairment, fatique, emesis, other side effects (as defined by the physician) and Qtc prolongation were recorded. LFT's elevation was defined as aspartate aminotransferase and alanine aminotransferase elevations, renal function impairment was defined as creatinin elevation in blood tests. Febrile neutropenia, emergency room (ER) admissons/hospitalization related with adverse event of study drug, infection requiring antibiotic use, and drug discontinuation were defined as 'serious adverse events' (SAEs). Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (v5.0).

2.3. The G8 Questionnaire

The G8 questionnaire is a screening tool for geriatric syndromes in oncology [9,10]. This frailty screening tool, which was developed based on the MNA and age, consists of eight items concerning multiple geriatric domains, including nutritional status, physical capacity, mood, and polypharmacy. It is an easy-to-use screening tool with a total score ranging from zero to seventeen. In a prospective multicentric cohort study, G8 was evaluated in 364 cancer patients older than 70 years prior to chemotherapy [9]. Results suggested that the area under the curve was maximized when the threshold was 14, equivalent to a 90% sensitivity, and a 60% specificity. Based on these findings, we used a G8 cut-off score of ≤14 to define an abnormal screening test. The validity and reliability study of G8 in the Turkish language was previously reported by Atakul et al. [11], with a Cronbach's alpha coefficient of 0.655.

2.4. The Groningen Frailty Indicator

The GFI was developed as a screening instrument for the level of frailty in geriatrics that specifically also included psycho-social components. The GFI screens for the loss of functions and resources in four domains of functioning: physical (mobility functions, multiple health problems, physical fatigue, vision, hearing), cognitive (cognitive functioning), social (emotional isolation), and psychological (depressed mood and feelings of anxiety). The total score ranges from 0 to 15, with a higher score indicating more serious frailty. In the original GFI, a score of 4 and above indicated frailty [12,13]. Thus, like the G8, a distinct cut-off point is an advantage of the GFI. This tool has already been used in various patient groups, including older patients with cancer [14–17]. The Turkish validation of the GFI was performed by Aygör et al. [18]. Cronbach Alpha coefficient was 0.72. For GFI, when the threshold value is accepted as ≥3, the sensitivity is 87%, the specificity is 70%, and when it is ≥4, the sensitivity is 66%, while the specificity is 87% [19]. Since the GFI test was included in the study considering its specific feature, the cut-off point was accepted as ≥4 to define frailty.

2.5. Statistical Analysis

Descriptive statistics were used in the study. Non-normally distributed continuous variables were presented as median ± range. Relationships between categoric variables were analyzed with the Chi-Square test. All analyses were carried out using the Statistical Package for Social Sciences, version 25.0 (SPSS, Chicago, IL). Two-tailed *P*-values < 0.05 were considered statistically significant.

3. Results

A total of 160 patients were included; 76 patients received palbociclib and 84 ribociclib (the two drugs will be presented in this order unless otherwise stated). A total of 43 (26.9%) patients were 75 years or older [(19 (25%) and 24 (28.6%) respectively]. Thirty-two (44.4%) and 33 (40.7%) patients were obese (BMI ≥30), and 14 (18.6%) and 10 (11.9%) had an ECOG-PS of ≥2. Polypharmacy was seen in 9 (13.4%) and 11 (14.5%) patients. Forty-two (55.2%) and 53 (63.2%) patients used the study drug as a second line therapy or higher. Visceral metastatic disease was present in 42 (55.3%) and 41 (48.8%) patients. Among the whole patient group, the hormonal treatment for those with bone-only disease were fulvestrant 31 (54.4%) and letrozole 26 (45.6), and the treatment for those with visceral metastases was fulvestrant 51 (61.4%) and letrozole 30 (36.1%). The demographic and clinical characteristics of all patients are shown in Table 1.

The number of patients who started palbociclib and ribociclib at full dose was 64 (84.2%) and 79 (94%), respectively. The number of patients who did not experience any dose reductions or dose interruptions were 32 (50%) and 34 (43%). The initial dose modification was dose reduction alone in 5 (7.7%) and 6 (7.6%) patients, dose interruption alone in 7 (10.8%) and 12 (15.2%) patients, and both interruption and reduction in 23 (35.4%) and 31 (39.2%) patients. Dose reductions were implemented byadministering the next known lower dose for both drugs. The median time to first dose modification was 36 and 31 days, respectively. The most common cause for first dose modification was neutropenia for both drugs [33 (97%) and 34 (69%)]. LFT's elevation (10%) and renal function impairment (6%), were other causes for ribociclib dose reduction. The most common cause for a second dose modification was also neutropenia for both drugs (13.8% and 16.2%). For ribociclib, renal function impairment was a reason for second dose modification in two patients (2.6%). The dose modifications of patients who started a full-dose are shown in Table 2.

Grade 3–4 side events were observed in 41 (53.9%) patients receiving palbociclib and in 43 (51.2%) patients receiving ribociclib. For both drugs, neutropenia was the most common adverse event. The median time to deepest neutropenia was 35 days for palbociclib and 43.5 days for ribociclib. All adverse events for both drugs are shown in detail in Table 3.

Factors associated with grade 3–4 neutropenia were also examined. In the ribociclib arm, neutropenia was significantly higher in those receiving ≥3rd line therapy, in those with visceral metastases, and in those with hematological side effects other than neutropenia. When the association between starting dose and grade 3 or 4neutropenia was assessed no significant difference between the patients with standard dose and those with reduced dose was observed. Grade 3–4 neutropenia was less common among obese patients than in those with a normal BMI. Factors associated with neutropenia are shown in Table 4. Serious adverse events were seen in 9 (11.8%) and 13 (15.5%) patients, respectively, as shown in Table 5.

Factors found to be related with increased risk of severe adverse events included presenting with visceral disease and and ECOG PS ≥2 for patients taking palbociclib; while only being older than 75 years was significant for those taking ribociclib (Table 6).

During the 6-month follow-up period, the number of patients whose disease progressed was 7 (9.2%) for palbociclib and 9 (10.7%) for

Table 1
Demographic and clinical characteristics.

Variables No (%)*	Palbociclib (*N* = 76)	Ribociclib (*N* = 84)
Age at diagnosis		
Median yr** (range)	66 (35–86)	68 (38–87)
Age at the time of CDK4/6 inhibitor therapy		
Median yr (range)	71 (65–87)	72 (65–87)
<75 yr	57 (75)	60 (71.4)
≥75 yr	19 (25)	24 (28.6)
BMI – no (%)		
<18.5* (underweight)	0	0
18.5–24.9 (normal weight)	11 (15.3)	20 (24.7)
25–29.9 (overweight)	29 (40.3)	28 (34.6)
≥30 (obese)	32 (44.4)	33 (40.7)
ECOG performance status		
0	26 (34.7)	28 (33.3)
1	35 (46.7)	45 (53.6)
2	12 (16)	7 (8.3)
3	2 (2.6)	3 (3.6)
4	0	1 (1.2)
Geriatric 8 (G8) Score		
Median (range)	13 (8–17)	13 (6–16)
Frail	39 (52)	49 (58.3)
Groningen Frailty Indicator Score		
Median (range)	7 (0–13)	6 (1–14)
Frail	63 (82.9)	68 (81)
Recurrent disease		
Yes	40 (52.6)	43 (51.2)
No (De novo)	36 (47.4)	41 (48.8)
Number of comorbid diseases		
<3	51 (76.1)	55 (71.4)
≥3	16 (23.9)	22 (28.6)
Polypharmacy (≥5 drugs used)	9 (13.4)	11 (14.5)
Metastatic regions		
Visceral[a]	42 (55.3)	41 (48.8)
Non-visceral[b]	34 (44.7)	43 (51.1)
Bone only	22 (28.9)	35 (41.7)
Treatment line		
1.	34 (44.7)	31 (36.9)
2.	22 (28.9)	30 (35.7)
≥3.	20 (26.3)	23 (27.5)
Type of hormonal therapy		
Fulvestrant	39 (51.3)	53 (63.1)
Letrozole	35 (46.1)	31 (36.9)
Other aromatase inhibitors	2 (2.6)	0
Chemotherapy in the last 6 months	10 (11.8)	16 (19)

* Number (percent) if not otherwise specified.
** Year.
[a] Visceral means visceral metatatic disease including lung, liver, sürrenal etc.
[b] Non-visceral means metatastic disease other than visceral organs such as bone, lymph nodes, skin etc.

Table 2
Summary of dose management in patients that started the optimal dose drug.

Variables *n* (%)*	Palbociclib (*N* = 76)	Ribociclib (*N* = 84)
Received full starting dose	64 (84.2)	79 (94)
Did not require any drug reduction or interruption during follow-up	32 (50)	34 (43)
Maximum tolerated dose		
125 mg (600 mg)	38 (58.5)	41 (52.6)
100 mg (400 mg)	21 (32.3)	31 (39.7)
75 mg (200 mg)	6 (9.2)	6 (7.7)
Required a first dose modification	34 (53.1)	49 (62)
First dose modification		
Only dose reduction	5 (7.7)	6 (7.6)
Only dose interruption	7 (10.8)	12 (15.2)
Both	23 (35.4)	31 (39.2)
Time to first dose modification in days		
Median (range)	36 (8–239)	31 (7–210)
Cause for first dose modification		
Neutropenia	33 (97)	34 (69)
Thrombocytopenia	2 (5)	3 (6)
Anemia	0	1 (2)
LFT's elevation	0	5 (10)
Renal function impairment	0	3 (6)
Diarrhea	1 (2)	1 (2)
Emesis	0	1 (2)
Hypertension	0	1 (2)
Qt prolongation***	0	2 (4)
Required a second dose modification	9 (13.8)	15 (19)
Second dose modification		
Only dose reduction	3 (4.6)	1 (1.3)
Only dose interruption	0	2 (2.5)
Both	7 (10.8)	12 (15.2)
Cause for second dose modification		
Neutropenia	9 (13.8)	12 (16.2)
Renal function impairment	0	2 (2.6)
Skin rash	0	1 (1.3)
Time to second dose modification in days Median (range)	67 (42–203)	36 (30–185)

* Number (percent) if not otherwise spesified. **Palbociclib dose (ribociclib dose) *** QTcF >480 msec

Table 3
Treatment related adverse events.

Adverse event *n* (%)*	Palbociclib (*N* = 76)			Ribociclib (*N* = 84)		
	All grade	Grade 3	Grade 4	All grade	Grade 3	Grade 4
Neutropenia	74 (97.3)	27 (35.5)	14 (18.4)	80 (93)	29 (35.8)	11 (13.6)
Anemia	41 (58.5)	0	0	40 (52)	2 (2.6)	0
Trombocytopenia	17 (24.3)	1 (1.4)	2 (2.9)	16 (21.1)	3 (3.9)	0
Diarrhea	10 (13.1)	1 (1.3)	0	9 (11)	1 (1.2)	0
LFT's elevation	6 (7.9)	0	0	11 (13.4)	4 (4.9)	0
Renal function impairment	9 (11.9)	1 (1.3)	0	19 (17.1)	2 (2.4)	0
Fatigue	28 (37.3)	0	0	41 (49.7)	0	0
Emesis	17 (23)	0	0	17 (22.6)	0	0
Loss of apetite	1 (1.5)	0	0	3 (3.9)	0	0
Peripheral edema	2 (3)	0	0	1 (1.3)	0	0
Constipation	0	0	0	2 (2.6)	0	0
Alopecia	0	0	0	1 (1.3)	0	0
Skin rash	1 (1.5)	0	0	0	0	0
Cough	1 (1.5)	0	0	0	0	0
Stomatitis	1 (1.5)	0	0	0	0	0
Qt prolongation	0	0	0	2 (2.4)	2 (2.4)	0

* Number (percent).

Table 4
Factors related with grade 3–4 neutropenia.

Variables *n* (%)*	Palbociclib (*N* = 76)		Ribociclib (*N* = 84)	
		P value		*P* value
Age at diagnosis		0.690		0.782
≥75 y/o	11 (57.9)		12 (50)	
65–74 y/o	30 (52.6)		28 (46.7)	
Geriatric 8		0.540		0.768
Frail	20 (51.3)		24 (49)	
Not frail	21 (56.8)		16 (45.8)	
Groningen Frailty Indicator		0.536		0.442
Frail	35 (55.6)		31 (45.6)	
Not frail	6 (46.2)		9 (56.3)	
ECOG		0.390		0.254
≥2	9 (64.3)		7 (63.7)	
0–1	32 (51.6)		33 (45.2)	
Treatment line		0.527		**0.013**
≥3	12 (60)		16 (69.6)	
<3	29 (51.8)		24 (39.3)	
Metastatic regions		0.343		**0.039**
Visceral	31 (57.4)		28 (36.4)	
Bone only	10 (45.4)		12 (25.5)	
Number of comorbidities		0.102		0.564
>2	6 (37.5)		12 (54.5)	
0–2	31 (60.8)		26 (47.3)	
Polypharmacy		0.485		0.744
Yes	4 (44.4)		5 (45.5)	
No	33 (56.9)		33 (50.8)	
Hematologic adverse event other than neutropenia		0.776		**0.045**
Yes	24 (53.3)		26 (57.8)	
No	17 (56.7)		14 (35.9)	
BMI		**0.011**		**0.034**
Obese	12 (37.5)		26 (42.6)	
Non-obese	27 (67.5)		14 (70)	

Chi square test was used for statistics.
* Number (percent). Significant values ($p<0.05$) are marked in bold.

Table 5
Treatment-related serious adverse events.

	Palbociclib (*N* = 76)	Ribociclib (*N* = 84)
Adverse event no (%)*		
Febrile neutropenia	1 (1.3)	3 (3.7)
Infection requiring antibiotic use	7 (9.6)	9 (10.7)
Emergency room admissions/hospitalization related with study drug	4 (5.6)	8 (9.8)
Drug discontinuation	3 (3.9)	5 (6)

* Number (percent).

Table 6
Factors related with serious adverse events (SAE's).

Variable no (%)*	Palbociclib ($N = 76$)		Ribociclib ($N = 84$)	
		P value		*P* value
Age		0.539		**0.028**
65–74 y/o	6 (10.5)		6 (10%)	
≥75 y/o	3 (15.8)		7 (29.2%)	
G8		0.099		0.799
Not-frail	2 (5.5)		5 (14.3%)	
Frail	7 (18)		8 (16.3%)	
GFI		0.147		0.714
Not-frail	0		2 (12.5%)	
Frail	9 (14%)		11 (16.2%)	
ECOG performance status		**0.002**		0.790
0–1	4 (6%)		11 (15.1%)	
≥2	5 (35.5%)		2 (18.2%)	
Metastatic setting		0.852		0.693
De novo disease	4 (11.1)		7 (17.1)	
Recurrent disease	5 (12)		6 (13.9)	
BMI		1		0.229
Obese/	4 (13)		3 (10)	
Non-obese	5 (13)		9 (18.8)	
Polypharmacy		0.307		0.333
Yes/	2 (22.2)		3 (27.2)	
No	6 (10.3)		10 (15.3)	
Number of concomitant diseases		0.336		0.124
>2	3 (18.7)		6 (27.2)	
/0–2	5 (9)		7 (12.7)	
Bone only metastatic disesase		**0.041**		0.799
No	9 (16.6)		8 (16.3)	
Yes	0 (0)		5 (14.2)	
Treatment line		0.766		0.766
0–1	7 (12.5)		9 (14.8)	
>2	2 (10)		4 (17.4)	

Chi square test was used for statistics.
* Number (percent). Significant values ($p<0.05$) are marked in bold.

ribociclib. In the same period, 6 (7.9) patients stopped palbociclib and 8 (9.5%) ribociclib, all of them due to progression.

4. Discussion

In this prospective study, the side effects and dose management of palbociclib and ribociclib in older pateints with HR + HER2- metastatic BC were examined in a "real-world" cohort.

Older adults are under-represented in clinical trials and as a result, clinicians are forced to extrapolate from findings in younger and healthier patients when making treatment decisions for older patients. Moreover, older patients included in clinical trials often have better performance scores. In the PALOMA 2 study, there were 133 patients aged 65–74 years using palbociclib, of which 48 were 75 years and older. Only seven patients (2.3%) had an ECOG-PS of 2 and above [3]. Likewise, in the Monaleesa 2 study using ribociclib, patietns with ECOG 2 PS and above were not included [20]. Therefore, we believe that our study, which included older and frailer patients, has useful information for daily oncology practice.

Another study in which the safety of palbociclib in older patients was investigated was conducted in France under the name of PALOMAGE [21]. Like in our study, the G8 was utilized to measure frailty. Patients aged 70 years and older were included, with a median age of 79 years and a median follow-up of 6.7 months. The proportion of patients with ECOG 2 and above was 17.9%, similar to our study and 68.3% were considered frail, which was higher than in our study. While 32.1% of the patients had only bone metastases, 44% had visceral metastases. In our study, bone metastasis only were present in 28.9% of patients, while the rate of visceral metastases was 55%. This indicates that our study included patients with a higher burden of disease. In PALOMAGE, the rate of patients who received full dose (125 mg) palbociclib when starting treatment was 76%, while it was 84.2% in our study. This difference could be explained by the younger median age in our study (79 vs. 71). In the safety analysis, grade 3–4 neutropenia was seen in 32.3% of patients, while the incidence of febrile neutropenia was 1.1%. In our study, grade 3–4 neutropenia was observed in 53.9% of patients, and febrile neutropenia in 1.3%. The most common adverse events at all grades in PALOMAGE were neutropenia (43.2%), anemia (17.5%), asthenia (16.3%), and thrombocytopenia (13.6%). In our study, neutropenia (97.3%), anemia (58.5%), asthenia (37.3%), thrombocytopenia (24.3%) and emesis (23%) were most common in all grades. Apart from neutropenia, thrombocytopenia (4.3%), diarrhea (1.3%), and impaired renal function (1.3%) were observed in a small number of patients as grade 3–4 side effects. Another report of palbociclib's toxicity among older patients (65 years and older) comes PALOMA 2; grade 3 and higher adverse events were reported as neutropenia in 66.1%, thrombocytopenia 1.9%, anemia 5.5%, infections 8.5%, nausea 0.06%, and fatigue 4.2%. was reported [22]. The reason why the rates were lower in our study may be that palbociclib was started at a lower dose in patients who were considered at high risk by physicians.

In a literature search, we couldn't find any study in which ribociclib was prospectively investigated among a cohort of older adults. In MONALEESA-2, 295 patients (44%) were ≥ 65 years of age, of which 150 patients were randomized to receive ribociclib + letrozole. In the subgroup analysis of the study in which patients aged 65 and over were examined [20] the most common grade 3–4 adverse events were neutropenia (60%), leukopenia (21%), and liver enzyme elevation (9%) (only side effects occuring in ≥15% of participants were reported). According to our results, while most adverse events were low-grade, liver and renal function should be followed more closely. In the randomized study, discontinuation was 13%, compared to 6% in our study, which may be due to lower doses of ribociclib prescribed by physicians for patients who were considered at high risk of complications.

Neutropenia is the most common side effect associated with CDK 4/6 inhibitors. In our study, neutropenia was the most common side effect for both drugs and the most common reason for dose modification. Since CDK 4/6 inhibitors do not have cytotoxic effects on neutrophils like chemotherapy does, neutropenia is a more manageable side effect and dose modification is recommended only when grade 3–4. Factors associated with grade 3–4 neutropenia in our study included receiving third line or higher therapy, having visceral metastasis, the presence of other hematological side effects other than neutropenia, and obesity. Similarly, in a recent pooled analysis of the PALOMA 1–2-3 studies, palbociclib was associated with less neutropenia among pateients with a BMI ≥30 kg/m2 [23]. Another CDK 4/6 inhibitor, abemaciclib, was shown to be associated with less neutropenia in obese patients [24]. A potential reason may be the higher neutrophil counts among obese individuals as a result of an increased inflammatory state, which has also been found in people without cancer [25,26]. More importantly, since both drugs show lipophilic properties [27], an increased body fat ratio may reduce the myelosuppressive effects of drugs, which is also true for chemotherapy [28].

We found a low incidence of febrile neutropenia, hospitalizations, emergency room visits and treatment discontinuation. In a retrospective study evaluating the toxicity of palbociclib in 160 older adults with cancer, febrile neutropenia was observed in 2.1%; 19.3% ($n = 117$) had documented infection requiring antibiotic use; and 10.4% ($n = 63$) needed emergency room admissions or hospitalization secondary to an infectious complication [29]. One reason for the differences seen in our study may be that the rate of de novo patients was higher in our study (47.4% vs. 24.5%). In other words, patients treated in the recurrent metastatic setting can have worse outcomes and complications. We also evaluated the course of SAEs seen with palbociclib and ribociclib in the pivotal studies, PALOMA and MONALEESA. Febrile neutropenia was observed in 0.6% of patients in PALOMA 3, 1.5% in MONALEESA 2, and 1% in MONALEESA 3 [20,30,31]. These rates were similar to our study. Discontinuation due to AE was observed in 2.6% of patients in PALOMA 3 [30] and it was 5.5% in the 65 years old subgroup [22], which is 3.9% in our study. Discontinuation due to AE was 7.5% in MONALEESA 2, and

8.4% in MONALEESA 3, which were also similar to our findings [20,31]. Factors that may be related with the incidence of severe adverse effects included having an ECOG-PS ≥2 and visceral disease in patients treated with palbociclib; and being ≥75 years of age those treated with ribociclib. These findings are generally consistent with previous studies, with bone-only metastatic disease associated with a safer clinical course.

In the study, together with age and ECOG-PS, the G8 and the GFI scales were used to assess frailty. While a comprehensive geriatric assessment is the gold standard for evalauting older adults, it may not possible to apply it to every patient in daily practice. G8 assesses different geriatric aspects, including nutrition, disability, consciousness, depressed mood, and comorbidities. So far, it has been shown that it can predict survival [10,32] and chemotherapy toxicity [33] in older patients, including those living in Turkey [34]. Moreover, G8 can also be used to predict the toxicity of other oral treatments for breast cancer, including aromatase inhibitors [35]. GFI is another highly specific screening test for geriatric syndromes [19]. Previous studies showed that it may be associated with mortality in patients with cancer receiving chemotherapy [15,36]. No correlation was found between the incidence of Grade 3–4 neutropenia and G8 and GFI.

The strengths of the study come from its prospective design and gathering of "real-world" data. Another strength is that relatively less common side effects such as fatique and emesis, which were not mentioned in other studies, were also examined. In addition, polypharmacy and comorbid diseases, which can frequently seen in older patients, were also included in the analysis. In the second part of the ongoing study, the efficacy data of the drugs will also be analyzed. Among the study limitations we can mention the lack of randomization. Not having any health-related quality of life (HR-QoL) measurement is another limitation in this study. We believe that studies with larger numbers of patients will contribute more to the literature.

This study prospectively investigated the adverse events of palbociclib and ribociclib among older patients with breast cancer in a "real world" cohort. We did not identify any new safety signals among older adults other than those previously reported in the literature. In patients at higher risk of adverse events such as ECOG-PS ≥2, ≥75 years of age, having non-bone-only metastatic disease, having hematological side effects other than neutropenia, etc. additional attention should be paid and early interventions initiated. The low incidence of severe neutropenia among obese patients should be kept in mind when deciding on dose modifications.

Funding Acknowledgement

Authors report no funding.

Author Contributions

Conceptualization: OA, Yİ, EÇ, KK, ESŞ
Data curation: OA, Yİ, EÇ, KK, ESŞ
Formal analysis: OA, Yİ, EÇ, KK, ESŞ
Funding acquisition: OA, Yİ, EÇ, KK, ESŞ
Investigation: OA, Yİ, EÇ, KK, ESŞ
Methodology: OA, Yİ, EÇ, KK, ESŞ
Project administration: OA, Yİ, EÇ, KK, ESŞ
Resources: OA, Yİ, EÇ, KK, ESŞ
Software: OA, Yİ
Supervision: OA, ESŞ
Validation: OA, ESŞ
Visualization: OA, Yİ, EÇ, KK, ESŞ
Writing - original draft: OA
Writing - review & editing: OA, ESŞ

Declaration of Competing Interest

Authors report no conflicts of interest.

References

[1] Arnold A, Papanikolaou A. Cyclin D1 in breast cancer pathogenesis. J Clin Oncol 2005;23:4215–24. https://doi.org/10.1200/JCO.2005.05.064.
[2] Witkiewicz AK, Knudsen ES. Retinoblastoma tumor suppressor pathway in breast cancer: prognosis, precision medicine, and therapeutic interventions. Breast Cancer Res 2014;16:207. https://doi.org/10.1186/bcr3652.
[3] Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016;375:1925–36.
[4] Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 2016;375:1738–48.
[5] Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol 2017;35:3638–46.
[6] Extermann M, Aapro M, Bernabei R, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol 2005;55:241–52.
[7] Aaldriks AA, Giltay EJ, le Cessie S, et al. Prognostic value of geriatric assessment in older patients with advanced breast cancer receiving chemotherapy. Breast 2013; 22:753–60. https://doi.org/10.1016/j.breast.2013.01.011.
[8] Scheepers ERM, van der Molen LF, van den Bos F, et al. The G8 frailty screening tool and the decision-making process in older breast cancer patients. Eur J Cancer Care (Engl) 2021;30:e13357. https://doi.org/10.1111/ecc.13357.
[9] Bellera CA, Rainfray M, Mathoulin-Pelissier S, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol 2012;23: 2166–72. https://doi.org/10.1093/annonc/mdr587.
[10] Soubeyran P, Bellera C, Goyard J, et al. Screening for vulnerability in older cancer patients: the ONCODAGE prospective multicenter cohort study. PloS One 2014;9: e115060. https://doi.org/10.1371/journal.pone.0115060.
[11] Atakul E, Akyar I, Tanyer DK. Geriatric assessment in oncology: G8 screening too validation and reliability study. 2019.
[12] Steverink N. Measuring frailty: developing and testing the GFI (Groningen frailty Indicator). Gerontologist 2001;41:236.
[13] Schuurmans H, Steverink N, Lindenberg S, et al. Old or frail: what tells us more? J Gerontol A Biol Sci Med Sci 2004;59:M962–5.
[14] Kellen E, Bulens P, Deckx L, et al. Identifying an accurate pre-screening tool in geriatric oncology. Crit Rev Oncol Hematol 2010;75:243–8.
[15] Aaldriks A, Maartense E, Le Cessie S, et al. Predictive value of geriatric assessment for patients older than 70 years, treated with chemotherapy. Crit Rev Oncol Hematol 2011;79:205–12.
[16] Pol R, Van Leeuwen B, Visser L, et al. Standardised frailty indicator as predictor for postoperative delirium after vascular surgery: a prospective cohort study. Eur J Vasc Endovasc Surg 2011;42:824–30.
[17] Meessen J, Leichtenberg CS, Tilbury C, et al. Frailty in end-stage hip or knee osteoarthritis: validation of the Groningen Frailty Indicator (GFI) questionnaire. Rheumatol Int 2018;38:917–24. https://doi.org/10.1007/s00296-017-3868-1.
[18] Aygör H, Sahin S, Aykar FS, et al. P131: testing the reliablity and validity of the 'Groningen Frailty Index'in Turkish population. Eur Geriatr Med 2014;S124.
[19] Baitar A, Van Fraeyenhove F, Vandebroek A, et al. Evaluation of the Groningen Frailty Indicator and the G8 questionnaire as screening tools for frailty in older patients with cancer. J Geriatr Oncol 2013;4:32–8.
[20] Sonke GS, Hart LL, Campone M, et al. Ribociclib with letrozole vs letrozole alone in elderly patients with hormone receptor-positive, HER2-negative breast cancer in the randomized MONALEESA-2 trial. Breast Cancer Res Treat 2018;167:659–69. https://doi.org/10.1007/s10549-017-4523-y.
[21] Caillet P, Pulido M, Brain E, et al. PALOMAGE, a French real-world cohort of elderly women beyond age 70 with advanced breast cancer receiving palbociclib: baseline characteristics and safety evaluation. In: Wolters Kluwer health; 2021.
[22] Rugo HS, Turner NC, Finn RS, et al. Palbociclib plus endocrine therapy in older women with HR+/HER2- advanced breast cancer: a pooled analysis of randomised PALOMA clinical studies. Eur J Cancer 2018;101:123–33. https://doi.org/10.1016/j.ejca.2018.05.017.
[23] Ettl J, Im SA, Ro J, et al. Hematologic adverse events following palbociclib dose reduction in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: pooled analysis from randomized phase 2 and 3 studies. Breast Cancer Res 2020;22:27. https://doi.org/10.1186/s13058-020-01263-0.
[24] Franzoi MA, Eiger D, Ameye L, et al. Clinical implications of body mass index in metastatic breast cancer patients treated with Abemaciclib and endocrine therapy. J Natl Cancer Inst 2021;113:462–70. https://doi.org/10.1093/jnci/djaa116.
[25] Herishanu Y, Rogowski O, Polliack A, Marilus R. Leukocytosis in obese individuals: possible link in patients with unexplained persistent neutrophilia. Eur J Haematol 2006;76:516–20. https://doi.org/10.1111/j.1600-0609.2006.00658.x.
[26] Yilmaz H, Ucan B, Sayki M, et al. Usefulness of the neutrophil-to-lymphocyte ratio to prediction of type 2 diabetes mellitus in morbid obesity. Diabetes Metab Syndr 2015;9:299–304. https://doi.org/10.1016/j.dsx.2014.04.009.
[27] George MA, Qureshi S, Omene C, et al. Clinical and pharmacologic differences of CDK4/6 inhibitors in breast cancer. Front Oncol 2021;11:693104. https://doi.org/10.3389/fonc.2021.693104.
[28] Carroll J, Protani M, Walpole E, Martin JH. Effect of obesity on toxicity in women treated with adjuvant chemotherapy for early-stage breast cancer: a systematic review. Breast Cancer Res Treat 2012;136:323–30. https://doi.org/10.1007/s10549-012-2213-3.
[29] Clifton K, Min Y, Kimmel J, et al. Progression-free survival (PFS) and toxicities of palbociclib in a geriatric population. Breast Cancer Res Treat 2019;175:667–74. https://doi.org/10.1007/s10549-019-05181-4.

[30] Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016;17:425–39.

[31] Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer: MONALEESA-3. J Clin Oncol 2018;36:2465–72.

[32] [32] Agemi Y, Shimokawa T, Sasaki J, et al. Prospective evaluation of the G8 screening tool for prognostication of survival in elderly patients with lung cancer: a single-institution study. PloS One 2019;14:e0210499. https://doi.org/10.1371/journal.pone.0210499.

[33] [33] Stokoe J, Pearce J, Sinha R, Ring A. G8 and VES-13 scores predict chemotherapy toxicity in older patients with cancer. J Geriatr Oncol 2012;3:S81.

[34] [34] Cavdar E, Iriagac Y, Karaboyun K, et al. Prospective comparison of the value of CARG, G8, and VES-13 toxicity tools in predicting chemotherapy-related toxicity in older Turkish patients with cancer. J Geriatr Oncol 2022;13:821–7. https://doi.org/10.1016/j.jgo.2022.03.004.

[35] [35] Dottorini L, Catena L, Sarno I, et al. The role of Geriatric screening tool (G8) in predicting side effect in older patients during therapy with aromatase inhibitor. J Geriatr Oncol 2019;10:356–8. https://doi.org/10.1016/j.jgo.2018.10.007.

[36] [36] Aaldriks AA, van der Geest LG, Giltay EJ, et al. Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy. J Geriatr Oncol 2013;4:218–26. https://doi.org/10.1016/j.jgo.2013.04.001.