Araştırma Makalesi / *Research Article*

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IS THERE A DIFFERENCE BETWEEN PATIENTS UNDER 65 AND PATIENTS AGE 65 AND OVER IN THE EFFECT AND SAFETY OF CDK 4/6 INHIBITOR + ENDOCRINE THERAPY?

65 YAŞ ALTINDAKİ HASTALARLA 65 YAŞ VE ÜZERİ HASTALAR ARASINDA CDK 4/6 İNHİBİTÖR + ENDOKRİN TEDAVİSİNİN ETKİ VE GÜVENLİĞİNDE FARK VAR MI?

Hüseyin Salih SEMİZ[1] Merve KESKİNKILIÇ[2] Tuğba YAVUZŞEN[1]

[1]Dokuz Eylul University, Institute of Oncology, Department Of Medical Oncology, Izmir/Turkey
[2]Dokuz Eylul University Faculty of Medicine, Department of Medical Oncology, Izmir / Turkey

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SUMMARY

Introduction: *Metastatic breast cancer (MBC) has a significant mortality and morbidity rate despte all development in treatment modalities. The clinical course of MBC could be differnt in geriatric (≥65 years old) and non-geriatric (<65 years old) population. Toxicities due to targeted therapies could be different in geriatric population. We aimed to investigate whether there is a difference between the treatment characteristics of CDK 4/6 inhibitor + ET use in the geriatric and non-geriatric populations.*

Material and Method: *HR-positive HER-2 negative MBC patients using CDK 4/6 inhibitors + ET were included. Data about sociodemographic, histopathologic and treatment modalities of patients collected from hospital database retrospectively.*

Results: *In our study, which included 81 patients, 29% (n=17) of the patients were ≥65 years. Median OS in the non-geritric group was 17.5 months (95% CI; 15.6-19.5), and 17 months (95% CI; 15.2-19.8) in the geriatric group. There was no statistically significant difference between geriatric and non-geriatric patients in terms of survival. PFS in the non-geriatric group was 14.3 months (95% CI; 12.2-16.3), 15.4 months in the geriatric group (95% CI; 12.9-17.7).PFS was longer numerically in the geriatric group than in non-geriatric group. But this was not statistically significant. The treatment response rate was almost 2 times higher in the geriatric group than the non-geriatric group (87.6% vs 48.4%, respectively)(p=0.047). The incidence of side effects was similar in both groups, while dose reduction was performed in 35.3% of the geriatric group, 17.2% of the non-geriatric group. However, this was not statistically significant (p=0.242).*

Conclusion: *In our study, OS was similar in both groups, while PFS was longer in the geriatric group. Contrary to the literature, the response rate was higher for geriatric group, while the incidence of side effects was similar in both groups.*

ÖZ

Giriş: *Metastatik meme kanseri (MBC), tedavi modalitelerindeki tüm gelişmelere rağmen önemli bir mortalite ve morbidite oranına sahiptir. MBC'nin klinik seyri geriyatrik (≥65 yaş) ve geriyatrik olmayan (<65 yaş) popülasyonda farklı olabilir. Geriyatrik popülasyonda hedefe yönelik tedavilere bağlı toksisiteler non-geriyatrik popülasyondan*

farklı olabilir. Geriatrik ve geriatrik olmayan popülasyonda CDK 4/6 inhibitörü + ET kullanımının tedavi özellikleri arasında fark olup olmadığını araştırmayı amaçladık.

Gereç ve Yöntem: *CDK 4/6 inhibitörleri + ET kullanan HR-pozitif HER-2 negatif MBC hastaları dahil edildi. Hastaların sosyodemografik, histopatolojik ve tedavi uygulamalarına dair veriler hastane veri tabanından geriye dönük olarak toplandı.*

Bulgular: *81 hastayı içeren çalışmamızda hastaların %29'u (n=17) 65 yaş üstü idi. Non-geriyatrik grupta medyan OS 17.5 ay (%95 GA; 15.6-19.5) ve geriyatrik grupta 17 ay (%95 GA; 15.2-19.8) idi. Geriyatrik ve geriyatrik olmayan hastalar arasında sağkalım açısından istatistiksel olarak anlamlı fark yoktu. Non-geriyatrik grupta PFS 14.3 ay (%95 GA; 12.2-16.3), geriyatrik grupta ise 15.4 aydı (%95 GA; 12.9-17.7). PFS geriatrik grupta sayısal olarak non-geriyatrik gruptan daha uzundu. Fakat bu istatistiksel olarak anlamlı değildi. Tedaviye yanıt oranı geriyatrik grupta non-geriyatrik gruba kıyasla neredeyse 2 kat daha yüksekti (sırasıyla %87.6 ve %48.4) (p=0.047). Yan etki insidansı her iki grupta benzer bulunurken geriatrik grubun %35.3'ünde, geriatrik olmayan grubun %17.2'sinde doz azaltımı yapılmıştır. Ancak bu istatistiksel olarak anlamlı değildi (p=0,242).*

Sonuç: *Çalışmamızda OS her iki grupta da benzer iken, geriyatrik grupta PFS daha uzundu. Literatürün aksine, geriyatrik grupta yanıt oranı daha yüksek iken, yan etki insidansı her iki grupta benzerdi.*

INTRODUCTION

The most common subtype is hormone receptor (HR) positive human epidermal growth factor receptor 2 (HER2) negative breast cancer, occurring in 75% to 80% of patients diagnosed aged 65 years and over, and its incidence increases with age(1,2). Since the inclusion of patients aged 65 and over in clinical studies is limited, it has always been a matter of curiosity whether there is a difference in the efficacy and safety of treatments in the geriatric age group. To answer this question, patients aged 65 years and older in studies on CDK 4/6 inhibitor and endocrine therapy (ET) combination therapy in HR positive HER-2 negative metastatic breast cancer were also analyzed. The common result obtained from both the pooled analysis of palbociclib PALOMA studies in elderly HR-positive HER2-negative breast cancer patients and the pooled analyzes of Phase 3 studies (MONALEESA-2, MONARCH-3, PALOMA-2) in which combinations of aromatase inhibitör (AI) and cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor were evaluated, these treatments show similar efficacy in the elderly population compared to the population under 65 years of age, and their side effects are tolerable. As a result, if there is no visceral crisis in the treatment of HR-positive HER2-negative metastatic breast cancer, CDK 4/6 inhibitor and ET combination is recommende as first-line therapy in all age groups.

Cyclin-dependent kinase (CDK) 4/6 inhibitors prevent cell cycle progression and tumor cell proliferation by causing cell cycle arrest during the transition from G1 phase to S phase in the cell cycle(3). Although the mechanisms of action of the three CDK 4/6 inhibitors palbociclib, ribociclib and abemaciclib are similar, the side effects that develop are also different because their effects on CDK 4 and 6 are different(4). In fact, abemaciclib with higher CDK 4 affinity has a lower rate of myotoxicity, while gastrointestinal and fatigue are more prominent side effects, myelotoxicity is more common in ribociclib and palbociclib due to more CDK 6 inhibition. There appears to be limited information when considering toxicity in patients aged 65 years and older in Phase 3 studies of all three agents in treatment-naïve and previously treated subjects. In treatment-naïve patients, neutropenia was observed in 81% and febrile neutropenia in 1% in the population aged 65 and over in the Paloma-2 study of palbociclib, in the ribociclib MONALEESA-2 study nausea, alopecia, diarrhea and vomiting in >10% of patients; it has been reported that >10% increase in fatigue and grade 1–2 anemia. In the PALOMA-3 study of palbociclib, it was reported that grade 3-4 neutropenia was 13.9% in patients aged 70 years and older who had received previous treatment. In the ribociclib study, toxicity according to age was not evaluated in treatment-naïve subjects, and neither in treatment-naive nor in treatment-naïve studies of abemaciclib study of toxicity according to age was evaluated(3). As seen in the studies, there is a lack of information about the side effects and real-life data related to the use of CDK 4/6 inhibitors in patients aged 65 and over. In our study, we aimed to review the response status and treatment-related side effects related to the use of CDK 4/6 inhibitor and

ET combination in the group under 65 years of age and those aged 65 and over, and contribute to the literature on this commonly used drug group.

MATERIAL AND METHODS

Patients aged 18 years and older, diagnosed with metastatic HR positive HER2 negative breast cancer, and treated with a combination of CDK 4/6 inhibitor (ribociclib and palbociclib) and ET, between January 2020 and December 2021, were included in the study**.** Exclusion criteria was inability to access patient data from the hospital database. The patients' age, gender, diagnosis, menopausal status, histological subtype, pathological features, CDK 4/6 inhibitor therapy type used, the time they received CDK 4/6 inhibitor therapy, type of endocrin therapy agent (anastrazole, letrozole, fulvestrant), CDK 4/6 pretreatment laboratory values, treatment response status, side effects, development time of side effects, need for dose reduction and comorbidities were recorded. Sociodemographic and clinicopathological characteristics of the patients were obtained retrospectively from the hospital database.

The patients were grouped as 65 years old and over and under 65 years old. The response rates of both groups, adverse events, progression-free survival (PFS), mean overall survival (OS), and side effects during treatment were compared using the chi-square test. Descriptive statistics (mean ± standard deviation, percentage (%)) were used as appropriate for statistical analysis. Survival analysis was evaluated by Kaplan Meier. All data analyzes were performed using the Statistical Package for Social Science (SPSS) (version 26.0 SPSS Inc, Chicago, IL, USA). Statistical significance was determined as $p<0.05$.

Ethical approval for this study was obtained from the Ethics Committee of Dokuz Eylul University Faculty of Medicine (Approval date: 09.02.2022; Decision no. 2022/05-09).

RESULTS

Our study included 81 patients who received CDK 4/6 inhibitor + ET combination therapy. The median age of the patients was 53.96 years (29.69-83.13 years). Sociodemographic and clinicopathological features of the patients are shown in Table 1.

Sixty three percent (n=51) of the patients were de novo metastatic, and the remaining patients were metastatic patients who developed recurrence during follow-up (37%, n= 30). 11.1% (n=9) of our patients are dead and 88.8% (n=72) are still alive. Considering the type of CDK 4/6 inhibitor applied to the patients, 54.3% (n=44) used palbociclib and 45.7% (n=37) used ribociclib. Considering the endocrine treatment options combined with CDK 4/6 inhibitors, 59.3% (n=48) of the patients were using fulvestrant and 40.7% (n=33) were using letrozole.

The median treatment line of using cdk4/6 inhibitor was 4.21 (range 1-9). Only 9.9% (n=8) of the patients received CDK 4/6 inhibitor +ET in the first line. We have three patients over the age of 65 who used CDK 4/6 inhibitor as the first line treatment, one of these patients died in the 3rd month of treatment, and two of them are still continuing their treatment. Five patients under the age of 65 are still under treatment, and since the number of our patients who used CDK 4/6 inhibitor in the first line was low, a comparison with the group over 65 years of age could not be made.

The follow-up period in our study was 19 months. The median cancer-specific survival (CSS) time in the whole group was 68.11 (range; 3.23-284.90) months. Median OS of all study group patients included in the study was 17.9 months (95% CI; 16.2-19.6), in the <65 years old group <17.5 months (95% CI; 15.6-19.5), ın the ≥65 years group, it was 17 months (95% CI; 15.2-19.8), and there was no statistically significant difference in survival in the geriatric age group (Figure 1). PFS in the whole group was 14.8 months (95% CI; 13-16.6), for the <65 years old group 14.3 months (95% CI; 12.2-16.3), for the >65 years and older group ıt was 15.4 months (95% CI; 12.9-17.7) and numerically longer PFS was observed in the geriatric group (Figure 2).

Twenty-point nine percent (n=17) of the patients who received CDK 4/6 inhibitor treatment were 65 years and older. When the patients were divided into 2 groups as under 65 years and 65 years and older, the clinopathological and treatment characteristics of the patients were shown in Table 2.

Table 1. Sociodemographic and Clinicopathologic Characteristics of Patients

Characteristics (All of group)	n (%)
Sex	
Female	79 (97,5 %)
Male	2 (2,5 %)
Performance Status	
ECOG PS 0	71 (71 %)
ECOG PS 1	21 (21 %)
ECOG PS 2	8 (8 %)
Comorbidity	
None	41 (50,6 %)
One	22 (27,1%)
Two or more	18 (22,2 %)
Menopause Status	
Postmenopausal	61 (75,3%)
Premenopausal	16 (19,7%)
Perimenopausal	2 (2,4 %)
Histological Subtype	
Invasive ductal carcinoma (IDC)	26 (32,5 %)
Invasive carcinoma	21 (25,9 %)
Invasive lobular carcinoma (ILC)	15 (18,5 %)
Mixed type (IDC+ ILC)	8 (9,9 %)
Mucinous	1 (1,2%)
Tubulolobuler	1 (1,2 %)
Unknown	9 (11,1 %)
Metastasis Site	
Bone	64 (79 %)
Lymph node	57 (70,4 %)
Liver	26 (32,1 %)
Lung	25 (30,9 %)
Brain	7 (8,6 %)
Others (pleura,adrenal,cardiac,bone marrow, meninges,skin)	23 (28,2 %)

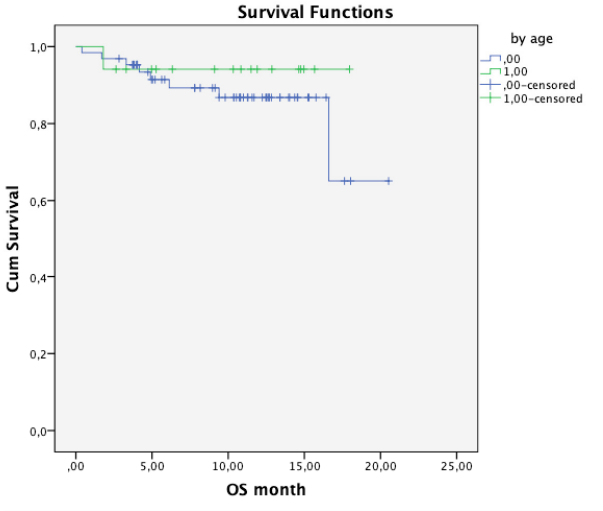

Figure 1. Overall Survival by Age

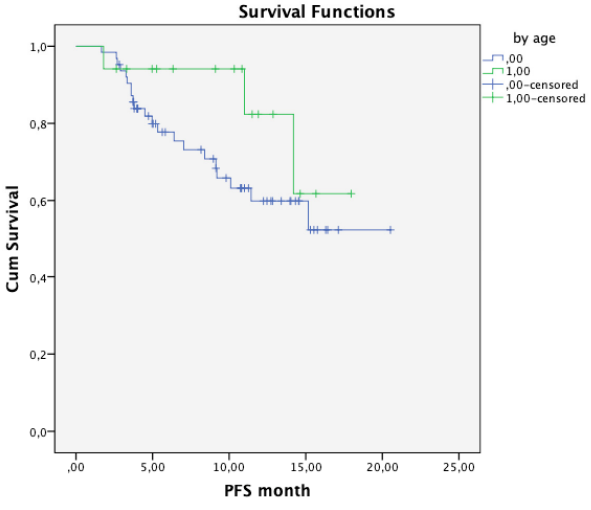

Figure 2. Progression Free Survival by Age

Table 2. Comparison of the characteristics of the under-65 and 65-and-over group

Characteristics n (%)	<65 years group	≥65 years group	P value
Performance Status			
ECOG PS 0	49 (77,8 %)	7 (41,2 %)	p=0,014
ECOG PS 1	10 (15,9 %)	7 (41,2 %)	
ECOG PS 2	4 (6,3 %)	3 (17,6 %)	
Comorbidity			
Hypertansion	14 (21,9 %)	12 (70,6 %)	p <0,001
Tip 2 DM	9 (14,1 %)	4 (23,5 %)	p=0,345
Coronary Arter Disease (CAD)	0	2 (11,8 %)	p=0,005
Metastasis Site			
Bone	50 (78,1 %)	14 (82,4 %)	p=0,704
Lymph node	41 (64,1 %)	16 (94,1 %)	p=0,016
Liver	22 (34,4 %)	4 (23,5 %)	p=0,395
Lung	18 (28,1 %)	7 (41,2 %)	p=0,300
Previous line Chemotherapy			
Absent	15,6 %	58,8 %	p=0,002
1 line	21,9 %	29,4 %	
2 line	39,1 %	5,9 %	
3 line	23,5 %	5,9 %	
CDK 4 /6 Agent Choice			
Palbociclib	36 (56,3 %)	8 (47,1 %)	p=0,499
Ribociclib	28 (43,8 %)	9 (52,9 %)	
Endocrin Treatment			
Fulvestrant	40 (62,5 %)	24 (37,5 %)	p= 0,249
Letrozole	8 (47,1 %)	9 (52,9 %)	
Response Status			
Overall Response	31 (48,4 %)	14 (87,6 %)	p=0,027
Partial	24 (37,5 %)	11 (68,8 %)	
Stable	7 (18,8 %)	3 (10,9 %)	
Progression	22 (34,4 %)	0	
Unknown	11 (17,2 %)	2 (12,5 %)	

As stated in Table 2, the rate of those aged 65 and over who have never received chemotherapy before is 58.8%, the rate of those who receive first line chemotherapy is 29.4%, the rate of those who receive second lines of chemotherapy is 5.9%, and the rate of those who receive third lines of chemotherapy is %. while 5.9; The rate of those under 65 years of age who did not receive any chemotherapy was 15.6%, the rate of those who received first line chemotherapy was 21.9%, the rate of those who received second lines of chemotherapy was 39.1%, and those who received third lines or more chemotherapy was 23.5%. Significantly, it was observed that chemotherapy treatment was applied at a lower rate (p=0.002).

When evaluated in terms of treatment-related side effects, there was no statistically significant difference between the age groups in terms of neutropenia, anemia, prolongation of QTc value and increase in creatinine value, which are the most common side effects. While 35.3% of the geriatric group had dose reduction, 17.2% of the group under 65 years of age had a dose reduction, but this was not statistically significant (p=0,242). Treatment of one patient in the group under 65 years of age was discontinued. While dose reduction was performed in 23.5% (n=19) of the whole group, 12.3% (n=10) of these patients had cytopenia, 9.9% (n=8) had QTc prolongation and 1%, dose reduction was performed in 1,2% (n=1) patients due to atrial fibrillation.

DISCUSSION

In metastatic HR-positive HER2-negative breast cancer, both national and international guidelines recommend CDK 4/6 inhibitor + endocrine therapy (AI or fulvestrant) as first-line therapy. Phase-3 studies (MONARCH-3, PALOMA-2 AND MONALEESA-2) have shown that all three CDK 4/6 inhibitors (abemaciclib, palbociclib and ribociclib) contribute to PFS in first-line treatment in metastatic HR + HER-2 negative breast cancer (5-7). On the other hand, ribociclib + letrozole

combination. was the first CDK 4/6 inhibitor agent to show its contribution on OS with 63.9 months versus 51.4 months in postmenopausal patients with HR-positive, HER2–negative advanced breast cancer(7).

In the MONARCH-3, PALOMA-2 and MONALEESA-2 Phase-3 trials, in which the first-line use of CDK 4/6 inhibitor agents were evaluated, the population aged 65 and over constituted 45.1%, 40.8% and 44.9% of the study population in the treatment arms, respectively (5-7). Compared to the only study with OS data, the MONALEESA-2 study, the OS duration of the population over 65 was longer at 68 months versus 59.7 months (7). Overall survival durations in the combined studies with second-line fulvestrant were 46.7, 34.9 and 39.7 months compared to the Phase 3 MONARCH-2, PALOMA-3 and MONALEESA-3 trials, respectively (8-10).

In the MONARCH-2 study, the hazard ratio (HR) on OS duration was minimally higher in the abemaciclib+ fulvestrant arm in the population under 65 years of age, and the HR on OS on the ribociclib+ fulvestrant arm in the MONALEESA-3study was similar in the under-65 and over-65 age group. In the Paloma-3 study, OS was statistically significantly longer in the palbociclib + fulvestrant arm in the population aged 65 and over (39.7 versus 31.4)(8,9,10). In our study, which consisted of 20.1% of the 65-year-old and older age group, the OS duration of the geriatric group and the group under 65 years was 17 months versus 17.5 months, and although it was not statistically significant, they had a similar survival time as in the MONALEESA-3study.

In the ribociclib MONALEESA-3study, in which the second-line use of CDK 4/6 inhibitors was evaluated in the subgroup analysis, the OS duration was 39.7 months, and in the palbociclib PALOMA-3 and abemaciclib MONARCH-3 study, there was no such stratification, although the OS durations in the entire group were 34.9 and 46.7 months, respectively(8,9,10). In our study, the median OS duration of all patients was 17.9 months, and the median OS duration was shorter compared to both first-line and second-line studies. Considering that only eight of our patients (%9,9) used CDK 4/6 inhibitor treatment in the first line, CDK 4/6 inhibitor treatment use order was median 4.21 (range: 1-9) and the follow-up period was short, it is thought that this explains the short duration of survival of our study.

Combination with endocrine therapy in metastatic HR + HER2-negative breast cancer improved PFS for all three agents compared with either a first- and second-line AI or fulvestrant. In elderly patients (75 years of age and older), the combination of CDK4/6 inhibitor and endocrine therapy showed an improvement in median PFS from 13.7 to 31.1 months compared with AI alone (11). In a study in the literature comparing the PFS of those under the age of 70 and those aged 70 and over, it was observed that the PFS was longer in the over 70 age group, at 33.1 months versus 27.4 months[1]. Similarly, in the pooled analysis of Palbociclib studies (PALOMA-1, PALOMA-2, PALOMA-3), the under-65 age group had a shorter PFS duration than the 65-74 age group (22 months vs 27.5 months, respectively). Although we had a short follow-up period of 19 months, in our study, the PFS was longer at 15.4 versus 14.3 months in the 65 and older group.

In terms of toxicity, in randomized clinical trials (RCTs) evaluating safety, neutropenia was the most common adverse event with palbociclib and ribociclib, while diarrhea was the most common adverse event with abemaciclib. Qtc prolongation and liver toxicity due to ribociclib are more prominent, and gastrointestinal toxicity consisting of nausea, vomiting and diarrhea and an increase in serum creatinine level are more prominent in abemaciclib compared to the other two agents (12). When the literature is reviewed, the incidence of grade 1-2 side effects is similar in both groups, while the incidence of grade 3-4 side effects is higher in the 75 years and older group. In our study, the most common adverse event in both groups was neutropenia, with almost similar rates. (<65 years 90.6%; >65 years 94.1%). In the study conducted by Howie et al., the dose reduction rate was 79.3% higher than 70% in the group aged 70 and over, and the rate of discontinuation was also higher in the 75-year-old and older group, as 11.4% vs. 23.2% (1). As expected in our population, the dose reduction rate was higher in the 65-year-old and older group. (35.3% vs 17.2%, respectively)

Although it is stated in the literature that the response rates of CDK 4/6 inhibitor + ET are

similar regardless of age, in our study, despite the short follow-up period, the treatment response rate was almost 2 times higher in the 65 and older group, which was statistically significant. (87.6% vs 48.4%, respectively) (p=0.047). This was thought to be due to the use of the CDK 4/6 inhibitor treatment line in younger patients, with an average of 1.7 versus 2.1 in later treatment lines.

CONCLUSION

CD 4/6 inhibitor + ET is the standard treatment in hormone receptor positive HER2 negative metastatic breast cancer. In our study, in which we compared the treatment characteristics of the under-65 and 65-year-old and older groups, it was concluded that the efficacy was similar in both groups, and that the 65-year-old and older group should be more careful in terms of side effects. Prospective studies on this subject will make more important contributions to the literature.

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Sorumlu yazar

Hüseyin Salih SEMİZ (Dr. Öğretim Üyesi)
Dokuz Eylül Üniversitesi Onkoloji Enstitüsü, Tıbbi Onkoloji Kliniği, İzmir
Tel: 05337182006
E- mail: hsalihsemiz@hotmail.com
ORCID: 0000-0002-7083-8517

Merve KESKİNKILIÇ (Uzm. Dr.) ORCID: 0000-0002-3342-3144
Tuğba YAVUZŞEN (Prof. Dr.) ORCID: 0000-0001-9375-8133