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Efficacy and toxicity of everolimus plus exemestane in third and later lines treatment of hormone receptor-positive, HER2-negative metastatic breast cancer

Hormon reseptör pozitif HER2-negatif metastatik meme kanseri tedavisinde üçüncü ve sonraki basamaklarda everolimus/eksemestan tedavisinin etkinliği ve toksisitesi

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Abstract

Aim: In daily practice, everolimus plus exemestane therapy has begun to be used in the later-lines as it has been demonstrated that treatments such as cyclin-dependent kinase (CDK) 4/6 inhibitors and fulvestrant, alone or in combination, are more effective in hormone receptor (HR)-positive metastatic breast cancer (MBC). The aim of this study is to evaluate the efficacy and toxicity of everolimus plus exemestane in the third line and later-lines on HR-positive Human Epidermal Growth Factor Receptor 2 (HER2)-negative MBC treatment with real-life data.

Methods: Patients who received everolimus plus exemestane with the diagnosis of HR-positive and HER2-negative MBC between November 2013 and March 2020 were included in this retrospective cohort study. Clinicopathological characteristics of patients and treatment related toxicities were evaluated retrospectively.

Results: The median age of the 33 patients included in the study was 59 (30-77) years. Twenty-three (69.7%) of the patients had visceral metastasis, while 10 (30.3%) had only bone metastasis. Everolimus plus exemestane was used in the third line in 22 (66.6%) patients and later-lines in 11 (33.3%) patients. The median follow-up time was 15.5 months (0.3-35.5). Median progression-free survival (PFS) and overall survival (OS) were 7.0 (5.1-9.0, 95% CI) months and 21.3 (13.4-29.2, 95% CI) months, respectively. Median PFS of patients with only bone metastasis and visceral metastasis were similar (7.2 vs 6.4 months, *P*=0.96).

Conclusion: Everolimus plus exemestane is an effective and tolerable treatment choice in the later-lines in the treatment of HR-positive HER2-negative MBC.

Keywords: Everolimus, Exemestane, Breast cancer

Öz

Amaç: Siklin bağımlı kinaz 4-6 inhibitörü ve fulvestrant gibi tedavilerin tek başına ya da kombinasyon halinde kullanılmasının hormone reseptör (HR)-pozitif metastatik meme kanseri (MMK) tedavisinde daha etkin olduğunun gösterilmesiyle günlük pratikte everolimus/eksemestan tedavisi daha ileriki basamaklarda kullanılmaya başlamıştır. Bu çalışmanın amacı HR-pozitif HER2-negatif MMK tedavisinde üçüncü ve sonraki basamaklarda everolimus/eksemestan kombinasyon tedavisinin etkinliğini ve toksisitelerini gerçek yaşam verileri ile değerlendirmektir.

Yöntemler: Bu çalışma retrospektif kohort çalışmasıdır. Kasım 2013 - Mart 2020 tarihleri arasında merkezimizde HR-pozitif HER2-negatif MMK tanısıyla everolimus/eksemestan kombinasyon tedavisi alanlar çalışmaya dahil edilmiştir. Hastaların klinikopatolojik özellikleri ve tedavi ilişkili toksisiteler retrospektif olarak incelenmiştir.

Bulgular: Çalışmaya dahil edilen 33 hastanın ortanca yaşı 59'du (30-77). Hastaların 23'ünün (%69,7) visseral metastazı varken 10 (%30,3) hastanın yalnızca kemik metastazı vardı. Everolimus/eksemestan tedavisi 22 (%66,6) hastaya üçüncü basamakta, 11 (%33,3) hastaya ise sonraki basamaklarda verilmişti. Ortanca takip süresi 15,5 (0,3-35,5) aydı. Ortanca progresyonsuz sağkalım (PS) 7,0 (5,1-9,0, 95% CI) ay; ortanca genel sağkalım ise 21,3 (13,4-29,2, 95% CI) aydı. Yalnızca kemik metastazı olan hastalarla visseral metastazı olan hastalar arasında ortanca PS açısından fark yoktu (7,2–6,4 ay; *P*=0,96).

Sonuç: Everolimus/eksemestan kombinasyonu HR-pozitif HER2-negatif MMK tedavisinde ileriki basamaklarda da etkin ve tolere edilebilir bir tedavi seçeneğidir.

Anahtar kelimeler: Everolimus, Eksemestan, Meme kanseri

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Introduction

Breast cancer is the most common type of cancer in women and ranks second after lung cancer in cancer-related deaths [1]. It is not a single type of disease and is divided into three subgroups with different pathological and clinical features: 'Hormone Receptor (HR)-Positive', 'Human Epidermal Growth Factor Receptor 2 (HER2)-Positive' and 'Triple-Negative' [2-12]. In the last four decades, there have been significant advances in the treatment of 'HR-positive metastatic breast cancer (MBC)' through the process that started with tamoxifen in 1977 [13,14]. Apart from endocrine therapy (ET), significant improvements in survival have been achieved through targeted therapies such as 'phosphoinositide 3-kinase', 'mammalian target of rapamycin (mTOR)' or 'cyclin-dependent kinase (CDK) 4/6' inhibitors [15-21].

The first phase-3 study on efficacy of mTOR inhibitors in the treatment of MBC was conducted in 2012 [17]. In patients with HR-positive and HER2-negative MBC, administration of everolimus in addition to exemestane has been shown to provide an advantage in progression-free survival (PFS). In a later phase-2 study comparing everolimus plus exemestane with capecitabine or exemestane, median PFS were similar between the arms of exemestane plus everolimus and capecitabine [20]. In both prospective studies, everolimus with exemestane was administered as second line treatment. In later retrospective reports, most patients were using everolimus plus exemestane as second line treatment [22,23]. In daily practice, everolimus plus exemestane therapy has begun to be used in the later lines as it has been demonstrated that treatments such as CDK 4/6 inhibitors and fulvestrant, alone or in combination, are more effective in HR positive MBC [24,25].

Our aim in this study is to evaluate the efficacy and toxicity of everolimus plus exemestane in the third and later lines in HR-positive HER2-negative MBC treatment with real-life data.

Materials and methods

This single-center retrospective cohort study was conducted on patients who received everolimus plus exemestane with the diagnosis of HR-positive and HER2-negative MBC between November 2013 and March 2020.

Male patients and those under 18 years of age were excluded from the study.

Demographic features, pathological features (estrogen receptor (ER) expression, Ki67 proliferation index), breast cancer diagnosis date, metastasis date, metastasis regions, everolimus plus exemestane treatment start and end dates, and treatment-related toxicities were evaluated retrospectively via the electronic registration system and manually through the patient files. Side effects were graded by Common Terminology Criteria for Adverse Events version (CTCAE) V.4.03.

Statistical analysis

The analyses were carried out through SPSS software. The time from the onset of everolimus plus exemestane to progression was defined as PFS and time to death was defined as overall survival (OS). Kaplan-Meier curve was used for survival analysis. Log-rank analysis was used for median PFS comparison in subgroups. Values of P <0.05 were considered significant.

Results

The median age of 33 women included in the study was 59 (30-77) years. Characteristics of the patients are presented in table 1. ER status of 26 patients (78.7%) was >80%, and Ki-67 status of 20 patients (60.6%) was >30%.

Table 1: Patient characteristics

	n=33	%
Age		
Median (range) – years	59 (30-77)	
ECOG performance status score		
0 or 1	29	87.9
2	4	12.1
Estrogen receptor expression		
≥ 80%	26	78.7
< 80%	7	21.2
Ki-67 Proliferation index		
≤ 30%	21	63.6
> 30%	12	36.3
Metastatic site		
Bone	29	87.9
Lymph node (non-regional)	21	63.6
Lung	19	57.6
Liver	8	24.2
Brain	3	9.1
Everolimus plus exemestane sequence		
Third line	22	66.6
Fourth line	9	27.2
Fifth line and later	2	6.0

While 23 (69.7%) of the patients had visceral metastasis, 10 (30.3%) had only bone metastasis. Everolimus plus exemestane was used in 22 (66.6%) patients in the third line and 11 (33.3%) patients in later lines. Stable disease (SD) was achieved in 21 (63.6%) patients, while partial response (PR) was achieved in 2 (6.1%) patients.

During the median follow-up period of 15.5 months (0.3-35.5), the disease progressed in 30 (90.9%) patients and 19 (57.6%) patients died. Median PFS was 7.0 (5.1-9.0, 95% CI, figure 1) months, and median OS was 21.3 (13.4-29.2, 95% CI, figure 2) months. There was no significant difference in median PFS between patients with only bone metastasis and those with visceral metastasis (7.2 vs 6.4 months; P=0.96; figure 3).

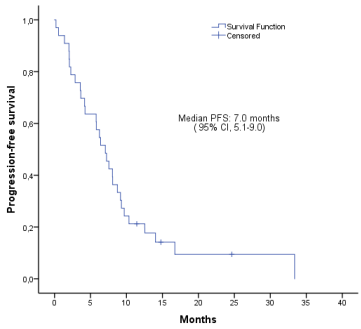

Figure 1: Kaplan–Meier estimates of progression-free survival

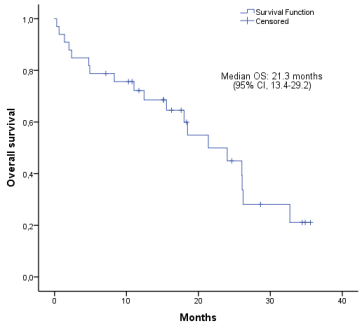

Figure 2: Kaplan–Meier estimates of overall survival

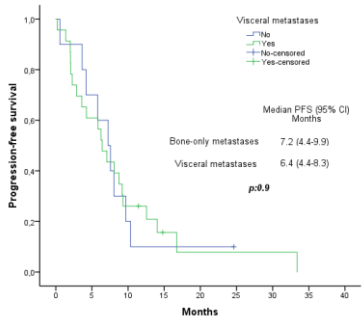

Figure 3: Median PFS on visceral vs bone-only metastases

One (3%) patient died due to acute coronary syndrome and 1 (3%) patient died due to acute renal failure. Eleven (33.3%) patients could not continue with the treatment due to toxicity. Eight (24.2%) patients had dose delay and 7 (21.2%) patients had dose reduction. The most common side effects were stomatitis (n=14, 42.4%) and fatigue (n=13, 39.3%). Treatment-related side effects are shown in table 2.

Table 2: Everolimus related toxicity (n=33)

	Grade 1-2	Grade 3	Grade 4
Stomatitis	12 (36.3%)	2 (6.0%)	0
Fatigue	11 (33.3%)	2 (6.0%)	-
Pneumonitis	5 (15.1%)	0	0
Diarrhea	5 (15.1%)	1 (3.0%)	0
AST/ALT increased	5 (15.1%)	0	0
Anemia	5 (15.2%)	1 (3.0%)	0
Hyperglycemia	4 (12.1%)	1 (3.0%)	0
	n (%)		
Treatment delay	8 (24.2%)		
Dose reduction	7 (21.2%)		
Discontinuation due to toxicity	11 (33.3%)		
Death	2 (6.0%)		

Discussion

To the best of our knowledge, this study is one of the limited number of studies demonstrating the efficacy of everolimus in HR-positive HER2-negative MBC treatment after at least one line of chemotherapy and hormonotherapy in the third and later lines. The median PFS obtained in our study showed that everolimus plus exemestane may be an effective treatment choice in the later lines.

The first study to investigate the effect of mTOR inhibitors in the treatment of HR-positive HER2-negative MBC is BOLERO-2 [17]. This phase-3 study published in 2012 included postmenopausal patients who were refractory to nonsteroidal aromatase inhibitor treatment. Compared to exemestane plus placebo, longer PFS was obtained with everolimus plus exemestane (6.9 vs 2.8 months).

In the phase-2 BOLERO-4 study published in 2018, the efficacy of everolimus combined with letrozole in first line and exemestane in the second line was investigated in HR-positive and HER2-negative MBC patients. Median PFS achieved with everolimus plus letrozole was 22.0 months in the first line and median PFS with everolimus plus exemestane was 3.7 months in the second line [19].

In another phase-2 study, BOLERO-6, published in the same year, the same patient group was randomized into three groups [20]. Median PFS for everolimus, everolimus plus exemestane and capecitabine was 6.8, 8.4 and 9.6 months, respectively. According to the results, everolimus plus exemestane and capecitabine were better than everolimus alone.

In the large retrospective series on 264 HR+ HER2- MBC patients published from Italy, PFS was 11.6, 9.7 and 7.5 months with everolimus plus exemestane in the first, second and third lines, respectively [22]. The median PFS value obtained in our study is similar to the results in BOLERO-2, BOLERO-6 and the study published from Italy. However, our median PFS was better than the 3.7-month PFS in the BOLERO-4 study [17,19,20,22], the difference between which was thought to stem from study design: In BOLERO-4, some patients who received everolimus with exemestane in the second line had received everolimus and letrozole in the first line.

When the tumor response achieved with everolimus plus exemestane was analyzed in the original study, 12% PR and 73% SD were reported compared to central assessment [17]. In our study, the proportion of patients with both PR and SD was slightly lower. The reason for this difference might be the fact that our patients received the treatment in further lines as compared to BOLERO-2.

In the final analysis of BOLERO-2, OS was reported as 31.0 months, while it was reported as 33.0 months in the wide retrospective series [22,27]. In our study, the median OS was 21.3 months. The median PFS we achieved was akin to the pivotal study and retrospective series, while the median OS was shorter. OS difference is thought to be caused by the treatments given after progression.

In visceral metastatic disease, the effectiveness of everolimus with exemestane treatment has been a matter of curiosity. In final analysis of BOLERO-2, it was reported that everolimus plus exemestane treatment was more effective than placebo in the presence of visceral metastasis [17]. In our study 69.7% of the patients had visceral metastasis, and there was no difference in median PFS between visceral metastatic patients and those with only bone metastasis.

The phase 3B BALLET study published in 2017 is one of the most comprehensive studies on the safety of everolimus plus exemestane [28]. In this study, which was conducted on 429 patients, 1% of patients had treatment-related death, 15% could not continue treatment due to side effects and 56% had dose reduction due to side effects. In BOLERO-2, these rates were slightly higher: 1.4% death, 26% could not continue treatment due to side effects, 66% dose reduction or interruption of treatment [17]. In our study we experienced 6% death, 33% of our patients could not continue treatment due to side effects, and 21% of the patients needed dose reduction. Compared to these two comprehensive studies, the rate of patients who could not continue treatment was higher in our real-life experience. Dose reduction in fewer patients was thought to cause more cases to discontinue the treatment.

One of the most common side effects of everolimus plus exemestane is stomatitis, which occurs in approximately 60% of patients [17,28]. In our study, this side effect was observed in 40% of our patients. In our center, the recommendation of prophylactic oral care to each patient at least one week before starting treatment and close follow-up during the treatment has lowered the rate of this side effect. In daily practice, fatigue, pneumonitis, and diarrhea, which are the most common side effects that cause treatment discontinuation, were experienced in our patient group at a rate similar to the previous studies [17,22,28].

Limitations

The limitations of our study were retrospective design and small number of patients. In retrospective studies, the unrecorded side effects are a handicap. However, our study is one of the few studies with real-life data evaluating the efficacy and safety of everolimus plus exemestane in the third and later lines in the treatment of HR-positive HER2 negative MBC.

Conclusion

In conclusion, everolimus plus exemestane is an effective and tolerable treatment choice in the later-lines in the treatment of HR-positive HER2-negative MBC. Novel studies are needed to evaluate the effectiveness of everolimus plus exemestane in patients who progressed with CDK 4-6 inhibitors and fulvestrant.

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