

Ixabepilone in Metastatic Breast Cancer: Real-World Experience

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ABSTRACT Objective: This study assessed the efficacy of ixabepilone and compared two regimens of this drug (weekly vs. every 3 weeks) in patients with heavily treated metastatic breast cancer during daily clinical practice. **Material and Methods:** Between 2012 and 2018, all cases of metastatic breast cancer treated with ixabepilone were evaluated. **Results:** We evaluated data from 75 patients diagnosed with metastatic breast cancer. Eighty-eight percent of patients had hormone-positive Human Epidermal Growth Factor Receptor 2-negative metastatic breast cancer. Most patients had visceral and bone metastases (65%). Most patients were heavily pretreated; 96% had received at least three lines of prior chemotherapy in the metastatic setting. The median use of ixabepilone was the sixth line. The objective response rate was 32%. Patients had a median progression-free survival (PFS) of 4 months, and there was no statistical difference in the PFS of two chemotherapy regimens (weekly: 3.2 months vs. every 3 weeks: 5 months, $p=0.31$). Patients had a median overall survival (OS) of 12.7 months, and there was no statistical difference in the OS of two chemotherapy regimens (weekly: 16 months vs. every 3 weeks: 12 months, $p=0.91$). The incidence of Grade 1-2 hematologic toxicity events (neutropenia and thrombocytopenia) was 10% in patients on the weekly regimen. Grade 3 neutropenia was seen in 20% of patients and grade 3 thrombocytopenia was seen in 6% of patients treated every 3 weeks. **Conclusion:** This study showed that ixabepilone is effective in patients with heavily treated breast cancer, and weekly treatment is less toxic and safer than treatment every 3 weeks for these patients.

Keywords: Breast cancer; metastatic; ixabepilone

Breast cancer is the most frequent diagnosis encountered in oncology clinics and the second cause of cancer-related mortality besides lung cancer among women worldwide.¹ Although the methods of early detection have evolved, around 6% of women are still diagnosed with metastatic breast cancer at their first visit. In addition, as many as 30% of patients with non-metastatic early stage breast cancer will be diagnosed with distant metastatic disease during their disease course.² Although there is currently no cure for metastatic

breast cancer, newer systemic therapies have improved survival.

Ixabepilone is an epothilone, a class of non-taxane microtubule-stabilizing agents that have activity in taxane-resistant patients. Many trials have demonstrated the efficacy of ixabepilone in chemotherapy-resistant tumors.³⁻⁵ This study assessed the efficacy of ixabepilone and compared two regimens of this drug in patients with metastatic breast cancer in daily clinical practice.

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MATERIAL AND METHODS

INCLUSION/EXCLUSION CRITERIA

Between 2012 and 2018, all cases of metastatic breast cancer were evaluated. We retrospectively identified 75 patients treated with ixabepilone. Data were primarily obtained from three hospital files: Antalya Memorial Hospital, Hacettepe University Hospital, and Samsun Medical Park Hospital. ¹⁸F-fluorodeoxyglucose positron emission tomography-computed tomography or computed tomography was used to assess treatment responses. Medical charts were reviewed to obtain patient demographic data, including age, performance status, pathologic subtype, treatment modality, and prior chemotherapy.

STATISTICAL ANALYSIS

SPSS software version 20.0 (SPSS Inc., Chicago, Illinois) was used to perform statistical analyses. Kaplan-Meier methodology was used to determine progression-free survival (PFS) and overall survival (OS). The log-rank test was utilized to compare survival curves. P-values lower than 0.05 were considered statistically significant. Overall response rate (ORR) was calculated for all patients treated with ixabepilone.

RESPONSE CRITERIA

Radiologic response was evaluated by response evaluation criteria in solid tumors.⁶

Complete response (CR): Vanishing of all target lesions.

Partial response (PR): By taking the sum of diameters of lesions as the reference baseline, minimum 30% decrease in the total diameters of target lesions.

Progressive disease (PD): The emergence of one or more new lesions not present initially. In addition, by taking the smallest sum on the study as the reference baseline, patients with relatively 20% or more increase in the total diameters of target lesions (this total diameter must also prove an increase of 5 mm or more) were considered as having PD.

Stable disease: Patients who did not show enough shrinkage of tumors to classify as PR or who

did not show an increase to classify as PD compared with the smallest sum diameters.

Objective Response: CR+PR.

CHEMOTHERAPY

Ixabepilone was delivered either weekly as 15 mg/m² on days 1, 8, and 15 of a 28-day cycle or once every 3 weeks as 40 mg/m² on day 1 of a 21-day cycle.

ETHICAL STATEMENT

Because of the retrospective nature of the study, the ethical consent requirement has been waived, and this study has been approved by the institutional review board of the concerned tertiary center. All procedures performed in the scope of this study were in line with the Declaration of Helsinki.

RESULTS

CLINICAL CHARACTERISTICS

In this study, the data from 75 patients who were diagnosed with metastatic breast cancer and treated with ixabepilone between March 2012 and May 2018 were evaluated. Patients were enrolled in three cancer centers: Antalya Memorial Hospital, Hacettepe University Hospital, and Samsun Medical Park Hospital. The median follow-up duration was 64 (12-303) months. The median age of patients was 49 years (range: 24-75 years). All patients were women. Eighty-eight percent of patients had hormone-positive Human Epidermal Growth Factor Receptor 2 (HER2)-negative metastatic breast cancer. Most patients had visceral and bone metastases (65%). Thirty-two percent of patients were given ixabepilone every 3 weeks. Patient characteristics are provided in [Table 1](#).

Most patients were heavily pretreated; 96% had received at least three lines of prior chemotherapy in line with the metastatic setting. The median use of ixabepilone was the sixth line (range 3-13). The objective response rate (complete and PRs) was 32% ([Table 2](#)).

SURVIVAL ANALYSIS:

The median follow-up period was 64 months. A median PFS of 4 months [95% confidence interval (CI) for hazard ratio (HR) (2.71-5.30)] was observed in all patients. There was no statistical difference be-

TABLE 1: Patients Characteristics.

	Patients n=75 (%)
Age	
Median	49
Range	24-75
Breast cancer type	
ER positive and/or PR positive HER2 negative	66 (88)
ER positive and/or PR positive HER2 positive	5 (6.7)
ER negative, PR negative, HER2 negative	4 (5.3)
Metastasis area	
Visceral	11 (14.7)
Bone	15 (20)
Visceral and bone	49 (65.3)
Prior therapy metastatic setting	
Taxane	75 (100)
Anthracycline based therapy	75 (100)
Capecitabine	75 (100)
Hormonal therapy	73 (94.7)
Ixabepilone use	
Weekly	51 (68)
Every Three weeks	24 (32)
Ixabepilone line in the metastatic setting	
Median	6
Range	4-12
Median cycles of ixabepilone	3 (1-41)

ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human Epidermal Growth Factor Receptor 2.

tween the chemotherapy regimens (weekly: 3.2 months vs. every 3 weeks: 5 months, p=0.31) (Figure 1).

The patients had a median OS of 12.7 months [95% CI for HR (4.50-20.87)]. OS was not statisti-

cally different between the chemotherapy regimens (weekly: 16 months vs. every 3 weeks: 12 months, p=0.91) (Figure 2).

ADVERSE EVENTS

There was no dose reduction needed in the weekly regimen. The incidence of Grade 1-2 hematologic toxicity events (neutropenia and thrombocytopenia) was 10% in patients on the weekly regimen. There was no grade 3-4 side effect seen in patients with treated weekly regimens. Grade 3 neutropenia was evident in 20% of patients, and an event of Grade 3 thrombocytopenia was observed in 6% of patients, while Grade 2 thrombocytopenia was seen 6% of patients treated every 3 weeks.

DISCUSSION

Our study demonstrated the efficacy of ixabepilone in real clinical practice. This study is the first to compare to a weekly ixabepilone treatment regimen vs. treatment every 3 weeks in patients with aggressively treated metastatic breast cancer.

Currently, many novel agents are being investigated for the treatment of breast cancer. Despite new advances in metastatic breast cancer, most patients develop drug resistance during their treatment course. Ixabepilone is an epothilone, a class of non-taxane tubulin polymerizing agents. Ixabepilone has demonstrated activity in taxane-resistant patients.⁷ Many trials have shown the activity of ixabepilone in patients after heavy treatment as well as at earlier stages of metastatic breast cancer. It is both effective as monotherapy and in combination therapy with capecitabine. One meta-analysis showed that ix-

TABLE 2: Radiological response of ixabepilone.

	All patien n=75 (%)	Weeklyt n=51 (%)	Every three weeks n=24 (%)
Complete response	2 (2.7)	2 (3.9)	0
Partial response	22 (29.3)	12 (23.5)	10 (41.7)
Stable disease	3 (4)	2 (3.9)	1 (4.2)
Progressive disease	31(41.3)	24 (47.1)	7 (29.2)
Clinical progression	3 (4)	3 (5.9)	0
Not assessed	14 (18.7)	8 (15.7)	6 (25)

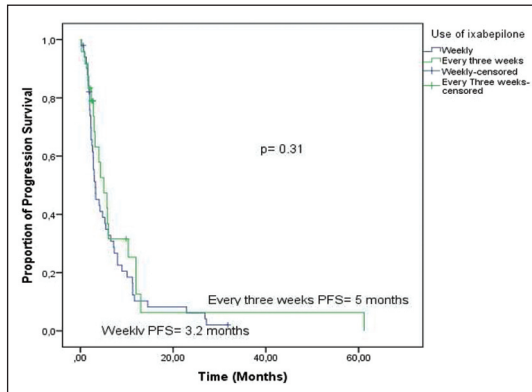


FIGURE 1: Progression-free survival curve in patients treated with ixabepilone weekly vs. ixabepilone every 3 weeks.
PFS: Progression free survival.

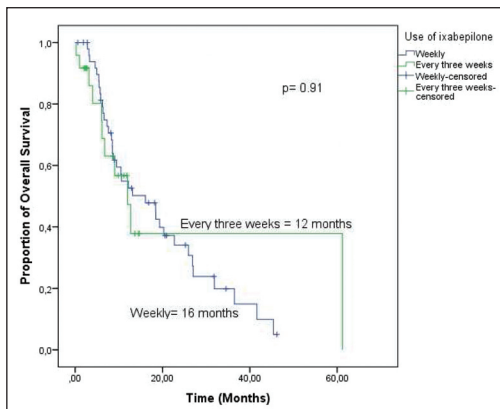


FIGURE 2: Overall survival curve in patients treated with ixabepilone weekly vs. ixabepilone every 3 weeks.

ixabepilone-capecitabine combination therapy leads to the better OS, PFS, and ORR than ixabepilone monotherapy.⁸ Ixabepilone is approved by Food and Drug Administration for patients with metastatic breast cancer who have progressed after anthracycline and taxane therapy. However, the use of ixabepilone currently requires progression after anthracycline, taxane, gemcitabine, and capecitabine treatment in Turkey. Thus, all of our patients had been treated with anthracycline, taxane, gemcitabine, and capecitabine before treatment with ixabepilone. As a single-agent treatment, a previous trial showed that ixabepilone therapy resulted in an ORR of 19%, median PFS of 3.1 months, and median OS of 8.6 months.⁹ Our study included patients with heavily treated metastatic breast cancer, and they had an ORR of 32%, median PFS of 4 months, and median OS of 12.7 months.

One clinical study showed that weekly ixabepilone treatment led to shorter PFS compared with treatment with taxanes. These data showed that weekly ixabepilone is less active than taxanes, but may be better tolerated.¹⁰ However, this trial provided ixabepilone as a first-line treatment in chemotherapy-naïve patients with metastatic breast cancer. All of our patients had been heavily treated prior to our trial.

One important aspect to consider is the toxicity in patients with heavily treated breast cancer. Several meta-analyses have shown that sequenced single-agent chemotherapy is effective and less toxic than combination chemotherapy in breast cancer patients with distant metastasis. Since there is currently no cure for metastatic breast cancer, the goal of the treatment was based on prolonging survival and improving the quality of life.¹¹⁻¹³ Thus, with equally effective agents, the first aim should be to use the least toxic and most effective treatment plan. We have shown that the weekly ixabepilone regimen is as effective as the regimen of every 3 weeks, and it is more tolerable and less toxic in patients with heavily treated metastatic breast cancer.

Some breast cancer types, especially the hormone receptor-positive and HER2-negative types, are associated with longer life expectancy than others.^{14,15} This situation has come about due to new chemotherapy agents such as cyclin-dependent kinase 4/6 inhibitors. However, most of these patients will need a new drug because of drug resistance.^{16,17} Eighty-eight percent of our patients had hormone receptor positive and HER2-negative tumors. Ixabepilone was used as the median sixth line agent.

This study showed that ixabepilone is effective in patients with heavily treated breast cancer, and weekly treatment is less toxic and safer than treatment every 3 weeks for these patients. Ixabepilone is a good option for patients with metastatic breast cancer treated with many drugs and having a good performance status.

CONCLUSION

Currently, there are many novel agents for the treatment of breast cancer. Although much progress has been achieved in the treatment of metastatic breast cancer, most patients develop drug resistance.

This study aimed to assess the efficacy of ixabepilone and compare two different regimens of this drug (weekly vs. every 3 week) in patients with heavily treated metastatic breast cancer during daily clinical practice. The objective response rate to ixabepilone was 32%. Our patients had a median PFS of 4 months, and there was no statistical difference between PFS of two chemotherapy regimens (weekly: 3.2 months vs. every 3 weeks: 5 months, $p=0.31$). The incidence of Grade 1-2 hematologic toxicity events (neutropenia and thrombocytopenia) was 10% in patients on the weekly regimen. Grade 3 neutropenia was evident in 20% of patients, and Grade 3 thrombocytopenia was seen in 6% of patients treated every 3 weeks.

This study showed that ixabepilone is effective in patients with heavily treated breast cancer, and weekly treatment is less toxic and safer than treatment every 3 weeks for these patients. Ixabepilone is a good option for those with metastatic breast cancer treated with many drugs and having a good performance status.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Dilek Erdem, İrem Karaman; **Design:** Dilek Erdem, İrem Karaman; **Control/Supervision:** Dilek Erdem, Şeyda Gündüz; **Data Collection and/or Processing:** Deniz Can Güven, İrem Karaman, Sercan Aksoy; **Analysis and/or Interpretation:** Akin Yıldız, Aysegül Kargı, Mustafa Özdoğan, İrem Karaman; **Literature Review:** Şeyda Gündüz, Mükremin Uysal, Aysegül Kargı; **Writing the Article:** Deniz Can Güven, Aysegül Kargı, Dilek Erdem; **Critical Review:** Aysegül Kargı, Mükremin Uysal, Sercan Aksoy; **References and Fundings:** Mustafa Özdoğan, Aysegül Kargı, Akin Yıldız; **Materials:** Şeyda Gündüz.

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