Efficacy and Safety of Ixabepilone Monotherapy and Ixabepilone-Capecitabine Combination in Patients with Heavily Pretreated Metastatic Breast Cancer

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ABSTRACT

Ixabepilone is a semisynthetic epothilone-B analogue, targeting microtubule structures in mitosis analog, that can be used after anthracycline and taxane treatment in patients with metastatic breast cancer. We aimed to analyze the results of ixabepilone and ixabepilone-capecitabine combination in heavily pretreated metastatic breast cancer patients. In this single-center study, records of 24 patients with hormone receptor positive and HER negative or triple negative metastatic breast cancer who received at least one cycle of ixabepilone or ixabepilone-capecitabine in our clinic between 2015 and 2019 were analyzed retrospectively. Kaplan-Meier survival analysis was used for progression-free survival (PFS), and overall survival (OS) analyzes. A total of 24 patients with metastatic breast cancer were eligible and included. The median age of the patients was 53.6 (range 33.7-77.3). Patients were heavily pre-treated with a range of 3-6 previous chemotherapy lines before ixabepilone. At the and of the follow up-up period (September 2019) all patients received a median of 4.5 cycles of ixabepilone. Partial response (PR) was achieved in 8 patients (33%) and stable disease (SD) was achieved in 7 patients (29%). Median PFS was 3.9 (95% CI: 3.4-5.6) months. The overall median PFS was 3.9 months, 4.0 months in hormone receptor-positive patients and 3.7 months in triple-negative patients. There was no statistically significant difference between histological subtypes in terms of PFS (p= 0.77). The most common grade 3-4 adverse events were neutropenia (n=11, 45,8%) and neuropathy (n=15, 62.5%). Ixabepilone only or combination with capecitabine may be considered as an effective treatment option for heavily pre-treated patients with metastatic breast cancer, regard to its side effects.

Keywords: Ixabepilone, Capecitabine, Metastatic breast cancer, Efficacy, Safety

INTRODUCTION

Breast cancer is the most common cancer type in women. In addition, it is the second most common cause of cancer-related death in women. Approximately 6% of all breast cancer cases at the time of diagnosis are in the metastatic stage. In these patients, the 5-year survival rate is 26%.[1] There is no standard treatment algorithm for the treatment of metastatic breast cancer. In hormone-positive disease, hormonotherapy is the basis of treatment as long as there is no resistance and visceral crisis. On the other hand, chemotherapy is still the basis of the treatment in triple-negative patients.[2]

Ixabepilone is a semisynthetic epothilone-B analogue, targeting microtubule structures in mitosis. It stabilizes microtubule polymerization by binding to beta-tubulin, which is in the structure of microtubules, more potently than taxanes. In this way, cell-cycle arrest and apoptosis are provided. Ixabepilone has been shown to attenuate potential drug resistance resulting in decreased sensitivity to p-glycoprotein and multi-drug resistance-related protein-1 (MDRP-1) pumps.[3,4] In phase-II studies performed with ixabepilone in advanced breast cancer patients, objective response rates (ORR) were observed at rates ranging from 11.5% to 42%.[5,6]

In two Phase-III studies in which ixabepilone and capecitabine were used in combination, progression-free survival increased significantly with 6.2 months versus 4.2 months compared to capecitabine alone.[7,8] With these data, ixabepilone has been approved by the FDA for use alone or in combination with capecitabine in breast cancer patients who are metastatic or locally advanced hormone-positive or triple-negative, resistant to anthracycline and taxane treatments.[9]

In this study, it was aimed to retrospectively evaluate the results of ixabepilone treatment administered alone or in combination with capecitabine in patients with metastatic breast cancer who has seen the progression and who had been treated with hormone receptor-positive or triple-negative chemotherapy regimens including an anthracycline, taxane, gemcitabine, and vinorelbine previously.

PATIENTS and METHODS

A total of 24 patients with hormone receptor-positive and HER-2 negative or triple-negative metastatic breast cancer who received at least one cycle of ixabepilone between September 2015 and September 2019 were included in the study. Ixabepilone 40 mg/m^2 was administered on day one of the 3-week cycles. Capecitabine was given 1750-2000 mg/m^2 for the patients who did not receive capecitabine before. All patients have received at least one cycle of anthracycline, taxane, gemcitabine, and vinorelbine previously in the adjuvant or metastatic setting. Patients with bone metastases continued receiving bisphosphonate or denosumab. Endocrine treatment was not given concomitantly during ixabepilone treatment. Granulocyte colony-stimulating factor (G-CSF) prophylaxis was used in subsequent cycles for patients with grade 3-4 neutropenia. Dose reduction was performed for patients who have grade 3 or 4 toxicity according to National Cancer Institute Common Toxicity Criteria for Adverse Events v 4.0.

The demographic features of patients, tumor histopathology, previous chemotherapy, radiotherapy and endocrine therapy, sites of metastases, treatment-related adverse effects, overall response rates (ORR), and progression-free survival (PFS) were recorded. Radiological, laboratory, and clinical evaluations were performed for efficacy analyzes. Treatment response was assessed with imaging performed in 2-3 monthly intervals according to RECIST criteria version 1.1. Tumor marker and clinical evaluation were performed at least once in 2 monthly intervals. Adverse events were registered retrospectively according to standard terminology criteria for adverse events, version 4.0. For this retrospective study, ethical approval was obtained from Academical and Ethics Board of Medicana International Hospital (06.10.2020 / 2020/10).

Statistical Analysis

Standard descriptive statistics were used to characterize the sample dataset. PFS was defined as the time from the start of ixabepilone therapy to the progression due to any cause. PFS was the primary endpoint of this study. Kaplan-Meier survival analysis was used for PFS analyzes. The objective response rate (ORR) was defined as the sum of partial response (PR) and complete response (CR). The clinical benefit rate (CBR) was defined as the sum of PR, CR, and SD. In all assessment, a p-value < 0.05 were considered statistically significant. SPSS 18.0 program was used for statistical analyzes.

RESULTS

A total of 24 patients whose demographic and clinical characteristics were summarized in Table 1, and all patients were evaluated retrospectively. While 13 of the patients were triple-negative, 11 patients had hormone receptor-positive. The median age of all patients was 53.6 (33.7 - 77.3), triple-negative patients was 51.2 years (33.7 - 69.2), and the median age of hormone-receptor-positive patients was 56.6 years (37.5-77.3). While the ECOG performance status (ECOG PS) of 12 patients was 0, the ECOG PS of 7 patients was evaluated as 1, and the ECOG PS of 5 patients was evaluated as 2. The most common metastasis locations were bone, liver, lung, lymph node, and brain metastasis, respectively. Bone metastasis was the most common in hormone receptor-positive patients (9 patients), while the most common metastatic site was the liver in triple-negative patients (7 patients). The num-

Table 1. Patient demographic and baseline clinical features

	All patients (n: 24)	Triple negative (n: 13)	Hormone receptor positive (n: 11)
Age	53.6 (33.5-77.3)	51.2 (33.5-69.2)	56.6 (37.5-77.3)
ECOG PS			
0	12	6	6
1	7	4	3
2	5	3	2
Site of metastases			
Lymph node	9	3	6
Bone	17	8	9
Liver	12	7	5
Lung	11	6	5
Brain	9	6	3
Others	5	3	2
Stage at time of diagnosis			
I	1	1	0
II	5	3	2
III	13	6	7
IV	5	3	2
Previous chemotherapy lines			
3	4	2	2
4	11	6	5
5	7	3	4
6	2	2	0
Previous hormonotherapy lines			
3	3	0	3
4	6	0	6
5	2	0	2
Treatment			
Ixabepilone	19	10	9
Ixabepilone-Capecitabine	5	3	2

ECOG PS: Eastern Cooperative Oncology Group performance status

ber of metastatic patients at the time of diagnosis was four, 58.3% of the patients had Stage-II disease at the time of diagnosis. Five patients had previously received three-lines treatment, 11 patients who received four-lines treatment, six patients who received five-lines treatment, and two patients who received six-lines. A total of 19 patients received single-agent ixabepilone, and five patients received ixabepilone-capecitabine combination therapy (Table 1). At the and of the follow up-up period (September 2019) all patients received a median of 4.5 cycles of ixabepilone. None patients achieved complete radiological response with treatment in both triple-negative and hormone receptor-positive patients. A partial radiological response was observed in 8 patients (33.3%). Five of the patients with a partial response were triple-negative, and 3 patients were hormone receptor-positive. Seven of the remaining 16 patients (29.1%) had radiologically stable disease at the first response evaluation. In the remaining eight patients, increased tumor marker or radiological progression was observed. ORR was 33.3% and CBR was 62.5%. Progression was observed in all patients after a total of 9 months of follow-up period (Table 2). The median PFS was 3.9 months. Median PFS was found for 4.0 months in hormone receptor-positive patients and 3.7 months in triple-negative patients. PFS was detected between 2.2 months and 9.1 months. There was no statistically significant difference between histological subtypes in terms of PFS (p= 0.77). It was observed that the ixabepilone-capecitabine combination regimen did not provide a significant PFS advantage compared to ixabepilone alone. While PFS was 3.6 months with single-agent ixabepilone and 3.7 months with

Table 2. Efficacy outcomes

Histology	All patients (n: 24)	Triple negative (n: 13)		Hormone receptor positive (n: 11)	
Treatment	Ixabepilone (n: 19) Ixabepilone-Capecitabine (n: 5)	Ixabepilone (n: 10)	Ixabepilone-Capecitabine (n: 3)	Ixabepilone (n: 9)	Ixabepilone-Capecitabine (n: 2)
CR	-	-	-	-	-
PR	8 (33%)	4 (40%)	1 (33%)	2 (22%)	1 (50%)
SD	7 (29%)	2 (20%)	2 (66%)	2 (22%)	1 (50%)
ORR	8 (33%)	4 (40%)	1 (33%)	2 (22%)	1 (50%)
CBR	15 (62%)	6 (60%)	3 (100%)	4 (44%)	2 (100%)

CR= complete reponse, PR= partial response, SD= stabile disease, ORR= overall response rate, CBR= clinical benefit rate

combination therapy in triple-negative patients, it was observed that PFS was 3.8 months with single-agent ixabepilone and 4.1 months with combination therapy in hormone receptor-positive patients. There was no statistically significant difference between single agent ixabepilone and combination treatment in terms of PFS (Hormone receptor positive vs negative p= 0.72 in ixabepilone arm and p= 0.54 in combination arm) (Table 3). The most common treatment-related grade 3-4 toxicity was neuropathy (62.5%). Hematologic toxicities were the second most common. Neutropenia was observed in 45.8% of the patients, and febrile neutropenia was observed in 16.6%. Thrombocytopenia was detected at a rate of 33.3%, and anemia was 29.1%. Grade 3-4 diarrhea was present in 29.1% of the patients. The other treatment-related grade 3-4 toxicity was hand-foot syndrome observed in 3 patients (Table 4). Depending on the treatment's side effects, three patients required hospitalization, and ten patients required a dose reduction. In four patients, treatment could not be continued.

DISCUSSION

There is no standard algorithm for the use of chemotherapeutic agents to treat metastatic breast cancer.[2] Ixabepilone alone and the combination of ixabepilone-capecitabine are used as one of the treatment options in triple-negative and hormone receptor-positive patients. In our study, treatment response rates and progression-free survival times of 24 patients who had previously received at least three steps of chemotherapy, including an anthracycline, taxane, gemcitabine, and vinorelbine, were evaluated retrospectively. This study showed that ixabepilone is an effective treatment alternative in patients with heavily pretreated patients metastatic breast cancer despite its adverse effects. The overall response rate was 41%, the median PFS was 4 and 3.7 months for hormone receptor positive-patients and triple-negative patients, respectively.

Ixabepilone is a semisynthetic epothilone B analogue. Numerous in vitro studies have shown that ixabepilone has activity in cancer cells with upregulated beta III-tubulin expression associated with taxanes.[10,11]

Table 3. PFS analysis in subgroups of patients

	All histology	Triple negative	HR positive	P value
All patients	3.9	3.7	4.0	0.77
Ixabepilone	3.7	3.6	3.8	0.72
Ixabepilone-Capecitabine	4.0	3.7	4.1	0.54

HR= Hormone receptor

Table 4. Treatment-related grade 3-4 adverse events

Adverse events	n (%)
Anemia	7 (29.1)
Neutropenia	11 (45.8)
Thrombocytopenia	8 (33.3)
Febrile neutropenia	4 (16.6)
Diarrhea	7 (29.1)
Neuropathy	15 (62.5)
Hand and foot syndrome	3 (12.5)
Transaminase elevation	3 (12.5)

In many phase 2 and phase 3 studies, the efficacy of ixabepilone has been shown in patients with advanced-stage metastatic breast cancer who progressed after anthracycline and taxane treatment.[5-9] Median PFS was reported between 5.8 months and 7.6 months in ixabepilone studies after taxane and anthracycline treatments.[7,8] In combined applications with capecitabine, PFS advantage was obtained between 1.7 months and 4.2 months.[9] In our retrospective analysis of metastatic breast cancer patients who received ixabepilone, the median PFS was observed as approximately 3.8 months in patients who received both ixabepilone as a single-agent and ixabepilone in combination with capecitabine. In our study, it can be said that the administration of ixabepilone in more advanced steps and mainly as a single agent caused the PFS advantage obtained in combination therapy studies not to be provided.

In this study, only 5 of the patients received the ixabepilone-capecitabine combination regimen. All 19 patients who received single-agent ixabepilone had received capecitabine alone or in combination with gemcitabine, vinorelbine, paclitaxel, or docetaxel in previous treatment steps. The low number of patients receiving ixabepilone-capecitabine combination therapy might be attributed to the fact that all but five patients had previously received capecitabine.

In our study, similar to the results of ixabepilone Phase-III studies, it was observed that similar progression-free survival times were obtained in patients with both hormone receptor-positive and triple-negative histology, and ixabepilone provided similar PFS advantage regardless of hormone receptor status.[9] However, the fact that the hormone receptor-positive patients whose data were evaluated in our study received at least three steps of chemotherapy and at least two steps of hormonotherapy in the metastatic stage, and that ixabepilone was applied in the sixth step at the earliest, may have caused a shorter progression-free survival.

In the meta-analysis of ixabepilone Phase-III studies conducted by Rugo HS et al., neutropenia was observed with a rate of 21%, thrombocytopenia 1.3%, and anemia 3.3%.[9] In our study, the rates of grade 3-4 hematological toxicity were much higher in patients. The possible reason for this situation is that patients have decreased bone marrow reserves due to previous treatments. Similarly, the rate of neuropathy was 62.5% in our study, while it was 17% in the meta-analysis of Rugo HS et al.[9] In our study, patients received taxane treatments both in adjuvant therapy and in the metastatic stage, and both docetaxel and paclitaxel were administered in one part of treatment. Moreover, since all patients took vinorelbine, it probably contributed to the development of neuropathy before ixabepilone. Therefore, more neuropathic complaints can be expected with ixabepilone.

In another Phase-III study conducted by Rugo HS et al., combined paclitaxel applications, nab-paclitaxel, and ixabepilone with bevacizumab in chemotherapy-naive metastatic breast cancer patients were compared, and PFS was determined as 11 months, 7.4 months, and 9.3 months, respectively. Although ixabepilone is less effective in first-line treatment than paclitaxel and nab-paclitaxel treatments, it was found to be 7.4 months PFS in the first-line treatment. This study data also reveals that ixabepilone is more appropriate to be used in taxane-resistant patients. However, hematological toxicities, neuropathy, and the need for dose reduction were found to be higher in patients taking taxane compared to patients who received ixabepilone.[12] In our study, nearly half of the patients needed dose reduction, and four patients could not continue the treatment due to side effects. In this study, it was seen that the side effect problem was more common. In advanced steps, the increased side effects and toxicities associated with ixabepilone could be thought to be due to cumulative toxicity.

Especially, peripheral neuropathy is a serious problem with the use of ixabepilone. In a phase-II study by Vahdat LT et al., ixabepilone and eribulin mesylate were compared in metastatic breast cancer patients with progression with anthracycline and taxane treatments. ORR and CBR ratios were similar in 104 patients included in the study, and it was observed that ixabepilone was not superior to eribulin. Eribulin and ixabepilone were associated with neutropenia, peripheral neuropathy, and hematological toxicities, but there were no statistically significant differences in the adverse events rates. Neuropathy rates 48.0% vs. 33.3% and peripheral neuropathy rates 44.0% vs 31.4%. However, the difference was not statistically significant. Median PFS was 104 days vs. 95 days, which was longer in favor of eribulin, but the difference is not statistically significant.[13] On the other hand, the number of patients who could not continue treatment due to neuropathy was higher in the ixabepilone group. In addition, in the eribulin group, patients had previously received more step chemotherapy. However, neuropathy was less common in the eribulin mesylate group. This study's results reveal that eribulin mesylate may be more advantageous than ixabepilone in terms of neuropathy. In our study, the neuropathy rate of 62.5% was much higher than the rates in this study. On the other hand, PFS was similar. This situation may indicate that the use of ixabepilone in further steps can give similar results in terms of efficiency, but the side effects are significantly increased.

Our study is important in terms of evaluating the efficacy and reliability of ixabepilone in metastatic breast cancer patients who have consumed almost all of the classical chemotherapy options. On the other hand, the retrospective nature of our study, the small number of patients, and the fact that most of the patients took ixabepilone as a single agent, not in combination with capecitabine, are important limitations of our study.

Conclusion

Single-agent ixabepilone with or without capecitabine can be considered an option regimen to be used in both hormone receptor-positive / HER2 negative and triple-negative metastatic breast cancer patients. Although response is still possible in further lines of chemotherapy in the treatment of metastatic breast cancer, risk benefit ratio should always be considered since high rates of toxicity could hamper quality of life.

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