Epothilones in breast cancer: review of clinical experience

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Background: Drugs that target microtubules, including paclitaxel (Taxol) and docetaxel (Taxotere), are among the most commonly prescribed anticancer therapies. However, the utility of taxane-based therapies is limited by difficulties with formulation, administration, and resistance induced by P-glycoprotein. The epothilones are a novel class of antimicrotubule agents that have demonstrated antitumor activity in the setting of resistance.

Design: This review summarizes clinical studies of epothilones in patients with metastatic breast cancer. Data were identified by searches of PubMed and the Proceedings of the American Society of Clinical Oncology annual meetings from 2000 to 2006.

Results: The epothilones have demonstrated promising antitumor activity and manageable toxicity in phase II studies of heavily pretreated patients with metastatic breast cancer, including patients with resistance to taxanes and other cytotoxic agents. Neuropathy associated with ixabepilone appears to be schedule dependent and comparable to that observed with paclitaxel. Ixabepilone appears to be active in combination with capecitabine.

Conclusions: Ongoing and planned trials promise to elucidate the benefits of ixabepilone in combination with other agents including capecitabine, bevacizumab, and trastuzumab in patients with metastatic breast cancer as well as those receiving neo-adjuvant therapy.

Key words: epothilone, ixabepilone, KOS-862, metastatic breast cancer, phase II clinical trial, taxane-resistant

Introduction

Over the last 20 years, antimicrotubule agents have emerged as a mainstay of chemotherapeutic regimens for the treatment of breast cancer. Among these agents, the taxanes paclitaxel (Taxol, Bristol-Myers Squibb, New York) and docetaxel (Taxotere, Sanofi-Aventis, Bridgewater, NJ) are used most widely because of their proven efficacy in the metastatic and adjuvant settings, manageable toxicity profile, and lack of cross-resistance with anthracyclines. Although the introduction of these agents marked a significant advance for the treatment of breast cancer, their clinical utility is often limited by the rapid emergence of drug resistance conferred by cellular P-glycoprotein and alterations in β-tubulin. Other limitations include dose-limiting neurotoxicity and a Cremaphor® EL (BASF, Ludwigshafen, Germany)-based formulation that requires premedication to prevent hypersensitivity reaction [1].

Epothilones are naturally occurring macrolides that share a similar mechanism of action with taxanes but possess more potent antiproliferative activity in various tumor cell lines, particularly in the setting of taxane resistance [2–4]. Several epothilones have exhibited potent antitumor activity against multidrug-resistant in vitro cell culture and in vivo in human xenograft models [3]. Of greatest interest is the preclinical activity of epothilones in cell lines resistant to paclitaxel [2, 4, 5]. Moreover, the side-effect profiles of the epothilones appear to be comparable to those observed following taxane therapy.

Currently, two derivatives of epothilone B and D, ixabepilone and KOS-862, are under clinical investigation for the treatment of metastatic breast cancer. In phase I studies, ixabepilone and KOS-862 demonstrated promising antitumor activity in patients with taxane-refractory breast cancer [6–8]. Data from several phase II studies of ixabepilone have been published, and phase III investigations are under way in patients with advanced breast cancer previously treated with taxane and anthracycline therapy, including some patients with taxane-resistant disease. This review briefly summarizes the current clinical experience with epothilones in patients with metastatic breast cancer.

Phase I studies

Two phase I studies of ixabepilone reported objective responses in patients with resistant metastatic breast cancer [6, 7]. In the first trial, Abraham et al. [6] investigated a schedule of ixabepilone given as a 1-h infusion for 5 days every 21 days in 27 patients with advanced cancer. The maximum tolerated dose (MTD) was 6 mg/m²/day. Two partial responses (PR), assessed using Standard Response Evaluation Criteria in Solid Tumors (RECIST), in patients with breast cancer were observed. Objective responses were also observed in patients with cervical and basal cell carcinoma. The most
common toxicity was neutropenia; neurotoxicity in patients treated with ixabepilone was mild. In the second study, Mani et al. [7] investigated escalating dose levels of ixabepilone, 7.4–59.2 mg/m², administered as a 1-h infusion every 21 days. This study involved 25 patients with advanced malignancies. With ixabepilone 50 mg/m², neutropenia again was the dose-limiting toxicity, and the most common non-hematologic toxic effects were fatigue and generalized weakness (grade 3–4, seen in 9% of patients), followed by peripheral neuropathy and gastrointestinal discomfort. At lower doses, fatigue, abdominal pain, diarrhea, and neuropathy were observed, but at a much lower incidence. The MTD was 40 mg/m². Objective PRs occurred in two patients with paclitaxel-refractory ovarian cancer, one patient with taxane-naive breast cancer and one patient with docetaxel-refractory breast cancer.

phase II studies

Based on the promising activity of epothilones observed in phase I studies, several phase II studies (four of ixabepilone and one of KOS-862) were initiated in patients with metastatic breast cancer. Data from these studies have been reported in the literature and in abstract form (Table 1) [9–14].

Low et al. [10] reported the results of a phase II clinical trial (NCI-0229) that evaluated the safety and efficacy of ixabepilone in 37 women with metastatic and locally advanced breast cancer. All patients with measurable disease had received paclitaxel, docetaxel, or both, as prior neo-adjuvant, adjuvant, or metastatic therapy. Ixabepilone was administered at a rate of 6 mg/m²/day i.v. on days 1 through 5 every 3 weeks. Patients were excluded if they had brain metastases and/or neuropathy of grade 1 or higher at baseline, although an unlimited number of previous treatment regimens were allowed. All patients underwent a baseline biopsy before receiving ixabepilone. A post-treatment biopsy was obtained during the second cycle. In addition, glutamate (glu)-terminated and acetylated α-tubulin levels (posttranslational modifications reflecting an increased stability of microtubules) were measured in a subset of matched pre- and post-treatment tumor biopsy specimens. One patient achieved a complete response (CR), assessed using RECIST, and a PR was noted in seven patients, for an overall objective response rate of 22%. Stable disease (SD), assessed using RECIST but with neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since treatment started, was observed in 13 additional patients (35%). The most common grade 3 and 4 toxic effects included neutropenia (35%), febrile neutropenia (14%), fatigue (14%), diarrhea (11%), nausea and vomiting (5%), and myalgia and arthralgia (3%). The frequency of grade 3 or 4 sensory peripheral neuropathy was low (only 3%). Five patients had to discontinue treatment because of prolonged grade 2 or 3 neurotoxicity or other grade 3 and 4 non-hematologic toxic effects. Notably, levels of both glu-terminated and acetylated α-tubulin were increased in tumor biopsy samples after treatment, as compared with baseline. This trial demonstrated clinical activity for ixabepilone in heavily taxane-pretreated patients with breast cancer. Furthermore, the markers of microtubule stabilization appeared to correlate with a response to treatment.

Three additional studies reported in abstract form have evaluated a schedule of ixabepilone 40 mg/m² given as a 3-h infusion every 3 weeks [9, 11–13]. An international, multicenter, open-label phase II trial (CA-163009) assessed the safety and activity of ixabepilone in patients with taxane-resistant metastatic breast cancer. The results have been reported in abstract form [9]. Eligible patients were 18 years of age or older and had metastatic breast cancer that had progressed during or within 4 months of taxane therapy or within 6 months of adjuvant taxane only. In total, 49 patients received ixabepilone administered as a 3-h infusion at a dose of 40 mg/m² every 3 weeks. The majority of the patients had received at least two lines of prior taxane therapy and had progressed within 1 month of their last taxane dose. The overall objective tumor response rate was 12% [95% confidence interval (CI), 4.7% to 26.5%]. All the responders (n = 6) had an PR, five of six patients had not responded to prior taxane therapy. The responders received a median of 10.5 cycles (range, 5–15 cycles) and had a median duration of response of 10.4 months (95% CI, 6.3–22.0 months). Disease stabilization was achieved in 20 patients (41%). The majority of these patients (16 of 20; 80%) received more than four cycles of ixabepilone therapy. The median time to progression (TtP) was 2.2 months (95% CI, 1.4–3.2 months), and the median survival time was 7.9 months (95% CI, 6.1–14.5 months). Toxic effects associated with ixabepilone were mild to moderate and included grade 3 and 4 neutropenia (57%), grade 3 and 4 febrile neutropenia (4%), and grade 3 sensory neuropathy (12%). None of the enrolled patients suffered from grade 4 neuropathy while in the study [13].

Roche et al. [11] reported the results of a nonrandomized, phase II study that evaluated ixabepilone 40 mg/m² given as a 3-h infusion every 3 weeks in patients with metastatic breast cancer who had progressed following treatment with an anthracycline in the adjuvant setting. Of the 65 patients in the intent-to-treat analysis, 27 patients achieved a PR for an overall response rate of 42% (95% CI, 29.4% to 54.4%). The median duration of response was 8.2 months (95% CI, 5.7–10.2 months). Among the 27 patients who responded, six were progression free for >12 months. Median TtP was 4.8 months (95% CI, 4.2–7.6 months) and median survival was 22.0 months (95% CI, 15.6–27.0 months).

Data from a third phase II trial (CA-163081) of ixabepilone in patients with metastatic breast cancer with resistance to anthracycline, taxane, and capecitabine also have been reported in abstract form [12]. This single-arm phase II trial was designed to assess the objective response rate among patients treated with ixabepilone administered at a dose of 40 mg/m² >3 h every 3 weeks. Dosing continued for a maximum of 16 cycles or until evidence of disease progression. All of the patients were resistant to an anthracycline, a taxane, and capecitabine as defined by progression within 8 weeks in patients with metastatic disease or recurrence within 6 months in patients receiving adjuvant or neo-adjuvant treatment. Response was assessed by an independent radiology review committee (primary analysis) and by each investigator per response evaluation criteria in solid tumors. Of the 126 patients treated, 113 patients provided data assessable for response. The overall response rate as determined by the independent
radiology review committee was 11.5% (95% CI, 6.3% to 18.9%). PR was achieved in 13 patients and was sustained for a median of 5.7 months (range, 4.4–7.3 months). SD was the best outcome in 50% of patients, and 14% of patients had SD for >6 months. Median progression-free survival was 3.1 months; overall survival (OS) was 8.6 months. The most common grade 3/4 treatment-related adverse events were peripheral sensory neuropathy (14%), fatigue (10%), myalgia (7%), and stomatitis (6%). In general, neuropathy was cumulative and reversible through dose reduction. The time to resolution (to grade 1 or baseline) for grade 3/4 neuropathy was 5.4 weeks by Kaplan–Meier analysis. Grade 3/4 neutropenia and thrombocytopenia occurred in 54% and 7% of patients, respectively. Febrile neutropenia was reported in 3% of patients.

### KOS-862

A phase II trial of KOS-862 in women with anthracycline- and taxane-pretreated metastatic breast cancer has been reported in abstract form [14]. Twelve patients received KOS-862 100 mg/m² for 3 of every 4 weeks, administered as a 90-min infusion. At the time of reporting, 10 patients had provided data assessable for response. Of these, two patients achieved a PR, including one patient with hepatic metastases who achieved >50% tumor reduction and normalization of CA-163009 [9]. Median progression-free survival was 3.1 months; overall survival (OS) was 8.6 months. The most common grade 3/4 treatment-related adverse events were peripheral sensory neuropathy (14%), fatigue (10%), myalgia (7%), and stomatitis (6%). In general, neuropathy was cumulative and reversible through dose reduction. The time to resolution (to grade 1 or baseline) for grade 3/4 neuropathy was 5.4 weeks by Kaplan–Meier analysis. Grade 3/4 neutropenia and thrombocytopenia occurred in 54% and 7% of patients, respectively. Febrile neutropenia was reported in 3% of patients.

### ixabepilone

An ongoing phase II trial (CA-163080) is evaluating the pathologic response to ixabepilone as neo-adjuvant therapy in women with stage IIIA/IIIB breast cancer [15, 16]. Following treatment with ixabepilone 40 mg/m² given as a 3-h infusion once weekly for a 21-day cycle, patients underwent surgical resection and adjuvant anthracycline-based therapy. At the time of reporting, 164 patients had been enrolled, and data were available for 96 patients. A complete pathologic response in the breast was achieved by 29 patients (19%), 17 (11%) of whom also had complete pathologic response in axillary lymph nodes. Subanalysis of a cohort of estrogen receptor (ER)/HER-2-negative patients showed that 11 patients (26%) had a complete pathologic response in the breast, and eight patients (19%) also had complete pathologic response in axillary lymph nodes. Reported toxic effects included grade 3/4 neutropenia (34%), grade 2/3 arthralgia/myalgia (34%), neuropathy (13%), and mucositis (8%). In this study, ER status, as measured by FISH, was predictive of response to ixabepilone, with higher responses noted in ER-negative patients. Data from this study indicate that ixabepilone has a manageable toxicity profile and may offer promising clinical benefit to patients receiving neo-adjuvant treatment. The pathologic complete tumor response rate observed after four cycles of single-agent ixabepilone is comparable to that reported in studies of single-agent taxanes (Table 2) [15, 17–21].

Preliminary data from a second phase I/II study (CA-163031) of two different schedules of ixabepilone in combination with capecitabine in women with metastatic breast cancer were recently reported [22, 23]. This study involved patients previously treated with a taxane and an anthracycline in the adjuvant or metastatic setting. Patients who had received more than three prior chemotherapeutic regimens in the metastatic setting were excluded. Ixabepilone was given either as a 3-h infusion on day 1 or as a 1-h infusion for three consecutive days in combination with capecitabine given orally on days 1 through 14 every 21 days. At the time of reporting, 50 patients treated with ixabepilone 40 mg/m² as a 3-h infusion and capecitabine 2000 mg/m² were assessable for response. Of these, one patient (2%) achieved a CR and 14 patients (28%) achieved a PR, for an overall response rate of 30% (95% CI, 17.9% to 44.6%). An additional 16 patients (32%) experienced...
been noted at lower doses, and the 100-mg/m² cohort was given as a 90-min infusion weekly for 3 weeks following a loading dose of trastuzumab 4 mg/kg, followed by a weekly schedule of ixabepilone. The recommended phase II (and phase III) schedule is ixabepilone 40 mg/m² (3-h infusion on day 1 every 21 days). Of these patients, nine patients developed grade 2/3 peripheral neuropathy and two patients developed grade 3 peripheral neuropathy. The median time to onset was 144 days (range, 6–189 days). Among these 11 patients, peripheral neuropathy resolved in eight patients, within a median of 15 days (range, 6–346 days) after onset, but in three patients the peripheral neuropathy did not resolve during follow-ups at 76, 361, and 746 days after onset. These findings indicate that serious ixabepilone-induced neuropathy was relatively rare in patients who received the ixabepilone once daily for 5 days every 21 days.

In general, the rate of ixabepilone-associated neurotoxicity appears to be comparable to that for the neuropathy observed in patients treated with weekly paclitaxel [27]. Additionally, neuropathy associated with ixabepilone appears to be schedule dependent, with a lower frequency of neuropathy observed in phase I trials of three- and five-times-daily schedules [6, 28]. However, these schedules were associated with an increased frequency of severe diarrhea. As with the taxanes, the formulation of ixabepilone in polyoxyethylated castor oil may contribute, in part, to the neurotoxicity observed in clinical trials [29].

### ongoing studies

In phase II studies, the combination of ixabepilone and capecitabine demonstrated promising synergistic antitumor activity and a manageable safety profile in patients with metastatic breast cancer previously treated with a taxane and an anthracycline. Based on these findings, two randomized phase III studies have been initiated. These studies will evaluate ixabepilone 40 mg/m² administered every 3 weeks in combination with twice daily capecitabine 1000 mg/m² every 14 days, as compared with single-agent, twice daily capecitabine 1250 mg/m² every 14 days in patients with advanced breast cancer treated previously with an anthracycline or a taxane. The first study (CA-163046) has enrolled ~1200 patients. The primary end point of this study is OS. The second study (CA-163048) has enrolled 750 patients, and its primary end point is TTP.

Two phase II studies are currently evaluating the combination of ixabepilone and trastuzumab in patients with HER-2-positive breast cancer. The first phase II trial is ongoing in minimally pretreated patients with metastatic breast cancer.

### safety

Phase II studies have confirmed the findings of phase I studies indicating that sensory neuropathy is the primary toxicity associated with ixabepilone. In phase I studies, dose-limiting grade 3/4 neutropenia and sensory neuropathy were observed with both schedules of ixabepilone tested: once every 21 days and once weekly [7, 25]. The nature and incidence of peripheral neuropathy associated with ixabepilone treatment was specifically assessed among 47 patients with metastatic breast cancer who received more than two cycles of ixabepilone 6 mg/m² once daily for five consecutive days every 21 days [26]. Of these patients, nine patients developed grade 2/3 peripheral neuropathy and two patients developed grade 3 peripheral neuropathy. The median time to onset was 144 days (range, 6–189 days). Among these 11 patients, peripheral neuropathy resolved in eight patients, within a median of 15 days (range, 6–346 days) after onset, but in three patients the peripheral neuropathy did not resolve during follow-ups at 76, 361, and 746 days after onset. These findings indicate that serious ixabepilone-induced neuropathy was relatively rare in patients who received the ixabepilone once daily for 5 days every 21 days.

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the combination of carboplatin and trastuzumab plus ixabepilone in patients with stage IV breast cancer and recurrent breast cancer. Patients will receive trastuzumab on days 1, 8, 15, and 22, with ixabepilone and carboplatin given on days 1, 8, and 15. Treatment is repeated every 28 days for up to six courses if toxicity is deemed acceptable. The projected accrual is 10–60 patients >6 months, and the primary objective is to determine response rate. A second study is evaluating ixabepilone combined with trastuzumab in women with stage IV or recurrent breast cancer. Patients will receive trastuzumab >30–90 min and ixabepilone >3 h on day 1. Cycles are repeated every 21 days in the absence of disease progression or unacceptable toxicity. Patients are being stratified according to prior trastuzumab therapy, and a total of 60 patients (30 per stratified group) is planned for accrual. The study population will include patients who have received no prior treatment for metastatic breast cancer except hormone therapy and another cohort who have received prior chemotherapy plus trastuzumab. The primary objective of this trial is to determine response rate.

A third phase II, open-label, randomized study (CA-163115) is being planned to investigate two schedules of ixabepilone plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer. Patients will be randomized to one of three treatment arms: ixabepilone 16 mg/m² administered as a 1-h infusion weekly for 3 weeks plus bevacizumab 10 mg/kg every 2 weeks; ixabepilone 40 mg/m² administered as a 3-h infusion every 3 weeks plus bevacizumab 15 mg/kg every 3 weeks; or paclitaxel 90 mg/m² administered as a 1-h infusion weekly for 3 weeks plus bevacizumab 10 mg/kg every 2 weeks. The target enrollment for this study is 120 patients. The primary objective of this study is to determine the response rate. Secondary objectives include duration of response, time to response, progression-free survival at week 24, progression-free survival, and OS.

The combination of ixabepilone with liposomal doxorubicin in patients with metastatic breast cancer is also under clinical investigation. This phase I/II trial involves patients with previously treated metastatic breast, ovarian, epithelial, primary peritoneal cavity, or fallopian tube cancer. The target enrollment is 20–50 patients. All study patients will receive liposomal pegylated doxorubicin and ixabepilone at the MTD determined in the phase I portion of the trial. They will be followed for up to 2 years after treatment to determine safety and efficacy.

Conclusion

The epothilones have demonstrated promising antitumor activity and manageable toxicity in phase II studies of heavily pretreated patients with metastatic breast cancer, including patients who are resistant to taxanes and other cytotoxic agents. Neuropathy associated with ixabepilone appears to be schedule dependent and comparable to that observed with paclitaxel. Moreover, ixabepilone can be administered without steroid premedication and does not cause alopecia. Ixabepilone appears to be active in combination with capecitabine. Ongoing and planned trials promise to elucidate the benefits of ixabepilone in combination with other agents, including capecitabine, bevacizumab, and trastuzumab, in patients with metastatic breast cancer as well as in the neo-adjuvant setting.

Disclosures

MNF has reported no financial relationships with companies whose products are mentioned in this supplement.

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