New Drug

Ixabepilone (Ixempra), a novel microtubule inhibitor for the treatment of breast cancer

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ABSTRACT Ixabepilone, a semisynthetic analogue of epothilone B, a novel microtubule-stabilizing agent, has been approved by the FDA for treatment of advanced breast cancer. Preclinical data suggest that its mechanisms of actions are different from those of the most commonly used microtubule-stabilizing agent, paclitaxel. This information in addition to the cytotoxicity of this drug in taxane-resistant cell lines in multiple solid tumors supports the fact that ixabepilone may be active in taxane-resistant tumors. It is indicated for use in combination with capecitabine (Xeloda Roche) for treatment of locally advanced or metastatic breast cancer after failure of an anthracycline such as doxorubicin (Adriamycin) and a taxane such as paclitaxel (Taxol, and others). It is also approved as monotherapy for treatment of metastatic or locally advanced breast cancer after an anthracycline, a taxane and capecitabine have failed.

KeyWords: Ixabepilone; breast cancer

Ixabepilone, a semisynthetic analogue of epothilone B, a novel microtubule-stabilizing agent, has been approved by the FDA for treatment of advanced breast cancer. Preclinical data suggest that its mechanisms of actions are different from those of the most commonly used microtubule-stabilizing agent, paclitaxel. This information in addition to the cytotoxicity of this drug in taxane-resistant cell lines in multiple solid tumors supports the fact that ixabepilone may be active in taxane-resistant tumors. It is indicated for use in combination with capecitabine (Xeloda Roche) for treatment of locally advanced or metastatic breast cancer after failure of an anthracycline such as doxorubicin (Adriamycin) and a taxane such as paclitaxel (Taxol, and others). It is also approved as monotherapy for treatment of metastatic or locally advanced breast cancer after an anthracycline, a taxane and capecitabine have failed.

MECHANISM OF ACTION — Epothilones are cytotoxic macrolides derived from bacterial fermentation. They are similar to taxanes in that they bind to and stabilize microtubules resulting in mitotic arrest and apoptosis, but they differ structurally and are not affected by the common mechanisms of taxane resistance (1). (Fig. 1)

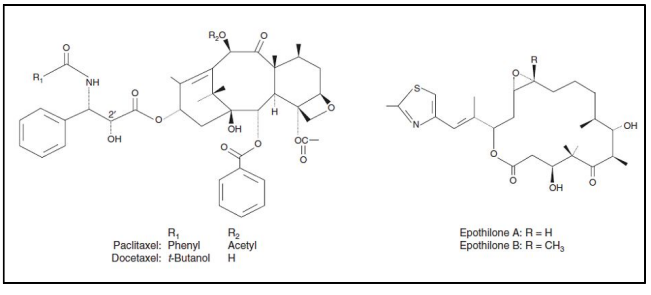

Fig.1 Taxanes and epothilones are structurally unrelated microtubule stabilizing agents but share a common pharmacophore that allows binding to tubulin.

PRECLINICAL STUDIES — In preclinical models, ixabepilone induced objective responses in 18 of 29 solid tumor xenograft models at the maximum-tolerated dose (MTD) of 10 mg/kg (2). Paclitaxel (15 20 mg/kg) administered on the same schedule failed to induce regression of three cell lines highly sensitive to ixabepilone (3). The ixabepilone exposure achieved at 10 mg/kg in mice was similar to that reached with the 40-mg/m2 dose given once every three weeks (q3w) in phase II and III clinical trials (2,3)—a regimen that produced significant antitumor activity in patients. Additional preclinical studies have demonstrated the synergistic antitumor activity of ixabepilone with other chemotherapeutic and biologic agents including capecitabine (4), cetuximab (4), trastuzumab

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(5), and bevacizumab (6).

Ixabepilone possesses high microtubule-stabilizing activity and low susceptibility to key mechanisms of drug resistance such as P-gp and MRP-1, as well as β III-tubulin overexpression (7-9). Although its action is similar to that of paclitaxel (10), the in vivo antitumor activity of ixabepilone is superior to that of paclitaxel in both paclitaxelsensitive and paclitaxel-resistant cell lines and tumors (8). Based on preclinical data supporting its efficacy in paclitaxel-sensitive and paclitaxel-resistant cell lines, the clinical development of ixabepilone in breast cancer has focused on patients with tumors that had failed prior treatment with anthracyclines and/or taxanes (8,9).

CLINICAL STUDIES — *Monotherapy* In a clinical trial of ixabepilone (40 mg/m2 as a 3-hour infusion once every 21 days for a median of 4 cycles) in patients with metastatic or locally advanced breast cancer resistant to an anthracycline, a taxane and capecitabine, 13 of 113 patients (11.5%) had a partial objective response. The median duration of response was 5.7 months. An additional 15 patients (13%) had stable disease for >6 months. Median progression-free and overall survival were 3.1 and 8.6 months, respectively (11). In the neoadjuvant setting, ixabepilone has also shown activity as a single agent, with 61% of patients achieving an objective tumor response in a phase II study (12). A pathologic complete response in the breast (pCRB) was achieved in 19% of patients after a maximum of four cycles of ixabepilone at a dose of 40 mg/m2 on a 21-day cycle; this figure was higher than values for up to four cycles of a singleagent taxane described in other studies (7% 10%) (13). Although higher pCR rates have been reported with taxanes, these usually require a greater number of cycles and/or combination regimens (14,15). The breast-conserving surgery rate after ixabepilone treatment was 32% (12).

Combination Therapy In a randomized open-label trial in 752 women with metastatic or locally advanced breast cancer resistant to anthracyclines and taxanes, patients received either ixabepilone 40 mg/m2 once every 21 days plus capecitabine 2000 mg/m2/day on days 1-14 every 21 days for a median of 5 cycles, or capecitabine monotherapy 2500 mg/m2/day on days 1-14 every 21 days for a median of 4 cycles. The combination arm prolonged progression-free survival (the primary endpoint) compared to capecitabine alone (median 5.8 vs. 4.2 months p=0.0003). (Fig. 2) The objective tumor response rate was also greater in the combination arm (35% vs. 14%; p<0.0001). The median response duration with the combination was 6.4 months compared to 5.6 months with monotherapy (16).

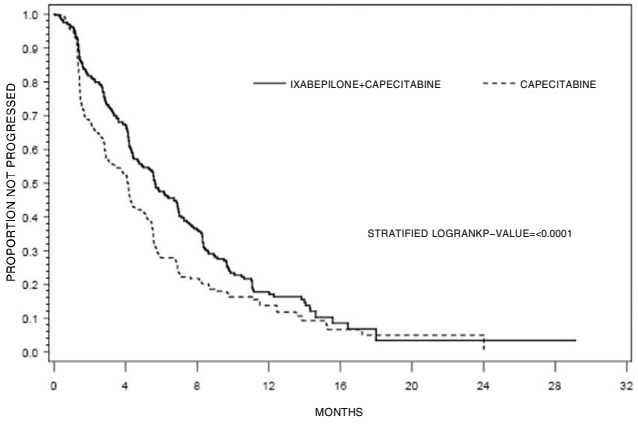

Fig.2 The combination ixabepilone and capecitabine prolonged progression–free survival compared to capecitabine alone. (Ref. 16)

ADVERSE EFFECTS — The incidence of adverse effects was generally higher in patients treated with both ixabepilone and capecitabine than in those who received ixabepilone alone. Periph eral sensory neuropathy was common and occurred early in treat ment. Other adverse effects reported in >20% of patients with com bination therapy or monotherapy were fatigue/asthenia, myal gia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea and musculoskeletal pain. Patches of hyperpigmentation and erythema have been reported (17). Grade 3 or 4 neutropenia oc curred in 68% of patients who received combination therapy and in 54% of those treated with ixabepilone alone.

DRUG INTERACTIONS — Ixabepilone is a CYP3A4 sub strate. The strong 3A4 inhibitor ketoconazole (Nizoral, and others) increased the AUC of ixabepilone by 79%. Concomitant adminis tration of strong CYP3A4 inducers, such as rifampin, may result in subtherapeutic concentrations of ixabepilone. In vitro, ixabepilone is a weak inhibitor of CYP3A4, but it does not inhibit any CYP en zymes at clinically relevant concentrations and is unlikely to affect the plasma concentrations of concomitantly administered drugs.

DOSAGE, ADMINISTRATION AND COST —Ixabepilone is administered in a castor oil/alcohol solution (Cremophor EL), which has been associated with hypersensitivity reactions; prophy lactic H1- and H2-antihistamines are recommended, but severe hy persensitivity reactions occurred nevertheless in 1% of patients in clinical trials. The recommended dose of ixabepilone is 40 mg/m2 (max 88 mg) administered over 3 hours once every 3 weeks. The dose should be reduced by half if strong CYP3A4 inhibitors are taken concomitantly (18). Patients with an AST or ALT >2.5xULN or an elevated serum bilirubin concentration should not be treated with ixabepilone and capecitabine. The cost for ixabepilone thera py (generally about four cycles of monotherapy or five cycles of combination therapy) for an average patient would range from about $20,000 to $25,000.

CONCLUSION — Ixabepilone (Ixempra) in combination with capecitabine can prolong progression-free survival in patients with metastatic or locally advanced breast cancer resistant to an anthra cycline and a taxane. It has also been modestly effective when used as monotherapy after anthracyclines, taxanes and capecitabine have failed. Major toxicities include peripheral sensory neuropathy

and neutropenia. Ixabepilone's role in treating early breast cancer remains to be determined.

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