ABSTRACT

Drugs that target microtubules, such as the taxanes and vinca alkaloids, are among the most frequently prescribed antitumor therapies used today. Microtubules are a major structural part of cells found in the cytoskeleton, and they have a fundamental role in critical cellular functions. Presently, standard chemotherapy regimens used in early-stage breast cancer generally include a taxane, such as paclitaxel or docetaxel, and an anthracycline, such as doxorubicin or epirubicin. For patients who present with recurrent advanced/metastatic breast cancer, multidrug chemotherapy resistance is a potential treatment challenge, particularly in the triple-negative (estrogen receptor negative, progesterone receptor negative, and human epidermal growth factor receptor 2 [HER2/NEU] negative) patient population. The epothilones are a new class of antitumor cytotoxic therapy that target microtubules and are presently being studied in the metastatic breast cancer setting, as well as in other tumor types. The cytotoxic activity of epothilones, like that of taxanes, has been linked to the stabilization of microtubules resulting in mitotic arrest and apoptosis (cell death). Although the 2 classes of cytotoxic therapies share many similarities, epothilones maintain a distinctly different structure from that of taxanes and do not seem to be affected by common mechanisms of drug resistance. This new class of therapy has demonstrated activity in multiple cell lines that are resistant to other agents, including taxanes, anthracyclines, and capecitabine. Several phase II and phase III studies have evaluated use of one of the epothilones, ixabepilone, in the treatment of advanced breast cancer. Ixabepilone has been generally well tolerated by patients and has demonstrated antitumor activity in patients who have been heavily pretreated, as well as in the treatment-naive patient setting. The most common adverse effects have included fatigue, neuropathy that was observed to be cumulative but reversible, and neutropenia. Most recently, a large, randomized, double-blind clinical trial compared combination therapy with capecitabine and ixabepilone to capecitabine alone in patients with advanced breast cancer who had previously been treated with an anthracycline and a taxane. This study demonstrated that the combination treatment strategy was superior to capecitabine alone. The US Food and Drug Administration recently approved ixabepilone in combination with capecitabine for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane. Ixabepilone also was approved as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine. Other epothilones are in earlier stages of clinical testing for breast cancer.


The management of breast cancer has evolved significantly during the past several decades, with the use of less invasive surgical techniques and the incorporation of new agents, such as the anthracyclines, taxanes, aromatase inhibitors, trastuzumab, and lapatinib. The use of anthracycline-and taxane-containing regimens in the adjuvant setting has improved the overall survival of patients with breast cancer considerably. Despite these treatment advances in early-stage breast cancer, approximately 30% of women will develop recurrent...
advanced/metastatic disease. The 5-year survival rate for patients with stage IV breast cancer is still only approximately 20%, and the median duration of survival following a diagnosis of metastatic disease is roughly 2 to 3 years. As summarized in the Figure, the management of metastatic breast cancer is based on several factors, including the extent of metastases (limited or visceral crisis), hormone receptor status, human epidermal growth factor receptor 2 (HER2)/NEU status, and recurrence-free interval.

It is anticipated that increased numbers of patients will have pretreated metastatic breast cancer that has developed mechanisms of resistance to multiple prior agents, including anthracyclines and taxanes, and novel strategies are needed for the management of metastatic breast cancer, particularly in the triple-negative (estrogen receptor negative, progesterone receptor negative, HER2 negative) setting.

**Figure. Management of Metastatic Breast Cancer**

- **Advanced Breast Cancer**
  - Limited metastases
  - Positive hormone receptors (60%–70%)
  - Hormone-sensitive
  - Recurrence-free interval ≥1–2 years
  - HER2 + (20%–25%)

- **Extensive metastases or visceral crisis**
  - Negative hormone receptors
  - Not sensitive to hormones
  - HER2 + (20%–25%)

**First-line hormonal therapy**

- +/-HER2 targeted therapy

**Response**

- No Response
- No progression
- Progression of disease

**If disease progresses, second-line hormonal therapy**

- Second-line chemotherapy

HER2 = human epidermal growth factor receptor 2.


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**Table 1. Indications, Dosing, Warnings, and Precautions for Ixabepilone**

| Indications | In combination with capecitabine for treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane.
|            | As monotherapy for treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine. |
| Dosing information | Recommended dose: 40 mg/m² IV over 3 h q3wk
|                     | Doses for body surface area >2.2 m² should be calculated based on 2.2 m².
|                     | The combination of ixabepilone and capecitabine is contraindicated in patients with AST or ALT >2.5 x the upper limit of normal or bilirubin >1 x the upper limit of normal.
|                     | Use of strong inhibitors of CYP3A4 should be avoided (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, amprenavir, indinavir, nelfinavir, delavirdine, or voriconazole).
|                     | If used with a strong inhibitor of CYP3A4, dose should be decreased to 20 mg/m².
| Preparation and IV administration | Patients with previous hypersensitivity reactions to ixabepilone should be premedicated with corticosteroids, in addition to H₁ and H₂ antagonists.
|                     | Only supplied diluent must be used to reconstitute ixabepilone.
|                     | Ixabepilone should be stored under refrigeration at 2°C–8°C (36°F–46°F) in original packaging and protected from light.
|                     | Remove from packaging and allow to stand at room temperature for 30 min before reconstituting.
|                     | Constituted solution must be further diluted with lactated Ringer’s solution in DEHP-free [di-(2-ethylhexyl)] bags.
|                     | Final concentration for infusion should be between 0.2 mg/mL and 0.6 mg/mL.
|                     | Reconstituted solution is stable at room temperature for up to 6 h.
| Warnings and precautions | Peripheral neuropathy: Patients with new or worsening symptoms may require dose reduction or delay in treatment.
|                     | Myelosuppression: primarily manifested as dose-dependent neutropenia.
|                     | In combination with capecitabine, rates of febrile neutropenia and infection were 5% and 6%, respectively.
|                     | As monotherapy, rates of febrile neutropenia and infection were 3% and 5%, respectively.
|                     | Patients with history of severe hypersensitivity reaction to agents containing Cremophor EL or its derivatives (eg, poloxymethylefyl castor oil) should not receive ixabepilone.
|                     | Ixabepilone may cause fetal harm when administered to pregnant women (pregnancy category D).
|                     | Reconstituted product contains alcohol: may cause cognitive impairment or other effects of alcohol.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; IV = intravenous.

and HER2 negative) patient population. The epothilones are a new class of antitumor agents that are being evaluated for the treatment of breast cancer and other cancer types. Several recent clinical studies have suggested that epothilones are effective against tumor cells that are resistant to other therapies. Ixabepilone, the first of these agents to enter clinical practice, was recently approved in the United States for the treatment of metastatic or locally advanced breast cancer. Ixabepilone is indicated in combination with capecitabine for patients who have not responded adequately to treatment with an anthracycline and a taxane, or who have not responded adequately to taxane therapy and for whom anthracycline therapy is contraindicated. Ixabepilone also is indicated as monotherapy for patients with metastatic or locally advanced breast cancer who have tumors that are resistant or refractory to anthracyclines, taxanes, and capecitabine. The indications and usage of ixabepilone, dosage and administration, instructions for preparation, and warnings and precautions are summarized in Table 1. Guidelines for dosing of ixabepilone are summarized in Tables 2 and 3.

**OVERCOMING MULTIDRUG RESISTANCE: TARGETING MICROTUBULES**

Agents that target specific phases of the cell cycle during mitosis play a critical role in most cancer therapies. Microtubules are filaments that act as major structural components of cells and play a fundamental role in diverse cellular functions, including cell division, growth, motility, cell shape, and cell signaling. Microtubules are a critical component of the mitotic spindle, the intracellular structure by which chromosomes are aligned during the process of cell division.

Microtubules are formed by the polymerization of heterodimeric subunits, α tubulin, and β tubulin. The polymerization and depolymerization of microtubules lead to the formation and functioning of the mitotic spindle. Agents that target microtubules are the most commonly used antitumor therapies and include the taxanes and vinca alkaloids. By targeting microtubules there is interference with the function of the mitotic spindle and the process of cell division is blocked. Agents that target microtubules may be divided into 2 groups: destabilizing agents (which interfere with the polymerization of tubulin and decrease the formation of microtubules) and stabilizing agents (which prevent microtubule breakdown and cause the formation of microtubule bundles within cells). Taxanes are potent microtubule stabilizers, have been the mainstay for treatment of metastatic breast cancer for many years, and have recently become the standard of care for the treatment of metastatic breast cancer.

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<table>
<thead>
<tr>
<th>Table 2. Dose Adjustment Guidelines for Ixabepilone*</th>
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<tbody>
<tr>
<td><strong>Ixabepilone (monotherapy or combination therapy)</strong></td>
</tr>
<tr>
<td>Nonhematologic:</td>
</tr>
<tr>
<td>Grade 2 neuropathy (moderate) lasting ≥7 d</td>
</tr>
<tr>
<td>Grade 3 neuropathy (severe) lasting &lt;7 d</td>
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<tr>
<td>Grade 3 neuropathy (severe) lasting ≥7 d or disabling neuropathy</td>
</tr>
<tr>
<td>Any grade 3 toxicity (severe) other than neuropathy</td>
</tr>
<tr>
<td>Transient grade 3 arthralgia/myalgia or fatigue</td>
</tr>
<tr>
<td>Grade 3 hand-foot syndrome (palmar-plantar erythrodysthesia)</td>
</tr>
<tr>
<td>Any grade 4 toxicity</td>
</tr>
<tr>
<td>Hematologic:</td>
</tr>
<tr>
<td>Neutrophil &lt;500 cells/mm³ for ≥7 d</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>Platelets &lt;25 000/mm³ or platelets 50 000/mm³ with bleeding</td>
</tr>
</tbody>
</table>

| Capecitabine (when used in combination with ixabepilone) | Capecitabine Dose Modification |
|---------------------------------------------------------|
| Nonhematologic: | |
| Platelets <25 000/mm³ or 50 000/mm³ with bleeding | Hold for concurrent diarrhea or stomatitis until platelet count >50 000/mm³, then continue at same dose. |
| Hematologic: | |
| Neutrophils <500 cells/mm³ for ≥7 days or febrile neutropenia | Hold for concurrent diarrhea or stomatitis until neutrophil count >1000 cells/mm³, then continue at same dose. |

treatment of early breast cancer. In contrast, vinca alkaloids are microtubule destabilizers. Vinca alkaloids are also frequently used in the metastatic breast cancer setting.9

A new class of nontaxane microtubule stabilizing agents—the epothilones—has received recent attention as potential anticancer agents. The epothilones were discovered in 1987 in soil bacteria from southern Africa and are produced by the fermentation of the myxobacterium Sorangium cellulosum.10 By binding to and stabilizing β tubulin, epothilones induce the polymerization of tubulin into microtubules. This disrupts the normal formation and breakdown of microtubules, resulting in cell cycle arrest and apoptosis.6,11 Epothilone analogues that are being evaluated for the treatment of patients with cancer include ixabepilone, patupilone, BMS-310705, ZK-EPO, and KOS-862.8,10 At present, nearly all of these agents are at early stages of clinical testing. Epothilones cause the arrest of the cell cycle by affecting tubulin polymerization, but with a mode of action that is distinct from the taxanes. In vitro studies suggest that the epothilones are approximately 5- to 25-fold more potent antitumor agents than the taxanes. They appear to be less susceptible to mechanisms that produce treatment resistance than taxanes.10 In vitro and in vivo studies have demonstrated high levels of antitumor activity of the epothilones in tumor cell lines with multidrug resistance or with mutations affecting tubulin, both of which are associated with reduced efficacy when treated with paclitaxel.10

**EPOTHILONES: CLINICAL STUDIES OF PATIENTS WITH BREAST CANCER**

Ixabepilone, a semisynthetic analogue of the natural macrolide antibiotic epothilone B, has been evaluated more extensively than the other epothilones for the treatment of breast cancer. It is a potent inducer of microtubule stabilization with demonstrated efficacy in taxane-resistant tumors and in other cell lines in preclinical studies.8 Ixabepilone is a poor substrate for efflux transporters, such as the multidrug resistance related protein and P-glycoprotein that are involved in drug resistance mechanisms. Phase I studies evaluated different dosing regimens of ixabepilone. Safe and tolerable dosing schedules included 40 mg/m² intravenous (IV) over 3 hours every 3 weeks, 6 mg/m² IV over 1 hour for 5 consecutive days every 3 weeks, 25 mg/m² IV over 1 hour weekly on a 21 day cycle (3 weeks on with 1 week off), and 20 mg/m² IV over 1 hour weekly on a 28-day cycle. The most commonly observed adverse events were peripheral neuropathy, fatigue, and neutropenia.8

**PHASE II CLINICAL TRIALS**

A phase II study of ixabepilone in taxane-naïve patients with metastatic breast cancer demonstrated response rates comparable to those observed with single-agent taxane therapy (25%–68%).13 Twenty-three patients were treated with ixabepilone 6 mg/m² IV, over 1 hour, daily for 5 days, once every 3 weeks. Patients were premedicated with diphenhydramine 25 mg to 50 mg IV or orally, or hydroxyzine 25 mg orally, with ranitidine 50 mg IV 30 to 60 minutes before treatment. Treatment was generally well tolerated: 5 of 23 patients experienced grade 3 or grade 4 neutropenia, and the most frequent nonhematologic events observed were fatigue, peripheral neuropathy, and nail changes. The efficacy of treatment was evaluated for all 23 patients. The objective response rate was 57%, with 13 patients having partial responses and 26% of the patients maintaining stable disease for at least 6 weeks. The median time to progression was 5.5 months.

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**Table 3. Dose Adjustment Guidelines for Ixabepilone Monotherapy in Patients with Hepatic Impairment**

<table>
<thead>
<tr>
<th>Transaminase Levels</th>
<th>Bilirubin Levels *</th>
<th>Ixabepilone,† mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>AST and ALT ≤2.5 x ULN and ≤1 x ULN</td>
<td>40</td>
</tr>
<tr>
<td>Moderate</td>
<td>AST or ALT ≤10 x ULN and &gt;1.5 x ULN</td>
<td>32</td>
</tr>
</tbody>
</table>

* Excluding patients whose total bilirubin is elevated due to Gilbert’s disease.
† Dosage recommendations are for first course of therapy; further decreases in subsequent courses should be based on individual tolerance.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Reprinted with permission from Ixabepilone [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2007.6
Another phase II study examined ixabepilone in heavily pretreated taxane-resistant patients with metastatic breast cancer. In this study, ixabepilone was administered as a 3-hour IV infusion at a dose of 40 mg/m² every 3 weeks. Treatment was continued until disease progression or until the development of an unacceptable toxicity. Fatigue and sensory neuropathy were the most commonly reported adverse events. Grade 3 fatigue was reported by 27% of patients, and grade 3 sensory neuropathy by 7%. Treatment efficacy was evaluated in 49 patients. The objective tumor response rate was 12%, with all responders achieving a partial response and 41% of patients maintaining stable disease. The median duration of response was 10.4 months, and the median time to progression was 2.2 months. Ixabepilone demonstrated antitumor activity in heavily pretreated patients with metastatic breast cancer with extensive disease resistant to taxane therapy.

A third phase II trial evaluated ixabepilone in women with metastatic breast cancer resistant to taxane, anthracycline, and capecitabine therapy. Patients received ixabepilone at a dose of 40 mg/m² over 3 hours on day 1 of a 21-day cycle. Eligibility for this study included: diagnosis of metastatic breast cancer; resistance to anthracyclines, taxanes, and capecitabine; disease progression while receiving therapy in metastatic setting within 8 weeks of last treatment or recurrence within 6 months of adjuvant or neoadjuvant anthracycline or taxane therapy; completion of at least 2 cycles of each regimen in any order; no more than 5 regimens in total, with 3 in the metastatic setting allowed; and hormone receptor-positive patients who have progressed and are no longer candidates for endocrine therapy. Independent review suggested that 13% of patients achieved a partial response; response rates are summarized in Table 4. In this study, adverse events included sensory neuropathy, were associated with increasing cumulative ixabepilone exposure, and were usually managed by reducing the dose. A total of 17 patients developed grade 3 or grade 4 neuropathy after a median of 4 treatment cycles. For 13 patients, neuropathy resolved to baseline or to grade 1, with a median time to resolution of 5.4 weeks.

In another recent phase II study, the use of ixabepilone as neoadjuvant therapy in patients with breast cancer was examined. A total of 164 women with stage IIA to IIIB breast cancer with tumors larger than 3 cm at diagnosis received 4 cycles of ixabepilone 40 mg/m² over 3 hours on day 1 of a 21-day cycle, followed by surgery within 3 to 4 weeks of completion of therapy. Adjuvant chemotherapy with an anthracycline combination regimen followed by radiotherapy and hormone therapy where indicated followed surgery. A complete pathological response in the breast was noted for 19% of patients, and 11% achieved a complete pathological response in the breast and axilla. Genomic studies indicated that patients with hormone receptor-negative disease were more likely to respond to ixabepilone in this study. As shown in Table 5, the complete pathological response rates with single-agent ixabepilone are comparable to other neoadjuvant regimens studied.

Ixabepilone is a novel epothilone that has demonstrated antitumor activity in multiple phase II trials in patients with metastatic breast cancer who have been extensively treated with other therapies. Neuropathy and other treatment-related adverse events have been manageable for these patients. Studies are also examining the safety and efficacy of ixabepilone in combination with trastuzumab in patients with HER2/NEU-positive metastatic breast cancer, and in combination with bevacizumab in patients with metastatic breast cancer.

PHASE III CLINICAL TRIAL

In a recent large, randomized, double-blind phase III study in patients with metastatic breast cancer, ixabepilone in combination with capecitabine was evaluated in comparison to capecitabine alone. A total of...

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Objective Response Rate, % (CI)</th>
<th>Partial Response, n (%)</th>
<th>Stable Disease, n (%)</th>
<th>Progressive Disease, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator</td>
<td>18.6 (11.9–27)</td>
<td>21 (19)</td>
<td>51 (45)</td>
<td>33 (29)</td>
</tr>
<tr>
<td>Independent review</td>
<td>11.5 (6.3–18.9)</td>
<td>13 (12)</td>
<td>57 (50)</td>
<td>36 (32)</td>
</tr>
</tbody>
</table>

CI = confidence interval.
Data from Perez et al. 13
of 752 patients with advanced breast cancer who were previously treated with an anthracycline and a taxane participated in this study. Patients were randomly assigned to treatment with ixabepilone 40 mg/m² IV over 3 hours on day 1 of a 21-day cycle in combination with capecitabine 1000 mg/m² orally twice daily for 14 days consecutively followed by 1 week off, or to single-agent capecitabine 1250 mg/m² orally twice daily for 14 days consecutively followed by 1 week off. Patients were eligible to participate in the trial if they had adequate organ function, a life expectancy of at least 12 weeks, had previously been treated with an anthracycline and a taxane, and had received no more than 2 previous cytotoxic regimens. Visceral disease was present in 84% of the patients. Treatment with ixabepilone in combination with capecitabine was superior to single-agent capecitabine. Patients in the combination treatment arm had significantly greater progression-free survival and had an objective response rate that was more than double the objective response rate of capecitabine alone (Table 6). Grade 3 and 4 adverse events included neuropathy (26% with combination treatment vs 0% for capecitabine alone), hand-foot syndrome (18% vs 17%), fatigue (9% vs 3%), and neutropenia (grade 3, 32% vs 9%; grade 4, 36% vs 2%).

Other epothilones are in the early stages of clinical development, and the efficacy and safety of these agents for the treatment of breast cancer are being studied. Patupilone was evaluated in a phase I dose-finding clinical trial in patients with advanced breast cancer and other solid tumors who had failed to respond to standard therapy. BMS-310705 has been evaluated in preclinical studies, and in early clinical trials of breast cancer; the results of these clinical trials have not yet been reported. Other agents, such as KOS-862 and ZK-EPO, have not yet been evaluated for breast cancer therapy.

**Nursing Implications of Epothilone Therapy**

Ixabepilone is a semisynthetic agent that is formulated in Cremophor. Premedications include an H₁ blocker and H₂ blocker. In clinical trials, ixabepilone has been evaluated at a dose of 40 mg/m² IV over 3 hours on day 1 of a 21-day cycle. Adverse effects that should be anticipated with ixabepilone therapy include neuropathy, myelosuppression, alopecia, fatigue,

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients, n</th>
<th>Agent</th>
<th>Cycles, n</th>
<th>pCR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B18</td>
<td>683</td>
<td>AC</td>
<td>x4</td>
<td>13</td>
</tr>
<tr>
<td>Gradishar</td>
<td>41</td>
<td>Docetaxel</td>
<td>x4</td>
<td>3</td>
</tr>
<tr>
<td>Buzdar</td>
<td>87</td>
<td>Paclitaxel</td>
<td>x4</td>
<td>9</td>
</tr>
<tr>
<td>Current study</td>
<td>161</td>
<td>Ixabepilone</td>
<td>x4</td>
<td>18</td>
</tr>
<tr>
<td>Amat</td>
<td>88</td>
<td>Docetaxel</td>
<td>x6</td>
<td>20/36</td>
</tr>
<tr>
<td>Estevez</td>
<td>56</td>
<td>Docetaxel Qwk</td>
<td>x12 wk</td>
<td>16*</td>
</tr>
</tbody>
</table>

*Response in breast or axilla.
AC = doxorubicin-cyclophosphamide; NSABP B18 = National Surgical Adjuvant Breast and Bowel Project B18; pCR = pathologic complete response.

Data from Fisher et al.17; Gradishar et al.18; Buzdar et al.19; Amat et al.20; and Estevez et al.21

<table>
<thead>
<tr>
<th>Ixabepilone + Capecitabine (n = 375)</th>
<th>Capecitabine (n = 377)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival (range)</td>
<td></td>
</tr>
<tr>
<td>Independent review committee</td>
<td>5.8 mo (5.5–7)</td>
</tr>
<tr>
<td>Investigator review</td>
<td>5.3 mo</td>
</tr>
<tr>
<td>12-wk progression-free rate, %</td>
<td>71</td>
</tr>
<tr>
<td>Objective response rate</td>
<td>35</td>
</tr>
</tbody>
</table>

Table 5. Pathologic Complete Response to Ixabepilone in Neoadjuvant Phase II Trials

Table 6. Survival and Cancer Progression in a Clinical Trial of Capecitabine Alone or Capecitabine with Ixabepilone

Reprinted with permission from the American Society of Clinical Oncology, Vahdat et al. J Clin Oncol. 2007;25(suppl):1006.22
hypersensitivity reactions, and gastrointestinal toxicity. Nursing measures include monitoring laboratory values (liver function tests), monitoring for hypersensitivity reactions, administering premedications, assessing for preexisting allergies, administering growth factor support, and assessing for preexisting neuropathies, as well as ongoing assessments for the development of new or worsening neuropathies.

CONCLUSIONS

Despite the introduction of a large number of new therapies during the past several decades, long-term survival rates for patients with metastatic breast cancer remain low. Many patients progress despite therapy or have difficulty tolerating treatment-related adverse events. Therapies are limited for patients with multiple drug resistance, particularly in the triple-negative patient population. The epothilones are a new class of cytotoxic therapy that target microtubules and interrupt cell division. These new agents appear in vitro to be more potent than the taxanes against tumor cells and to be more effective against multidrug-resistant tumor cells lines. Several phase II and phase III clinical trials have demonstrated that the epothilone ixabepilone is well tolerated by patients and active as treatment of patients with or without a history of previous taxane therapy. Other epothilones are in earlier stages of clinical development for breast cancer.

DISCUSSION

Ms Stein: I think that the key messages here are that we have great medications (eg, taxanes) that we have added to the adjuvant setting, really improving patient outcomes. But we are also creating drug resistance. When patients do have recurrences, the epothilones are novel agents that may overcome some of this resistance.

Ms Frye: One of the things that impressed me when learning about the epothilones was the importance of resistance mechanisms. We as nurses become very concerned when we observe over and over our patients becoming resistant to agents and regimens, especially if it is after a short period of time. When I talk with nurses in the community or in academic settings, their interest in using epothilones with current regimens is increased when they learn of the potential for reduced resistance.

Ms Shivan: One thing that I am wondering about is the high percentage of “triple-negative” patients—those who are negative for estrogen receptor, progesterone receptor, and HER2—who have responded to the epothilones. Can you comment about that?

Ms Stein: These patients often respond well to taxanes, and both taxanes and the epothilones affect microtubule function. The data are exciting, because that is one group that we are trying to target—the triple-negative population. We really have not had successful drugs in the past that we could use. The triple-negative population certainly responds better to these new cytotoxic therapies; possibly it has something to do with the epothilones’ ability to bypass mechanisms of drug resistance, such as P-glycoprotein.

Ms Frye: One concern as we use many agents with potential for neuropathy is that a percentage of treated patients do not totally recover from this side effect. This becomes an important discussion as we now introduce epothilones as a new chemotherapy choice, because they are agents that may cause neuropathic toxicity or increase the severity of current symptoms.

Ms Stein: The data with the epothilones showed that neuropathy was reversible and that the vast majority of patients with neuropathy were exposed to prior taxane therapy. In the first phase II study I referred to, the patients had not had taxane exposure, and the incidence of neuropathy was relatively low. Thus, it seems to reflect a treatment effect compounded by a history of exposure to several neuropathic agents.

REFERENCES