Potential clinical applications of epothilones: a review of phase II studies

J. M. G. Larkin & S. B. Kaye*
Department of Medicine, The Royal Marsden Hospital, Sutton, Surrey, UK

Background: Epothilones are cytotoxic macrolides that share a similar mechanism of action with the taxanes but demonstrate antitumor activity in taxane-resistant settings. Six epothilones are in early clinical trials for cancer treatment.

Design: This review summarizes data from phase II clinical studies of the epothilones ixabepilone (BMS-247550), patupilone (EPO906), and KOS-862. Data were identified by searches of PubMed and of the proceedings of the American Society of Clinical Oncology annual meetings and the Federation of European Cancer Societies biennial conference for the period 2000–2006. Studies were included if safety and efficacy data were available for at least 10 patients with a given tumor type in a standard phase II design.

Results: Epothilones have demonstrated activity in lung, ovarian, breast, prostate, and renal carcinomas and in non-Hodgkin’s lymphoma in phase II studies. Little or no evidence of clinical activity has been reported in studies of epothilones in other tumor types. Preliminary data indicate that epothilones can be combined safely with other cytotoxic agents such as carboplatin.

Conclusions: The epothilones may play a role as an alternative to taxanes if activity in resistant settings can be confirmed together with an acceptable toxicity profile. Randomized studies are awaited to investigate the utility of epothilones in single-agent and combination regimens.

Key words: cancer, epothilones, ixabepilone, KOS-862, patupilone, phase II clinical trials

Introduction

Epothilones are microtubule-stabilizing cytotoxic macrolides that are under evaluation for the treatment of cancer. These agents were originally described when antifungal and cytotoxic activity was found in the culture supernatant of the cellulose-degrading myxobacterium Sorangium cellulosum [1] and cytotoxicity mimicking the effects of the taxanes was noted [2]. The taxanes have efficacy in a number of tumor types; as a result, there has been interest in the development of the epothilones in the hope that problems with both taxane resistance and formulation might be overcome.

Epothilone B (EPO906; patupilone), like epothilone A, is a natural product [1], and five synthetic epothilones are under investigation for the treatment of cancer: BMS-247550 (aza-epothilone B; ixabepilone), BMS-310705 (a water-soluble BMS-247550 derivative), KOS-862 (epothilone D; desoxyepothilone B), KOS-1584, and ZK-EPO (ZK 219477). In phase I trials, patupilone, ixabepilone, and KOS-862 have demonstrated promising antitumor activity in a broad spectrum of solid tumor types [3–8]. Based on promising antitumor activity and side-effect profiles observed in phase I studies, several epothilones are currently in phase II studies. This review will highlight emerging clinical data from phase II studies of the epothilones ixabepilone, patupilone, and KOS-862. Preliminary data from phase I/II trials of epothilones in combination with other cytotoxic agents are also presented. The review concludes with a discussion of the potential role of epothilones in the setting of taxane resistance.

Phase II Studies

Phase II studies of the epothilones for cancer therapy were identified from the PubMed database, the proceedings of the American Society of Clinical Oncology annual meetings, and the Federation of European Cancer Societies biennial conference. The search terms used were ‘epothilone’, ‘epothilone B’, ‘EPO906’, ‘patupilone’, ‘BMS-247550’, ‘aza-epothilone B’, ‘ixabepilone’, ‘BMS-310705’, ‘KOS-862’, ‘epothilone D’, ‘desoxyepothilone B’, ‘KOS-1584’, ‘ZK-EPO’, and ‘ZK 219477’. Studies identified have been included in this discussion if safety and efficacy data were available for at least 10 patients with a given tumor type in a standard phase II design. Combinatorial phase I studies have been included as well, but studies recruiting patients with only breast or prostate cancer have been excluded; these tumor types are reviewed elsewhere.

Twenty-one phase II studies published in abstract form or in peer-reviewed journals of the epothilones ixabepilone (n = 13), patupilone (n = 7), and KOS-862 (n = 1) were identified (Table 1) [9–29]. These studies are reviewed by tumor type; toxicity is discussed in a separate section.
Two studies have investigated a weekly schedule of ixabepilone in patients with non-Hodgkin’s lymphoma (NHL) [9, 10]. In the first study, by Smith et al. [9], ixabepilone was administered at a dose of 20 mg/m² on days 1, 8, and 15 of a 28-day cycle to 18 patients, 14 of whom provided data evaluable for response. Twelve patients had a confirmed histologic subtype (diffuse large B cell, n = 7; mantle cell, n = 4; grade 3 follicular, n = 1). All patients were heavily pretreated, and three patients had previously received high-dose therapy. Two patients demonstrated a partial response to treatment (14% response rate), and another patient with radiographic stable disease was positron emission tomography negative after treatment and went on to receive a successful allograft.

In the second study, by O’Connor et al. [10], ixabepilone was administered at a dose of 25 mg/m² on the same schedule to 18 patients, 12 of whom provided data assessable for response. Patients had undergone no more than four prior courses of therapy, and all had a confirmed histologic subtype (mantle cell, n = 12; follicular, n = 3; small lymphocytic lymphoma, n = 3). Four patients (33%) responded to treatment: one patient each with mantle cell, follicular, and small lymphocytic lymphoma had a partial response, and a fourth patient with mantle cell lymphoma had a complete response.

### non-Hodgkin’s lymphoma

Two studies have investigated a weekly schedule of ixabepilone in patients with non-Hodgkin’s lymphoma (NHL) [9, 10]. In the first study, by Smith et al. [9], ixabepilone was administered at a dose of 20 mg/m² on days 1, 8, and 15 of a 28-day cycle to 18 patients, 12 of whom provided data evaluable for response. Twelve patients had a confirmed histologic subtype (diffuse large B cell, n = 7; mantle cell, n = 4; grade 3 follicular, n = 1). All patients were heavily pretreated, and three patients had previously received high-dose therapy. Two patients demonstrated a partial response to treatment (14% response rate), and another patient with radiographic stable disease was positron emission tomography negative after treatment and went on to receive a successful allograft.

In the second study, by O’Connor et al. [10], ixabepilone was administered at a dose of 25 mg/m² on the same schedule to 18 patients, 12 of whom provided data assessable for response. Patients had undergone no more than four prior courses of therapy, and all had a confirmed histologic subtype (mantle cell, n = 12; follicular, n = 3; small lymphocytic lymphoma, n = 3). Four patients (33%) responded to treatment: one patient each with mantle cell, follicular, and small lymphocytic lymphoma had a partial response, and a fourth patient with mantle cell lymphoma had a complete response.

### non-small-cell lung cancer

There have been three studies of the treatment of non-small-cell lung cancer (NSCLC) with ixabepilone [11], patupilone [12], and KOS-862 [13].

In the study by Vansteenkiste et al. [11], patients with stage III/IV NSCLC who had failed platinum therapy were randomized to receive ixabepilone 40 mg/m² on day 1 of a 21-day schedule (n = 78) or 6 mg/m² on days 1 through 5 of a 21-day schedule (n = 74). A high incidence of mucositis and neutropenia in the first 18 patients treated at the 40 mg/m² dose level resulted in a reduction in dose of ixabepilone to 32 mg/m² in all subsequent patients. The response rate in 123 patients with evaluable data was 14% (6% after taxane pretreatment); responses were noted in both arms of the study.

Sánchez et al. [12] reported the preliminary results of a phase I/II trial of patupilone in patients with NSCLC. In the phase I part of the trial, 50 patients who had received treatment with platinum, 28% of whom had also received prior taxane therapy, were administered patupilone 6.3–13.0 mg/m², using an every-3-weeks schedule. The dose-limiting toxicity (DLT) was diarrhea, with 14% of patients overall reporting grade 3
diarrhea. The recommended phase II dose for patupilone was 10 mg/m². Partial response was noted in five patients, for an overall response rate of 11%. The phase II trial was still recruiting patients at the time of reporting, with 23 of 33 patients having been enrolled. The study by Yee et al. [13] reported a substantially lower response rate for a schedule of KOS-862 administered at a dose of 100 mg/m² on days 1, 8, and 15 of a 28-day cycle. In this study, only one patient (3%) out of 35 patients providing evaluable data responded to treatment.

**gynecologic cancer**

Two studies of the treatment of gynecologic cancers with ixabepilone [14] and patupilone [26] have been reported in abstract form. In the study by Chen et al. [14], 21 taxane-refractory patients with gynecologic malignancies were treated with ixabepilone 40 mg/m² every 21 days. Twenty-one additional patients with different tumor types (breast, n = 13; other, n = 8) were also included in the study. Of the 21 patients with gynecologic malignancies, two patients (one of 14 patients with ovarian carcinoma and one of three patients with endometrial carcinoma) responded to treatment for a response rate of 10%. A phase I/II study reported by Smit et al. [26] investigated the administration of patupilone 6.5–11.0 mg/m² every 3 weeks. This study involved 45 patients with refractory/resistant ovarian carcinoma, 94% of whom had received prior taxane therapy. The recommended phase II dose was 11.0 mg/m². Eight (25%) of 32 patients providing data evaluable for response had a complete (n = 1) or partial response (n = 7) to treatment with patupilone by the response evaluation criteria in solid tumors (RECIST).

**urologic carcinomas**

Three phase II studies investigating the efficacy of the epothilones in the treatment of urologic carcinomas have been reported in abstract form [27–29]. In the first study, Dreicer et al. [27] evaluated the administration of ixabepilone 40 mg/m² every 3 weeks to patients with urothelial carcinomas that had progressed following first-line therapy. A total of 45 patients were enrolled, 17 of whom had received prior taxane therapy. Of the 37 patients with assessable data, five responded to treatment for an overall response rate of 14%. Three of the responders had received prior taxane therapy. A second study, by Fojo et al. [28], investigated ixabepilone 6 mg/m² administered on days 1 through 5 of a 21-day cycle in patients with renal cell carcinoma (RCC). This study involved 67 patients; 91% had undergone prior nephrectomy and 39% had received at least one prior systemic therapy. Among 57 assessable patients with clear cell RCC who provided evaluable data, partial response was achieved in eight patients (14%) The third phase II study investigated patupilone 2.5 mg/m² administered on days 1, 8, and 15 every 28 days to patients with advanced (stage IV) RCC [29]. This study involved 53 patients (47 men; six women), 89% of whom had clear cell histology and 68% of whom had received prior immunotherapy. Of the 52 patients with response evaluable data, two patients (4%) had a partial response.

**pancreatic cancer**

One phase II study of ixabepilone in pancreatic cancer was recently reported in the literature [15]. In this study, ixabepilone 40–50 mg/m² was administered as a 3-h infusion on a 21-day schedule to 60 chemotherapy-naive patients with inoperable pancreatic adenocarcinoma and metastatic or recurrent disease. Shortly after the trial opened, the initial dose of 50 mg/m² was lowered to 40 mg/m² because of concerns about neurotoxicity. The most common toxic effects were neutropenia/granulocytopenia, nausea and vomiting, and neuropathy. Of 56 patients with measurable disease who were assessable for response, five patients achieved a confirmed partial response for an overall response rate of 9%. Unconfirmed partial responses were noted in an additional seven patients.

**other tumor types**

In phase II studies, ixabepilone and patupilone have demonstrated limited activity ranging from 5% to 8% in various other tumor types, including gastric [16, 17], head and neck [18], hepatobiliary [19], and soft tissue sarcoma [20] tumors (Table 1). Although no response was observed with ixabepilone at a dose of 40 mg/m² given every 3 weeks to patients with advanced colorectal cancer, minor activity (4% to 7%) has been reported with patupilone using different schedules of administration [23, 24]. The epothilones do not appear to be active against melanoma and neuroendocrine tumors [22, 25].

**toxicity**

A striking difference is observed in the toxicity profile of the epothilones. The side-effects of ixabepilone are similar to those of the taxanes in many ways, whereas patupilone predominantly causes diarrhea and fatigue. Ixabepilone has been administered according to three different schedules in phase II trials (Table 2): daily, weekly, and every 3 weeks [9–29]. The side-effect profile of ixabepilone appears to be schedule dependent. Although neuropathy, neutropenia, and fatigue were generally the most common toxic effects noted, the daily schedule (days 1–5 of a 21-day cycle) resulted in much less neuropathy and neutropenia than weekly or every-3-weeks treatment, and it also appeared to have been better tolerated overall. The phase II studies of patupilone largely confirmed the phase I data, inasmuch as diarrhea, fatigue, and nausea and vomiting were the most common toxic effects of both the weekly and the every-3-weeks schedules.

In contrast to the taxanes, neither ixabepilone nor patupilone causes significant alopecia, a potentially important consideration, particularly in the treatment of women.

**combination therapy**

A review of the literature identified three phase I/II studies that evaluated the combination of epothilones (patupilone or KOS-862) with other cytotoxic agents (carboplatin or gemcitabine).

In a phase IB trial in patients with relapsed ovarian carcinoma, the maximum tolerated dose of patupilone given on the every-3-weeks schedule in combination with carboplatin...
area under the time–concentration curve (AUC) = 6 was 4.8 mg/m² [30], and fatigue was the most common grade 3 or 4 toxicity, reported in 24% of patients. Patupilone pharmacokinetics were similar to those previously reported for single-agent therapy. Responses by RECIST were noted in 65% of patients with potentially platinum-sensitive disease, a figure comparable to that for other treatment regimens used in this setting.

Another study investigated the combination of KOS-862 with carboplatin in patients with various advanced malignancies. In this phase I trial, six patients were evaluated after treatment with carboplatin (AUC = 5), given on day 1, q21d, every 21 days; q28d, every 28 days; NHL, non-Hodgkin’s lymphoma; G, grade; NSCLC, non-small-cell lung cancer.

### Table 2. Toxicity and scheduling of epothilones in phase II studies

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Toxicity</th>
<th>Schedule</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ixabepilone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>27% G4 overall</td>
<td>q21d, 40 mg/m² 3 h</td>
<td>Dreicer et al. [27]</td>
</tr>
<tr>
<td></td>
<td>20% G4 neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>20% G3/4 neuropathy</td>
<td>q21d, 40 mg/m² 3 h</td>
<td>Eng et al. [21]</td>
</tr>
<tr>
<td></td>
<td>48% G3/4 neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>26% G3 nausea/vomiting</td>
<td>q21d, 50 mg/m² 1 h</td>
<td>Ajani et al. [17]</td>
</tr>
<tr>
<td></td>
<td>59% G3 fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynecologic</td>
<td>45% G3/4 neuropenia</td>
<td>q21d, 40 mg/m² 1 h</td>
<td>Chen et al. [14]</td>
</tr>
<tr>
<td></td>
<td>5% G3 neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>25% G3 fatigue</td>
<td>Days 1, 2, 3, 4, 5 q21, 6 mg/m² 1 h</td>
<td>Burtner et al. [18]</td>
</tr>
<tr>
<td></td>
<td>13% G3/4 anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30% G3 neuropathy</td>
<td>Days 1, 8, 15 q28 20 mg/m² 1 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24% G3 fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>39% G3/4 neuropenia</td>
<td>q21d, 40 mg/m² 3 h</td>
<td>Singh et al. [19]</td>
</tr>
<tr>
<td>Melanoma</td>
<td>29% G3/4 fatigue</td>
<td>Days 1, 8, 15 q28d, 20 mg/m² 1 h</td>
<td>Pavlick et al. [25]</td>
</tr>
<tr>
<td></td>
<td>25% G3/4 neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21% G3/4 diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHL</td>
<td>50% G3/4 neutropenia</td>
<td>Days 1, 8, 15 q28d, 25 mg/m² 1 h</td>
<td>O’Connor et al. [10]</td>
</tr>
<tr>
<td></td>
<td>28% G3/4 thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>43% G3/4 neutropenia</td>
<td>Days 1, 8, 15 q28d, 20 mg/m² 1 h</td>
<td>Smith et al. [9]</td>
</tr>
<tr>
<td></td>
<td>43% G3/4 fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>36% G3 neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>34% G3/4 overall</td>
<td>q21d, 32 mg/m² 3 h</td>
<td>Vansteenkiste et al. [11]</td>
</tr>
<tr>
<td></td>
<td>15% G4 neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22% G3/4 overall</td>
<td>Days 1, 2, 3, 4, 5 q21d, 6 mg/m² 1 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10% G3/4 fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td>25% G3/4 neutropenia</td>
<td>q21d, 40–50 mg/m² 3 h</td>
<td>Whitehead et al. [15]</td>
</tr>
<tr>
<td></td>
<td>23% G3 nausea/vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15% G3/4 neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>4% G3 neuropathy</td>
<td>Days 1, 2, 3, 4, 5 q21d, 6 mg/m²</td>
<td>Fojo et al. [28]</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>48% G3/4 neutropenia</td>
<td>q21d, 50 mg/m² 1 h</td>
<td>Okuno et al. [20]</td>
</tr>
<tr>
<td></td>
<td>26% G3/4 neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patupilone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>29% G3/4 diarrhea</td>
<td>q21d, 6 mg/m² on days 1, 8, 15 q28d, 2.5 mg/m²</td>
<td>Poplin et al. [23]</td>
</tr>
<tr>
<td></td>
<td>10% G3/4 nausea/vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21% G3 diarrhea</td>
<td>q21d, 6–10 mg/m² 1 or 5 days continuous i.v. 6–10 mg/m²</td>
<td>Casado et al. [24]</td>
</tr>
<tr>
<td>Gastric</td>
<td>27% G3/4 nausea/vomiting</td>
<td>Days 1, 8, 15 q28d, 2.5 mg/m²</td>
<td>Hsin et al. [16]</td>
</tr>
<tr>
<td></td>
<td>18% G3 diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>46% G3/4 diarrhea</td>
<td>Days 1, 8, 15 q28d, 2.5 mg/m²</td>
<td>Anthony et al. [22]</td>
</tr>
<tr>
<td></td>
<td>8% G3/4 nausea/vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>14% G3 diarrhea</td>
<td>q21d, 6.5–13 mg/m² 20 min</td>
<td>Sánchez et al. [12]</td>
</tr>
<tr>
<td>Ovary</td>
<td>19% G3 diarrhea</td>
<td>q21d, 6.5–11 mg/m² 20 min</td>
<td>Smit et al. [26]</td>
</tr>
<tr>
<td>Renal</td>
<td>8% G3 diarrhea</td>
<td>Days 1, 8, 15 q28d, 2.5 mg/m²</td>
<td>Thompson et al. [29]</td>
</tr>
<tr>
<td>KOS-862</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>Fatigue, neuropathy, nausea, vomiting</td>
<td>Days 1, 8, 15 q28d, 100 mg/m²</td>
<td>Yee et al. [13]</td>
</tr>
</tbody>
</table>
and KOS-862 50 mg/m², given on days 1 and 8 of a 21-day cycle [31]. One patient experienced DLT (prolonged neutropenia), but pharmacokinetic parameters for both drugs were the same as those for single-agent therapy. One patient with ovarian carcinoma had a radiologic and serologic complete response to treatment, and one patient with hepatocellular carcinoma had a 40% drop in α-fetoprotein level. A second cohort was being recruited to receive KOS-862 75 mg/m² at the time this study was reported.

A third phase I study evaluated the safety and antitumor activity of KOS-862 given in combination with gemcitabine. Preliminary data from this study indicated that KOS-862 and gemcitabine could be combined safely at doses of 750 and 60 mg/m², respectively, on days 1 and 8 of a 21-day cycle [32]. DLTs at higher doses of KOS-862 were neutropenia and diarrhea. There was no pharmacokinetic interaction between the two agents. Fourteen patients were treated; there was one partial response in a patient with carcinoma of unknown primary site.

**epothilones in taxane-resistant settings**

The epothilones ixabepilone and patupilone have demonstrated activity in phase II trials in a number of tumor types other than breast and prostate carcinoma in both taxane-sensitive and taxane-resistant settings.

**non-Hodgkin’s lymphoma**

Although only a small number of NHL patients have been treated with ixabepilone (n = 26 with response evaluable data), this drug has definite activity in NHL; response rates of 14% and 33% were reported in two phase II studies [9, 10]. Taxanes are not used routinely in the management of NHL, although response rates of up to 25% have been reported for paclitaxel (Taxol, Bristol-Myers Squibb, Princeton, NJ) as a single agent in phase II studies in refractory disease [33]. Unfortunately, the toxicity reported from one of the studies with ixabepilone [9] was not trivial: between one-third and one half of patients had grade 3 or worse neuropathy or fatigue, or both. Additionally, significant myelosuppression was reported in phase II studies. In the setting of NHL, this may have implications for the combination of epothilones with other cytotoxic agents.

**non-small-cell lung cancer**

Ixabepilone has clear activity in NSCLC. The response rate was 14% in a study of patients who had failed first-line platinum therapy [11], and in the taxane pretreated subset, the response rate was 6%. Patupilone may also be active in this setting. Among platinum pretreated patients, the response rate was 11% in the dose escalation stage of a phase I/II trial [12]. The standard treatment after the failure of platinum therapy in NSCLC is docetaxel (Taxotere Sanofi-Aventis, Bridgewater, NJ), which is associated with response rates ranging from ~9% to 14% [34–36]. On the basis of these data, docetaxel, ixabepilone, and patupilone appear to have similar efficacy, and further investigation of these epothilones in NSCLC is justified.

**ovarian cancer**

Patupilone is active in platinum- and taxane-resistant ovarian cancer; the reported response rate is 25% [26]. The response rate with ixabepilone in the same patient group is only 7% [14]. The activity of patupilone in taxane-resistant disease is encouraging. One phase II study of 60 patients with paclitaxel-resistant ovarian cancer demonstrated a 22% response rate to a regimen of docetaxel 100 mg/m² every 21 days [37]. However, hematologic toxicity was significant as 75% of patients experienced grade 4 neutropenia.

**renal cancer**

Metastatic clear cell RCC is resistant to cytotoxic chemotherapy, and immunotherapy has yielded responses in only 15%–20% of patients with good performance status [38]. Response rates to taxanes are negligible [39–41], a fact of interest in light of the 14% response rate to ixabepilone in the trial reported by Fojo et al. [28]. The response rate to patupilone was only 4% in a phase II study of similar size [29]. It is possible, given that >50 patients were treated in both studies, that this represents a true difference in efficacy between ixabepilone and patupilone, but these data await confirmation. The treatment of metastatic RCC is changing rapidly with the recent licensing of the tyrosine kinase inhibitors sunitinib [42, 43] and sorafenib [44]. If ixabepilone is to play a role in the management of metastatic RCC, it will be necessary to identify the patients who are most likely to benefit from cytotoxic therapy rather than the kinase inhibitors or immunotherapy [45].

**bladder cancer**

The activity of ixabepilone in urothelial carcinoma is of interest, but toxicity is a concern. In the phase II study reported by Dreicer et al. [27], in which ixabepilone was given at 40 mg/m² every 3 weeks, the response rate was 14% (8% after taxane). However, 27% of patients had grade 4 toxicity. This indicates that a lower dose of ixabepilone may be more appropriate in this patient group.

**pancreatic cancer**

The activity of ixabepilone in pancreatic cancer compares favorably with that of historical controls. In one study by Whitehead et al. [15], the estimated 6-month survival rate (the primary end point) with ixabepilone was 60%, and median survival time was 7.2 months. In comparison, the 6-month survival rate following the administration of gemcitabine in a phase III trial was 46%, and the median survival time was 5.7 months [46]. The median survival time in a phase II trial of paclitaxel given with granulocyte colony-stimulating factor was 5 months, and the response rate was 8% [47].

**conclusion**

Despite the fact that epothilones have shown activity in taxane-resistant settings in preclinical models, it is not yet clear from the phase II studies reviewed here that their clinical...
activity is superior to that of the taxanes. Nevertheless, responses to epothilones have been seen in taxane pretreated patients with bladder, lung, gastric, and ovarian cancers, whereas epothilones have shown minimal clinical activity in taxane-resistant tumor types with the exception of the modest response rate reported in RCC and the intriguing data from a small number of patients with NHL. Further experience is needed to clarify whether the side-effect profile of the two major epothilones, ixabepilone and patupilone, does or does not differ substantially from that of the taxanes. The initial impression that the major toxic effects for these two drugs—i.e., neurotoxicity and diarrhea, respectively—are different may be modified as more patients are treated. In any event, combination regimens with both drugs appear feasible. At this stage, it should be pointed out that the level of efficacy noted in various tumor types could have been expected with docetaxel (e.g., in ovarian [37] and breast cancers [48–50]). Randomized trials comparing the epothilones with standard treatments are now needed to further define the role of these drugs in cancer therapy.

disclosures

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

references