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The epothilone B analogue ixabepilone in patients with advanced hepatobiliary cancers: a trial of the University of Chicago Phase II Consortium

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Summary

Purpose—Hepatobiliary cancers respond poorly to cytotoxic chemotherapy. We evaluated the activity and safety of ixabepilone, an epothilone B analogue which stabilizes microtubules, in a phase II trial in patients with advanced cancers of the gallbladder, bile duct, and liver.

Methods—Eligible patients had previously-untreated, histologically-proven unresectable hepatobiliary cancer. Ixabepilone, 40 mg/m², was administered intravenously over 3 h every 21 days.

Results—Between January 2002 and April 2005, 54 patients (19 hepatocellular carcinoma, 13 cholangiocarcinomas, 22 gallbladder carcinomas) were enrolled; 47 patients were evaluable for efficacy. The objective response rate was 8.5%; 51% had stable disease. Median overall survival was 7.0 months (95% CI, 5.0 to 10.8 months) and median progression-free survival was 2.6

months (95% CI, 1.4 to 4.1 months). Grade 3/4 toxicities included neutropenia (39%), fatigue (9%), allergic/hypersensitivity reaction (4%) and sensory neuropathy (4%).

Conclusion—Single agent ixabepilone has limited activity in advanced hepatobiliary cancers.

Keywords

Epothilone; Hepatobiliary cancers

Introduction

It is estimated that there will be 30,890 new cases of the liver and biliary tree cancers diagnosed in the United States in 2008, with 21,750 deaths estimated annually [1]. Approximately one-half of these tumors are of the gallbladder, a third are tumors of the intrahepatic and extrahepatic biliary ducts, and the remainder are primary hepatocellular carcinomas [2].

Although hepatocellular carcinoma (HCC), cholangiocarcinoma (CC), and gallbladder cancer (GB) differ with respect to histological origin, etiology, and tumor bulk at presentation, the treatment considerations for patients with unresectable disease are similar. A majority (70% to 85%) of patients present with advanced or unresectable disease. These patients carry a poor prognosis with a median overall survival of less than 7 months [3–5].

Hepatocellular carcinomas are inherently chemotherapy-resistant tumors and are known to express the multidrug-resistant gene *MDR-1* [6–8]. In 1997, a meta-analysis evaluated the results of 37 randomized clinical trials of systemic and regional chemotherapy in 2,803 HCC patients and concluded that systemic chemotherapy is quite ineffective in HCC, as evidenced by low response rates and no survival benefit [9]. Although gemcitabine given either as a single-agent or in combination with either cisplatin, capecitabine or oxaliplatin has modest activity in gallbladder cancer and cholangiocarcinoma, the optimal regimen has not been defined by randomized trials [10, 11]. Clearly, novel agents deserve investigation in these diseases.

The epothilones are a new class of non-taxane tubulin polymerization agents obtained from the fermentation broth of the cellulose—degrading myxobacterium, *Sorangium cellulosum*. The cytotoxic mechanism of the epothilones, similar to taxanes, is linked to stabilization of microtubules, resulting in mitotic arrest [12]. However, epothilones bypass the multi drug resistance (MDR) protein and tubulin mutation modes of resistance, which play significant roles in taxane resistance [13].

Aza-epothilone B (ixabepilone; BMS-247550), a semisynthetic analog of the natural product epothilone B, has shown a broad spectrum of activity in vitro and in vivo against cancer models that are inherently insensitive to the taxanes or have developed resistance to them. Ixabepilone has greater activity than paclitaxel in paclitaxel-sensitive tumors, and in paclitaxel-resistant tumor xenografts including colon (HCT116/VM46), ovarian (Pat-7 and A2780Tax) and breast (Pat-21) cancer models [12, 13].

Phase I studies have established the maximum tolerated dose of ixabepilone as 6 mg/m²/day when given daily for 5 days every 3 weeks or 40 mg/m² when given once every 3 weeks [14–16]. Given the lack of activity of conventional chemotherapy in hepatobiliary malignancies, the novel mechanism of action of ixabepilone, and preclinical activity of this agent in gastrointestinal cancers, we initiated a phase II study of ixabepilone in patients with advanced hepatobiliary cancers.

Methods

Eligibility

Eligible patients (aged ≥ 18 years old) had previously untreated histologically-proven, measurable, metastatic, locally advanced or recurrent cancer of the liver (HCC), bile duct cholangiocarcinoma (CC) or gallbladder (GB). Adequate organ function was required, including: an absolute neutrophil count of ≥ 1,500/μL, platelet count of ≥ 100,000/μL, serum bilirubin ≤ 1.5 mg/μL, aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT) ≤ 2.5 times the upper institutional limit of normal and serum creatinine ≤ 1.5 mg/dL. Patients had to have a life expectancy of at least 3 months, and an ECOG performance status of 0 to 2. Patients were excluded if they had > grade 1 neuropathy, brain metastases, a history of an allergic reaction to Cremophor®, concurrent malignancy, pregnancy, were HIV positive, or had significant medical co-morbidities. The clinical trial was reviewed and approved by the Institutional Review Board at the University of Chicago Cancer Center and other participating institutions. All patients were informed of the investigational nature of this study and were required to provide written informed consent before study participation according to institutional and federal guidelines.

Pretreatment evaluation and follow-up studies

Before study entry, patients underwent a physical examination, and assessment of performance status. All patients had radiologic assessment of measurable disease by computed tomography scan (CT) or magnetic resonance imaging (MRI) within 28 days prior to registration. Baseline laboratory testing included CBC with differential and platelets, creatinine or calculated creatinine clearance, AST/ALT, bilirubin, serum B-HCG, AFP (HCC) or CA19-9 (CC, GB) and an electrocardiogram. All laboratory tests were obtained within 7 days prior to registration.

Patients were evaluated for response every two cycles (6 weeks), based on CT scan or MRI until progression of disease. Treatment was discontinued at any time for disease progression, unacceptable toxicity, patient withdrawal of consent, treatment delay for more than 3 weeks, patient non-compliance, or physician decision based on the patient's other medical conditions. All patients were evaluated clinically before each cycle and as medically indicated. Confirmatory scans were obtained at least 4 weeks following initial documentation of complete or partial response.

Treatment and dose modifications

All patients were premedicated 1 h before ixabepilone administration with an H1 blocker (diphenhydramine 50 mg administered orally) and an H2 blocker (ranitidine 150 mg,

famotidine 40 mg or nizatidine 150 mg administered orally) to prevent a hypersensitivity reaction due to Cremophor®. Ixabepilone was administered at 40 mg/m² intravenously over 3 h every 21 days. If patients experienced a grade 2 or higher hypersensitivity reaction following this premedication regimen, oral /i.v. dexamethasone 20 mg was added. CBC with differential, platelets, AST/ALT, and bilirubin were performed weekly.

The ixabepilone dose was reduced by one dose level (30 mg/m²) for grade 4 neutropenia, neutropenic fever lasting >7 days, platelet count <25,000 or bleeding with grade 3 thrombocytopenia. The dose was also reduced for grade 3 or higher non-hematological toxicities or treatment delays >7 days. Only two dose level reductions were allowed. Patients were removed from the study if they developed grade 3 neuropathy lasting >7 days.

Response assessment

Patients were evaluated for response and progression using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [17]. All patients who completed at least two cycles of ixabepilone were evaluable for response. Adverse events and other symptoms were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 2.0.

Statistical methods

The primary endpoint of this phase II study was the objective response rate (complete and partial response). A Simon optimal two-stage design was employed [18]. A 10% response rate precluded further study (null hypothesis), whereas a 25% response rate indicated that further study would be warranted (alternative hypothesis). Using α and β errors of 0.10 and 0.10, respectively, 21 assessable patients were to be enrolled in the first stage and if 2 responses were observed, the trial was to be terminated. Otherwise, an additional 29 patients were to be enrolled and if 8 responses were observed among all 50 patients then the drug would be considered sufficiently active to warrant further testing. This design had a 0.65 probability of stopping at the first stage if the true response rate was 10%.

An exact 95% confidence interval (CI) was calculated for the response rate based on the binomial distribution. Overall and progression-free survival curves were estimated using the Kaplan-Meier method. Median overall and progression-free survival times were calculated and their respective 95% CIs were constructed using the method of Brookmeyer and Crowley [19].

Results

Between January 2002, and April 2005, 54 patients were accrued. All patients were evaluable for toxicity, and 47 were evaluable for response. One patient was deemed ineligible due to uncertainty in their pathologic diagnosis. Two patients withdrew from the study after the first cycle because they decided not to pursue further treatment. Two patients died after the first cycle, one unexpectedly with an unclear cause of death, the other died from complicated neutropenic fever and sepsis. Another patient developed upper gastrointestinal bleeding, complicated by deep venous thrombosis and never resumed

treatment after the first cycle. The last patient developed fever, dehydration, and acute renal failure, was hospitalized, and decided not to pursue further treatment.

Baseline patient characteristics are listed in Table 1. Forty-one percent of the patients had gallbladder cancer, 35% had hepatocellular carcinoma and 24% had cholangiocarcinoma. The median age was 65 years (range 19 to 88 years). Most (96%) patients had an ECOG performance status of 0 or 1, and 76% had metastatic disease.

A total of 219 cycles of ixabepilone were administered (median 2, range 1–14). Of the seven patients who completed at least 10 cycles of ixabepilone, 4 had hepatocellular carcinoma.

Toxicity

The principal toxicities are summarized in Table 2. Hematologic toxicity was modest. Although grade 3/4 neutropenia developed in 39% of patients, only two patients (4%) developed neutropenic fever. The most problematic non-hematologic toxicity was sensory neuropathy, which developed in 33% of patients but was grade 3/4 in only 4%. Six percent of patients discontinued the study drug due to neurotoxicity. With premedication, grade 3/4 hypersensitivity reactions developed in only 4% of patients.

There were three toxic deaths. One patient died of an unclear cause 48 h after her first dose of ixabepilone. Another patient developed septic shock following a neutropenic fever. The third patient was a diabetic, taking an oral hypoglycemic, who died of metabolic encephalopathy secondary to hypoglycemia.

Response and survival

Forty-seven patients were evaluable for response, and 53 for survival (excluding the ineligible patient). Confirmed partial responses were observed in four patients (2 HCC, 1 GB, 1CC), lasting a median of 5.7 months (range 4.6–6.9), for an objective response rate of 8.5% (95% CI, 2.4% to 20.4%). Twenty-four patients (51%) developed stable disease.

The median survival was 7.0 months (95% CI, 5.0 to 10.8 months), and the one year survival probability was 0.27 (95% CI, 0.15 to 0.41) (Fig. 1). The median progression-free survival was 2.6 months (95% CI, 1.4 to 4.1 months).

Discussion

The limited survival time, poor performance status, deteriorating hepatic function, and inherent resistance of hepatobiliary cancers to conventional cytotoxic chemotherapy make it particularly challenging to test for novel agents in such a population. Taxanes have shown limited or no activity in hepatobiliary cancers, however preclinical data showed a lack of cross-resistance between epothilones and taxanes. We evaluated the novel agent, ixabepilone in patients with previously untreated advanced hepatocellular carcinoma, gallbladder cancer, and cholangiocarcinoma. Our study demonstrated limited activity for ixabepilone, with a partial response rate of 8.5%, and a median survival of 7.0 months. In addition, the toxic death rate was 6%, which is relatively high for a monotherapy. These results are comparable to other studies of epothilones in HCC. Venook et al. evaluated a

novel epothilone, patupilone, in patients with unresectable or metastatic, Child-Pugh Class A HCC, and reported an overall response rate of only 4% [20].

Historically, hepatocellular carcinomas, gallbladder cancers and cholangiocarcinomas have been evaluated together in clinical trials because of their similar clinical presentation, resistance to chemotherapy and the assumption that the tumor biology was very similar. Hepatocellular carcinoma has more recently emerged as a separate clinical entity with a distinct tumor biology. In our study, the number of patients enrolled was too small to detect any statistically significant differences in OS between the three cohorts of patients.

This is certainly not the only novel cytotoxic agent which has failed to demonstrate activity in hepatobiliary cancers. In general, efficacy with conventional cytotoxic chemotherapy is modest at best, and the duration of benefit is limited. Although few randomized trials have been conducted, no single regimen has emerged as superior to any other, and no drug or regimen until recently has been explicitly shown to improve survival.

The multicenter European SHARP phase III trial randomly assigned 602 patients with inoperable hepatocellular carcinoma and Child-Pugh A cirrhosis to sorafenib (400 mg twice daily) or placebo. The overall survival, the primary endpoint, was significantly longer in the sorafenib-treated patients (10.7 versus 7.9 months), as was TTP (5.5 versus 2.8 months) [21].

There appears to be a paradigm shift with this data on the efficacy of molecularly targeted agents which has brought these agents, particularly sorafenib, to the forefront of therapy for advanced hepatocellular cancers because of the potential for prolonged survival, although objective tumor remissions are rare. Whether this will be applicable to cholangiocarcinoma and gallbladder cancers remains to be seen.

Acknowledgments

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Fig. 1.
Kaplan Meier estimation of overall survival

Table 1Patient characteristics (*N*=54)

Characteristic	No.	%
Age, years		
Median	65	
Range	19–88	
Sex		
Male	28	52
Female	26	48
ECOG performance status		
0	26	48
1	26	48
1	2	4
Tumor type		
Liver-(Hepatocellular carcinoma)	19	35
Gallbladder-(Gallbladder carcinoma)	22	41
Bile duct-(Cholangiocarcinoma)	13	24
Stage of disease		
Locally advanced	13	24
Metastatic disease	41	76
Prior treatment		
Surgery	17	31
Radiotherapy	2	4

Table 2Worst toxicities per patient by common toxicity criteria version 2.0 ($N=54$)

Toxicity	Grade 3 % (of patients)	Grade 4 %	Grade 5 %
Hematologic			
Neutropenia	24	15	2
Neutropenic fever	2	0	2
Anemia	4	0	0
Thrombocytopenia	2	0	0
Non-hematologic			
Nausea	13	0	0
Vomiting	2	4	0
Constipation	2	0	0
Fatigue	9	0	0
Myalgia	2	0	0
Sensory neuropathy	4	0	0
Hypersensitivity	4	0	0
Hypoglycemia	0	0	2