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A Phase II Trial of the Proteasome Inhibitor Bortezomib in Patients with Advanced Biliary Tract Cancers*

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Abstract

Background—Patients with advanced biliary tract cancers have limited therapeutic options. Preclinical data suggest proteasome inhibition may be an effective therapeutic strategy. We thus evaluated the clinical efficacy of bortezomib in advanced biliary tract cancers.

Patients and Methods—Patients with locally advanced or metastatic cholangiocarcinoma or gallbladder adenocarcinoma who had received 0–2 prior therapies received bortezomib 1.3 mg/m² days 1, 4, 8, and 11 of a 21-day cycle. The primary endpoint was objective response rate. A Simon two-stage design was employed (null response rate of < 5% and response rate of 20% of interest).

Results—Twenty patients enrolled: bile duct/gallbladder cancer (14/6), prior treatments 0/1/2 (10/6/3). The trial was discontinued early due to lack of confirmed partial responses. No unanticipated adverse events were noted. There was one unconfirmed partial response. Ten patients achieved stable disease as best response. Median time to progression was 5.8 months (95% CI 0.7–77.6 months). Median survival was 9 months (95% CI 4.6–18.5 months). The 6-

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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month and 1-year survival rates were 70% and 38%. There was no difference in survival based on primary disease site.

Conclusions—Single agent bortezomib does not result in objective responses in biliary tract cancers. However, the rate of stable disease and time to progression benchmark is encouraging. Further development of bortezomib in combination with other therapies in this disease setting should be considered.

Keywords

bortezomib; biliary tract cancers; proteasome inhibition; cholangiocarcinoma

INTRODUCTION

Biliary tract cancers, including tumors of the gallbladder and bile ducts, are relatively uncommon in the United States. However, the incidence of intrahepatic cholangiocarcinomas is rising and is now among the top ten causes of cancer death in both men and women¹. Although surgical resection is the only curative therapy, most patients present with locally advanced or metastatic disease with limited systemic treatment options². Two year survival rates for metastatic disease in gallbladder and extrahepatic cholangiocarcinoma are 2% and 4%, respectively, while survival rates for intrahepatic cholangiocarcinoma are minimally better²⁻⁴.

At the time this trial was conceived, no randomized trial had demonstrated a survival benefit for systemic therapy. Fluoropyrimidine-based therapies produced response rates ranging from 9% to 34% in small single arm phase II trials, with median survival times ranging from 21 weeks to 12 months⁵⁻⁷. Single agent gemcitabine produced slightly better results, with response rates of 17.5% to 36% and median survival times of approximately 7.5 months^{8,9}. Single agent phase II trials of other cytotoxic agents were similarly disappointing, with median survival times of less than one year^{10,11}. Thus, development of novel agents and targets was, and remains, urgently needed in these tumors.

One such target is the ubiquitin-proteasome pathway. Inhibition of this pathway results in cell death via sensitization of cells to apoptosis. This may be accomplished through inhibition of nuclear factor kappa B (NFκB), increased activity of p53 and Bax proteins, accumulation of cyclin-dependent kinase inhibitors p27 and p21, increased c-myc and bcl-2 expression, and upregulation of heat shock proteins and caspase-mediated apoptotic pathways^{12,13}. Alterations in expression of many of these (p53, p27, bcl-2, NFκB) have been described in biliary tract cancers¹⁴⁻²⁰. Further, preclinical data in cholangiocarcinoma cell lines suggested proteasome inhibition was a possible therapeutic strategy via induction of endoplasmic reticulum dysfunction and caspase-independent cell death²¹⁻²³.

Bortezomib (Millenium Pharmaceuticals) is a dipeptide boronic acid and selective inhibitor of the 26S proteasome¹². Although bortezomib has broad spectrum activity against a range of tumor types in preclinical models and in breast and lung xenografts, bortezomib is currently only approved for the treatment of multiple myeloma and mantle cell lymphoma^{12,24,25}. Bortezomib is well-tolerated in patients with solid tumors and has a

predictable side effect profile^{25,26}. Given the tolerability of bortezomib in solid tumors and the preclinical data suggesting a therapeutic benefit for proteasome inhibition in biliary tract cancers^{21–23,26}, this single arm phase II trial of bortezomib in unresectable or metastatic adenocarcinoma of the bile duct or gallbladder was undertaken.

PATIENTS AND METHODS

Study Population

Eligible patients were age 18 years or older with histologically confirmed adenocarcinoma of the intrahepatic or extrahepatic bile ducts or gallbladder that was not amenable to surgical resection for cure. All patients were required to have measurable disease and provided informed consent. The initial protocol stipulated that patients could not have received prior chemotherapy for metastatic or locally advanced disease. However, as evolving evidence suggested a benefit to chemotherapy in this setting, the protocol was amended to allow up to two prior chemotherapy regimens^{27–31}. Chemotherapy used as a radiosensitizer was not considered a prior treatment regimen.

Key additional inclusion criteria included an Eastern Cooperative Oncology Group performance status of 0–2 and a total bilirubin up to 1.5 times the upper limit of normal (ULN), AST/ALT up to 2.5 times the ULN, and adequate hematologic and renal function. Exclusion criteria included known brain metastases, preexisting peripheral neuropathy of grade 2 or higher, known history of allergic reaction to bortezomib, history of immunodeficiency or uncontrolled intercurrent illness, or the receipt of more than two prior chemotherapy regimens for metastatic or locally advanced disease. The study was approved by the Institutional Review Board of Fox Chase Cancer Center and all patients provided written informed consent.

Study Design

This was a single arm, two-stage, open-label study. Bortezomib was administered at a dose of 1.3 mg/m² on days 1, 4, 8 and 11 of a 21-day cycle. Bortezomib was given as an intravenous bolus over 3–5 seconds. Treatment cycles were initiated on Mondays, Wednesdays, or Fridays to avoid treatment days falling on a weekend. Treatment was continued until disease progression, intercurrent illness precluding further dosing, unacceptable adverse events, patient withdrawal of consent, death, or changes in patient condition that rendered the patient unacceptable for further treatment in the judgment of the investigator. Toxicity was graded according to NCI Common Toxicity Criteria version 3.0³². Dose modifications were made for grade 3 non-hematologic toxicity, excluding neuropathy; grade 1 neuropathy with pain or grade 2 neuropathy without pain; and hematologic toxicity (neutrophil count < 750/mm³ or platelet count < 75,000/mm³). Dose reduction levels were 1 mg/m² and 0.7 mg/m² per dose. Patients requiring more than two dose reductions were removed from the study.

Study Evaluations

All patients were assessed for tumor response every 2 cycles, or 6 weeks, by radiologic assessment (computed tomography or magnetic resonance imaging) according to Response

Evaluation Criteria in Solid Tumors (RECIST) 1.0³³. Confirmatory scans were obtained at least four weeks following initial documentation of objective response. All patients who received at least one dose of bortezomib were considered evaluable for toxicity and response assessment.

Study Endpoints and Statistical Considerations

The primary endpoint was objective response rate (ORR) based on investigator assessment. Secondary endpoints included time to progression and overall survival (OS). The study design required 35 patients for 90% power to detect a response rate of at least 20% with a type I error of at least 0.05. Response rate was defined as the percent of patients who achieved a complete or partial response confirmed 28 days after initial documentation of response. An early stopping point of 20 patients based on efficacy was employed. If one or fewer of the first 20 patients enrolled had a complete or partial response to bortezomib, the trial would be terminated. Otherwise the study would continue to a total accrual of 35 patients.

Time to progression was defined as the time from initiation of therapy to first progressive disease. Overall survival was defined as the time from initiation of therapy to death or last follow-up. In an exploratory analysis done after study completion, the clinical benefit rate was also calculated, defined as the total number of patients who achieved a complete or partial response, unconfirmed response, or stable disease. Safety was evaluated in all patients who received at least one dose of bortezomib. The clinical benefit was compared between patients with and without prior therapy via Fisher's exact test. Survival analysis was assessed by Kaplan Meier estimation method and log rank test.

RESULTS

Between February 2004 and August 2008, twenty patients were enrolled. The median age was 62 years. Patient characteristics are listed in Table 1. The majority of patients had adenocarcinoma of the bile duct (cholangiocarcinoma) and had not received prior therapy for metastatic disease. Sixteen study participants presented with metastatic disease at baseline, while four patients were initially diagnosed with locally advanced disease and developed recurrence. These four patients had gallbladder carcinoma and underwent cholecystectomy and fluoropyrimidine-based chemoradiotherapy in the curative setting. Fourteen patients had metastatic disease to liver.

The median number of cycles received was three, with a range of one to nine. Accrual was halted after twenty patients were enrolled and treated based on the predefined early stopping rule. Median follow up was 9.6 months (range 1.3 to 77.6 months).

Toxicity

Table 2 summarizes adverse events experienced by all patients. The most common non-hematologic toxicities observed were fatigue (18 patients), nausea (11 patients), and vomiting (7 patients). Neuropathy was reported in six patients, with one patient having grade 3 neuropathy. The most common hematologic toxicities observed were anemia (15 patients), thrombocytopenia (14 patients), and leukopenia (5 patients). Grade 3/4 hematologic and

non-hematologic toxicities were rare and consistent with the adverse event profile of bortezomib²⁵. Eight serious adverse events were reported, four of which were felt to be at least possibly related to bortezomib and included grade 3 aseptic vasculitis in one patient, grade 4 cerebrovascular accident in one patient, grade 2 meningitis in one patient, and grade 2 renal insufficiency in one patient. Five patients discontinued treatment due to adverse events, all with at least stable disease at first disease evaluation (6 weeks). Dose reductions were required in seven patients. Fatigue (n=3) was the most common reason for dose reduction, followed by thrombocytopenia (n=2) and neuropathy (n=1).

Clinical Efficacy

One patient withdrew consent prior to the first disease evaluation. Of the remaining nineteen patients, one patient with intrahepatic cholangiocarcinoma achieved an unconfirmed partial response in thoracic lymph node metastases, but withdrew consent prior to confirmation of response. Ten patients (two with gallbladder carcinoma and eight with cholangiocarcinoma) achieved stable disease as best response. The median duration of stable disease was 11.3 weeks (range 3 weeks to 18 weeks). Thus, the clinical benefit rate was 53%. No confirmed partial or complete responses were observed. There was no difference in clinical benefit rate between patients who had and had not received prior therapy (21% versus 32% p=0.66). The median time to progression for the entire study population was 5.8 months (95% CI 0.7–77.6 months).

The median survival for the entire study population was 9 months (95% CI 4.6–18.5 months) (Figure 1). The 6-month and 1-year survival rates for the entire study population were 70% and 38%, respectively. Patients who had a clinical benefit had a 6 month and 1 year survival of 90% and 69%, respectively, as compared to patients whose best response was progressive disease (6 month and 1 year survival of 44% and 11%, respectively, p=0.01). There was no difference in survival at 6 months and 1 year based on primary disease site (gallbladder versus bile duct, p=0.63)

DISCUSSION

Our results demonstrate that objective responses with single agent bortezomib treatment are rare in biliary tract cancers. Since we did not observe a confirmed response, our pre-defined stopping rule triggered early discontinuation of this trial. However, our clinical benefit rate of 53%, time to progression of 5.8 months, and overall survival of 9 months are encouraging and compare favorably to prior studies of single agents such as 5-fluorouracil or gemcitabine in advanced biliary cancer. Previous studies of 5-fluorouracil with leucovorin in this disease have demonstrated a median survival of 6 months, while single agent gemcitabine trials have reported median survivals ranging from 6 to 11.5 months with varying doses and schedules. Time to progression was also similar between our results and those reported in other single agent studies^{8,9,34–36}.

While the low median number of cycles relative to prolonged time to progression may define a patient population with indolent disease, our results are intriguing given that half of the patients enrolled had received prior therapy. However, of those patients whose best response was stable disease, only three had received prior systemic therapy including

gemcitabine and/or fluoropyrimidines and one patient had undergone prior chemoembolization. In addition, many of the patients with stable disease had liver-only or liver-dominant metastases with some patients' metastases limited to regional intraabdominal lymph nodes. Intrahepatic disease is thought to be a good prognostic factor in resectable disease, and this may apply to our population as well³⁷. Additional prognostic factors from surgical series of resected cholangiocarcinomas include tumor differentiation, peripheral versus central location, and gross subtype (mass forming, intraductal growth, or periductal infiltrating)^{37,38}. We were unable to further analyze this in our study as most patients did not have surgical resection. Limited data exist in the literature regarding prognostic features in metastatic cholangiocarcinoma.

While these results may indicate that patient selection played a role in the high rate of stable disease, the clinical benefit rate suggests that proteasome inhibition may have some role in the management of this disease by delaying time to progression. The toxicity profile of bortezomib in this population was similar to other studies evaluating this agent in a variety of disease sites^{25,26}. Given that many of these patients had liver involvement with tumor with potential loss of functional hepatic parenchyma, it is worth noting that bortezomib was well tolerated in this population.

Since the initiation of this study, combination systemic therapy has proven effective in advanced biliary tract cancers and is associated with a survival benefit. Based on these data, combination therapy in the front-line setting is now recommended based on level one evidence for appropriate patients with unresectable or metastatic disease³⁹. The combination of cisplatin and gemcitabine has been established as a standard of care for advanced disease based on the results of a large randomized phase III study demonstrating an improvement in overall survival from 8.1 months to 11.7 months ($p < 0.001$) with the combination compared to gemcitabine alone⁴⁰. Other combination chemotherapy regimens have also demonstrated promising antitumor activity. Recent phase II trials of gemcitabine and oxaliplatin have produced response rates of 35% to 50%, and overall survival times of up to 18 months in the front-line setting^{28,31}. A pooled analysis of 104 chemotherapy trials in advanced biliary tract cancers further suggested that gemcitabine may be the most active agent in these diseases, with the addition of platinum agents to gemcitabine resulting in higher response rates and tumor control rates⁴¹. Combination therapy with gemcitabine and fluoropyrimidines has also demonstrated activity in the front-line setting. The addition of 5-fluorouracil to gemcitabine resulted in a response rate of 9.5% and a median overall survival of 9.7 months²⁷. The combination of gemcitabine and capecitabine may be more active, with response rates of slightly over 30%, a clinical benefit rate of over 60%, and a median overall survival of 14 months^{29,30}. Thus, combination chemotherapy has been established as a standard of care in advanced biliary cancers.

Given the increasing role of chemotherapy in biliary tract cancers, further combination studies with bortezomib should be considered. Preclinical data suggest that bortezomib enhances the activity of multiple chemotherapy agents including gemcitabine, 5-fluorouracil, and irinotecan, providing at least additive cell killing^{24,42-45}. This may be due to downregulation of NF κ B, a known candidate mediator of chemotherapy resistance⁴⁵. This principle is evident in the multiple myeloma setting, where recent studies have

consistently demonstrated improved response rates, longer progression-free survival times, and better survival with the addition of bortezomib to traditional therapeutic regimens^{46–50}. Further preclinical work to define the best cytotoxic combinations is clearly needed.

The limitations of our study include the nonrandomized, single arm trial design, the small sample size, and the inclusion of a heterogeneous patient population. The population was not uniform in treatment history, with some patients being treatment-naïve and others having received prior therapy for their advanced disease. However, the primary endpoint of our study was response rate. This is an endpoint which may be less affected by patient heterogeneity.

In contrast, the observation of prolonged time to progression and the high rate of stable disease despite a low number of treatment cycles received may be due to inherent biology of the disease, with some patients potentially harboring a biologically indolent disease. While a formal study of predictive and prognostic markers was planned at study inception, the majority of patients enrolled did not have surgical specimens nor biliary fluid available for analysis. In future evaluations of bortezomib for biliary tract cancers, correlative studies attempting to better characterize the clinicopathologic factors and biomarkers within tumors of those patients who experience clinical benefit from therapy and those that do not would be worthwhile.

CONCLUSION

Our data demonstrate that single agent bortezomib has minimal clinical activity as defined by tumor response in adenocarcinomas of the biliary tract. However, the rate of stable disease, TTP, and OS are comparable to other studies of single agents in this disease. Currently, combination chemotherapy with gemcitabine and cisplatin is the standard of care for biliary tract cancer. Given preclinical evidence of chemotherapy potentiation, future study of bortezomib with cytotoxic agents known to be active in these diseases is warranted.

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CLINICAL PRACTICE POINTS

- Combination therapy is recommended in the front-line setting for the treatment of advanced biliary cancers. Cisplatin and gemcitabine are a standard treatment option, with a known survival benefit over single agent gemcitabine.
- Therapeutic options are limited for those unable to receive platinum-based combination therapy or in patients who have failed front-line combination therapy.
- Bortezomib does not result in antitumor responses as a single agent in advanced biliary tract cancers.
- Investigation of bortezomib in combination with other active therapies for advanced biliary tract cancers is warranted.

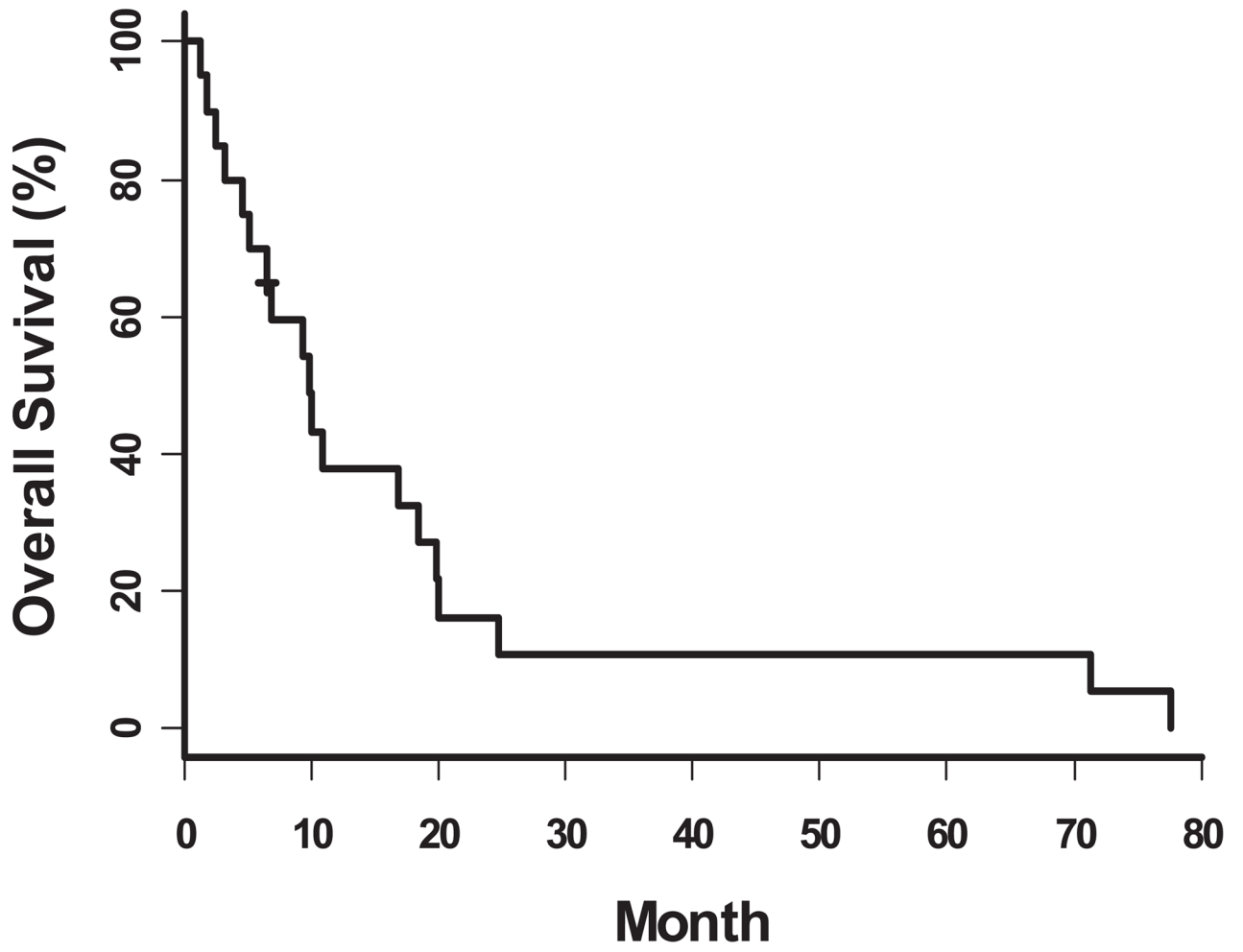


Figure 1.
Overall Survival for all patients treated with bortezomib

Table 1

Patient Characteristics

Demographic or Clinical Characteristics	Treatment Study Population (N=20) N (%)
Age	
Median	62
Range	41–79
Gender	
Male	11 (55%)
Female	9 (45%)
Site of Primary Tumor	
Gallbladder	6 (30%)
Cholangiocarcinoma (Intrahepatic or Extrahepatic)	14 (70%)
Site of Metastases	
Liver	14 (70%)
Lymph Nodes	7 (35%)
Lung	5 (25%)
Other	2 (10%)
ECOG PS	
0	7 (35%)
1	13 (65%)
Prior Treatment	
None	10 (50%)
Chemotherapy Only	4 (20%)
Chemotherapy/Radiation	5 (25%)
Other	1 (5%)
Prior Surgery	
Yes	5 (25%)
Cholecystectomy	4 (20%)
Liver Resection	1 (5%)
No	15 (70%)

Table 2

Adverse events by highest grade toxicity experienced per patient

Toxicity	All Grade Toxicity N (%)	Grade 3/4 Toxicity N (%)
<i>Hematologic</i>		
Anemia	15 (75%)	2 (10%)
Leukopenia	5 (25%)	0
Neutropenia	5 (25%)	1 (5%)
Thrombocytopenia	14 (70%)	3 (15%)
<i>Non-Hematologic</i>		
Dehydration	3 (15%)	2 (10%)
Dizziness	4 (20%)	0
Edema (all sites)	5 (25%)	0
Elevated Alkaline Phosphatase	3 (15%)	0
Elevated AST/ALT	7 (35%)	0
Elevated creatinine	3 (15%)	0
Fatigue	18 (90%)	4 (20%)
GI obstruction	0	2 (10%)
Hyperbilirubinemia	4 (20%)	3 (15%)
Hypertension	4 (20%)	0
Nausea	11 (55%)	2 (10%)
Pain (all sites)	9 (45%)	2 (10%)
Rash/Ulceration	4 (20%)	0
Sensory Neuropathy	6 (30%)	1 (5%)
Vomiting	7 (35%)	2 (10%)