A pilot study of bendamustine in advanced bile duct cancer

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We performed a pilot study to evaluate the safety and tolerability of bendamustine in patients with advanced hilar bile duct cancer and impaired liver function. Six patients with histologically proven, unresectable adenocarcinoma of the hilar bile duct were treated with bendamustine 140 mg/m^2 intravenously on day 1 of the first cycle and with bendamustine 100 mg/m^2 on days 1 and 2 of the second to fourth cycle. Treatment cycles were repeated every 21 days. Primary endpoint was the safety and tolerability of the treatment; secondary endpoints were response rate, time to progression and overall survival. Transient lymphopenia grade 3 occurred in all six patients. No other grade 3 or 4 toxicities were present. The most common nonhematologic toxicity was mouth dryness grade 2 in six patients. Three patients had stable disease. No partial or complete responses were observed. Median time to progression was 3.3 months; median overall survival was 6 months. Our study demonstrates that bendamustine can be safely administered in patients with hilar bile duct cancer and impaired liver function. A potential role of bendamustine in combination therapies for bile duct cancer will be a subject of further trials. ***Anti-Cancer Drugs*** **18:697–702 © 2007 Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2007, **18**:697–702

Keywords: bendamustine, biliary drainage, extrahepatic bile duct cancer, liver function, toxicity

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Received 6 November 2006 **Revised form accepted** 11 December 2006

Introduction

Carcinomas of the biliary tree are relatively rare tumors; however, their incidence is increasing worldwide [1–3]. About one-third of these tumors are extrahepatic bile duct tumors. Gallbladder and extrahepatic bile duct tumors have an estimated incidence of 6000 per year in Germany. Mortality rates from gallbladder and extrahepatic bile duct cancer in 2003 were 2.7 and 3.3 per 100 000 for men and women, respectively [4].

Approximately 60% of all bile duct cancers involve the biliary confluence (hilar cholangiocarcinoma) [5,6]. Surgical resection of hilar cholangiocarcinoma is the only potentially curative treatment. When initially diagnosed, not more than one-third of patients have resectable disease [7,8]. Five-year survival rates after resection of hilar bile duct cancer range from 20 to 35% [7–9].

For patients with nonresectable extrahepatic cholangiocarcinoma, biliary drainage is the standard palliative treatment. Palliative treatment leads to a median survival of 6–9 months [10,11]. Two randomized trials and several prospective single-arm studies demonstrated that photodynamic laser therapy in addition to stenting results in a relevant prolongation of survival reaching 9–21 months after diagnosis [12–16]. Median survival after palliative external irradiation of bile duct cancer is up to 12 months. The role of intraluminal brachytherapy is controversial and may be associated with adverse events [17–20].

A phase III trial studying palliative chemotherapy demonstrated a prolonged survival and an improved quality of life for biliary cancer patients treated with chemotherapy (5-fluorouracil, etoposide and leucovorin) as compared with best supportive care [21]. Epirubicin, cisplatin and infused 5-fluorouracil does not improve overall survival compared with 5-fluorouracil, etoposide and leucovorin [22]. Owing to the paucity of phase III studies, there is no established standard cytoreductive therapy in nonresectable disease. Median survival with palliative chemotherapy in phase II studies ranges from 7 to 15 months in advanced cholangiocarcinoma with objective response rates of 10–45% [23–27].

Bendamustine is a bifunctional alkylating agent combining a purine antagonist with an alkylating nitrogen mustard group. Its antineoplastic and cytotoxic properties are attributable mainly to crosslinking of the DNA single and double strands by alkylation. This leads to a disturbance of the matrix function of DNA and to hampered DNA synthesis [28,29]. Bendamustine has activity as single-agent therapy or in combination with

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other cytotoxic drugs in the treatment of plasmocytoma, chronic lymphocytic leukemia, non-Hodgkin's lymphoma and breast cancer [30–35].

Renal elimination was thought to be the predominant route of bendamustine excretion [36]. The drug should be given with caution to patients with impaired renal function. The drug is also metabolized in the liver and eliminated as cystein *S*-conjugates via the biliary system [37]. To what extent impaired liver function affects the pharmacokinetics, clinical safety and effectiveness of bendamustine is currently unknown.

We performed a pilot study of bendamustine in patients with hilar bile duct cancer to investigate the hepatic metabolism and pharmacokinetics of bendamustine in impaired liver function and to examine the safety of bendamustine in patients with this tumor. The pharmacokinetic studies published previously indicated the existence of phase II metabolites of bendamustine, which were identified as cysteine *S*-conjugates at the C-2 position of both ethylamino groups. The identification of cysteine *S*-conjugates provides evidence that a major route of bendamustine metabolism in humans involves conjugation with glutathione. The results indicate the importance of phase II conjugation in the elimination of bendamustine besides urinary excretion of the parent compound and its hydrolysis products [37]. We here report the clinical safety data and activity of the drug in patients with hilar bile duct tumors and impaired liver function.

Methods

Study population

Patients with histologically proven, unresectable adenocarcinoma arising from the hilar bile duct were eligible. Additional inclusion criteria were age 18–75 years, Karnofsky performance score $\geq 50\%$, life expectation of at least 3 months and adequate organ functions as follows: hemoglobin ≥ 5.5 mmol/l, leukocytes $\geq 4 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, bilirubin $\leq 3 \times$ upper limit of normal (UNL), transaminases $< 5 \times$ ULN, creatinine $\leq 2 \times$ ULN. Patients were ineligible if they had had surgery, chemotherapy or radiotherapy within the previous 4 weeks, or concomitant malignancies at other sites. Lactating or pregnant women were excluded. Written informed consent was obtained from each patient. The protocol was approved by the Ethics Committee at the University of Leipzig, Germany.

Endoscopic support

Biliary decompression was mandatory and consisted of nasobiliary tubes (7F, 290 cm, eight holes; Endo-Flex, Voerde, Germany) placed into the right and left hepatic duct during day 1 of cycle 1 for collection of bile samples. Thereafter, endobiliary prostheses (9F polyurethane stents) were inserted. Stents were exchanged every 3 months and in case of cholangitis. Photodynamic laser therapy was performed in all patients to optimize biliary drainage as previously described [12]. Briefly, photofrin (Axcan Pharma, Mount-Saint-Hilaire, Canada) was given at a dose of 2 mg/kg intravenously 24–48 h before endoscopic laser treatment. Photoactivation was performed at a wavelength of 630 nm using a light dose of 180 J/cm^2 and activation time of 800 s.

Chemotherapy

Bendamustine was administered as a 30-min intravenous infusion at a dose of 140 mg/m^2 on day 1 of the first cycle and at a dose of 100 mg/m^2 on days 1 and 2 of the second to fourth cycle. Treatment cycles were repeated every 21 days to a maximum of four cycles. Treatment was discontinued prematurely in case of progressive disease, unacceptable toxicity or withdrawal of patient consent. Chemotherapy was withheld for nonhematologic toxicities (with the exception of alkaline phosphatase and γ-glutamyl transpeptidase levels), thrombopenia, leukopenia and neutropenia Common Toxicity Criteria (CTC) grades 3 and 4 until recovery to $\leq$ grade 1 or baseline.

Assessment

Pretreatment evaluation included a medical history, physical examination, hematologic and biochemical testing, electroencephalography and chest radiography. Hematological and nonhematological toxicity was assessed once weekly and graded according to National Cancer Institute CTC (version 2.0). Mouth dryness was graded as follows: grade 0, normal; grade 1, mild perception of dry mouth lasting less than 2 weeks; grade 2, dry mouth and increased thirst more than 2 weeks; grade 3, intense but reversible perception of dry mouth with additional symptoms (hoarseness, dysphagia, burning sensation in the tongue); grade 4, irreversible mouth dryness.

Computed tomography or magnetic resonance imaging was obtained within 28 days before study entry, and repeated after the second and fourth cycle of bendamustine. Response to therapy was assessed according to World Health Organization. Time to progression was calculated from start of treatment to first documentation of disease progression. Overall survival was defined as time from start of treatment to death. Time from diagnosis to death was also recorded. Metric variables were described by median and standard deviation. Statistical analysis was done using MS Excel 2003.

Results

Between April and December 2003, six patients (median age 68 years, male:female ratio 3:3) with unresectable hilar bile duct cancer were enrolled. Four of them had had a laparotomy. All patients had histologically proven

adenocarcinoma. Median time from first diagnosis to start of treatment was 145.5 days (range 59–262 days). Pretreatment characteristics of the study population are summarized in Table 1.

Each patient received photodynamic laser therapy at least once during the study period and up to three times until death (Fig. 1).

Treatment toxicity

A total of 19 cycles of bendamustine were applied. Four patients completed treatment as intended per protocol. In two patients, treatment was stopped due to progressive disease after one (clinical progress) and two cycles, respectively. One erroneous treatment delay was observed for 1 week owing to leukopenia grade 2 but no dose reductions.

Hematological toxicity was mild except for grade 3 lymphocytopenia. Anemia (CTC grades 1 and 2) in four of six patients may have contributed to mild fatigue. Mild thrombopenia and leukopenia occurred in three and four cases, respectively, and did not cause any noticeable clinical problems (Table 2).

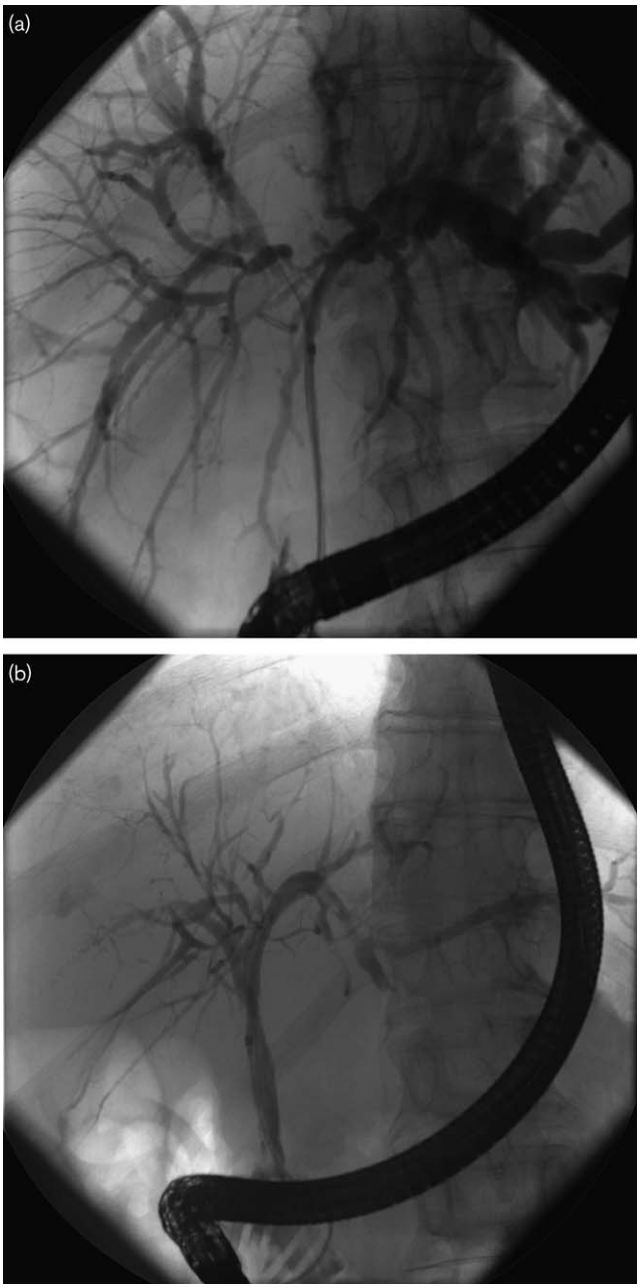
Transaminase and bilirubin levels remained stable throughout treatment with bendamustine. Median level of alkaline phosphatase was $10.3 \times$ ULN before treatment, $10.8 \times$ ULN after the first chemotherapy cycle and $5.9 \times$ ULN after the fourth cycle. Median γ-glutamyl transpeptidase levels were $12.2 \times$ ULN, $7.0 \times$ ULN and $2.5 \times$ ULN before treatment, after the first and after the fourth chemotherapy cycle, respectively. Apart from these abnormalities in liver function tests, no grades 3 and 4 nonhematological toxicities were observed. The most common mild adverse events were mouth dryness (CTC grade 2), nausea (CTC grades 1 and 2) and vomiting (CTC grade 1) in six, five and four patients, respectively (Table 2). Two patients developed liver abscesses 4 and 9 weeks after the last application of bendamustine, respectively. We consider these adverse events as a consequence of the underlying disease rather than a complication of bendamustine treatment. No further infectious episodes were observed.

Table 1 **Patient characteristics (*n* = 6)**

Age (years)	
Median	68
Range	61–74
Sex	
Male	3
Female	3
ECOG performance status	
1	4
2	2
Klatskin Bismuth–Corlette type	
III	1
IV	5
UICC tumor stage	
IIA (T3 N0 M0)	2
IIB (T3 N1 M0)	1
III (T4 Nx M0)	3
Interval since initial diagnosis (days)	
Median	145.5
Range	59–262

International Union against Cancer (UICC) tumor stage is indicated according to the TNM classification of malignant tumors [38].
ECOG, Eastern Cooperative Oncology Group.

Fig. 1



Endoscopic retrograde cholangiography showing an advanced Bismuth–Corlette type 4 bile duct cancer before (a), and after photodynamic therapy and four courses of bendamustine treatment (b).

Table 2 Maximum severity of hematologic toxicity and nonhematologic toxicity

	Grade 1/2	Grade 3/4
Hematologic		
Hemoglobin	4	–
Platelets	3	–
Leucocytes	4	–
Lymphocytes	–	6
Nonhematologic		
Nausea	5	–
Vomiting	4	–
Diarrhea	2	–
Obstipation	2	–
Appetite loss	6	–
Mouth dryness	6	–
Fatigue	6	–
Fever	2	–
Allergy	–	–
Cardiotoxicity	–	–
Bilirubin level	3	–
AP/GGT	0	6
Transaminases	3	1

AP/GGT, alkaline phosphatase/gamma-glutamyl transpeptidase.

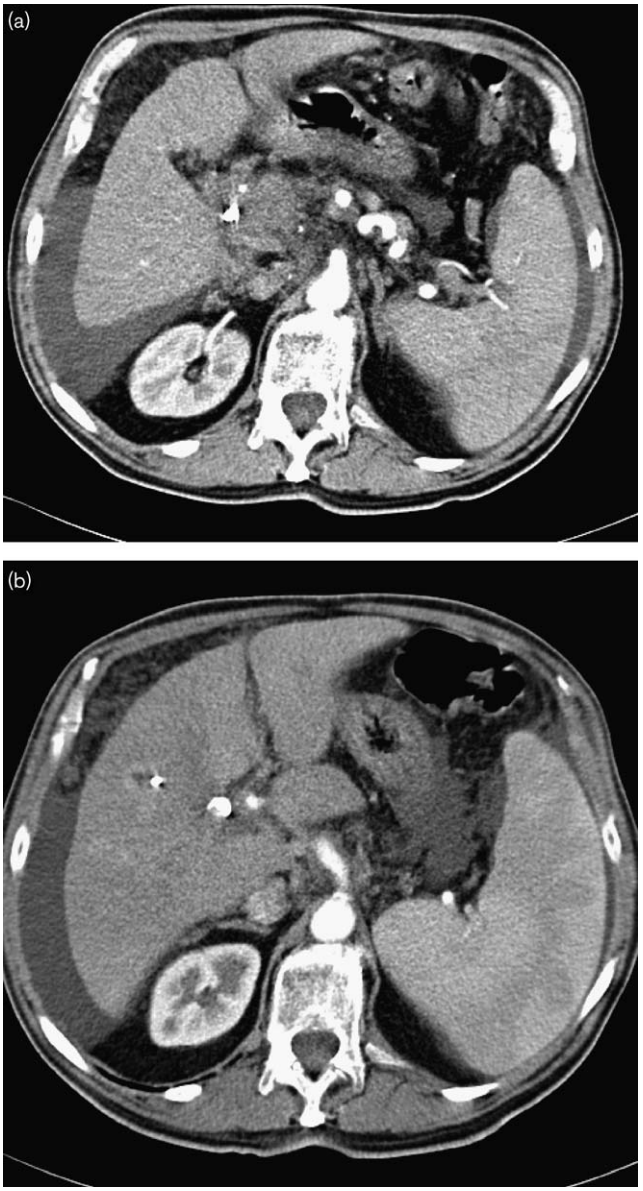
Response and survival

No complete or partial responses were noted. Stable disease was observed in three patients (Fig. 2). Median time to progression was 97.5 ± 41 days. Three patients had progressive disease as demonstrated by computed tomography or magnetic resonance imaging.

Serum carbohydrate antigen 19-9 increased in four patients (median 1023–3875 U/ml) and remained stable in two patients. No correlation between CA 19-9 levels and response to therapy was observed. This finding is probably due to the confounding effect of cholangitis and cholestasis on CA 19-9 levels.

The patients died 2, 4, 5.5, 7, 12.5 and 27 months after start of bendamustine treatment, respectively. Median overall survival was 183.5 ± 280 days. Median survival from diagnosis was 421.5 ± 243 days.

Fig. 2



Computed tomography scans are showing a perihilar tumor before (a) and after four courses of bendamustine treatment (b). The tumor response in this patient was classified as stable disease.

Discussion

No standard chemotherapy is currently known in advanced hilar bile duct cancer. The lack of consensus on the best treatment reflects not only the low incidence of the disease, but also the concern over detrimental toxicity. The patients' fate is often determined by cholangitis and liver failure [39,40]. Therefore, the mode of biliary decompression is a significant component of treatment [11,12,15,40] and biliary drainage is a prerequisite to cytotoxic therapy. Nevertheless, liver function tests remain elevated in the majority of cases. We have adopted a supportive strategy of regular biliary stent exchanges in combination with photodynamic therapy in hilar bile duct cancer [12]. During study treatment, no infectious complications were observed with this approach and chemotherapy was well tolerated. In two patients, however, with progressive disease liver abscesses occurred during follow-up, indicating the need for close attention to this problem.

In accordance with previously reported data, bendamustine at standard doses displayed a low toxicity profile [32–34]. In light of the impaired bile flow and abnormal liver function tests this is a noteworthy finding. Hematologic toxicity was mild except for transient lymphocytopenia grade 3. Grade 3 elevations of alkaline phosphatase

and γ-glutamyl transpeptidase levels improved over time. No severe adverse events occurred. Overall, toxicity was manageable on an outpatient basis. Our results broaden the potential applicability of bendamustine to patients with impaired bile flow. This is remarkable as recent evidence demonstrates that a major route of bendamustine metabolism in humans involves conjugation with glutathione followed by biliary excretion [37]. These findings suggest a broad therapeutic range of bendamustine. It is important to test the tolerability of the drug in impaired liver function because patients with liver metastases (e.g. breast cancer) and declining liver function may benefit from bendamustine treatment [34].

In our study, single-agent bendamustine led to disease stabilization in three patients (50%). No objective tumor responses were observed. Median overall survival was 6 months from start of therapy. Owing to the small number of patients treated, efficacy data should be interpreted with caution, though. With the exception of one older trial [21] there are no published studies demonstrating the superiority of cytotoxic therapy to supportive care alone in advanced biliary cancer. Hilar bile duct cancer constitutes a special entity with a slow and mostly local tumor growth, a marked desmoplastic stromal reaction, and in most cases no measurable tumor mass by cross-sectional imaging [41]. Thus, response to therapy as measured by imaging studies may be misleading. Nonetheless, no other in-vivo surrogate marker for cytotoxic activity is currently established in hilar bile duct cancer. Until we get results from randomized phase III trials, best supportive care including optimized biliary drainage and photodynamic therapy is still a valuable option in managing advanced hilar bile duct cancer. For new chemotherapeutic drugs to be introduced into the clinical armamentarium in obstructing bile duct tumors, tolerability remains an important aspect.

We conclude that bendamustine was well tolerated in all six patients with impaired hepatobiliary function. Efficacy of single-agent bendamustine in advanced hilar bile duct cancer cannot be reliably evaluated from this small series of patients. A potential role of bendamustine in combination therapies for bile duct cancer as well as its tolerability in impaired liver function will be a subject of further trials.

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