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ORIGINAL ARTICLE

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Phase II study of single-agent gemcitabine in patients with advanced biliary tract cancer

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Abstract *Purpose*: This phase II study was conducted to evaluate the efficacy and toxicity of single-agent gemcitabine in patients with advanced or metastatic biliary tract cancer. *Patients and methods*: Gemcitabine 1,000 mg/m^2 was administered as an intravenous 30-min infusion on days 1, 8, and 15 for every 28 days. *Results*: Forty chemonaive patients with a median age of 61 (range 33–73) were enrolled, and all 40 patients were involved in efficacy and safety analyses. Seven (17.5%) achieved partial response; 15 (37.5%) had stable disease; 17 (42.5%) had progressive disease; and 1 (2.5%) was not evaluated. The median survival time was 7.6 months, and the 1-year survival rate was 25.0%. Grade 3/4 neutropenia occurred in 12 patients (30.0%), leukopenia in five patients (12.5%), and anemia in four patients (10.0%). The most common grade 3/4 nonhematologic toxicities were elevated ALT (15.0%) and elevated γ-GTP (12.5%). One patient had grade 4 hemolytic uremic syndrome and recovered after discontinuation of gemcitabine. *Conclusions*: In single-agent therapy, gemcitabine demonstrated moderate efficacy with manageable toxicity in patients with advanced or metastatic biliary tract cancer. Further evaluations are warranted, including the exact impact of gemcitabine on the management of advanced or metastatic biliary tract cancer.

Keywords Biliary tract cancer · Chemotherapy · Clinical trial · Gallbladder cancer · Gemcitabine

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Introduction

The incidence of biliary tract cancer has increased markedly in Japan over the past several decades. In 2002, biliary tract cancer was the sixth leading cause of cancer death in Japan with approximately 16,000 deaths and a mortality rate of 12.5 per 100,000. A continued sharp increase in age-adjusted mortality is predicted over the next 10 years [22, 25, 30].

Of all the treatment modalities for biliary tract cancer, only resection offers the opportunity for cure. However, because of metastases or invasion of the tumor directly into the adjacent liver or the hepatic artery, only a small minority of biliary tract cancer patients are candidates for resection with curative intent. The prognosis for these patients is dismal, and the impact of existing chemotherapy is virtually negligible. Therefore, there is a clear need for new, effective, chemotherapeutic regimens in the management of biliary tract cancer.

Gemcitabine is a novel nucleoside analogue, which requires to be phosphorylated to its active metabolite, gemcitabine triphosphate. Gemcitabine triphosphate competes with deoxycytidine triphosphate for incorporation into DNA, inhibiting DNA synthesis [16]. Gemcitabine has shown broad activity in a variety of tumors and is currently approved for use in non-small-cell lung

cancer and pancreatic cancer in Japan. Based on the results obtained in early phase studies in other locales and the established safety profile of the agent [3, 7, 8, 12, 24, 34, 35, 40], our group has conducted a multicenter, phase II trial of single-agent gemcitabine to investigate the response rate, toxicity, and time-to-event variables (progression-free survival, duration of tumor response, and survival time) in patients with advanced or metastatic biliary tract cancer.

Patients and methods

Eligibility criteria

Enrolled patients had histologically or cytologically confirmed adenocarcinoma of biliary tract, extrahepatic bile duct, gallbladder, or ampulla of Vater. Each patient was required to meet the following eligibility criteria: unresectable biliary tract cancer with at least one bidimensionally measurable tumor; no history of prior chemotherapy; no history of prior antitumor treatment for biliary tract cancer except resection and intraoperative or postoperative adjuvant radiotherapy; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; 20–74 years of age; estimated life expectancy ≥2 months; adequate renal function (creatinine ≤ upper limit of normal [ULN]); adequate liver function (bilirubin ≤ 2 times ULN and aspartate/alanine transaminases [AST/ALT] ≤ 2.5 times ULN); adequate bone marrow reserve (white blood cells ≤ 4,000/mm^3, neutrophils ≥2,000/mm^3, platelets ≥100,000/mm^3, and hemoglobin ≥10 g/dl); and written informed consent. Patients with pre-existing obstructive jaundice were also eligible after their bilirubin levels met the criteria by biliary stent insertion or percutaneous biliary drainage.

Patients were excluded from the study if they had pulmonary fibrosis, interstitial pneumonia, New York Heart Association class III or IV congestive heart failure, myocardial infarction within the preceding 6 months, diabetes mellitus with severe complications, marked pleural or pericardial effusion, marked peripheral edema, or active infection. Additional exclusion criteria included pregnant or lactating females, patients of reproductive potential who did not use effective contraception, severe drug hypersensitivity, central nervous system metastases, active concomitant malignancy, other serious medical conditions, or patients receiving any investigational drug within 30 days before enrollment.

The study was conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represented the greater protection of the individual. In addition, the study design was approved by the appropriate ethical review boards.

Study treatment

Gemcitabine (supplied by Eli Lilly, Japan) 1,000 mg/m^2 was administered as an intravenous 30-min infusion on days 1, 8, and 15 for every 28 days. The treatment was continued until evidence of disease progression or unacceptable toxicity.

For white blood cells < 2,000/mm^3, neutrophils < 1,000/mm^3, platelets < 70,000/mm^3, bilirubin > 3 times ULN, or AST/ALT > 5 times ULN, gemcitabine was omitted on that day and postponed to the next scheduled treatment day.

In subsequent cycles, gemcitabine was reduced to 800 mg/m^2 if neutrophils < 500/mm^3 for 4 days, white blood cells < 1,000/mm^3 for 4 days, platelets < 25,000/mm^3, bilirubin > 3 times ULN, or AST/ALT > 5 times ULN. Gemcitabine was also reduced to 800 mg/m^2 if a platelet transfusion was performed due to thrombocytopenia or if gemcitabine was omitted twice in succession due to toxicity. No dose adjustment was allowed during the same cycle. The treatment was discontinued if a second dose reduction was needed, if bilirubin > 5.0 times ULN, AST/ALT > 20 times ULN, or tumor progression was observed. The use of granulocyte colony-stimulating factor (G-CSF) was permitted for any grade 4 leukopenia or neutropenia or grade 3 neutropenia with high fever (38.0°C). Prophylactic administration of antiemetics was allowed.

Baseline and treatment assessments

Pretreatment evaluation included complete history and physical examination. In addition, complete blood count, biochemistry tests, urinalysis, and chest X-ray were performed. Performance status and laboratory tests, except for urinalysis, were assessed weekly. Urinalysis was performed during days 15–28 in each cycle. Tumor size was measured by CT scan or MRI during days 22–28 in each cycle. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19–9) were quantified every 4 weeks. All 40 patients who received at least one dose of gemcitabine were involved in the efficacy analyses.Objective tumor response was assessed every 4 weeks using WHO criteria [41]. The duration of response was calculated from the first day of treatment until documentation of disease progression. Survival was measured from the first day of treatment.

Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria version 2.0 [27]. A monitoring committee independently evaluated the efficacy and safety of the study.

Statistical analysis

Considering the results of previous trials using gemcitabine for advanced or metastatic biliary tract cancer, we expected an overall response rate of 15–20% in this

study. With this population, response rates typically have not exceeded 10% in patients treated with 5-fluorouracil (5-FU); therefore, a response rate of at least 15% in our study would suggest a potential benefit.

Our goal was to enroll 40 eligible patients. If no response occurred in the first 18 patients, accrual was terminated because the chance of a 15% response rate was only 5.3%. If the response rate was 15%, the statistical power (the probability of a 5% response rate) would be 73% with type I error of 5% (one-sided). For a response rate of 17.5%, the statistical power would be 85%, and the statistical power would be 92% for a response rate of 20%.

All time-to-event measures were calculated using the Kaplan–Meier method.

Results

Patient characteristics and disposition

From October 2001 to September 2003, 21 males and 19 females, with a median age of 61 years (range 33–73 years), were enrolled. Table 1 shows the baseline patient characteristics. Twenty-three patients (57.5%) had no prior therapy, and 17 (42.5%) relapsed after resection for primary lesion. The major metastatic lesions were the abdominal lymph nodes (67.5%) and liver (55.0%). Prior to the initiation of study treatment, obstructive jaundice was palliated with percutaneous transhepatic catheter placement (11 patients) or endobiliary stent placement (3 patients).

The reasons for the treatment discontinuation included progressive disease (34 patients), elevated blood pressure associated with worsening of renal function (one patient), hemolytic uremic syndrome (one patient), blood bilirubin increased with progressive disease (one patient), relapse of pre-existing schizophrenia (one patient), patient's refusal due to nausea/vomiting (one patient), and general fatigue (one patient).

Table 1 Baseline patient characteristics ($n = 40$)

Characteristic	
Gender, *n* (%)	
Male	21 (52.5)
Female	19 (47.5)
Age, years	
Median (range)	61 (33–73)
ECOG performance status	
0	24 (60.0)
1	16 (40.0)
Primary lesion	
Extrahepatic bile duct	12 (30.0)
Gallbladder	22 (55.0)
Ampulla of Vater	6 (15.0)
CA19–9, *n* (U/ml)	
Median (range)	448.6 (1–77,820)
CEA, *n* (ng/ml)	
Median (range)	10.9 (0.5–1,790)
Metastatic sites, *n* (%)	
Abdominal lymph nodes	27 (67.5)
Liver	22 (55.0)
Peritoneum	4 (10.0)
Lung	2 (5.0)
Bone	1 (2.5)

ECOG Eastern Cooperative Oncology Group; *CA19–9* carbohydrate antigen 19–9; *CEA* carcinoembryonic antigen

Efficacy

All 40 patients were evaluated for efficacy and according to WHO criteria, seven patients achieved a partial response for an overall response rate of 17.5% (95% CI, 7.3–32.8%). The median duration of the response was 9.4 months (range, 2.6–9.4 months). Fifteen patients (37.5%) had stable disease, and 17 patients (42.5%) had progressive disease. Tumor response was not determined in one patient because she was transferred to another hospital before response evaluation. The serum CA 19–9 level was reduced by less than half in 11 (33%) of 33 patients who had a pretreatment level of above upper normal limit, and the CEA level was reduced by less than half in 6 (24%) of 25 patients. Of the 11 patients whose CA 19–9 level was reduced, 4 (36%) showed a partial response. Five (83%) of the six patients with the CEA response achieved a partial response.

At the time of analysis, 35 of 40 patients had died of cancer and two of five patients lived longer than 24 months after the initial administration of gemcitabine. The median progression-free interval was 2.6 months (95% CI, 1.7–3.8 months), and the median survival time was 7.6 months (95% CI, 5.4–9.3 months) (Fig. 1). The 1-year survival rate was 25.0%.

Toxicity

All 40 patients were evaluable for toxicity (Table 2). No toxic deaths occurred. Hematologic toxicity was reversible and manageable. Patients reported grade 3/4 neutropenia (30.0%), leukopenia (12.5%), and anemia (10.0%). Three patients had red blood cell transfusions due to hemolytic uremic syndrome, hemorrhagic shock, and anemia. No grade 3/4 thrombocytopenia was reported. Although two patients were treated with G-CSFs, there was no febrile neutropenia.

The most common nonhematologic toxicities, grades 1–4 were nausea (52.5%) and anorexia (52.5%), but only four patients (10%) required intravenous infusion due to these toxicities. The most common grade 3/4 nonhematologic toxicities were elevated ALT (15.0%) and elevated γ-glutamyltransferase (γ-GTP) (12.5%). Grade 4 elevated γ-GTP was observed in one patient, which was considered to be gemcitabine-related because the level returned to normal after treatment discontinuation. The patient, who had grade 3 uremia, grade 2 serum creatinine elevation, and grade 2 thrombocytopenia, was diagnosed with grade 4 hemolytic uremic syndrome and also recovered from these toxicities by

transfusion without dialysis after discontinuing gemcitabine. In another patient on day 25 of cycle 1, hemorrhagic shock occurred following unexpected hematemesis, which was unlikely to be gemcitabine related. Endoscopic examination showed acute gastric mucosal lesions, and prescribed nonsteroidal anti-inflammatory drugs to control abdominal pain were suspected to be the cause of hemorrhagic shock.

Dose intensity

A median of three cycles was administered (range, 1–14). Eleven patients (27.5%) completed one cycle; eight patients (20.0%) completed two cycles; and five patients (12.5%) completed three cycles. The planned mean dose intensity of gemcitabine was 750 mg/m^2; however, the actual mean dose intensity of gemcitabine was 688.7 mg/m^2. Thus, the dose intensity was 91.8% for gemcitabine. Of the 476 planned infusions, 37 dose omissions (7.8%) occurred, mainly due to neutropenia. There were no dose reductions.

Discussion

The vast majority of patients with biliary tract cancer are candidates for chemotherapy; however, chemotherapy for biliary tract cancer currently has only limited value in clinical practice. 5-FU is the mainstay of palliative chemotherapy, although response rates range from 0 to 13% in phase II trials [6, 11, 39]. It is generally accepted that combinations with 5-FU have little superiority over single-agent 5-FU, and the considerable toxicity often outweighs the benefit for the patients [11, 39]. Except for gemcitabine, no individual agent has shown a reproducible response rate over 15% [1, 12, 19, 29, 31, 33, 37]. Therefore, new agents need to be developed for truly effective chemotherapeutic regimens against this disease.

In a prospective randomized trial [4], gemcitabine is the only agent showing significant efficacy in respect to survival prolongation and symptom relief for patients with advanced pancreatic cancer; these results prompted trials for biliary tract cancer, which, to some extent, shares embryological and clinical features with pancreatic cancer. Several early-phase studies of single-agent gemcitabine at doses of 1,000–2,200 mg/m^2 have reported response rates of 8–60%, and median survival durations ranging from 6.5 to 11.5 months. [3, 7, 8, 14, 21, 24, 34, 35].

In our trial, gemcitabine 1,000 mg/m^2 was administered for 3 weeks with 1 week of rest; this schedule is currently approved in Japan for non-small-cell lung cancer and pancreatic cancer and is considered to be a standard regimen worldwide. Our overall response rate of 17.5% appeared to be comparable to previous trials with gemcitabine or other combination regimens and appeared near the highest results in single-agent therapy. In recent phase II trials of various single agents, responses were 8% in a study with cisplatin [29], 0% in paclitaxel [19], 0–25% in docetaxel [2, 31, 33], 11% in irinotecan [12], and 19% in capecitabine [23]. Our median overall survival of 7.6 months was also comparable to other trials of single-agent therapy, which ranged from 4.5 to 8.0 months [2, 12, 19, 23, 29, 31, 33, 37], and for combination therapies, which ranged from 5.0 to 14.0 months [5, 9, 10, 15, 18, 20, 26, 28, 32, 35, 36, 38]. However, it seemed to be longer when compared with other phase II trials for Japanese patients with advanced or metastatic biliary tract cancer, which was 5.3 months in uracil/tegafur, 5.9 months in cisplatin/

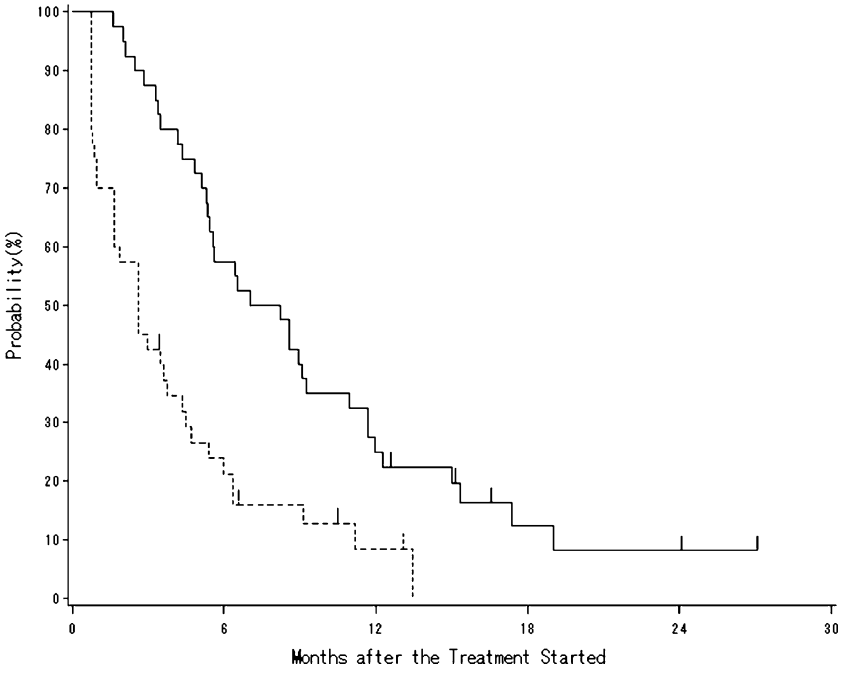

Fig. 1 Progression-free survival (*dashed line*) and overall survival (*solid line*) curves of patients with advanced biliary tract cancer receiving systemic chemotherapy with gemcitabine

Table 2 Adverse drug reaction

Adverse drug reaction	Grade 3		Grade 4	
	n	(%)	*n*	(%)
Hematologic toxicities				
Neutropenia	10	25.0	2	5.0
Leukopenia	5	12.5	0	0.0
Anemia	3	7.5	1	2.5
Thrombocytopenia	0	0.0	0	0.0
Nonhematologic toxicities				
Elevated ALT	6	15.0	0	0.0
Elevated γ-GTP	4	10.0	1	2.5
Elevated AST	2	5.0	0	0.0
Decreased serum sodium	2	5.0	0	0.0
Increased serum ALP	2	5.0	0	0.0
Urinary occult blood positive	1	2.5	0	0.0
Increased serum bilirubin increased	0	0.0	0	0.0
Increased serum creatinine	0	0.0	0	0.0
Proteinuria	0	0.0	0	0.0
Hematuria	0	0.0	0	0.0
Hemolytic uremic syndrome	0	0.0	1	2.5
Constipation	3	7.5	0	0.0
Vomiting	3	7.5	0	0.0
Nausea	2	5.0	0	0.0
Hematemesis	0	0.0	1	2.5
Diarrhoea	0	0.0	0	0.0
Stomatitis	0	0.0	0	0.0
Fatigue	0	0.0	0	0.0
Edema	0	0.0	0	0.0
Pyrexia	0	0.0	0	0.0
Biliary tract infection	1	2.5	0	0.0
Anorexia/Appetite impared	3	7.5	1	2.5
Rash	1	2.5	0	0.0
Alopecia	0	0.0	0	0.0
Hypertension	1	2.5	0	0.0
Hemorrhagic shock	0	0.0	1	2.5

ALT Alanine aminotransferase, *γ-GTP* γ-glutamyltransferase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase

epirubicin/5-FU, and 5.5 months in a study with cisplatin [18, 26, 29].

The toxicity profile in our study was generally acceptable. The major toxicities were myelosuppression; the incidences of grade 3/4 toxicities were 30.0% in neutropenia, 12.5% in leukopenia, and 10.0% in anemia. However, grade 4 toxicities were infrequent, and neither febrile neutropenia nor treatment-related deaths were observed. The toxicity profile in our study was consistent with past studies using gemcitabine in other tumors. For patients treated with cisplatin, epirubicin, and 5-FU [26], high incidences of grade 3/4 neutropenia (76.0%), leukopenia (59.0%), and death due to treatment-related sepsis 5.0% occurred despite a response rate (19%) similar to that in our study. There was only one episode of cholangitis in this study, although patients with biliary tract cancer are at high-risk for cholangitis, and sometimes severe sepsis occurs, which is derived from cholangitis during chemotherapy [26]. Transient elevations of hepatic enzymes have been reported in gemcitabine therapy for both pancreatic and biliary tract cancer; liver function may be easily affected by cholestasis due to existence of primary and/or metastatic tumors.

One patient developed hemolytic uremic syndrome, which was considered to be a manifestation of thrombotic microangiopathy, although gemcitabine-associated thrombotic microangiopathy is believed to be very rare, with estimated incidences of 0.008–0.31% [13, 17]. The event in this patient seemed to be a treatment-related adverse reaction; however, the patient recovered from hemolytic uremic syndrome without hemodialysis after discontinuation of gemcitabine. Grade 4 anemia was observed in one patient, who suffered grade 4 hematemesis and hemorrhagic shock. This was unlikely to be related to gemcitabine because no thrombocytopenia was observed in this patient. Also, upper gastrointestinal endoscopy revealed acute gastric mucosal lesions as the origin of the bleeding, which seemed to be related to prescribed non-steroidal anti-inflammatory drugs.

Our study was conducted among the largest group of patients with biliary tract cancer to date. In our study, gemcitabine was administered to patients who had biliary stent insertion or percutaneous biliary drainage, and no particular drug-related toxicity was observed in these patients. The result of our study is promising for patients with biliary tract cancer.

In conclusion, chemotherapy with single-agent gemcitabine was feasible and appeared to show efficacy in advanced or metastatic biliary tract cancer. Gemcitabine may provide a more favorable prognosis in patients with this disease compared to other chemotherapeutic regimes or best supportive care.

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Appendix

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