

## Efficacy and Safety of Gemcitabine Monotherapy for Patients with Advanced Biliary Tract Cancer

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### Abstract

**Objective:** The aim of this study was to analyze the efficacy and feasibility of gemcitabine monotherapy in patients with unresectable advanced or recurrent biliary tract cancer (BTC).

**Methods:** Six patients with unresectable advanced BTC and 12 patients with recurrent BTC received gemcitabine monotherapy. Gemcitabine (800–1,000 mg/m<sup>2</sup>) was administered intravenously over 30 minutes on days 1, 8, and 15 every 28 days. Disease and toxicity were assessed once a week in all patients until the completion of gemcitabine treatment. Computed tomographic/magnetic resonance imaging studies were done every 8 weeks during chemotherapy, and every 4 weeks if progressive disease was suspected. Tumor response was determined according to the Response Evaluation Criteria in Solid Tumors. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria version 2.0. The time to progression and survival time were also calculated.

**Results:** In patients with unresectable BTC, the overall response rate and the median time to progression for patients with partial response or stable disease was 66.7% and 5.68 months, respectively. Clinical benefit was observed in 3 patients with stable disease (50%). The median survival time was 5.2 months. In patients with recurrent BTC, 4 patients (33%) obtained partial responses and 2 patients (17%) had stable disease. The median time to progression was 8.2 months. Six of 12 patients (50%) obtained clinical benefit. The median survival time for cancer of the intrahepatic bile duct, the extrahepatic bile duct, and the ampulla of Vater were 2.8 months, 8.5 months, and 10.7 months, respectively. No significant correlation between the survival time and the resectability of the initial procedure (R number) was detected. The survival time for patients with a performance status of 0 or 1 was significantly longer than that for patients with a performance status of 2 ( $P=0.0051$ ). Neither grade 3/4 hematologic toxicity nor grade 3/4 nonhematologic toxicity was observed. No treatment-related deaths were observed.

**Conclusion:** Gemcitabine monotherapy may provide a more favorable prognosis in patients with advanced BTC than does best supportive care alone. Moreover, this regimen may represent a therapeutic option for the adjuvant setting in patients with BTC.

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**Key words:** gemcitabine, biliary tract cancer

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## Introduction

Biliary tract cancer (BTC) is a rare malignancy with a poor prognosis<sup>1</sup>. Although complete surgical resection offers the only chance for cure, BTC recurs in most patients, either locoregionally or metastatically<sup>1,2</sup>. Therefore, treatment focuses on a multidisciplinary approach including chemotherapy in the adjuvant, neoadjuvant, and advanced settings. Recently, several studies of chemotherapy for advanced BTC have been published<sup>2-12</sup>. Most of these studies, however, have been small, nonrandomized phase II trials<sup>2,5,6,8-10,12</sup>. Therefore, a standard treatment for BTC has not been established.

Gemcitabine is a novel nucleoside analogue that is phosphorylated to its active metabolite, gemcitabine triphosphate<sup>13,14</sup>. Gemcitabine triphosphate competes with deoxycytidine triphosphate for incorporation into DNA and thereby inhibits DNA synthesis<sup>14</sup>. Recently, gemcitabine monotherapy was developed as a first-line treatment for advanced pancreatic cancer<sup>14,15</sup>. Recent studies have reported longer survival and clinical benefit<sup>15-21</sup>. Moreover, gemcitabine monotherapy was more effective than any gemcitabine-based combination for relieving disease-related symptoms and prolonging survival in patients with advanced pancreatic cancer<sup>16-21</sup>. Recently, gemcitabine-based regimens for advanced unresectable BTC have achieved objective response rates of 20% to 45% and a median survival of 8 months<sup>22-35</sup>.

Since being approved by the Ministry of Health, Labour and Welfare in 2006, gemcitabine monotherapy has been used to treat BTC in Japan. The aim of the present study was to analyze the efficacy and feasibility of gemcitabine monotherapy in patients with unresectable advanced or recurrent BTC.

## Patients and Methods

### Eligibility Criteria

Six patients with unresectable advanced BTC and 12 patients with recurrent BTC received gemcitabine monotherapy from January 2002 through December 2007 at Nippon Medical School Tama Nagayama Hospital. The diagnosis of BTC

was confirmed as adenocarcinoma by means of histological examination or cytological examination or both. The eligibility criteria for this treatment were as follows: an Eastern Cooperative Oncology Group performance status (PS) of 0 to 2, adequate bone marrow function (white blood cell [WBC] count  $>3,000/\text{mm}^3$ , absolute neutrophil count  $>1,000/\text{mm}^3$ , and platelet count  $>70,000/\text{mm}^3$ ), and availability of written informed consent. Patients with severe complications were excluded. All patients with obstructive jaundice underwent percutaneous transhepatic or endoscopic retrograde biliary drainage before treatment. These patients were required to have serum bilirubin levels of  $<3.0 \text{ mg/dL}$  and serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels  $<5$  times the upper limit of normal (ULN).

### Treatment Design

Gemcitabine ( $800\text{--}1,000 \text{ mg/m}^2$ ) was administered intravenously over 30 minutes on days 1, 8, and 15 every 28 days. The treatment was continued until evidence of disease progression (PD), unacceptable toxicity, or the patient's refusal to continue treatment. Gemcitabine was omitted on that day and postponed to the next scheduled treatment day for WBC  $<2,000/\text{mm}^3$ , neutrophils  $<1,000/\text{mm}^3$ , platelets  $<70,000/\text{mm}^3$ , bilirubin  $>3$  times ULN, or AST/ALT  $>5$  times ULN. In subsequent cycles, gemcitabine was reduced to  $800 \text{ mg/body}$  if neutrophils  $<500/\text{mm}^3$  for 4 days, WBC  $<1,000/\text{mm}^3$  for 4 days, platelets  $<25,000/\text{mm}^3$ , bilirubin  $>3$  times ULN, or AST/ALT  $>5$  times ULN. Gemcitabine was also reduced to  $800 \text{ mg/body}$  if platelet transfusion was performed owing 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 was permitted for any grade 4 leukopenia or neutropenia or grade 3 neutropenia with fever ( $38.0^\circ\text{C}$ ). Prophylactic administration of an antiemetic was also allowed.

Table 1 Unresectable BTC

Age	Sex	Location	PS	IVR	N	H	P	Efficacy	TTP	ST	Clinical benefit	2nd line
56	M	Int.BD	1	EBD	+	+	-	SD	6.8	9.8	+	-
65	M	Int.BD	2	PTBD	-	+	+	PD	-	4.6	-	-
75	F	Ext.BD	1	EBD	+	+	+	SD	5.4	6.4	+	-
66	F	GB	0	PTBD	+	-	+	SD	5.7	6.8	+	-
78	F	GB	1	PTBD	+	-	+	PR	4.8	5.1	-	-
59	F	GB	2	PTBD	+	+	-	PD	-	3.5	-	-

Ext.BD: extrahepatic bile duct Int.BD: intrahepatic bile duct GB: gall bladder

N: lymph nodes metastasis H: liver metastasis P: peritoneal dissemination

TTP: time to progression (month) ST: survival time after the initial administration of gemcitabine (month)

PR: partial response SD: stable disease PD: progressive disease

EBD: endoscopic biliary drainage PTBD: percutaneous transhepatic biliary drainage

### Response and Toxicity Evaluation

All patients underwent assessment of disease and toxicity once a week until the completion of gemcitabine treatment. The antitumor effect of gemcitabine was evaluated with computed tomography (CT) or magnetic resonance imaging (MRI) or both. The CT/MRI studies were performed every 8 weeks during chemotherapy, and every 4 weeks if PD was suspected.

Tumor response was determined according to the Response Evaluation Criteria in Solid Tumors<sup>36</sup>. The size of measurable lesions was confirmed with contrast-enhanced CT or MRI. Toxicity was assessed with the National Cancer Institute Common Toxicity Criteria version 2.0<sup>37</sup>. The time to progression was calculated as the interval from the start of treatment with gemcitabine until the occurrence of PD. The survival time was defined as the interval from the start of treatment with gemcitabine until death.

### Statistical Analysis

Survival curves were estimated with the Kaplan-Meier method and were compared by means of the log-rank test. All probability values were determined from 2-sided tests.

## Results

### Patient Characteristics

The characteristics of patients with unresectable BTC are summarized in **Table 1**. Two patients had intrahepatic bile duct cancer, 1 had extrahepatic bile duct cancer, and 3 had gallbladder cancer. Four

patients (67%) maintained a good PS (0 or 1) before the start of gemcitabine monotherapy. All patients required bile duct drainage with the percutaneous transhepatic approach or the endoscopic approach for obstructive jaundice. Five patients (83%) had abdominal lymph node metastasis, 4 (67%) had liver metastasis, and 4 (67%) had peritoneal dissemination.

**Table 2** shows the characteristics of patients with recurrent BTC. Three patients (25%) had intrahepatic bile duct cancer, 6 (50%) had extrahepatic bile duct cancer, 1 (8%) had gallbladder cancer, and 2 (16%) had cancer of the ampulla of Vater. Previously, 7 patients (58%) had undergone R0 resection, 3 (25%) had undergone R1 resection. The median disease-free survival time after surgery was 42.5 months (range, 6.8–79.2). Ten patients (83%) had a PS of 0 or 1 before receiving gemcitabine. Five patients (42%) who underwent R1 or R2 resection received a combination of uracil and tegafur as adjuvant therapy. Three patients (25%) with intrahepatic bile duct cancer had recurrent tumors in the liver. Liver metastasis was also observed in 1 of 6 patients (17%) with extrahepatic bile duct cancer and in both patients (100%) with cancer of the ampulla of Vater. Two patients with extrahepatic bile duct cancer and 1 patient with cancer of the ampulla of Vater had peritoneal dissemination.

### Efficacy

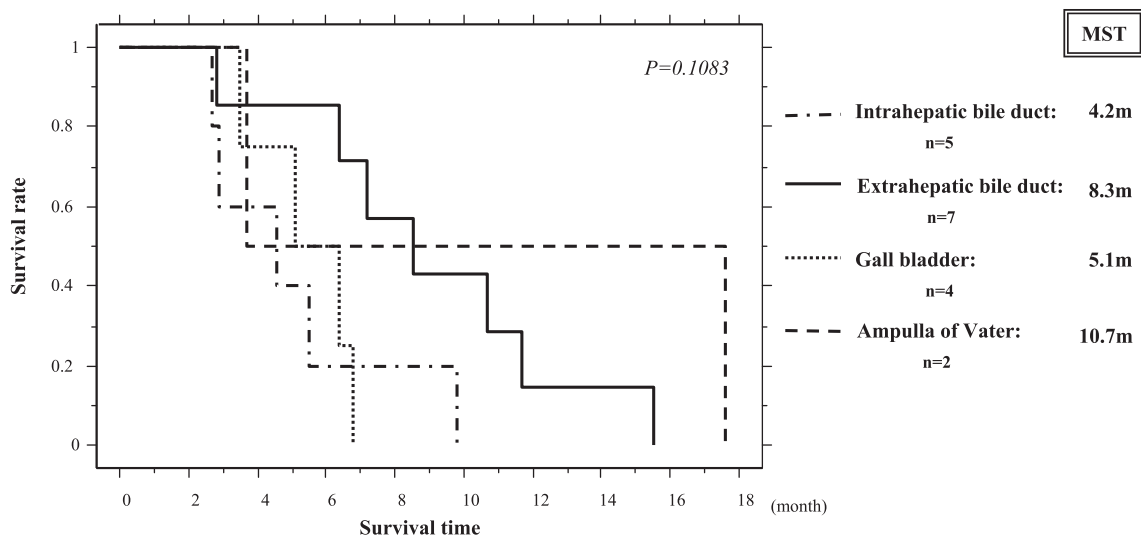
All BTCs

Five patients (33%) had partial responses (PRs), 5 patients (17%) had stable disease (SD), and 8 (50%) had PD. A PR was observed in 3 of 7 patients (50%)

Table 2 Recurrent BTC

Prior therapy			Recurrence												
Age	Sex	Location	Resection	DFI	PS	Adjuvant	N	H	P	Others	Efficasy	TTP	ST	Clinical benefit	2nd line
72	F	Int.BD	R0	6.8	0	-	-	+	-	-	PD	-	2.9	-	-
68	M	Int.BD	R0	15.3	0	-	-	+	-	-	PD	-	5.5	-	-
72	F	Int.BD	R0	11.7	0	-	-	+	-	-	PD	-	2.7	-	-
76	F	Ext.BD	R0	29.0	1	-	+	-	-	-	PR	10.1	15.5	+	RT
72	F	Ext.BD	R2	-	0	UFT	+	-	-	lung	PR	8.2	11.7	+	S-1
64	F	Ext.BD	R1	30.8	2	UFT	+	+	+	-	PD	-	2.8	-	-
72	M	Ext.BD	R1	79.2	0	UFT	+	-	+	-	PD	-	8.5	+	S-1
45	M	Ext.BD	R0	14.8	0	-	+	-	-	-	SD	6.0	7.2	+	GP
72	M	Ext.BD	R0	12.7	0	-	+	-	-	-	PR	8.3	10.7	+	GP
75	M	GB	R2	-	0	UFT	+	-	-	-	SD	4.8	6.4	+	-
67	M	Amp.	R1	27.4	1	UFT	+	+	+	-	PD	-	3.7	-	-
74	F	Amp.	R0	32.5	0	-	+	+	-	-	PR	13.2	17.6	+	-

Ext.BD: extrahepatic bile duct Int.BD: intrahepatic bile duct GB: gall bladder Amp.: ampulla of Vater  
 N: lymph nodes metastasis H: liver metastasis P: peritoneal dissemination  
 DFI: disease free interval (month) TTP: time to progression (month) ST: survival time after the initial administration of gemcitabine (month)  
 RT: radiotherapy S-1: tegafur/gimeracil/oteracil potassium GP: gemcitabine + cisplatin  
 PR: partial response SD: stable disease PD: progressive disease



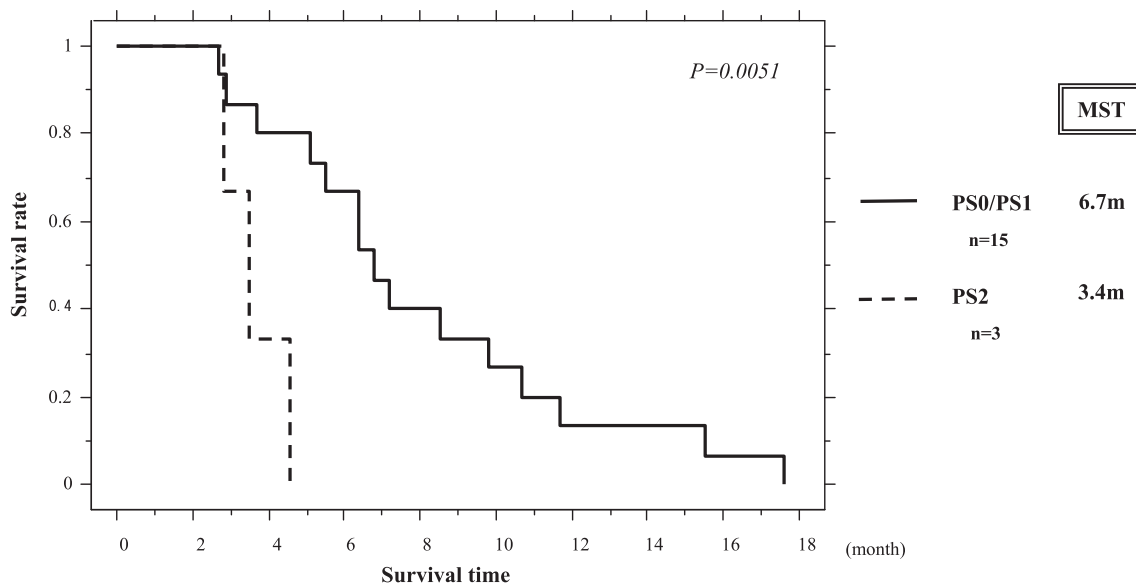
MST: median survival time (month)

Fig. 1 Survival curve of patients with all BTC according to the site of primary tumor

with extrahepatic bile duct cancer and 1 of 2 patients (50%) with cancer of the ampulla of Vater. The median time to progression after the start of treatment with gemcitabine was 6.0 months (range, 4.8–13.2 months). Clinical benefit was obtained by 5 of 7 patients (83%) with extrahepatic bile duct cancer, 2 of 4 patients (50%) with gallbladder cancer, and 1 of 2 patients (50%) with cancer of the ampulla of Vater. The median survival time after the start of

treatment with gemcitabine and the 1-year survival rate were 4.2 months and 0% for intrahepatic bile duct cancer (0 of 5 patients), 8.3 months and 14.3% for extrahepatic bile duct cancer (1 of 7 patients), 5.1 months and 0% for gallbladder cancer (0 of 4 patients), and 10.7 months and 50% for cancer of the ampulla of Vater (1 of 2 patients) (**Fig. 1**).

The median survival time and the 1-year survival rate were 6.7 months and 13.3% for patients who



MST: median survival time (month)

Fig. 2 Survival curve of patients with PS0/PS1 and PS2

had a PS of 0 or 1 (2 of 15 patients) and 3.4 months and 0% for patients who had a PS of 2 (0 of 3 patients). The survival time for patients with a PS of 0 or 1 was significantly longer than that for patients with a PS of 2 ( $P=0.0051$ ) (**Fig. 2**).

#### Unresectable BTCs

One patient (17%) with gallbladder cancer achieved a PR. Three patients (50%) had SD. SD was observed in 1 of 2 patients with intrahepatic bile duct cancer, in 1 of 1 patient with extrahepatic bile duct cancer, and in 1 of 3 patients with gallbladder cancer. Two patients (33%) had PD. The overall response rate was 66.7%. The median time to progression for patients with PR and SD was 5.68 months (range, 4.8–6.8). Clinical benefit was observed in 3 patients with SD (50%). The median survival time was 5.2 months, and the 1-year overall survival rate was 0%.

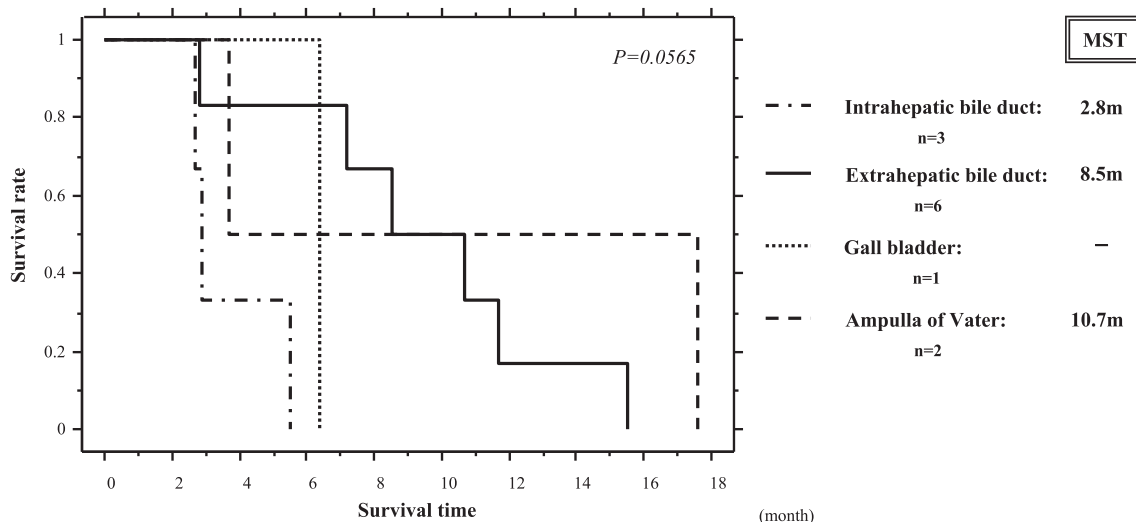
#### Recurrent BTC

Four patients (33%) obtained PRs, 2 (17%) had SD, and 6 (50%) had PD. A PR was observed in 3 of 6 patients (50%) with extrahepatic bile duct cancer and in 1 of 2 patients (50%) with cancer of the ampulla of Vater. The median time to progression after the start of treatment with gemcitabine treatment was 8.2 months (range, 4.8–13.2 months). Clinical benefit was obtained by 5 of 6 patients (83%) with extrahepatic bile duct cancer and 1 of 2 patients (50%) with cancer of the ampulla of Vater.

The median survival time after the start of treatment with gemcitabine and the 1-year survival rate were 2.8 months and 0% for patients with intrahepatic bile duct cancer (0 of 3 patients), 8.5 months and 17% for patients with extrahepatic bile duct cancer (1 of 6 patients), and 10.7 months and 50% for patients with cancer of the ampulla of Vater (1 of 2 patients). The overall survival time after the start of treatment with gemcitabine and the 1-year survival rate for patients with gallbladder cancer were 6.4 months and 0% (0 of 1 patient). There was no significant correlation between the disease site and survival time (**Fig. 3**). The median survival time for patients who underwent R0 resection and for patients who underwent R1 or R2 resection was 7.1 months and 6.4 months, respectively. No significant correlation was found between the survival time and resectability of initial procedure (R number) (**Fig. 4**). Five of 7 patients (71%) who had SD received second-line treatment: 2 patients received tegafur/gimeracil/oteracil potassium, 1 patient received radiotherapy, and 2 patients received a combination of gemcitabine and cisplatin.

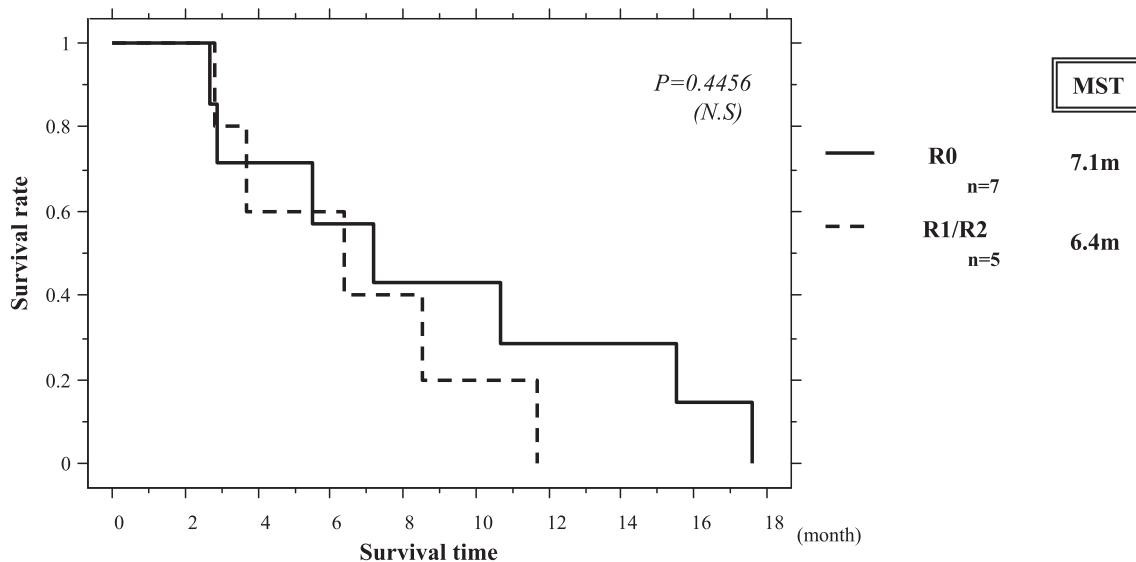
#### Toxicity

Neither grade 3/4 hematologic toxicity nor grade 3/4 nonhematologic toxicity was observed. Grade 0 to 2 hematologic toxicity consisted of neutropenia in 60% (11 of 18 patients) and thrombocytopenia in 9%



MST: median survival time (month)

Fig. 3 Survival curve of patients with recurrent BTC according to the site of primary tumor



MST: median survival time (month)

Fig. 4 Survival curve of patients with R0 resection and R1/R2 resection

(2 of 18 patients). Grade 0 to 2 nonhematologic toxicity consisted of fatigue in 60% (11 of 18 patients). No treatment-related deaths occurred.

### Discussion

Most patients with BTC are candidates for chemotherapy. Chemotherapy for BTC, however, has only limited value in clinical practice. So far, 5-fluorouracil (5-FU) is the mainstay of palliative chemotherapy, although response rates in phase II

trials have ranged from 0% to 13%<sup>34</sup>. It is generally accepted that combination therapy with 5-FU has few advantages over 5-FU monotherapy, and its considerable toxicity often outweighs its benefits<sup>47</sup>. Recently, gemcitabine has been developed as a key drug for unresectable advanced BTC, and gemcitabine-based regimens are widely used as first-line treatments for advanced BTC<sup>22-35</sup>. However, reliable evidence of the effectiveness of gemcitabine monotherapy in advanced BTC is still lacking.

The present study has found that gemcitabine

monotherapy is feasible for unresectable advanced BTC and obtained response rates and median survival times comparable to those reported previously. Several studies of gemcitabine monotherapy (1,000–2,200 mg/m<sup>2</sup>) for advanced BTC have reported response rates of 8% to 60% and median survival times of 4.6 to 14.0 months<sup>22–31</sup>. Our overall response rate for patients with unresectable BTC was 66.7%, and the median survival time was 5.2 months. In addition, all patients who had SD obtained clinical benefit (50%), and no episodes of grade 3–4 toxicity were detected. These results show that gemcitabine monotherapy has sufficient efficacy and safety to be a key regimen for advanced BTC. Indeed, although several single agents, such as cisplatin<sup>6</sup>, paclitaxel<sup>8</sup> and docetaxel<sup>9,10</sup>, have been used to treat advanced BTC, they have not achieved response rates and survival times superior to those of gemcitabine.

Gemcitabine monotherapy as an adjuvant treatment for recurrent BTC is expected to offer tumor response rates and clinical benefit that compare favorably with those for unresectable BTC. In particular, single agent gemcitabine monotherapy may play an important role in the adjuvant setting for extrahepatic bile duct cancer and cancer of the ampulla of Vater. Our response rate and clinical benefit response rate was 50%. These results were comparable to those in patients with unresectable BTC. Both PRs and clinical benefit were achieved in patients with extrahepatic bile duct cancer or cancer of the ampulla of Vater. For all BTCs, the median survival times in patients with extrahepatic bile duct cancer and in patients with cancer of the ampulla of Vater (8.3 months and 10.7 months, respectively) were longer than that in patients with intrahepatic bile duct cancer (4.2 months). For recurrent BTC, the median survival times in patients with extrahepatic bile duct cancer and patients with cancer of the ampulla of Vater (8.5 month and 10.7 months) were longer than that in patients with intrahepatic bile duct cancer (2.8 months). However, because of the small number of patients these differences did not reach the level of statistical significance. These findings suggest that gemcitabine monotherapy would be a safe and effective option in the adjuvant setting following surgical resection for patients with extrahepatic bile

duct cancer or cancer of the ampulla of Vater. Interestingly, no significant correlation was detected between the survival time after the start of gemcitabine therapy and the resectability of the initial procedure (R number). We speculate that adjuvant therapy using gemcitabine may have an antitumor effect on residual tumor.

The PS is an important prognostic factor for patients with advanced BTC, and patients with a PS of 0 or 1 are eligible for gemcitabine monotherapy. The PS is a simple but widely used index reflecting the physical condition of the patient which has been recognized as an important prognostic factor in patients with a variety of malignancies, including BTC<sup>38,39</sup>. In our study, the median survival time was 6.7 months in patients with a PS of 0 or 1 but was only 3.4 months in patients with a PS of 2.

The role of adjuvant chemotherapy after the surgical resection of resectable BTC remains to be defined, and no standard regimen has been established. At our institution, gemcitabine monotherapy has been used in the adjuvant setting for patients with recurrent BTC since gemcitabine was approved for BTC in 2006. Our present results demonstrate that this treatment could be an effective option, even for patients with recurrent BTC. In addition, we expect that gemcitabine monotherapy in the adjuvant setting for BTC will be developed in the near future.

In conclusion, gemcitabine monotherapy has antitumor activity with manageable toxicity in patients with unresectable and recurrent BTC. Gemcitabine may provide a more favorable prognosis in patients with advanced BTC than does best supportive care alone. Moreover, this regimen may represent a therapeutic option in the adjuvant setting for patients with BTC.

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