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ORIGINAL ARTICLE

A phase II study of uracil-tegafur plus doxorubicin and prognostic factors in patients with unresectable biliary tract cancer

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Abstract
Purpose The purpose of this study was to clarify the safety and efficacy of combination chemotherapy of uracil-tegafur (UFT) and doxorubicin (UFD regimen), and to identify the prognostic factors in patients with unresectable advanced biliary tract cancer who received systemic chemotherapy.
Methods Patients with histologically or cytologically confirmed, measurable biliary tract cancer, including intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, and ampullary cancer, who were not suitable candidates for surgery, were eligible for the study. Patients received oral UFT at 300 mg/m^2 per day divided into two doses on days 1–14 and intravenous doxorubicin at 30 mg/m^2 on day 1. This cycle was repeated every 21 days. The relationship between the patient characteristics and the prognosis was examined. Univariate and multivariate analyses were conducted to identify the prognostic factors associated with survival.
Results Sixty-one patients from 12 institutions were enrolled in the late phase II study between April 2005 and March 2006. Of the 61 patients, 4 patients had partial responses, for an objective response rate of 6.6% (95% CI: 1.8–15.9%); 28 patients had stable disease, 27 had progressive diseases, and 2 patients were not evaluated. The median progression-free survival was 1.6 months, and the overall median survival time was 6.5 months. In the 85 patients who received this UFD chemotherapy in previous and late phase II studies, multivariate analysis revealed the ECOG performance status 1 ($P = 0.001$), gallbladder as the

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primary cancer site ($P = 0.014$), T-factor 4 of the TNM classification ($P = 0.035$), and elevated serum lactate dehydrogenase levels ($P = 0.043$) as being associated with a significantly shorter survival.

Conclusions Combination chemotherapy of UFT and doxorubicin had minimum activity against advanced biliary tract cancer. Performance status was identified as the most important prognostic factor in patients who received systemic chemotherapy.

Keywords Biliary tract cancer · Systemic chemotherapy · Uracil-tegafur · Doxorubicin · Phase II study · Prognostic factor

Introduction

Biliary tract cancer consists of cholangiocarcinoma (CC), gallbladder cancer (GBC), and ampullary cancer (AC) [1]; intrahepatic cholangiocarcinoma is often included in clinical trials for biliary tract cancer. Each type of cancer has characteristic features, and the treatment strategy and prognosis are different. This heterogeneity has made it difficult to conduct and evaluate chemotherapy for biliary tract cancer. Biliary tract cancer is relatively uncommon in western countries, but it is a common cause of cancer-related death in Asia. In Japan, the mortality is estimated to be 16,000 deaths annually [2]. While surgery currently remains the only potentially curative treatment, most patients are found to have an unresectable advanced stage of disease. Although patients with unresectable disease receive various palliative treatments, including systemic chemotherapy, the prognosis remains extremely poor.

A previous report showed improved survival in patients with biliary tract cancer treated with 5-fluorouracil (5-FU)-based chemotherapy compared to the best supportive care [3]. Efforts have been made to develop promising regimens for biliary tract cancer using clinical trials of systemic chemotherapy [4]. In various reports on chemotherapy for biliary tract cancer, fluoropyrimidines have been considered as the basis of chemotherapy [5–7]. Furthermore, cisplatin or anthracycline antitumor antibiotic agents such as doxorubicin and epirubicin have been used as combination chemotherapy with 5-FU [8–10]. Recently, clinical trials of gemcitabine show moderate activity against biliary tract cancers, and gemcitabine-based regimens have been investigated [11–22]. However, no standard chemotherapy has currently been identified that can clearly prolong survival.

In Japan, until 2006, only three anticancer agents—uracil–tegafur (UFT), doxorubicin, and cytarabine—had been approved by the Ministry of Health, Labour, and Welfare for biliary tract cancer. Uracil-tegafur is an orally administered drug that is a combination of uracil and tegafur in a 4:1 molar concentration ratio. Tegafur is a 5-FU prodrug that is hydroxylated and converted to 5-FU by hepatic microsomal enzymes. Uracil prevents degradation of 5-FU by inhibiting dihydropyrimidine dehydrogenase, which leads to an increased level of 5-FU in plasma and tumor tissues [23, 24]. Doxorubicin is an anthracycline antibiotic that induces various biologic effects and has one of the widest spectra of antitumor activity against lymphomas, leukemias, soft tissue sarcomas, and a variety of carcinomas. Because, UFT + doxorubicin is the only doublet regimen currently covered by health insurance in Japan, we investigated the combination of UFT and doxorubicin (the UFD regimen) in patients with unresectable advanced biliary tract cancer as an early phase II study in 2004. In that study, the UFD showed modest activity; the response rate was 12.5%, the median progression-free survival (PFS) was 2.5 months, and the median overall survival (OS) was 7.6 months [25]. To examine the safety and efficacy in a larger number of patients, a multicenter late phase II study was conducted in a Japanese chemotherapy study group for biliary tract and pancreatic cancers. The objectives of the study were to evaluate response rate, toxicity, PFS, and OS. As an additional exploratory analysis, we examined the prognostic factors in patients with unresectable biliary tract cancer who had received the UFD regimen in the early and current phase II studies.

Patients and methods

Patient eligibility

The eligibility criteria for enrollment in this late phase II study were: (1) histologically or cytologically confirmed biliary tract cancer consisting of intrahepatic CC (ICC), extrahepatic CC (ECC), GBC, or AC; (2) measurable disease on computed tomography (CT) or magnetic resonance imaging (MRI); (3) unresectable disease; (4) no prior chemotherapy; (5) age $\geq$ 20 years, with a set upper limit of 74 years according to another Japanese trials of gemcitabine and S-1 [13, 26]; (6) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; (7) adequate bone marrow function (leukocyte count $\geq$ 4,000 cells/mm^3, platelet count $\geq$ 100,000 cells/mm^3, and hemoglobin $\geq$ 9.0 g/dL), renal function (serum creatinine concentration $\leq$ upper limit of normal range), and hepatic function [serum bilirubin level $\leq$ 2.0 mg/dL, serum albumin level $\geq$ 3.0 g/dL, and serum aspartate transaminase (AST) and alanine transaminase (ALT) levels $\leq$ 2.5 times the upper limit of normal range]; (8) life expectancy $\geq$ 8 weeks; and (9) written informed consent from the patient. Percutaneous biliary drainage was performed in patients with obstructive jaundice and these patients were

required to have serum bilirubin levels of ≤ 3.0 mg/dL, and serum AST and ALT levels ≤ 5 times the upper limit of normal before enrollment. Exclusion criteria were: serious complications such as active infection, active gastrointestinal ulcer, cardiac disease, or renal disease; central nervous system metastasis; marked pleural effusion or ascites; symptomatic interstitial pneumonitis; and pregnancy or lactation for women. This study was approved by the local institutional review boards at all participating centers.

In addition, prognostic factors were analyzed in patients treated with the UFD regimen in the earlier and current phase II studies. The eligibility criteria for enrollment in the previous study were the same as those mentioned above for the current study, except that the upper age limit of 74 years for enrollment was not set.

Treatment methods

Uracil-tegafur was administered orally at a dose of 300 mg/m^2 per day (400 mg/day in patients with body surface < 1.50 m^2 and 500 mg/body per day in patients with body surface $\geq$ 1.50 m^2) divided into two dosages, for 14 consecutive days followed by 1 week of rest. Doxorubicin was given as a 10-min intravenous infusion on day 1 of each cycle at a dose of 30 mg/m^2. This cycle was repeated every 21 days provided that patients had recovered sufficiently from the drug-related side effects.

Patients continued to receive additional courses of this regimen until a maximum of 15 courses, evidence of disease progression, or the appearance of unacceptable toxicity. When hematological toxicity greater than grade 3 or nonhematological toxicity greater than grade 2 was observed, treatment was delayed until the toxicity subsided to grade 1 or less. If the daily dose of UFT was considered to be intolerable, the dose was reduced by 100 mg/day (one capsule/day). In general, patients were treated as outpatients and admitted to the hospital only for management of toxicities and disease-related complications.

Assessment of response and toxicity

Physical examination, complete blood cell counts, serum chemistries, and urinalysis were performed at baseline and at least twice in 3 weeks after initiating treatment. Patients underwent dynamic CT or MRI to evaluate response at 4–6-week intervals after the start of treatment. Computed tomography or MRI was performed by obtaining contiguous transverse sections using the helical scanning method at a section thickness of 5 mm. Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors [27]. Objective responses were confirmed by a second evaluation performed at least 4 weeks later. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Study designs

The primary end point of this study was the overall response rate and the secondary endpoints were adverse events, OS, and PFS. In this study, the threshold response rate was defined as 5%, the expected response rate was set as 15%, and a sample size of 40 would ensure that there was a 74% power at a one-sided significance level of 5% in the late phase II study. The accrual period was set at 1 year and follow-up period was set at 1 year. When 40 patients were enrolled, the enrollment was extended until the end of the accrual time to improve the statistical power.

Factors analyzed

Twenty-three clinical variables were chosen at the time of study enrollment for the univariate and multivariate analyses. Each variable was divided into two categories as follows: age (<64 or $\geq$64 years), sex (male or female), PS (0 or 1), pretreatment (surgery or no treatment), biliary drainage (yes or no), diagnosis (GBC or non-GBC including ICC, ECC, and AC), white blood cell count (<8,000 or $\geq$8,000/mL), hemoglobin level (<11.0 or $\geq$11.0 g/dL), platelet count (<150,000 or $\geq$150,000/mL), serum total bilirubin level (<2.0 or $\geq$2.0 mg/dL), serum albumin level (<3.5 or $\geq$3.5 g/dL), serum lactate dehydrogenase (LDH) level (<300 or $\geq$300 IU/L), serum AST and ALT levels (<40 or $\geq$40 IU/L), serum alkaline phosphatase (<400 or $\geq$400 IU/L), size of maximum targeted tumor (<60 mm or $\geq$60 mm), T-factor of TNM classification (Tx-3 or T4) [1], extent of disease (locally advanced and local recurrence after surgery, or metastatic), liver metastasis (presence or absence), ascites or peritoneal dissemination (presence or absence), lymph node metastasis (presence or absence), serum carcinoembryonic antigen (CEA) level (<10 or $\geq$10 ng/mL), and serum carbohydrate antigen 19-9 (CA 19-9) level (<1,000 or $\geq$1,000 U/mL). The size of the primary tumor was measured by enhanced CT. Peritoneal dissemination was defined as recognition of peritoneal nodules in CT scans or accumulation of ascites.

Statistical analysis

Progression-free survival was calculated from the first day of treatment until evidence of tumor progression, clinical progression, or death due to any cause. Overall survival was calculated from the first day of treatment until death due to any cause. Survival data were analyzed using the Kaplan–Meier method. The tumor response, toxicity, and survival were evaluated on an intention-to-treat basis.

As an additional and unplanned analysis, the Cox proportional hazards model was used to evaluate prognostic variables associated to survival in patients with unresectable biliary tract cancer who received the UFD regimen in two phase II studies. Forward and backward stepwise regression procedures based on the partial likelihood ratio were used to determine the major independent predictors of survival. Statistical analyses were performed using the SPSS II 11.0 J software package for Windows (SPSS Japan, Tokyo, Japan). The statistical significance of differences between the survival curves was determined using the log-rank test. Two-sided *P*-values of less than 0.05 were considered significant.

Results

Patient characteristics

A total of 61 patients were enrolled between April 2005 and March 2006 in the late phase II study. Patient characteristics are shown in Table 1. The 61 patients received 244 cycles of the UFD regimen. The median number of cycles administered per patient was two (range 1–16 cycles). All patients discontinued this treatment: 50 experienced disease progression, six patients refused further treatment, two patients experienced serious adverse events of disseminated intravascular coagulation (DIC), or thrombocytopenia, and in three patients doxorubicin reached the upper limit dose. After abandoning the UFD treatment, 28 (45.9%) patients received second-line treatment; 30 patients had systemic chemotherapy with gemcitabine in 18 patients, UFT in 7, doxorubicin in 1; 1 patient had chemoradiotherapy and the other had immunotherapy. Three patients were unknown because of moving to another hospital. The remaining 30 (49.2%) patients received only best supportive care after the UFD treatment.

Table 1 Patient characteristics

	Current phase II study	Previous phase II study
N	61	24
Sex		
Male	27 (44%)	13 (54%)
Female	34 (56%)	11 (46%)
Median age (range)	65 (46–74) years	63 (46–75) years
ECOG performance status		
0	45 (74%)	16 (67%)
1	16 (26%)	8 (33%)
Location of primary tumor		
Gallbladder cancer	29 (48%)	13 (54%)
Intrahepatic cholangiocarcinoma	18 (30%)	10 (42%)
Extrahepatic cholangiocarcinoma	11 (18%)	1 (4%)
Ampullary cancer	3 (5%)	0 (0%)
Extent of disease		
Locally advanced or local recurrence after surgery	10 (16%)	5 (21%)
Metastatic	51 (84%)	19 (79%)
Metastatic sites		
Lymph node	43 (70%)	15 (63%)
Liver	35 (57%)	16 (67%)
Lung	6 (10%)	4 (17%)
Peritoneum	7 (11%)	1 (4%)
Bone	2 (3%)	1 (4%)
Adrenal grand	1 (2%)	0 (0)
Pleura	1 (2%)	0 (0)
Pretreatment		
No	44 (72%)	18 (75%)
Surgery	17 (28%)	6 (25%)

Tumor response

Partial response was achieved in 4 of the 61 patients (2 with GBC and 2 with ECC), but no complete response was observed. Overall response rate was thus 6.6% [95% confidence interval (CI), 1.8–15.9%], and 8.7% (95% CI, 2.6–14.7%) in 85 patients including 24 patients in the early phase II study. Stable disease (SD) was noted in 28 (45.9%) of the 61 patients and progressive disease (PD) was noted in 27 patients (44.3%). The remaining two patients who refused the treatment before the evaluation were not evaluated for response.

Toxicity

Toxicities of the 61 patients are shown in Table 2. During treatment, the most common toxicities were gastrointestinal effects such as anorexia in 38 patients (62.3%) and nausea in 35 patients (57.4%). Other major symptoms were fatigue in 35 patients (57.4%), hematological toxicities of anemia in 23 patients (32.8%), and leukopenia in 17 patients (27.9%). Grade 3 or 4 toxicity was observed in 4 of the 61 patients (6.6%), with anorexia, nausea, fatigue, DIC, and/or hematological toxicities. There were no treatment-related deaths during the study.

Survival

Disease progression was finally observed in 57 of the 61 patients. The progression pattern was progression of target lesions in 24 patients (42.1%), developments of new lesions in 10 (17.5%), both of these in 11 (19.3%), symptomatic deterioration without objective evidence of disease progression in 9 (15.8%), progression of non-target lesion and new

Table 2 Toxicity ($n = 61$)

Toxicity	Grade 1–4	Grade 3	Grade 4
Hematological			
Leukopenia	17 (28%)	2 (3%)	0 (0)
Neutropenia	14 (23%)	0 (0%)	0 (0)
Anemia	23 (38%)	1 (2%)	2 (3%)
Thrombocytopenia	9 (15%)	2 (3%)	0 (0)
Non-hematological			
Anorexia	38 (62%)	5 (8%)	1 (2%)
Nausea	35 (57%)	2 (3%)	0 (0)
Fatigue	35 (57%)	3 (5%)	1 (2%)
Alopecia	19 (31%)	0 (0)	0 (0)
Vomiting	13 (21%)	0 (0)	0 (0)
Abdominal pain	12 (20%)	0 (0)	0 (0)
Mucositis	10 (16%)	0 (0)	0 (0)
Fever	7 (11%)	0 (0)	0 (0)
Diarrhea	5 (8%)	0 (0)	0 (0)
Transaminase elevation	4 (7%)	0 (0)	0 (0)
Rash	4 (7%)	0 (0)	0 (0)
Pigmentation	3 (5%)	0 (0)	0 (0)
Arrhythmia	2 (3%)	0 (0)	0 (0)
Taste disturbance	1 (2%)	0 (0)	0 (0)
Edema	1 (2%)	0 (0)	0 (0)
Constipation	1 (2%)	0 (0)	0 (0)
Total bilirubin	1 (2%)	0 (0)	0 (0)
Sore throat	1 (2%)	0 (0)	0 (0)
Hand–foot skin reaction	1 (2%)	0 (0)	0 (0)
BW loss	1 (2%)	0 (0)	0 (0)
DIC	1 (2%)	1 (2%)	0 (0)

BW body weight, *DIC* disseminated intravascular coagulation

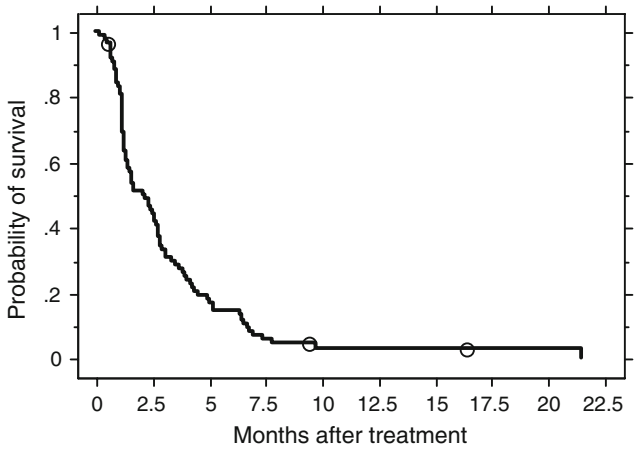

Fig. 1 Progression-free survival of all 85 patients. The median progression-free survival was 2.2 months and the 6-month survival rate was 14.3%

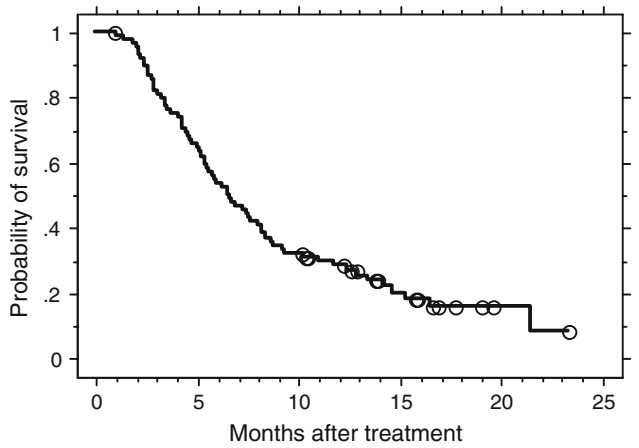

Fig. 2 Overall survival of all 85 patients. The median overall survival was 6.6 months and the 1-year survival rate was 28.2%

lesions in 3 (5.3%). Fifty of the 61 patients died: 49 patients died of cancer progression, and in the case of the other patient, the death was reported and the cause was unknown. The median PFS was 1.6 months in the 61 patients. The median OS time was 6.5 months and the 1-year survival rate was 30.0%.

Univariate and multivariate analyses

Among the 23 variables in 85 patients who received the UFD chemotherapy in the early and late phase II studies, six variables were identified as being significantly associated with shorter survival time: PS of 1, diagnosis of GBC, serum CA 19–9 level of >1,000 U/mL, T-factor of 4, serum LDH level of ≥300 IU/L, and serum total bilirubin level of ≥2.0 mg/dL by univariate analysis. The median PFS was 2.2 months in the 85 patients (Fig. 1). The median OS time was 6.6 months and the 1-year survival rate was 28.2% (Fig. 2). The median OS of patients with PS 0 was 8.2 months and that of patients with PS 1 was 4.3 months. There was a statistically significant difference in the survival curves between the two groups ($P < 0.0001$). Figure 3 shows survival curves for patients with non-GBC of ICC, ECC, or AC and for patients with GBC. The median OS of the patients with GBC was 5.4 months and that of the patients without GBC was 8.4 months. There was a statistically significant difference in the survival curves between the two groups ($P = 0.0019$). On the other hand, there was no statistically significant difference in the survival among patients with ICC, ECC, or AC.

Multivariate regression analysis was conducted for the six variables found to have prognostic significance in the univariate analysis. The four factors of PS, disease site, T-factor, and serum LDH were identified as independent prognostic factors (Table 3).

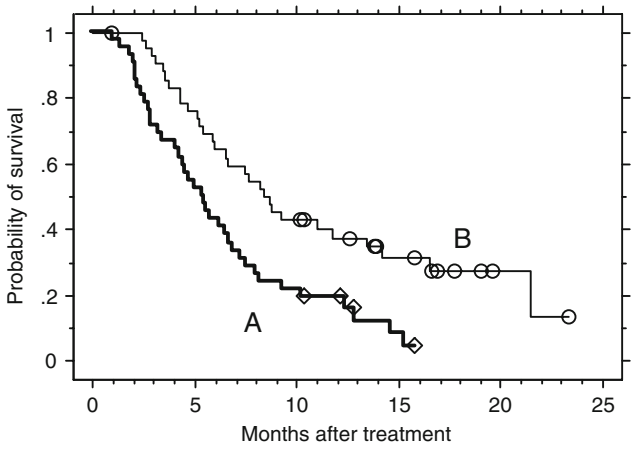

Fig. 3 Survival curves of patients with gallbladder cancer (**a**, $n = 42$) and with non-gallbladder cancer (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or ampullary cancer (**b**, $n = 43$) ($P = 0.0019$)

Table 3 Multivariate analysis of prognostic factors in patients with unresectable biliary tract cancer

Variables	*N*	Median OS (mo)	Hazard ratio	95%CI	*P*-value
ECOG PS					
0	61	8.2	1		0.001
1	1	4.3	2.52	1.44–4.42	
Disease site					
ICC/ECC/AV	43	8.4	1		0.014
GB	42	5.4	1.88	1.14–3.12	
T-factor					
T1–3	62	8.1	1		0.035
T4	23	5.0	1.93	1.05–3.56	
LDH					
<300	67	8.1	1		0.043
≥300	18	4.8	1.85	1.02–3.35	
CA19-9					
<1,000	59	8.1	1		0.067
≥1,000	26	5.2	1.73	0.96–3.11	
T-Bil					
<2.0	77	6.6	1		0.27
>2.0	8	5.2	1.85	0.70–3.49	

OS overall survival, *CI* confidence interval, *PS* performance status, *ICC* intrahepatic cholangiocarcinoma, *ECC* extrahepatic cholangiocarcinoma, *GB* gallbladder cancer, *AV* ampullary cancer, *LDH* lactate dehydrogenase, *CA19-9* carbohydrate antigen 19-9, *T-Bil* serum total bilirubin

Discussion

Chemotherapy is generally indicated in patients with unresectable advanced cancer and patients with recurrence after resection. However, no standard chemotherapy for biliary tract cancer has yet been established, because only few randomized controlled trials with large numbers of patients have been conducted till date. Since only UFT and doxorubicin had been approved for biliary tract cancer for more than 20 years in Japan, the efficacy and safety of combinations of UFT and doxorubicin were examined in two phase II studies. The expected response rate was set as 15%, because biliary tract cancer was considered to be chemoresistant. The overall response rate in the two phase II studies was 8.7% (95% CI, 2.6–14.7%). The upper limit of the 95% confidence interval did not reach 15%, and the combination of UFT and doxorubicin was decided to have minimum activity against biliary tract cancer.

Response rate is sometimes not correlated with OS. Eckel et al. reported a pooled analysis of clinical trials in biliary tract cancer [28]. Based on the analysis of 104 phase II studies comprising of 112 trial arms, there was a highly significant correlation between time to progression (TTP) and OS ($r = 0.73$, $P = 0.000$), but there was a significant weak correlation between response rate and OS ($r = 0.2$, $P = 0.043$). Furthermore, it was reported that the pooled tumor control rate was 57.3% (95% CI: 55.3–59.3%), the median TTP was 4.1 months, and the median OS was 8.2 months. In the current studies, the tumor control rate (CR + PR + SD) was 56.4% (95% CI: 44.1–66.1%), which was almost equal to the pooled TCR, but the median PFS and OS were inferior to those of the pooled analysis, only 2.2 months and 6.6 months, respectively. The TTP or PFS seems appropriate as a surrogate marker of OS compared to the TCR.

It is difficult to conduct clinical trials consisting of a large number of patients with biliary tract cancer, because complications such as obstructive jaundice or cholangitis make it difficult to recruit eligible patients. Therefore, most of the clinical trials of chemotherapy for biliary tract cancer consist of less than 50 patients. Owing to the lack of clinical trials with large patient numbers, few analyses of prognostic factors in patients with advanced biliary tract cancer who received chemotherapy have been conducted till date. In the current phase II studies, 85 patients who received the same regimen of chemotherapy were enrolled and the patient characteristics in the two studies were almost the same. Therefore, we tried to determine the prognostic factors with univariate and multivariate analyses. Although some limitations of these methods should be recognized, such as insufficient patient number to allow adequate statistical power to be obtained, four factors, namely, the PS, disease site, T-factor, and serum LDH were identified as independent prognostic factors; PS was the most important prognostic factor with a hazard ratio of 2.52 ($P = 0.001$).

It has been reported for the advanced stage of various cancers, including pancreatic cancer, that the survival differs significantly depending on the extent of disease, that

is, depending on whether the disease is locally advanced or metastatic. In the current study, the median OS of the patients with locally advanced cancer was longer than that of patients with metastatic disease (8.2 months vs. 5.8 months), although there was no statistically significant difference in survival between the two patient groups ($P = 0.18$). We believe that this could possibly be explained by the smaller number of patients with locally advanced disease ($n = 15$) compared to that with metastatic disease ($n = 70$).

Performance status is often mentioned as an important independent prognostic factor in various cancers such as pancreatic cancer and hepatocellular carcinoma. The clinical practice guideline for the management of biliary tract cancer in Japan recommends that patients with a PS of two or more should not receive chemotherapy at the present time [29]. Since most clinical trials of chemotherapy for biliary tract cancer conducted till date have included patients with a PS of 2, the protocol of the current study also allowed the entry of patients with a PS of 2. However, only patients with a PS of 0 or 1 were actually enrolled. We investigated the prognostic factors to distinguish between PS 0 and 1, and found a statistically significant difference in survival between PS 0 and 1. The median OS in patients with a PS of 0 was 8.2 months and in patients with a PS of 1 was 4.3 months. Patients with a PS of 1 may be candidates for chemotherapy, but the survival is shorter than that in patients with a PS of 0.

The heterogeneity of biliary tract cancer is recognized to be one of the most important issues in considering prognosis of patients with biliary tract cancer. Regarding the primary site, the median OS in patients with gallbladder cancer was statistically significantly shorter than that in patients with intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma or ampullary cancer in the current study ($P = 0.014$). Some other trials showed this tendency [16, 20] but some did not [11, 12, 26]. The reason for this discrepancy is not clear but the small number of patients in each trial may be one of the reasons. In a retrospective analysis of a large number of patients ($n = 179$) [30], the median OS was 8.44 months for intrahepatic cholangiocarcinoma, 10.15 months for extrahepatic cholangiocarcinoma, and 6.50 months for gallbladder cancer. There was a statistically significant difference between extrahepatic cholangiocarcinoma and gallbladder cancer ($P = 0.029$). In the current study, a multivariate analysis in patients with unresectable biliary tract cancer who received the same regimen revealed that the site of disease was one of the significant prognostic factors. Therefore, PS and tumor site of gallbladder cancer or non-gallbladder cancer should be considered in randomized clinical trials for unresectable biliary tract cancer.

No standard chemotherapy for biliary tract cancer has yet been established till date. In Japan, recently, two registration phase II studies of a single agent, gemcitabine and S-1, have been reported [13, 26]. Gemcitabine achieved a better response rate, PFS, and OS compared with the UFT or UFD regimens. Furthermore, S-1 also seems active. Both gemcitabine and S-1 were well tolerated. Based on these results, gemcitabine and S-1 were approved for the treatment of biliary tract cancer in June 2006 and August 2007, respectively.

In conclusion, combination chemotherapy with UFT and doxorubicin (the UFD regimen) was well tolerated but showed minimum activity against advanced biliary tract cancer. Further studies of gemcitabine, S-1, and other cytotoxic or molecular targeted agents are expected to lead to the establishment of a standard chemotherapy for biliary tract cancer.

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