Table 2. Number of patients (Pt) who accepted or declined participation

	Pt invited to RCT	Participant (%)	Non-participant		
			Total	Surgery	Local ablation therapies
Institution A	10	3 (30)	7	1	6
Institution B	8	1 (12)	7	1	6
Institution C	12	1 (8)	11	0	11
Institution D	11	1 (9)	10	4	6
Total	41	6 (15)	35	6	29

Reasons for Participation or Non-participation

Table 3 summarizes participants' reasons for deciding to participate in the parent-trial. All participants answered that they thought participation in the trial would contribute to the development of medicine. When asked about their major reason for participation, three participants marked 'the contribution to medical development' and two participants noted 'clinicians asked me to participate'.

Table 4 shows non-participants' reasons for refusing to enroll in the parent-trial. Four patients (13%) answered that they preferred surgery to LAT whereas 23 (77%) noted that they preferred LAT. One of two patients who received LAT stated 'I disliked surgery'; although the other stated 'clinicians did not ask strongly to participate'. Twelve patients (40%) stated that they were not satisfied with the random allocation into a treatment group. Among these 12 patients, 7 (58%) answered that patients should decide their own treatment whereas 3 (25%) answered that clinicians should decide. Two patients (17%) answered that randomization was inhumane. One patient (8%) stated that random allocation was problematic when two treatments were very different. One patient (8%) stated that he/she could not understand randomization.

Table 3. The frequency of agreement to each statement according to participation among six patients

Statement[a]	Number of respondents (%)
I thought participation in the trial would contribute to the development of medicine	6 (100)
Clinician asked me to participate	2 (33)
I thought there were no differences between two treatments	1 (17)
Other	
I had no preference because my tumors were small	1 (17)
I could not decide which treatment to have	1 (17)

[a]More than one response was allowed.

Table 4. The reasons of 30 non-participants for refusal

Statement[a]	Number of respondents (%)
I was not satisfied to be assigned to the treatment by randomization	12 (40)
Patient should decide the treatment	7 (58)
Clinician should decide the treatment	3 (25)
Randomization was inhumane	2 (17)
Two treatments were very different	1 (8)
I could not understand randomization	1 (8)
I wanted to receive local ablation therapies	23 (77)
I wanted to receive surgery	4 (13)
Other	
Clinician did not ask me to participate	1 (3)
I disliked surgery	1 (3)

[a]More than one response was allowed.

Reasons for Refusing Trial Entry Among Non-participants

Table 5 shows non-participants' reasons for why they subsequently decided to undergo surgery or LAT. All four patients who received surgery and one patient who receive LAT answered that they had thought the probability of recurrences would be lower. Among the patients who had LAT, the majority (20/25, 75%) stated that LAT imposed a lower amount of burden and invasiveness to their body than surgery. In addition, about half of the non-participants (12/25, 48%) stated that the hospitalization period would be shorter with LAT than with surgery. One patient stated that the medical cost of LAT was fewer.

Table 6 summarizes the results of how non-participants made their treatment decisions. Among these four patients who had surgery, three answered that they followed their surgeons' recommendation and one answered he/she followed physicians' recommendation. Among these 25 patients who had LAT, 2 (8%) answered that they referred to their surgeons, 21 (84%) answered that they relied on their attending physicians' recommendation and 9 (36%) answered that they relied on general practitioners' recommendation. Thirteen out of 25 patients who had LAT answered they had already decided to obtain this treatment before they were invited to the trial.

DISCUSSION

In this study, we found that patients who declined trial entry had a strong preference for LAT, which was less invasive and offered a shorter hospitalization course. We also found that this patient preference had stemmed from patient consultations with either a clinician or general practitioner who

Table 5. The reasons of 30 non-participants for preferring surgery or local ablation therapies

Statements[a]	Number of respondents (%)	
	Pt with surgery ($n = 4$)	Pt with local ablation therapies ($n = 25$)
I thought the probability of recurrences would be lower	4 (100)	1 (4)
I thought the survival period would be longer	0	0
I thought the treatment was less burdensome	0	20 (80)
I thought the hospitalization period was shorter	0	12 (48)
I thought the medical cost was fewer	0	1 (4)
Other	0	
I heard that the prognosis were the same		1 (4)
I did not want to increase wound any more		1 (4)

[a]More than one response was allowed.

Table 6. What non-participants referred to when they made a decision

	Number of respondents (%)	
	Pt with surgery ($n = 4$)	Pt with local ablation therapies ($n = 25$)
What non-participants referred to[a]		
Informed consent form	0	13 (52)
Consultation with surgeon in charge	3 (75)	2 (8)
Consultation with physician in charge	1 (25)	21 (84)
Consultation with general practitioner	0	9 (36)
Opinion of other patients	0	2 (8)
Opinion of my family	1 (25)	3 (12)
Other		
My close friend who was clinician suggested	1 (25)	
My friend suggested		1 (4)
The explanation about the prognosis		1 (4)
The information from internet		1 (4)
The information from newspaper		2 (8)
When they made a decision		
Before invitation to the study	1 (25)	13 (52)
After invitation to the study	1 (25)	8 (32)
Do not know or no answer	2 (50)	4 (16)

[a]More than one response was allowed.

referred them to a specialist hospital. Non-participants who received surgery believed in the survival benefits from surgery and relied on surgeon recommendations. On the other hand, patients without strong preference participated in the trial largely because of altruistic motivations. In summary, we found that patients tended to choose less invasive treatment methods even if there is a lack of superiority evidence or an inferiority possibility compared with the standard treatment. Many studies have reported a number of complex barriers in appropriately conducting RCTs (13–18), and we found a couple of these factors that contributed to the incompletion of this trial.

One barrier is that LAT, which had been performed in patients with unrespectable hepatic malignancies, has become popular in treating patients with small HCC due to its superiority in local tumor control and minimal invasiveness. It has become so popular that even without appropriate evidence that LAT has equivalent survival benefits compared with surgery, many general practitioners have recommended it to their patients as an alternative therapy.

Another barrier was patient fear towards a possible allocation into a treatment group that they did not prefer. Although some studies reported that a barrier to trial entry was patient difficulty in understanding the randomization concept and associated patient uneasiness (19–21), our study did not find this as an issue. Only one in 12 respondents that disliked randomization could not understand the randomization concept. Consequently, unbiased and objective explanations by clinicians are crucial in the consent process. However, in our study, we found that the more we stressed the clinical equipoise, the more the patients preferred LAT.

Although the lack of participation was based on these simple reasons, the solution is not simple. In order to increase the number of participants, there are a few possible study designs. One is a randomized consent design, where patients are randomly allocated into a specific treatment group before they provide consent (22,23). If patients decline the allocated treatment, they are then possibly allocated to the other treatment. Even if we apply this design, apart from its ethical problems, the effort will likely fail because most patients allocated to the surgery group will decline. Another possible solution is a randomized trial with a non-randomized part. Specifically, consenting patients are randomized into the two treatment groups, and those that refuse their allocated treatment are enrolled into a non-randomized study. At the conclusion of such a study, the endpoints of the randomized group and the non-randomized group are compared. In such a design, the results may include biases. Moreover, if there is an imbalance in the number of patients between the treatment groups in the non-randomized study, it is difficult to obtain appropriate results.

Furthermore, when there is a discrepancy in results between the randomized and non-randomized study groups, there is difficulty in the interpretation of the results.

In conclusion, when innovative and less burdensome treatments become widespread, they are difficult to compare with standard therapy utilizing a RCT. In light of the increasing number of organ preserving therapies, investigators should evaluate the efficacy and safety of innovative treatments with RCTs as early as possible (24).

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Conflict of interest statement

None declared.

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with liver-limited metastatic disease who responded in the CRYSTAL study. These promising outcomes with cetuximab-containing regimens are the result of years of optimisation to define the target population of this drug. The high proportion of responders, and especially the 34% with an R0 resection in patients with liver-limited initially unresectable disease, represent what can be achieved in this indication. Additionally, the number of R1 resections leading to a total resection rate of 46% can be considered a benefit of treatment, since recent reports showed similar long-term survival benefits between R0 and R1 resections.[8] Can we expect the number resected to further increase in patients with more than five or technically challenging lesions? It would be interesting to see on a per-patient basis how responses to chemotherapy affect resectability—ie, what is the gain for a lesion adherent to main vascular structures at baseline, versus the gain for a patient with bilobar multifocal disease. A higher resection rate might also be expected in the future by the development of highly specialised surgical teams. Future trials should address the clinically relevant endpoint of overall survival, and compare regimens that contain biologicals such as bevacizumab or cetuximab in combination with chemotherapy.

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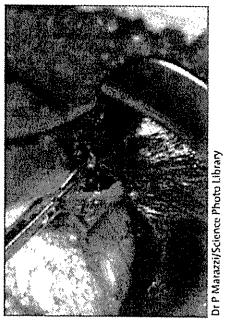
Targeted therapy for biliary-tract cancer

Surgery is the only curative treatment option for biliary-tract cancer, but many patients are diagnosed at an unresectable stage. Furthermore, patients who undergo curative surgery often develop recurrences. Although chemotherapy is recognised as the standard treatment for patients with unresectable or recurrent biliary-tract cancer, a standard regimen was not previously defined because of a paucity of large randomised clinical trials.[1] A recent, large phase 3 study[2] showed a survival benefit with the combination of gemcitabine and cisplatin, compared with gemcitabine alone, in patients with unresectable biliary-tract cancer. The combination of gemcitabine and oxaliplatin also showed efficacy and safety in several phase 2 studies.[3,4] Thus, the combination of gemcitabine and a platinum analogue, cisplatin or oxaliplatin, has been recognised as the standard chemotherapy for patients with biliary-tract cancer. One of the next questions is whether a molecularly targeted agent can provide benefits in addition to those of chemotherapy.

In a phase 2 study in this issue of *The Lancet Oncology*, Zhu and colleagues[5] report that a combination of gemcitabine and oxaliplatin plus bevacizumab (GEMOX-B) showed significant antitumour activity and a tolerable safety profile in patients with advanced biliary-tract cancer. Bevacizumab is a recombinant, humanised monoclonal antibody against vascular endothelial growth factor (VEGF), and phase 3 studies of bevacizumab have shown a survival benefit in addition to chemotherapy in patients with several types of malignancies, including colorectal and lung cancers. VEGF is also related to cancer progression in biliary-tract cancer,[6] and antiangiogenic treatment using bevacizumab is expected to enhance the efficacy of chemotherapy.

Zhu and colleagues found an objective response rate of 40%, median progression-free survival of 7·0 months, and overall survival of 12·7 months with GEMOX-B. These results show promising antitumour activity compared with the results for gemcitabine and cisplatin or oxaliplatin. However, this study had some limitations,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including a small number of patients, selection bias, and a heterogeneous disease background (cholangiocarcinoma, gall-bladder carcinoma, and ampullary cancer) in a single-group study. A previous phase 2 study[3] assessed oxaliplatin at a dose of 100 mg/m² when combined gemcitabine. In the current study, an oxaliplatin dose of 85 mg/m² was planned but the median dose was 64 mg/m²; gemcitabine and bevacizumab were given at the planned doses of 1000 mg/m² and 10 mg/kg, respectively.[5] Thus, the optimum dose of oxaliplatin for the treatment of biliary-tract cancer remains unclear.

The antitumour response is usually assessed using Response Evaluation Criteria in Solid Tumors (RECIST). However, more appropriate methods are needed for chemotherapy regimens that include molecularly targeted agents, because antiangiogenic therapy cannot be properly assessed if only the reduction in tumour size is considered. Zhu and colleagues investigated the efficacy of GEMOX-B in patients with advanced biliary-tract cancer using 18-fluorodeoxyglucose ([^{18}F]FDG)-PET, and reported that changes in the standardised uptake value correlated with progression and overall survival. These findings were limited to a small series of patients and should be confirmed in a larger prospective trial. However, the use of [^{18}F]FDG-PET to assess chemotherapy regimens that include molecularly targeted agents at an early stage might be appropriate for determining whether treatment should be continued.

Biliary-tract cancer is recognised as a rare disease and no large clinical trials have been conducted, particularly for new compounds such as molecularly targeted agents. However, the incidence of biliary-tract cancer is not negligible, and most patients require effective chemotherapy. Thus, the investigation of better treatments is anticipated and global collaboration might be necessary to achieve this objective.

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First-generation genomic tests for breast cancer treatment

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The 21-gene recurrence score assay was developed to predict which patients with oestrogen-positive breast cancer can avoid adjuvant chemotherapy. Although reported as a continuous variable, the score is usually split into three categories: low risk (score <18), intermediate risk (18–30), and high risk (≥31). Three published studies[1] have reported that the risk of metastatic relapse is below 10% at 10 years in patients with low recurrence score, node-negative breast cancer treated with adjuvant tamoxifen. One of these studies also reported that patients with a high recurrence score are more likely to benefit from adjuvant chemotherapy consisting of cyclophosphamide, methotrexate, and fluorouracil (CMF).[1] On the basis of these studies, guidelines from the American Society of Clinical Oncology (ASCO) now include the 21-gene recurrence score assay as an acceptable tool for making treatment decisions.[2]

In *The Lancet Oncology* today, Kathy Albain and colleagues[3] report the prognostic and predictive value of the 21-gene recurrence score in a population of postmenopausal women with node-positive, hormone-receptor-positive breast cancer who were randomly assigned to receive tamoxifen alone or anthracycline-based chemotherapy (cyclophosphamide, doxorubicin, and fluorouracil; CAF) followed by tamoxifen (SWOG-8814, INT-0100 trial[4]). Their results accord with previous findings that recurrence score is a prognostic variable for women treated with tamoxifen alone (hazard ratio 2·64, 95% CI 1·33–5·27, for a 50-point difference in score). However, their main finding, based on a clinically high-

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ORIGINAL ARTICLE

A phase II study of induction chemotherapy with gemcitabine plus S-1 followed by chemoradiotherapy for locally advanced pancreatic cancer

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Abstract
Purpose The aim of this study was to investigate the feasibility and efficacy of induction chemotherapy with gemcitabine and S-1 followed by chemoradiotherapy for locally advanced pancreatic cancer.
Methods Patients with locally advanced unresectable pancreatic cancer received four cycles of induction chemotherapy consisting of 30-min intravenous infusions of gemcitabine 1,000 mg/m^2 on days 1 and 8 and oral S-1 40 mg/m^2 twice daily on days 1–14 of a 21-day cycle. Those without disease progression received chemoradiotherapy of 30 Gy in ten fractions with 250 mg/m^2 of gemcitabine on days 1 and 8.
Results A total of 20 patients were treated. Median follow-up time was 431 days (range 133–1,014 days). Four cycles of induction chemotherapy were completed in 18 patients, and 16 patients received chemoradiotherapy, which was completed without delay in all. Grade 3–4 toxicities associated with induction chemotherapy were neutropenia (50%); anemia (20%); thrombocytopenia (10%); febrile neutropenia (5%); nausea (10%); anorexia (10%); and vomiting, fatigue, dehydration, stomatitis, and rash (5%). Grade 3–4 toxicities among those receiving chemoradiotherapy were neutropenia (13%) and anemia (6%). Median progression-free survival was 8.1 months. Median overall survival was 14.4 months, with a 1-year survival rate of 54.2%.
Conclusions The regimen of induction chemotherapy with gemcitabine and S-1 followed by chemoradiotherapy used in the present study demonstrated promising activity in locally advanced pancreatic cancer. Further consideration of radiation schedule and duration of induction chemotherapy is required to enhance the efficacy of this strategy.

Keywords Chemotherapy · Pancreatic neoplasms · Radiotherapy · Gemcitabine · S-1

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Introduction

Pancreatic cancer is the fifth leading cause of cancer death in Japan and one of the most lethal types of cancer; approximately, 20,000 patients are diagnosed and about the same number of patients die from this disease every year [1]. The majority of patients present with unresectable disease at the time of diagnosis, because of local involvement or metastatic spread. Unresectable pancreatic cancer due to vascular involvement (celiac, hepatic, or supra-mesenteric artery) without radiographically distant metastases is categorized as locally advanced disease.

Traditionally, chemoradiotherapy has been considered as a standard treatment for locally advanced pancreatic cancer, because randomized trials conducted by Moertel et al. [2–4]

and the Gastrointestinal Tumor Study Group (GITSG) demonstrated a survival advantage for chemoradiotherapy compared with chemotherapy or radiotherapy alone. However, a recent French randomized controlled trial reported that chemotherapy with gemcitabine was superior to chemoradiotherapy (median survival 13.0 vs. 8.6 months) [5]. On the other hand, The Eastern Cooperative Oncology Group (ECOG) reported that chemoradiotherapy conferred a survival advantage when compared with gemcitabine chemotherapy (median survival 11.0 vs. 9.2 months) [6]. Thus, the role of chemoradiotherapy is controversial, especially because of the introduction of gemcitabine.

Most patients with locally advanced pancreatic cancer treated with chemoradiotherapy eventually develop metastatic progression. Moreover, minute hepatic or peritoneal metastases are found in one-third of patients with radiographically diagnosed locally advanced pancreatic cancer at staging by laparoscopy or laparotomy [7–9]. Thus, even in locally advanced disease, it is necessary to deliver more effective systemic chemotherapy earlier as well as to give loco-regional treatment to improve the outcome.

Gemcitabine has been widely used as a standard systemic chemotherapeutic agent for advanced pancreatic cancer. Although some combination therapies including gemcitabine have shown survival benefit, these are not considered as standard regimens. S-1 is an oral fluoropyrimidine derivative that combines tegafur (FT) with two modulators; 5-chloro-2, 4-dihydroxypyridine (CDHP) and oteracil potassium (Oxo) in a 1:0.4:1 molar concentration ratio. The efficacy of S-1 has already been shown in a variety of solid tumors, particularly gastric cancer [10, 11]. A phase II trial of S-1 monotherapy for metastatic pancreatic cancer has shown a response rate of 37.5% and median survival of 9.2 months [12]. Moreover, phase II trials of a combination of gemcitabine and S-1 have demonstrated objective response rates of 44–48% and median survival of 10–12 months [13, 14].

In the present study, we conducted the early phase II trial consisting of induction chemotherapy using gemcitabine and S-1 to prevent or evaluate early metastatic progression followed by consolidative chemoradiotherapy for locally advanced pancreatic cancer.

Patients and methods

Patient eligibility

Patients with histologically confirmed locally advanced pancreatic adenocarcinoma were eligible for this study. Inclusion criteria were as follows: diagnosis of unresectable disease due to vascular involvement (i.e., celiac, hepatic, or supra-mesenteric artery) or to occlusion of superior mesenteric or portal vein on contrast-enhanced computed tomography (CT); age of ≥20 years; ECOG performance status of 0 or 1; no prior anticancer treatment; adequate bone marrow function (white blood cell count >4,000 cells/mm^3, absolute neutrophil count >2,000 cells/mm^3, hemoglobin level >9.0 g/dL, platelet count >100,000 cells/mm^3), liver function (serum total bilirubin <2.0 mg/dL, transaminase <150 IU/L), and renal function (serum creatinine <1.2 mg/dL); life expectancy of ≥3 months; and provision of written informed consent. Exclusion criteria were as follows: the presence of pleural effusion or ascites, severe complications, such as heart disease, renal disease, mental disorder, infection, intestinal paresis, uncontrolled diabetes mellitus, drug allergy, and lactation or pregnancy. This study was approved by the institutional review board at the National Cancer Center and conducted in accordance with the Good Clinical Practice guidelines of Japan. This was a single center, open-label phase II trial.

Treatment

Patients received four cycles of induction gemcitabine plus S-1 chemotherapy consisting of gemcitabine 1,000 mg/m^2 (Eli Lilly Japan K.K., Kobe, Japan) via a 30-min intravenous infusion on days 1 and 8 and oral S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) 40 mg/m^2 twice daily on days 1–14 every 3 weeks. Three dose levels of S-1 were established according to the body surface area (BSA) as follows: BSA <1.25 m^2, 80 mg/day; BSA 1.25−1.50 m^2, 100 mg/day; and BSA >1.50 m^2, 120 mg/day. These dosing schedules were investigated in a previous phase I study for advanced pancreatic cancer [15]. If patients experienced absolute neutrophil count <1,000 cells/mm^3, platelet count <70,000 cells/mm^3, or unacceptable non-hematological toxicities (≥grade 3), both gemcitabine and S-1 were withheld until recovery. If patients experienced absolute neutrophil count <500 cells/mm^3 or platelet count <25,000 cells/mm^3 or if they could not receive gemcitabine on day 8 or S-1 for more than 7 days because of any toxicities, the dose of gemcitabine was reduced to 800 mg/m^2 and the dose of S-1 was reduced by 20 mg/day in the subsequent cycle.

Subsequently, patients without disease progression received chemoradiotherapy within 2–6 weeks, after the last dose of chemotherapy. A total dose of 30 Gy/10 fractions using once-daily fractionation was delivered with a 10 MV X-ray unit. Treatment planning was performed with a CT-based planning system; the gross tumor volume (GTV) was defined as the primary tumor and metastatic lymphadenopathy as visualized on each CT image with contrast enhancement. The clinical target volume (CTV) was defined as the GTV plus a 1.0-cm margin, to account for subclinical tumor spread. The planning target volume (PTV) was defined as the CTV plus a 1.0- to 2.0-cm margin along the cranio-caudal axis and a 1.0-cm lateral margin,

to account for physiological organ motion and daily set-up error. The prescribed dose was determined at the central part of the PTV. A 4-field technique was used to minimize irradiated volume of the liver and the kidneys. Prophylactic lymph node irradiation was not performed. Gemcitabine at a dose of 250 mg/m^2 was administered intravenously for 30 min before radiotherapy on days 1 and 8.

After chemoradiotherapy was completed, maintenance chemotherapy with gemcitabine was started within 2–4 weeks. Gemcitabine was administered once weekly at a dose of 1,000 mg/m^2 in a 30-min intravenous infusion for three consecutive weeks, followed by a week of rest. Two cycles of gemcitabine were defined as the protocol treatment. Treatments were continued until disease progression, patient refusal, or unacceptable toxicity.

Evaluation

Physical and laboratory examination were performed at least once every week. Contrast-enhanced CT was performed every two cycles of induction chemotherapy, after the completion of chemoradiotherapy, and every two cycles of maintenance gemcitabine chemotherapy. Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST). Progression-free survival (PFS) was calculated from the day of initial therapy until the day of disease progression. Progression was defined as confirmation of progressive disease on the RECIST or deterioration of the patients' general condition. Overall survival (OS) was calculated from the day of initial therapy until the day of death from any cause. Carbohydrate antigen 19-9 (CA19-9) was measured once every month. Toxicities were evaluated according to the National Cancer Institute—Common Toxicity Criteria version 2.0.

Statistical design and analyses

The primary end point was PFS at 6 months. A PFS rate of 50% at 6 months was expected in this trial. The planned sample size was 20 patients. If $\leq$5 of the 20 patients were progression free at 6 months, the treatment would have been assessed as invalid because the upper limit of the 95% confidential interval (CI) was calculated as 49.1%. PFS and OS were analyzed using the Kaplan–Meier methods.

Results

Patient characteristics

A total of 20 patients were enrolled in this study between February 2005 and October 2006. Patient characteristics are shown in Table 1.

Protocol treatments were completed in all 20 patients by April 2007. Data were collected in May 2008. Median follow-up time was 431 days (range 133–1,014 days).

Treatment administration

A schema of the trial is shown in Fig. 1. All 20 patients received at least one cycle of induction chemotherapy; 2 of the 20 patients showed disease progression (general deterioration and progression at the primary site with duodenal obstruction) during the induction chemotherapy. Four cycles of the induction chemotherapy were completed in 18 patients. Two of these 18 patients showed disease progression (peritoneal dissemination and obstructive jaundice) after the completion of the induction chemotherapy. Relative dose intensity for induction gemcitabine and S-1 was 0.92 and 0.89, respectively. Subsequently, 16 patients received chemoradiotherapy, which was completed without delay in all. Of these 16, one developed liver metastasis after the completion of chemoradiotherapy. Therefore, a final total of 15 patients received 2 cycles of maintenance chemotherapy with gemcitabine. Relative dose intensity for maintenance gemcitabine was 0.88.

Laparotomy was performed in six patients after the evaluation of the above-mentioned protocol treatments. Of these, two underwent laparotomy with the intention of intraoperative radiotherapy, and four with the intention of curative resection. None of the six patients had extra-pancreatic disease. Two received intraoperative radiotherapy, three underwent surgical resection with pathological negative margin, and one had exploratory laparotomy alone because of vascular involvement.

Safety

During the induction chemotherapy, toxicities were evaluated in all 20 patients. The data are summarized in Table 2.

Table 1 Patient characteristics (n = 20)

Characteristic	Number
Age, years: median (range)	63.5 (33–75)
Sex: male/female	10/10
Performance status: 0/1	15/5
Primary site: pancreatic head/body	11/9
Tumor size, mm: median (range)	40.5 (13–100)
Stage of tumor	
IIA: T3 N0 M0	3
III: T4 N0 M0	10
III: T4 N1 M0	7
Baseline CA19-9, U/ml: median (range)	444 (0.1–10760)

CA19-9 carbohydrate antigen 19-9

Tumor stage was evaluated according to TNM classification 6th edition

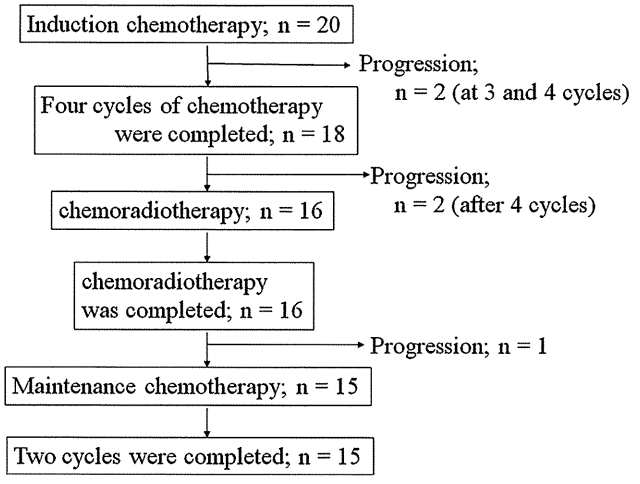

Fig. 1 Outcomes of treatment

Grade 3 or 4 hematological toxicities were observed in 13 (65%) patients. These recovered promptly after the withdrawal of gemcitabine and S-1, and were manageable by dose modification in the next cycle. Febrile neutropenia occurred in one patient, associated with grade 3 infection, stomatitis and anorexia. Nausea, anorexia, rash, and stomatitis were common non-hematological toxicities. Dose reduction in gemcitabine and S-1 was required in six patients.

Chemoradiotherapy was started on schedule up to 4 weeks after finishing chemotherapy. Toxicities for chemoradiotherapy were evaluated in 16 patients (Table 3). Grade 3 hematological toxicities were observed in two (12.5%) patients. No patients developed grade 3 or 4 non-hematological toxicities, and chemoradiotherapy was completed in all patients without delay.

Efficacy

Tumor response and survival data were assessable in all 20 patients (Table 4). Five patients (20%) achieved partial response. The median duration of response was 281 days (range 244–930). At the first evaluation, no patients had progressive disease. In 12 (92.3%) of the 13 patients with pretreatment, serum CA19-9 level of 100 IU/ml or greater, the level was decreased more than 50%.

Median PFS was 8.1 months (95% CI 5.5–10.8 months) (Fig. 2). Proportion of patients with PFS at 6 months was 70.0% (95% CI 45.7–88.1%). Patterns of progression are summarized in Table 5. Disease progression was observed in 17 patients at the time of analysis. One patient died without disease progression because of surgical complications. Fifteen patients died of the disease. Two patients remained alive without progression at the time of analysis. Median overall survival was 14.4 months (95% CI 8.7–20.0 months) and 1-year survival was 54.2% (Fig. 3).

Table 2 Toxicities of induction chemotherapy (n = 20)

	Any grade		Grade 3/4	
	n	%	n	%
Hematological				
Neutropenia	14	70	10	50
Anemia	11	55	4	20
Thrombocytopenia	11	55	2	10
Febrile neutropenia	1	5	1	5
Non-hematological				
Nausea	9	45	2	10
Vomiting	7	35	1	5
Anorexia	8	40	2	10
Fatigue	6	30	1	5
Dehydration	1	5	1	5
Stomatitis	5	25	1	5
Rash	7	35	1	5
Diarrhea	3	15	0	0

Toxicities were evaluated according to the National Cancer Institute-Common Toxicity Criteria version 2.0

Table 3 Toxicities of chemoradiotherapy (n = 16)

	Any grade		Grade 3/4	
	n	%	n	%
Hematological				
Neutropenia	12	75	2	13
Anemia	4	25	1	6
Thrombocytopenia	2	13	0	0
Febrile neutropenia	0	0	0	0
Non-hematological				
Nausea	6	38	0	0
Vomiting	4	25	0	0
Anorexia	6	38	0	0
Fatigue	6	38	0	0

Toxicities were evaluated according to the National Cancer Institute-Common Toxicity Criteria version 2.0

Table 4 Objective response to treatment (n = 20)

Tumor response	n = 20 (%)
Partial response	5 (25)
Stable disease	15 (75)
Progressive disease	0
Baseline CA19-9	≥100 IU/ml, n = 13 (%)
Response (≥50% decline)	12 (92.3)
Non-response	1 (7.7)

Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumor

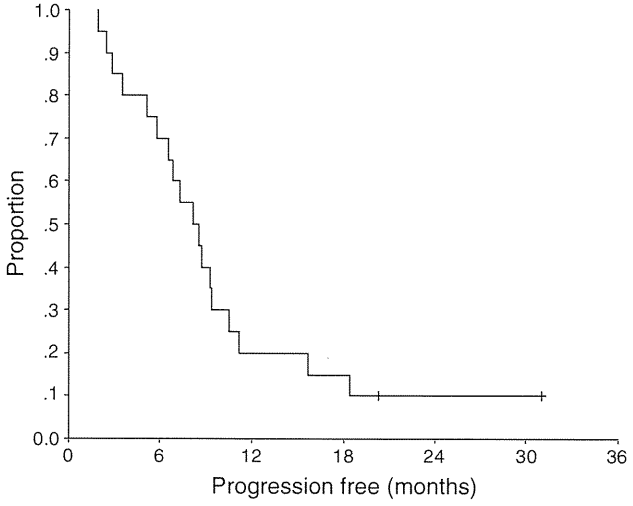

Fig. 2 Kaplan–Meier curve of progression-free survival. Median progression-free survival time was 8.1 months (95% CI 5.5–10.8). Proportion of patients progression free at 6 months was 65%

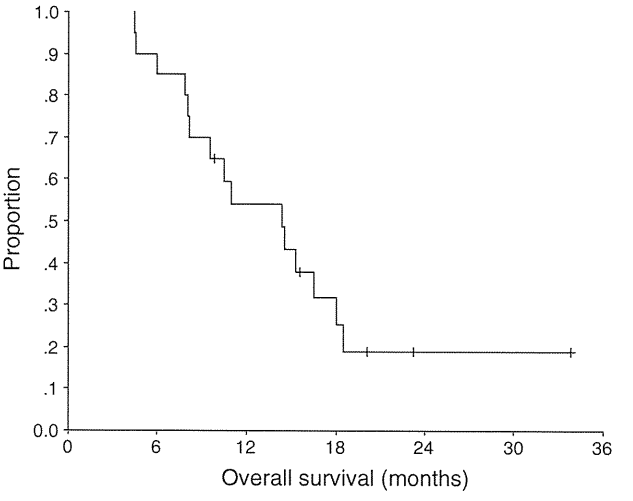

Fig. 3 Kaplan–Meier curve of overall survival. Median survival time was 14.4 months (95% CI 8.7–20.0); 1-year survival rate was 54.2%

Table 5 Patterns of progression

	Oveall $n = 17$	During chemotherapy $n = 4$
Local	3	2
Distant	12	1
Liver	2	0
Peritoneum	5	1
Liver and peritoneum	2	0
Others (lung, distant node)	3	0
General deterioration	2	1

Discussion

Although many clinical trials of chemoradiotherapy have been conducted for locally advanced pancreatic cancer, there has been not much improvement in survival rates for two decades. Median survival is around 10–12 months and accounts of long-term survivors are anecdotal. This indicates the limited efficacy of chemoradiotherapy as a loco-regional therapy. Secondary, latent metastases or early metastatic progressions are commonly observed, and effective systemic chemotherapy is required in this setting. It is difficult to administer sufficient doses of chemotherapeutic agents in maintenance therapy because myelosuppression is usually severe after chemoradiotherapy [5]. Moreover, doses of anticancer agents such as gemcitabine must be limited because of increasing toxicities in conjunction with a definitive dose of radiation [16, 17]. Induction chemotherapy is a reasonable strategy to resolve these problems and to improve treatment outcome. Up-front administration of effective antitumor agents might treat latent metastases and help in selecting appropriate patients for chemoradiotherapy.

The combination of gemcitabine and S-1 was selected as an induction regimen because it has already demonstrated an objective response rate of 44–48% in two phase II trials [13, 14]. A phase III trial to confirm the survival benefit of this regimen is continuing in Japan and Taiwan. Nausea, anorexia, and stomatitis were common non-hematological toxicities, which were manageable by supportive care. Disease progression was observed in four patients (20%) until the end of the chemotherapy. Therefore, these patients were probably not appropriate candidates for chemoradiotherapy at the time of diagnosis. Local progression, heralded by obstructive jaundice and duodenal obstruction, was observed in two of these four patients. It is possible that postponing chemoradiotherapy was a potential risk factor for lack of local control in such patients. Objective response was observed in 25% of all patients. CA19-9 response (a 50% decline in serum levels from a baseline of >100 IU/ml) was observed in 92.3% of patients. Most of the responses were observed during induction chemotherapy.

The concept on which this study was based is short-term radiotherapy. We previously performed a phase I trial of hypofractionated radiotherapy in which 3.0 Gy/day was confirmed to be feasible [18]. The same radiation schedule was investigated in a phase I trial at the MD Anderson Cancer Center. Gemcitabine is a potent radiosensitizer, and the phase I trial reported that a gemcitabine regimen of 350 mg/m^2 weekly had the potential for significant toxicity [19]. Gemcitabine at 250 mg/m^2 weekly was recommended in another phase I trial in which it was administered concomitantly with 50.4 Gy in 28 fractions of 1.8 Gy/day [16]. These trials used large irradiation fields, including prophylactic lymph node irradiation. On the other hand, investigators

at the University of Michigan and their colleagues reported that reduced irradiation fields enabled the concurrent administration of full-dose gemcitabine. They elected to irradiate the primary tumor only without prophylactic lymph node irradiation [29, 30]. Therefore, we performed chemoradiotherapy comprising 30 Gy in ten fractions of 3.0 Gy/day, in a 2-week schedule without prophylactic lymph node irradiation and gemcitabine 250 mg/m^2 weekly. As 30 Gy is a moderate radiotherapy dose, it might not be sufficient to achieve local control. However, lacking confirmatory evidence that high-dose radiotherapy leads to better outcome, this dose was chosen. Moertel et al. reported no statistical difference in survival between high dose (60 Gy) + 5-FU and moderate dose (40 Gy) + 5-FU radiotherapy. Sixteen patients received chemoradiotherapy, and all completed it without delay. No grade 3 or 4 gastrointestinal toxicities developed. The present schedule of chemoradiotherapy was, therefore, demonstrated to be feasible with limited toxicity, although a trial using the same dose and fraction conducted at MD Anderson Cancer Center did not seem to be tolerable. The reduced irradiation volume may make this approach possible. Further investigations of more intensified radiation schedules are warranted to enhance local tumor control.

Following the protocol therapy, laparotomy was performed in six patients. Of these, three underwent surgical resection with a pathologically negative margin. Relief of vascular encasement was observed in these cases. The antitumor activity encourages us to anticipate positive results in the neoadjuvant setting as well as in downstaging for locally unresectable or borderline resectable disease.

The strategy of induction chemotherapy for locally advanced pancreatic cancer has been proposed by several investigators. Prospective and retrospective studies of induction chemotherapy are summarized in Table 6 [20–26]. Huguet et al. [25] retrospectively analyzed 181 patients with locally advanced disease enrolled in the GERCOR prospective study. Of these, 72 received chemoradiotherapy on the basis of no distant metastases after 3 months of chemotherapy. They reported that chemoradiotherapy following chemotherapy improved outcome as compared to chemotherapy alone. Krishnan et al. [26] showed that chemoradiotherapy following chemotherapy improved outcome when compared with initial chemoradiotherapy. Among phase II trials, regimens consisting of gemcitabine plus platinum-based agents (which have shown high-tumor response compared with gemcitabine monotherapy in phase III trials) demonstrated better outcome than others [27, 28]. Hence, such a combination regimen for induction chemotherapy might enhance the results shown by this study. Nonetheless, the present study showed promising results: median survival and 1-year survival rate were 14.4 months and 54.2%, respectively.

In conclusion, our study demonstrated promising antitumor activity of induction chemotherapy with gemcitabine

Table 6 Summary of induction chemotherapy for locally advanced pancreatic cancer

References	*n*	Chemotherapy Chemoradiotherapy	Median OS (months)	1 year (%)
Huguet [25]	56	Gem, GEMOX, FOLFUGEM –	11.7	47.5
	72	Gem, GEMOX, FOLFUGEM 55 Gy/FU	15.0	65.3
Krishnan [26]	274	– 30 or 50.4 Gy/FU, Cape, Gem	8.5	–
	76	Gem/CDDP (2.5mo) 30 or 50.4 Gy/FU, Cape, Gem	11.9	–
Mishra [20]	20	Gem/CPT-11(1.5 months) 50.4 Gy/Gem	8.8	–
Ko [21]	25	Gem/CDDP (6 months) 50.4 Gy/Cape	13.5	62
Moureau-Zabotto [22]	59	GEMOX (2 months) 55 Gy/FU, Oxaliplatin	12.2	52.1
Kurt [23]	24	Gem/FU (2 months) 50.4-54 Gy/Gem	11	–
Goldstein [24]	41	Gem (1 months) 54 Gy/FU	11.7	46.3
Current study	20	Gem/S-1 (3 months) 30 Gy/Gem	14.4	54.2

OS overall survival, *Gem* gemcitabine, *GEMOX* gemcitabine and oxaliplatin, *FOLFUGEM* gemcitabine, leucovorin, and fluorouracil, *Cape* capecitabine, *FU* fluorouracil, *CDDP* cisplatin

plus S-1 followed by chemoradiotherapy in locally advanced pancreatic cancer. Further consideration regarding the radiation schedule and duration of induction chemotherapy is required in this regimen. A prospective randomized trial is needed to resolve whether the strategy of induction chemotherapy followed by chemoradiotherapy can improve survival when compared with initial chemoradiotherapy.

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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

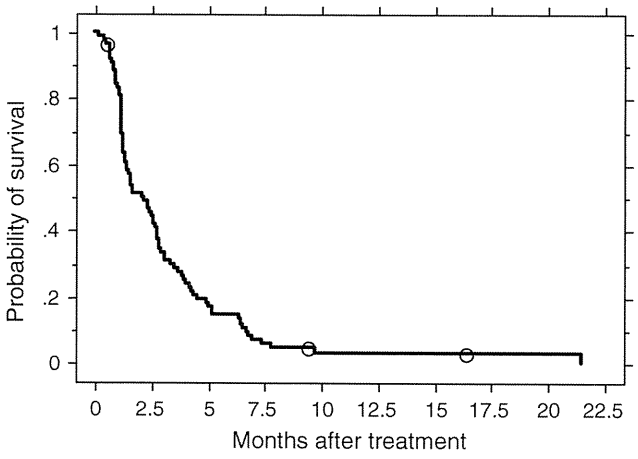

Fig. 1 Progression-free survival of all 85 patients. The median progression-free survival was 2.2 months and the 6-month survival rate was 14.3%

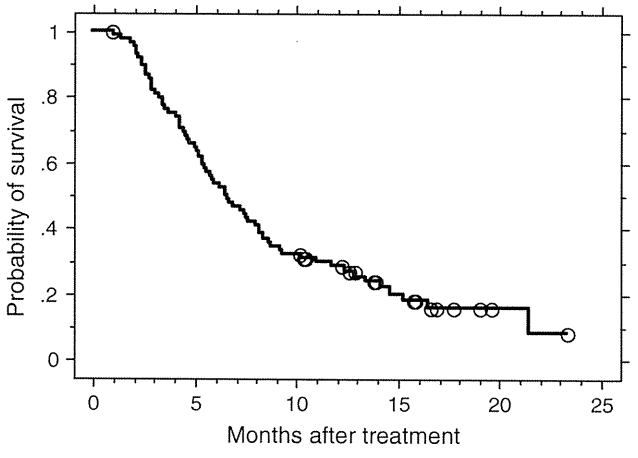

Fig. 2 Overall survival of all 85 patients. The median overall survival was 6.6 months and the 1-year survival rate was 28.2%

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).

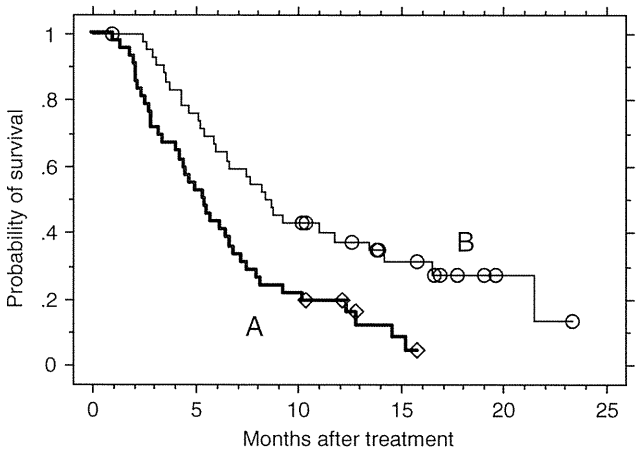

Fig. 3 Survival curves of patients with gallbladder cancer (**a**, $n = 42$) and with non-gallbladder cancer (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or ampullary cancer (**b**, $n = 43$) ($P = 0.0019$)

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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