date, since no large randomized controlled trials of adjuvant therapy have been conducted, no standard postoperative adjuvant treatment has been established. We consider S-1 as a potential candidate for adjuvant therapy, because a high response rate of 35% was demonstrated to S-1 in a Phase II study for unresectable biliary tract cancer (4). S-1 has also been already established as a standard adjuvant therapeutic agent for the treatment of gastric cancer. Surgical methods for the treatment of biliary tract cancer are highly diverse, including pancreaticoduodenectomy, hepatectomy, etc., when compared with those for gastric cancer. Therefore, a feasibility study of S-1 chemotherapy after surgery was conducted by a study group comprising some member institutes of the HBPO group. A treatment completion rate of 82% was achieved. The most common grade-3 toxicity was neutropenia (18%), and the rates of other grade 3 adverse events were under 5% (11). Therefore, S-1 is considered to be suitable as a postoperative adjuvant therapeutic agent for the treatment of patients with resected biliary tract cancer. Based on these results, we plan to conduct a Phase III study to compare S-1 as adjuvant therapy after surgery with surgery alone in patients with biliary tract cancer (JCOG PC1202).

PANCREATIC CANCER

Pancreatic carcinoma is a disease with one of the worst prognoses; the 5-year survival rate of patients diagnosed as having pancreatic cancer remains at 5–10%. Since it is difficult to diagnose pancreatic cancer at an early stage, 70–80% patients with pancreatic cancer have unresectable disease, including locally advanced or distant metastatic disease, at diagnosis. Since gemcitabine demonstrated a better survival benefit when compared with 5-fluorouracil (5-FU) in a Phase III study (12), it has been widely used as the standard chemotherapy for unresectable pancreatic cancer for >10 years. Despite a number of new compounds, including molecular-targeted agents, having been examined in combination with gemcitabine, no regimen, except for gemcitabine plus erlotinib, has been demonstrated to provide statistically significant improvement in the overall survival over gemcitabine alone (13,14). Thus, the prognosis of these patients with this cancer remains poor, and the development of more effective treatments for pancreatic cancer is urgently needed.

Under these situations, it is important to continue the development of new compounds in industry-initiated clinical trials and also participate in global registration trials. On the other hand, the HBPO group also considers itself as having the important role of establishing standard chemotherapy or chemoradiotherapy for unresectable locally advanced disease or postoperative adjuvant therapy.

With regard to treatments for unresectable locally advanced disease, we first conducted a Phase II study of gemcitabine alone to examine its efficacy and safety in patients with locally advanced disease of the JCOG 0506 study (15). This study was conducted to be foreseeing a Phase III trial comparing gemcitabine monotherapy with conventional chemoradiotherapy using 5-FU, which, at that time, was used as a standard therapy for locally advanced disease. The main eligibility criteria of the JCOG 0506 study were the following: (i) patients with histologically or cytologically proven pancreatic adenocarcinoma or adenosquamous carcinoma; (ii) International Union Against Cancer clinical stage III (T4N0-1 and M0); (iii) no previous chemotherapy or radiotherapy for any other malignancies; (iv) ECOG performance status of 0, 1 or 2 and (v) adequate organ function. The primary endpoint of this study was the 1-year survival rate. A sample size of 50 was required for a one-sided α of 0.20 and β of 0.10, with an expected 1-year survival rate of 40% and a threshold 1-year survival rate of 25%. Fifty patients were enrolled from January 2006 to February 2007 in this study. The results revealed a median overall survival of 15.0 months with a 1-year survival rate of 64.0% (Table 1), which significantly exceeded expectations. The toxicities were generally mild and the drug was well tolerated. Furthermore, a randomized controlled trial of gemcitabine vs. conventional chemoradiotherapy using 5-FU and cisplatin failed to show any survival benefit of chemoradiotherapy (16). Based on these results, gemcitabine monotherapy has come to be regarded as the provisional standard therapy by our group (Table 2).

Table 1. Recent randomized controlled trials using gemcitabine, cisplatin and/or S-1 for unresectable biliary tract cancer

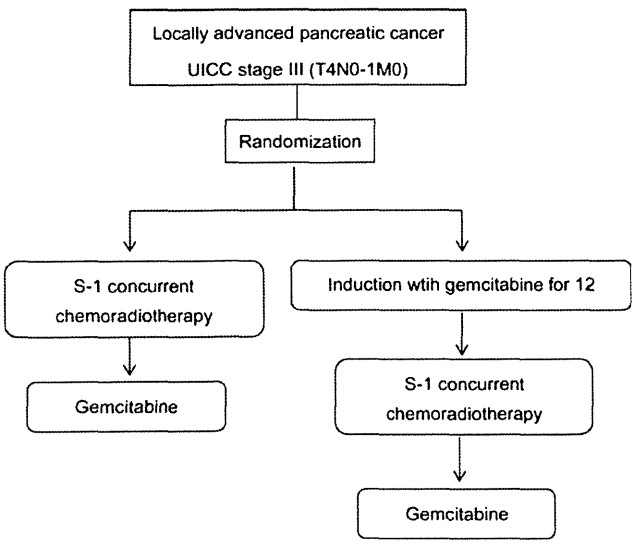
Study	Chemotherapy	*n*	Response rate (%)	Median PFS (months)	Median OS (months)	Study
ABC-02 study	Gemcitabine	206	15.5	5.0	8.1	Valle *et al.* (6)
	Gemcitabine + cisplatin	204	26.1	8.0	11.7	
BT-22 study	Gemcitabine	42	11.9	3.7	7.7	Okusaka *et al.* (7)
	Gemcitabine + cisplatin	41	19.5	5.8	11.2	
JCOG 0805 study	S-1	50	17.4	4.2	9.0	Ueno *et al.* (8)
	Gemcitabine + S-1	51	36.4	7.1	12.5	

PFS, progression-free survival; OS, overall survival.

Table 2. Recent clinical trials of chemotherapy or chemoradiotherapy for locally advanced pancreatic cancer

Study	Radiotherapy (Gy)	Chemotherapy	*n*	Median OS (month)	%1-year survival	Study
JCOG 0506 study	–	Gemcitabine	50	15.0	64	Ishii *et al.* (15)
S-1 radiation Phase II study	50.4	S-1	61	16.2	72	Ikeda *et al.* (18)
2000-01 FFCD/SFRO study	60	5-fluorouracil + cisplatin	59	8.6	32	Chauffert *et al.* (16)
	–	Gemcitabine	60	13.0	53	
ECOG 4201 study	50.4	Gemcitabine	34	11.1	50	Lochrer *et al.* (17)
	–	Gemcitabine	37	9.2	32	

%1-year survival, one-year survival rate.



Gemcitabine: 1000 mg/m^2 d1, 8, 15, repeated every 4 weeks
S-1: 80 mg/m^2/day on the day of irradiation

Figure 3. Study design of the JCOG 1106 study.

A clinical trial conducted in the USA comparing gemcitabine plus radiotherapy vs. gemcitabine alone reported that the overall survival rate was superior in the combined treatment group when compared with that in the gemcitabine-alone group in patients with locally advanced pancreatic cancer (17). Furthermore, chemoradiotherapy using S-1 demonstrated promising efficacy in a Phase II study, which was conducted as an in-house trial of some member institutes of the HBPO group; the median overall survival was 16.2 months (18). There is a possibility that new methods of chemoradiotherapy might improve the survival, especially prolonged survival of >2 years. Thus, in order to develop more promising new chemoradiotherapies, we conducted a randomized Phase II study of two chemoradiotherapeutic methods, one consisting of S-1 chemoradiotherapy and maintenance therapy with gemcitabine, and the other consisting of induction gemcitabine chemotherapy for 3 months followed by S-1 chemoradiotherapy and maintenance therapy with gemcitabine (JCOG 1106 study).

The JCOG 1106 study is a multi-institutional open-label randomized Phase II study to evaluate the efficacy of induction chemotherapy of gemcitabine in combination with S-1 chemoradiotherapy and select a candidate in a Phase III study comparing with gemcitabine alone (Fig. 3). The main eligibility criteria of the JCOG 1106 study were as follows: (i) clinically diagnosed with pancreatic cancer without distant metastasis, and histologically proven adenocarcinoma; (ii) no previous chemotherapy or radiotherapy for any other malignancies; (iii) ECOG performance status of 0 or 1 and (iv) adequate organ function. The primary endpoint is the overall survival, and we shall select the treatment method providing the better survival benefit between the two for use in a subsequent Phase III study. The 1-year survival rate of the two treatments would be expected to be >60% at least, because that of patients administered gemcitabine monotherapy was 64% in the JCOG 0506 study. The sample size is 100 patients and this study is under investigation in September 2012.

FUTURE DIRECTION

In hepatobiliary tract and pancreatic cancers, major advances have been made in relation to the establishment of standard treatments in recent years. However, the survival of patients with these cancers still remains dismal. The HBPO group considers it essential to actively conduct clinical trials to establish more effective standard treatments, including a combination of chemotherapy with local treatments including surgery or radiotherapy.

In HCC, many clinical trials using new agents are conducted as an Asian study including Japan or a global study. However, it is difficult to conduct investigator-initiated trials in HCC, because there are various differences in the etiology and treatment strategy among Asian countries, Japan and Western countries. However, it is also important for the HBPO group to discuss Asian studies on HCC and biliary tract cancer in the future, because these diseases are very common in Asia, compared with Western countries.

Establishment of standard therapies for relatively rare tumors is urgently needed. We are planning to conduct a

phase III study for the treatment of gastrointestinal neuroendocrine tumors in cooperation with other groups of the JCOG.

Although our HBPO group is growing in size, only 26 institutes are active members of the group. On the other hand, >30 institutes participate in our regular meetings as observers. It is therefore also important to increase the number of institutes as active members so as to make it possible to conduct larger clinical trials of higher quality in the future.

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Conflict of interest statement

None declared.

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Possibility of immunotherapy for biliary tract cancer: how do we prove efficacy? Introduction to a current ongoing phase I and randomized phase II study to evaluate the efficacy and safety of adding Wilms tumor 1 peptide vaccine to gemcitabine and cisplatin for the treatment of advanced biliary tract cancer (WT-BT trial)

Takuji Okusaka · Makoto Ueno · Tosiya Sato · Yuji Heike

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Abstract
Background/purpose In biliary tract cancer, few clinical studies evaluating immunotherapy have been reported. A phase I and randomized phase II study with Wilms tumor 1 (WT1) peptide vaccine plus gemcitabine and cisplatin (GC) for chemo-naïve patients with unresectable or recurrent biliary tract cancer was started, because the overexpression of WT1 is seen in the majority of patients with this disease, encouraging the potential of WT1-based immunotherapy. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000004886.
Methods and results The aim of this trial is to evaluate the efficacy and safety of the regimen and to determine whether the regimen should be compared with the current standard regimen, GC, in a subsequent phase III trial for patients with unresectable or recurrent biliary tract cancer. Six patients in the phase I study and a total of 100 patients in the phase II study will be accrued over a 2-year period. The patients in the phase II study will be randomized at a 2:1 ratio to receive GC either with or without WT1 peptide vaccine. The primary endpoint of the phase II study is the 1-year overall survival rate.
Conclusions This is the first randomized trial to evaluate the use of immunotherapy in patients with advanced biliary tract cancer.

Keywords Biliary tract cancer · Immunotherapy · Chemotherapy · Wilms tumor 1 (WT1) peptide vaccine · Randomized trial

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Introduction

Systemic chemotherapy is usually indicated for patients with unresectable advanced biliary tract cancer or for those who have relapsed after operation; however, no standard treatments with solid evidence of a survival benefit have been established for such patients [1]. Although gemcitabine (GEM) alone was regarded as the de-facto standard regimen for advanced biliary cancer until recently, gemcitabine plus cisplatin (GC) has become the new standard regimen, based on the results of the ABC-02 trial [2], which showed a significant survival advantage for the GC combination over GEM alone. Even with the establishment of a standard therapy for this disease, the prognosis of these patients remains dismal: their median survival period is only around 10 months [2, 3]. Therefore, a clear need exists for new, effective, treatments for the management of biliary tract cancer (Fig. 1).

Recent progress in understanding the basic aspects of immunology has led to the development of immune-based therapies for various types of cancers. The identification of

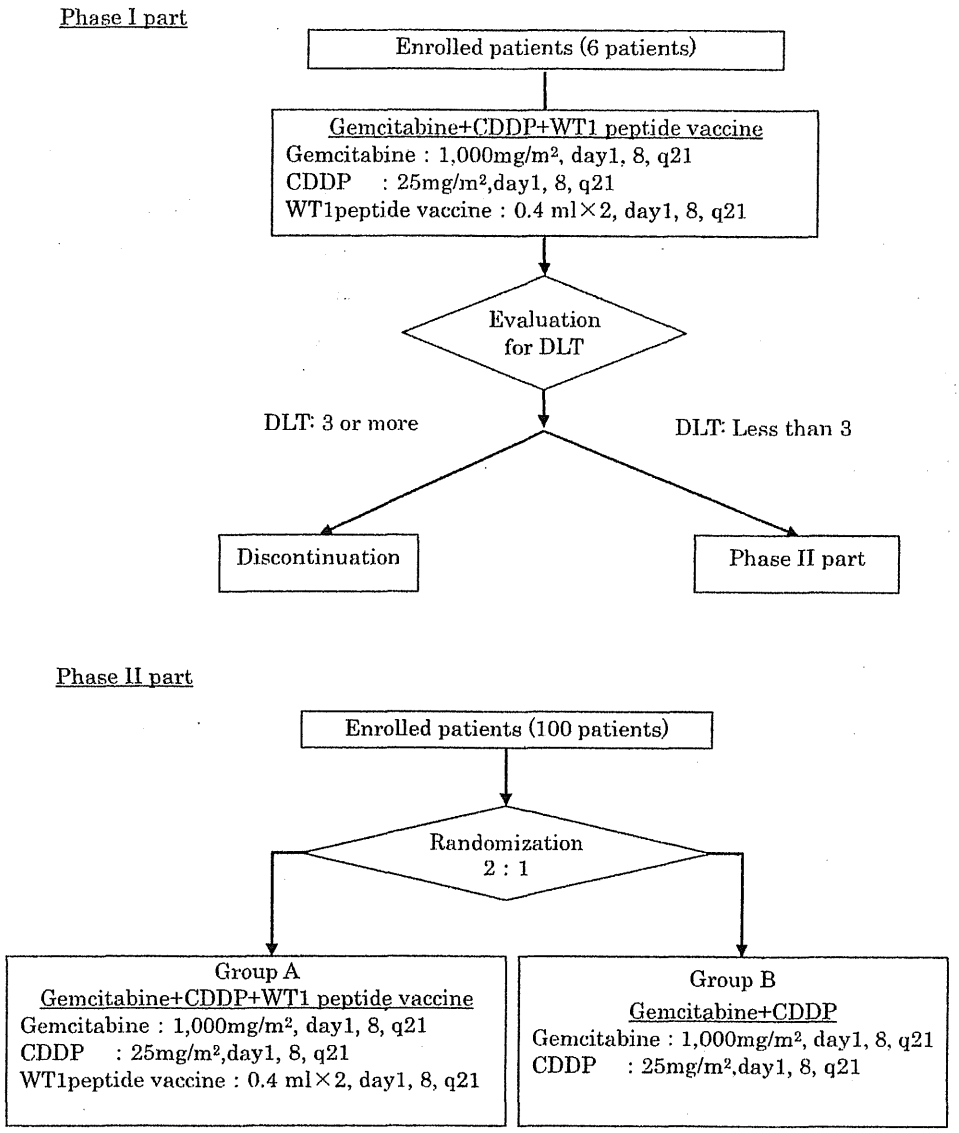

Fig. 1 Study design. *DLT* dose-limiting toxicity, *CDDP* cisplatin, *WT 1* Wilms tumor 1

various cancer antigens has facilitated many clinical trials of cancer vaccines that are expected to become new treatment strategies. Recently, sipuleucel-T immunotherapy for metastatic, asymptomatic hormone-refractory prostate cancer [4] and immunotherapy with ipilimumab for metastatic melanoma [5] have produced statistically significant improvements in survival, and both of these treatments have been approved by the United States Food and Drug Administration. Sipuleucel-T stimulates T-cell immunity against prostatic acid phosphatase, and ipilimumab blocks the potentiation of cytotoxic T-lymphocyte-associated antigen 4 and the antitumor T-cell response. Unfortunately, few preclinical studies examining biliary tract cancer have shown promising immune responses similar to those induced by sipuleucel-T against prostate cancer or those induced by ipilimumab against melanoma, and few clinical studies of immunotherapy for biliary tract cancer have been reported because of the rarity of this disease and the poor physical conditions of most patients at the time of the initial diagnosis. However, GEM has been reported not to suppress immunological cells, but to increase the population of dendritic cells that serve as antigen-presenting cells [6, 7]. Therefore, we conducted a phase I trial of Wilms tumor 1 (WT1) peptide vaccine and GEM combination therapy in patients with advanced pancreatic or biliary tract cancer [8]. Although the aim of that study was to assess the safety of the combination of WT1 peptide vaccine and GEM in a small population, it also showed that the WT1 peptide vaccine was safe enough to be employed in patients with advanced pancreatic or biliary tract cancer in combination with GEM, and

that the efficacy of the combination therapy seemed to be promising, as outlined below.

We recently initiated a phase I and randomized phase II study to evaluate the efficacy and safety of adding the WT1 peptide vaccine to GC in advanced biliary tract cancer (WT-BT trial), since GC has become the new standard and because the WT1 peptide vaccine is an attractive candidate as a partner for chemotherapy to improve survival in patients with advanced biliary tract cancer. WT1 protein is overexpressed in various types of cancer cells, including biliary tract cancer cells [9], and it was ranked as the No. 1 antigen in the cancer antigen prioritization project of the National Cancer Institute [10].

To our knowledge, this is the first randomized clinical trial to evaluate immunotherapy for biliary tract cancer. The study complied with the Declaration of Helsinki. Informed consent was obtained from all the patients, and the protocol was approved by the ethics committees at all participating institutions. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000004886 (http://www.umin.ac.jp/ctr/index.htm). The study was initiated in January 2011.

1. The results of a phase I trial of WT1 peptide vaccine and GEM combination therapy in patients with advanced pancreatic or biliary tract cancer

An open-labeled, dose-escalation phase 1 trial of WT1 vaccine and GEM combination therapy for patients with advanced pancreatic cancer or biliary tract cancer was performed. The primary endpoint was the evaluation of the toxicity, safety, and optimal immunological dose of the vaccine. Human leukocyte antigen (HLA)-A 0201, HLA-A 0206, and/or HLA-A 2402-positive patients with inoperable advanced pancreatic or biliary tract cancer who had not previously been treated with GEM were eligible for this study. Six doses of GEM and 4 doses of WT1 peptide (1 or 3 mg) emulsified in Montanide adjuvant were administered over 2 months. Twenty-five patients (13 male and 12 female) were enrolled. Nine patients had inoperable advanced pancreatic cancer, 8 had gallbladder cancer, 4 had intrahepatic, and 4 had extrahepatic bile duct cancer. The adverse events were comparable to those seen with GEM alone. Delayed-type hypersensitivity test was positive after vaccination in 2 patients, and WT1-specific T cells in peptide-stimulated culture were detected by tetramer assay in 59% (13 of 22) of the patients. The disease control rate at 2 months was 89% for pancreatic cancer and 50% for biliary tract cancer. With a median follow-up time of 259 days, the median survival time for patients with biliary tract cancer was 288 days, and that for patients with pancreatic cancer was 259 days. Although objective clinical efficacy was not apparent, the safety of the WT1 vaccine and GEM combination therapy was confirmed in this study.

2. An ongoing phase I and randomized phase II study to evaluate the efficacy and safety of adding WT1 peptide vaccine to GC in advanced biliary tract cancer (WT-BT trial).

Protocol summary of the WT-BT trial

Study setting

The study is a multi-institutional open-label phase I and randomized phase II trial.

Objectives and endpoints

The aim of this phase I/II study is to determine the recommended dosage of WT1 peptide vaccine when used in combination with GC chemotherapy and to clarify the safety and efficacy of GC plus WT1 peptide vaccine when administered at the recommended dose, in comparison with GC alone.

In the phase I study, we will investigate the frequency of the dose-limiting toxicity (DLT). The criteria for a DLT will include: Grade 4 neutropenia for 8 or more consecutive days, Grade 3 neutropenia accompanied by a fever (≥37.5°C), Grade 4 thrombocytopenia or the need for a transfusion, a Grade 4 aspartate transaminase (AST)/alanine transaminase (ALT) elevation or a Grade 3 AST/ALT elevation for 8 or more consecutive days, Grade 3 or 4 nonhematological toxicity (except for rash, hyperglycemia, gamma-GTP elevation, and any temporary events not affecting the protocol treatment), Grade 3 or 4 local skin inflammation at the vaccine injection sites, or Grade 1 or greater interstitial pneumonia.

In the phase II study, the primary endpoint will be the 1-year overall survival rate for all eligible patients. Overall survival will be defined as the number of days from randomization until death from any cause, and the data will be censored as of the last follow-up day on which the patient was alive. The secondary endpoints will be progression-free survival, response rate, median survival time, 2-year overall survival rate, percentage of adverse events, percentage of serious adverse events, and immunological responses (multimer assay and delayed-type hypersensitivity).

Eligibility criteria

Inclusion criteria

For inclusion in the study, patients are required to fulfill all the following criteria:

1. Clinically diagnosed with biliary tract cancer, including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer, and ampulla of Vater cancer.
2. Recurrent or unresectable biliary tract cancer.
3. Histologically proven papillary adenocarcinoma, tubular adenocarcinoma, or adenosquamous carcinoma for patients with extrahepatic cholangiocarcinoma, gallbladder cancer, and ampulla of Vater cancer; histologically proven adenocarcinoma for patients with intrahepatic cholangiocarcinoma.
4. Without central nervous system metastasis.
5. Without moderate or greater ascites/pleural effusion.
6. No previous therapy for biliary tract cancer.
7. No previous operation, chemotherapy, or radiotherapy for any other malignancies within the past 5 years.
8. No previous chemotherapy containing gemcitabine or cisplatin for any other malignancies.
9. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
10. Sufficient oral intake.
11. Age of 20–80 years.
12. Adequate organ functions.
13. HLA of A2402, A0201, or A0206.
14. Written informed consent.

Exclusion criteria

Patients will be excluded if they meet any of the following criteria:

1. Simultaneous or metachronous (within the past 5 years) double cancers, with the exception of intramucosal tumors curable with local therapy.
2. Pregnant or lactating women or women of childbearing potential and men who wish to father children.
3. Psychosis.
4. Patients requiring systemic steroid medication.
5. Interstitial pneumonia or fibroid lung disease.
6. Active bacterial or fungous infection.
7. Severe complications.
8. Drug allergies to drugs containing iodine compounds and/or gadolinium.
9. Inadequate physical condition, as diagnosed by the primary physician.

Randomization in the phase II study

After the fulfillment of the eligibility criteria has been confirmed, patient registration for both the phase I and II studies will be made by faxing the Data Center. Eligible patients in the phase II study will be stratified according to HLA (A2402/A02XX) and then randomized at the Data Center at a 2:1 ratio, using a minimization method and balancing the study arms according to institution, primary tumor (gallbladder cancer/other than gallbladder cancer), and history of surgical resection for the primary tumor (recurrent/advanced) to receive GC either with or without the WT1 peptide vaccine.

Treatment methods

For the patients in the phase I study, the GC and WT1 vaccine will be administered according to the following schedule: cisplatin (25 mg per m^2 of body-surface area) followed by gemcitabine (1000 mg per m^2) administered intravenously on days 1 and 8 every 3 weeks, with the vaccine (3 mg per body) injected subcutaneously alternating between 2 areas on the unilateral axillary fossa and inguen on days 1 and 8.

For both arms in the phase II study, GC will be administered according to the same dose and schedule as those used in the phase I study, but the vaccine will be administered only for the GC plus WT1 peptide vaccine arm.

The protocol treatments will be continued until disease progression, unacceptable toxicity, or patient refusal, although cisplatin will be continued for only a maximum of 24 weeks.

Follow-up

Enhanced abdominal computed tomography (CT)/magnetic resonance imaging, chest CT/X-rays, and tumor marker levels (carcinoembryonic antigen [CEA] and carbohydrate antigen [CA] 19-9) will be evaluated at least every 6 weeks during the protocol treatment. Patients will be seen on days 1 and 8 of every cycle for a physical examination to monitor their symptoms and the possible toxic effects of treatment. Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Study design and statistical analysis

In the phase I study, six patients will be recruited to determine whether a WT1 peptide vaccine dose of 3 mg per body can be recommended for use in combination with GC. A dose of 3 mg per body is the recommended dose for the WT1 peptide vaccine when used in combination with GEM alone, as determined in the previous phase I study. If treatment-related DLTs occur in no more than two of the six patients, transition to the phase II study will be

permissible with the approval of the independent data monitoring committee. If DLTs occur in three or more patients, transition to the phase II study will be terminated.

In the phase II study, 100 patients will be allocated to either of the two arms to evaluate the safety and efficacy of GC plus WT1 peptide vaccine, in comparison with GC alone. The sample size was determined based on the feasibility of the study after considering the research period, the number of participating institutions, and the available financial resources. A total of 66 patients in the GC plus WT1 peptide vaccine arm would enable the 1-year overall survival rate to be estimated with an accuracy of ±10%.

Interim analysis and monitoring

We do not plan to perform an interim analysis in this study. In-house monitoring will be performed every 6 months by the Data Center to evaluate the study progress and to improve the quality of the study.

Discussion

So far, no consensus exists regarding the "best criteria" for evaluating the effectiveness of cancer immunotherapy. Evidence of therapeutic activity may be difficult to obtain in early-phase trials using standard endpoints such as the antitumor response according to the Response Evaluation Criteria in Solid Tumors (RECIST), because most cancer immunotherapies are not expected to result in notable tumor shrinkage. Recently published FDA guidance suggests that the development of a cancer vaccine may present different considerations for clinical trial design than the development of a traditional cytotoxic drug or biological product for the treatment of cancer (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm).

We retrieved clinical trials using immunotherapy for biliary tract cancer through PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and ClinicalTrial.gov (http://clinicaltrials.gov/), although no reports or ongoing studies were found in this category, except for two trials: our previous phase I study examining GEM plus the WT1 peptide vaccine [8], and another study (phase II) examining chemoradioimmunotherapy, with interleukin 2 and 13-cis-retinoic acid being used for the immunotherapy [11]. Both studies conducted for pancreatic or biliary tract cancer showed some promise for a survival advantage, although the reported evidence was immature. We initiated the current phase I and randomized phase II studies to evaluate the efficacy and safety of adding the WT1 peptide vaccine to GC for the treatment of advanced biliary tract cancer. These studies are only the initial step in the development of immunotherapy for this disease, although we hope that the trial may provide useful data for assessing the true activities of this treatment.

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Conflict of interest None.

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ORIGINAL ARTICLE

Effect of biliary drainage on chemotherapy in patients with biliary tract cancer: an exploratory analysis of the BT22 study

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Abstract

Background/purpose: Complications from biliary drainage in biliary tract cancer (BTC) may influence the relative dose intensity of chemotherapy or increase adverse events during chemotherapy. BT22 was a randomized phase II trial, the results of which were consistent with those of a phase III trial in non-Japanese that demonstrated the effectiveness of gemcitabine plus cisplatin combination therapy (GC) in BTC. The purpose of this exploratory analysis of the BT22 study was to identify the possible effects of biliary drainage on the efficacy and safety of GC or gemcitabine monotherapy (G).

Patients and Methods: The 83 BTC patients who received GC or G in BT22 were retrospectively analysed in two subgroups dependent upon whether biliary drainage was performed before study entry. Efficacy and safety of treatment (GC vs. G) were compared in these two groups.

Results: The GC arm had a higher 1-year survival rate and longer median survival time (MST) than the G arm independent of prior biliary drainage. Patients in the drainage subgroup developed cholangitis more frequently, however, the frequency of grade 3/4 adverse events did not differ between the treatment regimens with/without drainage.

Conclusions: Biliary drainage before chemotherapy did not affect the therapeutic efficacy or tolerability of chemotherapy using G or GC.

Keywords

biliary drainage, chemotherapy, gemcitabine, cholangitis, cisplatin, biliary tract cancer

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Introduction

Biliary tract cancer (BTC), while relatively rare in Western countries, is more common in Japan where it is the sixth leading cause of cancer death with approximately 17 000 deaths every year.[1] The mortality caused by BTC in Japan is higher than any other country, and far exceeds all Western countries.[2]

Developing an effective BTC treatment has become a high priority for Japan. At present the only curative treatment is surgical resection, and although an increasing number of patients undergo surgery each year, outcomes have met with only a varying degree of success. Patients with unresectable disease can only be managed with chemotherapy and supportive care for palliation of disease including biliary decompression. However, prognosis remains extremely poor in these patients.

No standard chemotherapy for BTC has been established. Many clinical trials of systemic chemotherapy have been conducted in BTC patients, but most of these were phase II trials that had small sample sizes and lacked a control group because of the rarity and heterogeneity of BTC. In 2009, the results of a phase III study of gemcitabine plus cisplatin (GC) vs. gemcitabine monotherapy (G) conducted in the United Kingdom (ABC-02 Study) were reported.[3] This previous study included 410 patients and is the largest clinical trial to be conducted in this field. The GC arm had

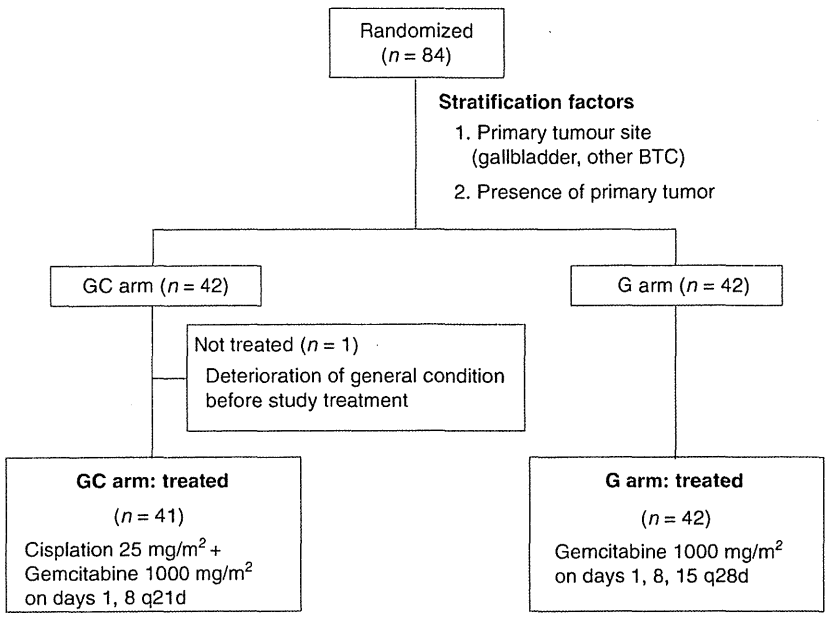

Figure 1 Patient disposition of the BT22 Study. BTC, biliary tract cancer; G arm, gemcitabine monotherapy; GC arm, combination therapy with gemcitabine and cisplatin

a significantly better median survival time (MST) [11.7 months (95% confidence interval (CI) 9.5 to 14.3) vs. 8.1 months (95% CI 7.1 to 8.7); $P < 0.001$] and progression-free survival (PFS) [8.0 months (95% CI 6.6 to 8.6) vs. 5.0 months (95% CI 4.0 to 5.9); $P < 0.001$] than the G arm. A comparison of grade 3 and 4 toxicities showed that the GC combination added little toxicity. From the results of the ABC-02 study, GC was recognized as the standard of care for the treatment of advanced BTC. A randomized phase II study comparing GC and G was also conducted in Japan (BT22 study; Clinical Trial.gov Identifier NCT00380588). Median survival time [11.2 vs. 7.7 months; hazard ratio (HR) 0.69 (95% CI 0.42 to 1.13)] and PFS [5.8 vs. 3.7 months; HR 0.66 (95% CI 0.41 to 1.05)] were similar to the results seen in the ABC-02 study confirming the status of GC as the worldwide standard.[4]

For patients with unresectable disease, biliary decompression is often required if chemotherapy is contemplated.[5] Usually, biliary obstruction will be managed by percutaneous or endoscopic drainage rather than a surgical approach because of the presence of incurable disease and high operative risk. However, complications resulting from insufficient biliary drainage, morbidities such as obstructive jaundice, cholangitis, and sepsis, often require that chemotherapy be interrupted or discontinued.[6] Obstructive jaundice may impact on prognosis by necessitating dose modification of chemotherapy or by complications as a consequence of biliary obstruction.

In the present study, we analysed the data from the BT22 study conducted in Japan to determine the impact of biliary drainage on the efficacy and adverse events associated with gemcitabine-based chemotherapy.

Patients and methods

Patients

This analysis included all patients who received at least one dose of study treatment in the BT22 study, a multicentre study conducted at nine medical institutions in Japan. From September 2006 to October 2008, 84 BTC patients were enrolled. The patients were randomized to either the GC arm [a weekly intravenous (i.v.) infusion of cisplatin 25 mg/m^2 followed by gemcitabine 1000 mg/m^2 for 2 weeks, followed by dose suspension at the third week, repeated as one course] or the G arm (weekly i.v. infusion of gemcitabine 1000 mg/m^2 for 3 weeks followed by dose suspension at the fourth week, repeated as one course). Randomization was stratified by primary tumour site (gallbladder cancer or other BTC) and the presence or absence of a primary tumour. One patient in the GC arm was discontinued before the start of the study treatment for deterioration of a general condition caused by another complication, so the analysis was conducted with 41 GC arm patients and 42 G arm patients (Fig. 1).

The specific criteria for study eligibility have been reported previously[4] and are only summarized here:

- patients with unresectable locally advanced or metastatic intrahepatic bile duct cancer, extrahepatic bile duct cancer, gallbladder cancer, or ampullary carcinoma that is histologically or cytologically confirmed adenocarcinoma (including adenosquamous carcinoma);
- patients with at least one measurable lesion;
- patients with no prior chemotherapy;
- patients with a performance status of 0 or 1;

Table 1 Patient characteristics at baseline

Characteristics	BD (n = 34)		Non-BD (n = 49)	
	n (%)		n (%)	
	GC arm (n = 16)	G arm (n = 18)	GC arm (n = 25)	G arm (n = 24)
Gender				
Male	7 (43.8)	9 (50.0)	11 (44.0)	12 (50.0)
Female	9 (56.3)	9 (50.0)	14 (56.0)	12 (50.0)
Age				
Median (years)	64.5	65.5	65.0	68.5
PS				
0	13 (81.3)	12 (66.7)	21 (84.0)	16 (66.7)
1	3 (18.8)	6 (33.3)	4 (16.0)	8 (33.3)
Primary tumour site				
Gallbladder	6 (37.5)	9 (50.0)	9 (36.0)	8 (33.3)
Non-gallbladder	10 (62.5)	9 (50.0)	16 (64.0)	16 (66.7)
Presence of a primary tumour				
Present	14 (87.5)	18 (100.0)	16 (64.0)	13 (54.2)
Absent	2 (12.5)	0 (0.0)	9 (36.0)	11 (45.8)
Extent of disease				
Locally advanced	5 (31.3)	7 (38.9)	0 (0.0)	1 (4.2)
Metastatic	11 (68.8)	11 (61.1)	25 (100.0)	23 (95.8)

BD, biliary drainage; G arm, gemcitabine monotherapy; GC arm, combination therapy with gemcitabine and cisplatin; PS, performance status.

- patients with an estimated life expectancy of more than 3 months; and
- patients with adequate organ function (e.g. bone marrow, liver and kidney).

Methods

The BT22 study was a randomized study that compared patients from two arms: GC vs. G.

Patients with obstructive jaundice had to achieve a certain degree of jaundice reduction with biliary drainage before study entry (i.e. total bilirubin was three times the upper limit of normal or less). The protocol contained no specific provisions about biliary drainage. The approach (endoscopic or percutaneous transhepatic), drainage type (internal biliary drainage or external biliary drainage) and stent material (plastic stent or metallic stent) could be decided by the investigator. The primary endpoint was 1-year survival rate. Sample size was calculated by the method proposed by Simon *et al.*[7] The 83 treated patients were retrospectively analysed and classified into subgroups of patients who had undergone biliary drainage before the start of the study (BD subgroup) and patients who had not (non-BD subgroup) to compare the efficacy and safety of the treatment regimens (GC vs. G arms). Progression-free survival and overall survival (OS) curves were constructed using the Kaplan–Meier method, and estimates of median OS and the respective 95% CIs were calculated from the Kaplan–Meier estimates. Cox's proportional hazard model was used to estimate the HR. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v. 3.0). A multivariate Cox proportional hazard model was used to identify prognostic factors.

Results

Of the 83 patients treated in the BT22 study, 34 were in the BD sugroup (16 in the GC arm and 18 in the G arm) and 49 were in the non-BD subgroup (25 in the GC arm and 24 in the G arm). Table 1 shows patient baseline characteristics. More of the patients in the BD subgroup (n = 34) had a primary tumour [GC: (14/16) 87.5%, G: (18/18) 100%], whereas the percentages of patients in the non-BD subgroup (n = 49) without a primary tumour were relatively higher [GC: (9/25) 36.0%, G: (11/24) 45.8%]. However, no substantial imbalances were noted between the two subgroups in gender, age or primary tumour site.

Efficacy

Efficacy data for the subgroups are shown in Table 2 and Fig. 2. In the BD subgroup, a comparison of OS in the GC and G arms showed 1-year survival of 40.9% vs. 27.8% and MST of 11.3 vs. 8.1 months [HR of 0.59 (95% CI 0.27 to 1.30)], respectively. In the non-BD subgroup, a comparison between the GC and C arms showed 1-year survival rate of 37.8% vs. 33.3% and MST of 9.6 vs. 7.5 months [HR of 0.76 (95% CI 0.40 to 1.45)], respectively.

Table 2 Overall survival and progression-free survival with or without biliary drainage by treatment arm

	BD (n = 34)		Non-BD (n = 49)	
	GC arm (n = 16)	G arm (n = 18)	GC arm (n = 25)	G arm (n = 24)
Overall survival				
1-year survival rate	40.9%	27.8%	37.8%	33.3%
Median survival time (months)	11.3	8.1	9.6	7.5
Hazard ratio (95% confidence interval)	0.588 (0.266–1.301)		0.758 (0.397–1.447)	
Progression-free survival				
6-month progression-free survival	53.3%	27.8%	43.7%	27.5%
Median progression-free survival (months)	7.1	3.9	4.5	3.3
Hazard ratio (95% confidence interval)	0.479 (0.222–1.032)		0.748 (0.407–1.374)	

BD, biliary drainage; G arm, gemcitabine monotherapy; GC arm, combination therapy with gemcitabine and cisplatin.

Subgroup analysis results based on HRs for OS by biliary drainage, performance status (PS), primary tumour site, presence of primary tumour and extent of disease are shown in Fig. 3. Hazard ratios (GC vs. G) for OS were less than one in every subgroup.

Safety

Adverse events observed in the GC and G arms with a frequency of at least 30% in the BT22 study have been reported.[4] In this analysis, the frequency of grade 3 and 4 events for the most common adverse events (frequency ≥30%) in the BD subgroup was compared with that in the non-BD subgroup (Table 3). Events in the BD subgroup that were more common in the GC arm were haemoglobin decrease (43.8% vs. 5.6%), thrombocytopenia (37.5% vs. 5.6%) and red blood cell decrease (37.5% vs. 5.6%). Events in the non-BD subgroup that were more common in the GC arm were leukopaenia (32.0% vs. 12.5%), neutoropenia (64.0% vs. 33.3%), and thrombocytopaenia (40.0% vs. 8.3%). There were no significant differences in the incidence of non-haematological events between the GC and G arms in either the BD or non-BD subgroup.

Although the incidence of cholangitis was higher in the BD subgroup than in the non-BD subgroup, the ratio of cholangitis in the GC arm to that in the G arm was not appreciably different in each of the BD and non-BD subgroups. For the BD subgroup, the incidence of Grade 3 and 4 cholangitis in the G arm was relatively higher than that in the GC arm (Table 4).

Prognostic factors

A multivariate Cox's proportional hazard model was used with the following six factors: biliary drainage, PS (0 vs. 1), primary tumour site (gallbladder vs. non-gallbladder), the presence of a primary tumour (present vs. absent), extent of disease (locally advanced vs. metastatic) and chemotherapy regimen (GC arm vs. G arm) (Table 5). The HR of the GC arm to the G arm was 0.72 [95% CI 0.44 to 1.20] after multivariate adjustment for several variables. The primary tumour site of non-gallbladder [HR of gallbladder vs. non-gallbladder 1.72 (95% CI 1.01 to 2.93)] and the absence of a primary tumour [HR of presence vs. absence 2.79 (95% CI 1.40 to 5.56)] were significantly related to a longer OS. Biliary drainage was suggested to have favourable clinical relevance [HR 0.72 (95% CI 0.39 to 1.32)], as well as PS 0 and locally advanced disease.

Discussion

Many studies on unresectable BTC retrospectively investigated whether biliary drainage should be performed endoscopically or with a percutaneous transhepatic approach,[8,9] and whether a plastic or metallic stent should be used.[10–15] Several of the few prospective studies conducted have stent patency or complication-free survival as a primary endpoint. However, only a few of those have considered the impact of drainage on chemotherapy efficacy or adverse events. This analysis represents an important exploratory investigation of the impact of biliary drainage on chemotherapy efficacy in the BT22 study which was a prospectively controlled study.

Insufficient biliary drainage leads to problems during chemotherapy, such as recurrent obstructive jaundice with or without cholangitis, which in turn often results in suspension or discontinuation of chemotherapy. In the BT22 study, the incidence of cholangitis during initial chemotherapy in the GC and G arms in the BD subgroup was higher than that in the respective arms of the non-BD subgroup. Although the profiles of grade 3 and 4 non-haematological adverse events in the GC and G arms did not differ, haematological toxicities were slightly more severe in the GC arm. GC therapy is expected to lead to an increased incidence of cholangitis or progression to severe cholangitis in patients undergoing biliary drainage who are at high risk of cholangitis mainly because the regimen has a more severe haematological toxicity profile than G. These events could undermine the efficacy of GC therapy.

In the BD subgroup, however, MST in the GC and G arms were 11.3 vs. 8.1 months, respectively, with an HR of 0.59 (95% CI 0.27 to 1.30). Median survival time in the GC arm was longer than MST in the G arm. As with adverse events overall, grade 3 and 4 adverse events in the BD subgroup were slightly more severe in the

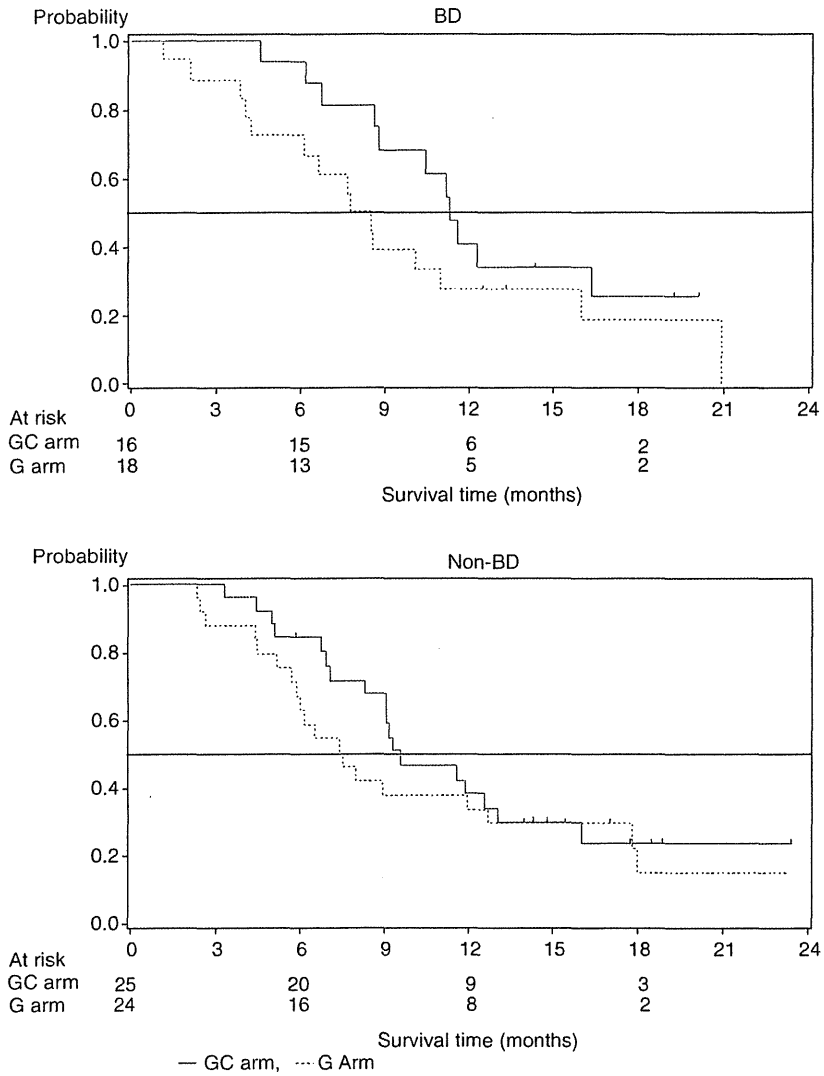

Figure 2 Survival curves in the BD subgroup (a) and non-BD subgroup (b) by the treatment arm. Solid line (—) indicates the GC arm and the broken line (---) the G arm. BD, biliary drainage; G arm, gemcitabine monotherapy; GC arm, combination therapy with gemcitabine and cisplatin

Subgroup		HR*	*P*-value	hazard ratio with 95% confidence interval
Biliary drainage	BD	0.588	0.1902	
	Non-BD	0.758	0.4006	
PS	0	0.759	0.3520	
	1	0.592	0.3344	
Primary tumour site	Gallbladder	0.852	0.6746	
	Non-gallbladder	0.578	0.1097	
Presence of primary tumour	Present	0.722	0.2525	
	Absent	0.602	0.3891	
Extent of disease	Locally advanced	0.591	0.4757	
	Metastatic	0.715	0.2181	

Figure 3 Hazard ratios for overall survival by patient baseline characteristics. HR*, hazard ratio of the combination therapy with gemcitabine and cisplatin (GC) arm to the gemcitabine monotherapy (G) arm

Table 3 Incidence of grade 3 or 4 events among most common adverse events[a]

Most common adverse events	BD (n = 34)		Non-BD (n = 49)	
	n (%)		n (%)	
	GC arm (n = 16)	G arm (n = 18)	GC arm (n = 25)	G arm (n = 24)
Hematologic				
WBC count decreased	4 (25.0)	5 (27.8)	8 (32.0)	3 (12.5)
Neutrophil count decreased	7 (43.8)	8 (44.4)	16 (64.0)	8 (33.3)
RBC decreased	6 (37.5)	1 (5.6)	8 (32.0)	5 (20.8)
Haemoglobin decreased	7 (43.8)	1 (5.6)	8 (32.0)	6 (25.0)
Haematocrit decreased	1 (6.3)	0 (0.0)	1 (4.0)	0 (0.0)
Platelet count decreased	6 (37.5)	1 (5.6)	10 (40.0)	2 (8.3)
Non-haematological				
Anorexia	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
Pyrexia	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)
Weight decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST increased	3 (18.8)	5 (27.8)	4 (16.0)	2 (8.3)
ALT increased	4 (25.0)	5 (27.8)	6 (24.0)	2 (8.3)
GGT increased	6 (37.5)	7 (38.9)	6 (24.0)	8 (33.3)
LDH increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ALP increased	1 (6.3)	3 (16.7)	2 (8.0)	4 (16.7)
Blood sodium decreased	4 (25.0)	2 (11.1)	3 (12.0)	2 (8.3)
C-reactive protein increased	0 (0.0)	2 (11.1)	0 (0.0)	1 (4.2)

[a]Most common, incidence ≥30% of all grades; events were graded according to CTCAE v3.0.
AST, aspartate aminotransferase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; BD, biliary drainage; G arm, gemcitabine monotherapy; GC arm, combination therapy with gemcitabine and cisplatin.

Table 4 Incidence of cholangitis with or without biliary drainage by treatment arm

	BD (n = 34)		Non-BD (n = 49)	
	n (%)		n (%)	
	GC arm (n = 16)	G arm (n = 18)	GC arm (n = 25)	G arm (n = 24)
Cholangitis (all grades)	5 (31.3)	7 (38.9)	2 (8.0)	3 (12.5)
Cholangitis (≥ grade 3)	2 (12.5)	5 (27.8)	0 (0.0)	1 (4.2)

BD, biliary drainage; G arm, gemcitabine monotherapy; GC arm, combination therapy with gemcitabine and cisplatin.

GC arm than in the G arm, but no particularly frequent events were encountered. In addition, patients with biliary drainage in the G arm had a relatively increased incidence of grade 3 and 4 cholangitis, possibly as a result of a lack of efficacy and inferior biliary drainage. Although careful monitoring of cholangitis is still needed, the above findings indicate GC to be an appropriate standard chemotherapy for unresectable BTC in both patients with and without biliary drainage.

Because this analysis was a retrospective investigation of the BT22 study, several biases could arise after this retrospective approach. Although the biases cannot be completely circumvented using a multivariate Cox's proportional hazard model, the results adjusted with other prognostic factors suggested that biliary drainage would not have a negative impact on the anticancer effect of chemotherapy. The results suggested that baseline biliary drainage did not adversely impact patient prognosis. The presence of a primary tumour (present vs. absent) and primary tumour site (gallbladder vs. non-gallbladder) had the greatest impact on the prognosis, which suggests that the stratification factors of the present study were appropriately selected.

Table 5 Multivariate analysis of prognostic factors using Cox's proportional hazard model

Covariate	*P*-value*	Hazard ratio (95% CI)
Biliary drainage (BD vs. non-BD)	0.2875	0.717 (0.389–1.323)
PS (1 vs. 0)	0.1620	1.532 (0.843–2.785)
Primary tumour site (gallbladder vs. non-gallbladder)	0.0454	1.722 (1.011–2.934)
Presence of primary tumour (present vs. absent)	0.0036	2.789 (1.398–5.564)
Extent of disease (metastatic vs. locally advanced)	0.4333	1.391 (0.609–3.176)
Treatment arm (GC arm vs. G arm)	0.2093	0.724 (0.437–1.199)

*Chi-square test.
BD, biliary drainage; CI, confidence interval; G arm, emcitabine monotherapy; GC arm, combination therapy with gemcitabine and cisplatin; PS, performance status.

As the BT22 study was conducted to compare chemotherapy regimens, the data available for investigating biliary drainage, e.g. the site of bile duct obstruction, the approach (endoscopic or percutaneous transhepatic) and the stent material (plastic stent or metallic stent), were limited. Thus, patient baseline characteristics varied substantially. A detailed subgroup analysis on biliary drainage was unfortunately infeasible with the limited sample size of the study. Moreover, this analysis was conducted to investigate the impact of whether or not biliary drainage was performed before starting chemotherapy, and patients requiring biliary drainage during chemotherapy were consequently included in the non-BD subgroup. Data on adverse events occurring during the primary treatment period are available, but adverse events occurring with more advanced cancer in secondary and subsequent treatments were not investigated. No definite conclusions about the relationship of biliary drainage to chemotherapy may therefore be drawn based on the findings of this analysis alone.

Conclusion

In this analysis, GC combination therapy was safely administered and the therapeutic efficacy of the GC arm was maintained in patients with or without biliary drainage. The presence or absence of biliary drainage was not found to impact the efficacy or adverse events in each treatment arm for unresectable BTC. Based on these results, it appears that adequate efficacy with gemcitabine-based chemotherapy can be expected in patients with BTC even with biliary drainage.

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Conflicts of interest

Masanori Taketsuna and Minori Koshiji are employees of Eli Lilly Japan K.K. Takuji Okusaka has received funding to research and attend/present at conference from Eli Lilly Japan K.K. Junji Furuse has received funding to attend/present at conference from Eli Lilly Japan K.K. The authors report no other conflicts of interest.

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膵胆道癌化学療法の最前線

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A. 膵　癌

緒　言

膵癌に対しては外科的治療が唯一の根治療法であるが，一般的には早期発見が困難で，診断時に約80％の症例が切除不能な状態であり，治癒切除例でもその大半に癌再発を認める．これらの切除不能な局所進行例，遠隔転移例，術後再発例に対しては，全身化学療法を含んだ治療が第一選択となり，今なお膵癌治療における全身化学療法の果たす役割は大きい．

標準治療―GEM中心の10年―

1997年にBurrisらが進行膵癌患者を対象とした比較試験で，ゲムシタビン塩酸塩(GEM：商品名ジェムザール)が5-FUと比較して症状緩和効果(23.8％ 対 4.8％，p＝0.0022)および生存期間中央値median survival time(MST)5.65ヵ月対4.41ヵ月，p＝0.0025で有意にすぐれていることを報告して以降，進行膵癌患者に対してはGEM単剤療法が標準治療とされた．わが国でも2001年に保険適用となってから約10年間にわたり切除不能膵癌に対する治療の中心的役割を担ってきたが，生存期間，治療成績は十分に満足できるものではない．その後も生存期間の延長を目指してGEM＋αの併用療法の臨床試験が複数行われてきたが(表1)，統計学的に有意にすぐれていたものはGEM＋エルロチニブ(erlotinib：商品名タルセバ)のみである．GEM＋エルロチニブに関しても予後の改善度はそれほど大きくなく，MSTでは0.3ヵ月の改善であった．2011年7月に治癒切除不能膵癌に対しての保険承認が追加され，わが

表1　GEM＋αの主な第Ⅲ相臨床試験の結果

試験	著者	発表年	MST(月)	p値
GEM vs GEM＋5-FU	Berlinら	2001	5.4 vs 6.7	0.09
GEM vs GEM＋シスプラチン	Colucciら	2002	4.6 vs 6.9	0.48
GEM vs GEM＋marimastat	Bramhallら	2002	5.5 vs 5.5	0.95
GEM vs GEM＋シスプラチン	Heinemannら	2003	6.0 vs 7.5	0.15
GEM vs GEM＋イリノテカン	Rocha Limaら	2003	6.6 vs 6.3	0.79
GEM vs GEM＋オキサリプラチン	Louvetら	2004	7.1 vs 9.0	0.13
GEM vs GEM＋ペメトレキセド	Oettleら	2004	6.3 vs 6.2	0.85
GEM vs GEM＋exatecan	Abou-Alfaら	2004	6.2 vs 6.7	0.52
GEM vs GEM＋tipifarnib	Van Cutsemら	2004	6.1 vs 6.4	0.75
GEM vs GEM＋5-FU＋LV	Riessら	2005	6.2 vs 5.9	0.68
GEM vs GEM＋カペシタビン	Herrmannら	2005	7.2 vs 8.4	0.23
GEM vs GEM＋エルロチニブ	**Mooreら**	**2005**	**5.9 vs 6.2**	**0.038**
GEM vs GEM＋オキサリプラチン	Poplinら	2006	4.9 vs 5.7	0.22
GEM vs GEM＋セツキシマブ	Philipら	2007	5.9 vs 6.4	0.23
GEM vs GEM＋ベバシズマブ	Kindlerら	2007	5.9 vs 5.8	0.95
GEM vs GEM＋カペシタビン	Cunninghamら	2009	6.2 vs 7.1	0.08
GEM vs GEM＋axitinib	Kindlerら	2009	8.5 vs 8.3	0.54

GEM＝ゲムシタビン塩酸塩

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◎切除不能進行膵癌に対しては全身化学療法が第一選択となる.
◎ゲムシタビン塩酸塩(GEM), S-1, 両者の併用療法, GEM+エルロチニブ療法などの選択肢があり, 患者の状態や希望を考慮して選択する.

表2 GEST試験における各群の投与法

レジメン	内容	投与日	投与間隔
GEM群	GEM 1,000 mg/m^2	day 1, 8, 15	4週ごと
S-1群	S-1 80 mg/body : BSA < 1.25 m^2 100 mg/body : 1.25 ≦ BSA < 1.50 m^2 120 mg/body : 1.50 ≦ BSA	day 1～28	6週ごと
GEM+S-1群	GEM 1,000 mg/m^2 S-1 60 mg/body : BSA < 1.25 m^2 80 mg/body : 1.25 ≦ BSA < 1.50 m^2 100 mg/body : 1.50 ≦ BSA	GEM : day 1, 8 S-1 : day 1～14	3週ごと

GEM=ゲムシタビン塩酸塩
BSA=Body Surface Area : 体表面積
(文献1)より引用)

国で使用可能となっている.

経口フッ化ピリミジン製剤のS-1(商品名ティーエスワン)はわが国で開発が進められた薬剤で, 遠隔転移を有する膵癌患者を対象としたS-1単独療法の第Ⅱ相試験で奏効割合は21.1～37.5%, MSTは5.6～9.2ヵ月と報告されており, 2006年8月に膵癌に対して保険適用となった. これらの結果から2007年よりわが国と台湾において, 進行膵癌に対するS-1の有効性を検証するための第Ⅲ相ランダム化比較試験(GEST)が行われ, その結果が2011年のアメリカ臨床腫瘍学会(ASCO)で報告された. GESTの各群レジメンを**表2**に示す. GESTはperformance status(PS)が0もしくは1と良好かつ未治療の切除不能進行膵癌患者に対し, GEM単剤治療を対照群としてS-1の非劣性, およびGEM+S-1併用(GS)療法の優越性を検討した3群間の比較試験であった. 主要評価項目のMSTは, GEM対S-1対GS : 8.8ヵ月対9.7ヵ月対10.1ヵ月で, 統計学的にS-1の非劣性は証明されたものの, GSの優越性は証明されなかった. ただ, 副次評価項目の無増悪生存期間は, GEM対S-1対GS : 4.1ヵ月対3.8ヵ月対5.7ヵ月であり, GEMに対してS-1の非劣性およびGSの優越性が証明された. 奏効割合は, GEM対S-1対GS : 13%対21%対29%で, S-1, GSともにGEMを上回った. GESTにより, 進行膵癌患者に対する治療としてS-1はGEMとほぼ同等の効果を有する標準治療であることが示され, GS療法も一つの選択肢になり得ることが示唆された[1].

局所進行膵癌

切除不能局所進行膵癌に対しては, 化学療法以外に化学放射線療法も選択肢になり得るが, GEMが登場して以降, 化学療法よりも化学放射線療法がすぐれているとする明確なエビデンスがないため, 化学療法が選択されることが多い. 局所進行膵癌に対するGEMの成績に関しては, 日本臨床腫瘍研究グループ(JCOG)により2005年から行われたGEM単独治療の第Ⅱ相試験(JCOG0506)で, MSTが15ヵ月, 1年生存割合64%であった. また, GESTのサブグループ解析では, 局所進行膵癌に対してGEM単剤のMSTは12.7ヵ月と報告されている. 化学放射線療法に関しては, S-1併用放射線療法(S-1 : 80 mg/m^{2}放射線治療日内服+放射線照射1.8 Gy/回×28回(5.5週))の第Ⅱ相試験が行われ, MSTが16.2ヵ月, 1年生存割合が72%と比較的良好な結果であったが, 化

膵癌の術後補助化学療法は，現時点ではGEMを使用して行われることが多い．
GEM耐性膵癌に対する二次治療は，日本でのS-1のほか，欧米では5-FUやオキサリプラチンを用いたものも検討されている．

学放射線療法が普及するには比較試験で化学療法よりもすぐれた結果を示す必要がある．

術後補助化学療法

欧州で行われた第Ⅲ相試験(CONKO-001)ではGEMによる術後補助化学療法が経過観察群を生存期間で上回り，わが国のJSAP-02試験でもそれを支持する結果であった．GEMは効果，安全性のバランス面ですぐれており，現時点における標準治療と考えられる．GEMの投与期間についての明確なエビデンスはないが，CONKO-001では投与期間が約6ヵ月に設定されており，同様の期間で行われることが多い．

GEM不応後の二次治療

GESTや後述するACCORD11試験の結果から，GEMを含まない一次治療を行う選択肢が増えたが，GEM不応例に対する治療開発は引き続き重要な課題である．GEM耐性膵癌を対象としたS-1単剤療法の第Ⅱ相臨床試験では奏効割合が15%と報告されている．その他，ASCO2008にはGEM不応後の二次治療としてのCONKO-003試験の報告があり，オキサリプラチン，5-FUと葉酸(folic acid)併用のOFF療法が5-FUと葉酸の併用のFF療法と比較し，MST(26週間 vs 13週間，$p=0.014$)と無増悪生存期間の中央値(13週間 vs 9週間，$p=0.012$)において有効性を示した[2]．ACCORD11試験の結果も含め，欧米においては初回あるいは二次化学療法として5-FUやオキサリプラチンを含む全身化学療法が用いられており，日本人患者においてもGEM耐性膵癌に対し有効な治療方法となる可能性がある．

今後の展望

フランスにおいて化学療法未治療の遠隔転移を有する膵癌患者を対象として，GEM単独療法とオキサリプラチン(L-OHP)+イリノテカン(CPT-11)+5-FU/ロイコボリン(LV)併用療法(FOLFIRINOX療法)を比較した第Ⅲ相試験(ACCORD11試験)が実施された．ASCO2010での報告によると，MSTの差が4.3ヵ月と，FOLFIRINOX療法において大幅な生存期間の延長を示した(GEM群対FOLFIRINOX群：6.8ヵ月対11.1ヵ月，$p<0.001$)[3]．2011年8月現在，わが国でも数施設で第Ⅱ相臨床試験が行われており，日本人における安全性と有効性が検討されている．分子標的薬に関しては，表1に示した通り，残念ながらエルロチニブ以外有効な薬剤が見つかっていないが，新しい薬の開発は続いており，今後の展開を期待したい．

癌ワクチン治療としては，血管内皮増殖因子受容体vascular endothelial growth factor receptor(VEGFR)-2/キナーゼドメイン受容体を特異的に認識し，腫瘍新生血管内皮細胞を特異的に傷害する細胞傷害性T細胞を誘導するペプチドワクチンであるOTS102の第Ⅲ相試験がすでに行われ，その解析結果が待たれている．

B. 胆道癌

緒　言

外科手術のみが根治を期待できる治療法であるが，乳頭部癌では1～2割，肝内胆管癌で3～4割，肝外胆管癌では6～7割が診断時に切除不能な進行癌である[4,5]．切除不能胆道癌に対する臨床試験は小規模なものが多く，MSTが7～10ヵ月程度と報告されてきた．また，胆道癌は治癒切除後も5～8割が再発する難治癌であり，やはり全身化学療法の果たす役割は大きい．なお肝内胆管癌は，外科手術での扱いが肝細胞癌と共通するため，UICC分類と日本の癌取扱い規約では原発性肝癌に分類されるが，胆管上皮から腺癌を主体と

◉進行胆道癌に対する標準治療はGEM＋シスプラチン(CDDP)である.
◉日本ではS-1も使用されている.

表3　わが国で行われた切除不能胆道癌に対する主な第Ⅱ相臨床試験

	患者数	奏効率(%)	無増悪生存期間	MST(月)	1年生存率(%)	報告者	報告年
CEF(シスプラチン，エピルビシン，5-FU)	37	19	NA	5.9	24	Morizane	2003
ユーエフティー	19	5	1.0	8.8	21.1	Ikeda	2005
ユーエフティー＋ゲムシタビン塩酸塩	24	12.5	2.5	7.6	19.7	Furuse	2006
ゲムシタビン塩酸塩	40	17.5	2.6	7.6	25	Okusaka	2006
S-1(前期)	19	21.1	3.5	8.3	21.1	Ueno	2004
S-1(後期)	40	35	3.5	9.4	32.5	Furuse	2008

して発生し，遠隔転移をきたしやすいという性質から，内科治療，特に薬物療法においては胆道癌に含めることが多い.

標準治療―GEMからGEM＋CDDPへ―◉

わが国では切除不能胆道癌に対して**表3**に示すような第Ⅱ相試験が行われてきた．比較的良好な成績を示したGEM，S-1はそれぞれ2006年6月，2007年8月に胆道癌に対し保険が適用され，一般臨床で使用されてきた．わが国において切除不能，再発胆道癌患者を対象としたGEM＋S-1療法対S-1単独療法の無作為化比較第Ⅱ相試験(JCOG0805)が行われており，その結果が待たれる.

2006年に英国を中心に行われたGEM単剤とGEM＋シスプラチン(CDDP：商品名ランダ，ブリプラチン)のランダム化比較第Ⅱ相試験(ABC-01)では，GEM単剤群対GEM＋CDDP群で，奏効割合は15.2%対24.3%，無増悪生存期間中央値は4.0ヵ月対8.0ヵ月，6ヵ月無増悪生存割合は47.7%と57.1%であった.

ASCO2008ではこのグループの第Ⅲ相試験(ABC-02)の結果が報告され，MSTは単剤群で8.3ヵ月，併用群で11.7ヵ月，ハザード比0.70とGEM＋CDDP群で有意な生存期間の延長を認め，有害事象も許容範囲内であった[6]．同時期に日本で行われたGEM対GEM＋CDDPのランダム化比較第Ⅱ相試験(BT22試験)でも，OSは単剤群で7.7ヵ月，併用群で11.2ヵ月とほぼ同様の結果であった．いずれもGEMは1,000 mg/m^{2}をday 1, 8, 15に投与し28日を1コースとし，GEM＋CDDPはGEM 1,000 mg/m^{2}とCDDP 25 mg/m^{2}をday 1, 8に投与し21日を1コースと設定した．BT22試験においては，CTCAE(Common Terminology Criteria for Adverse Events)におけるGrade 3, 4の有害事象は，GEM群対GEM＋CDDP群で，好中球減少が(38.1%対56.1%)，血小板減少(7.1%対39.0%)，白血球減少が(19.0%対29.3%)，ヘモグロビン減少が(16.7%対36.6%)，γ-GTP上昇が(35.7%対29.3%)であり，腎障害はGEM＋CDDP群41名のうち1名にGrade 3の急性腎不全がみられたのみであり，忍容性ありと判断された．以上から切除不能胆道癌に対する標準治療は，GEM＋CDDP療法と考えられるようになり，2011年8月にCDDPはわが国でも胆道癌において保険承認された．GEM＋CDDP療法においては外来通院治療可能であるが，腎機能障害や嘔気などの消化器毒性が強く現れることがあるため，十分な補液と制吐剤の使用が必要である．**表4**に当院におけるGEM＋CDDP療法のレ

進行胆管癌においても，ワクチンや分子標的薬を用いたレジメンでの臨床試験が行われており，結果が期待されている．

表4　当院における切除不能胆道癌に対するGEM＋CDDP療法の投与方法

Rp1	メインルート：3号維持液(ソリタT3，ソルデム3Aなど)	500 ml	3時間
	側管：生理食塩水	500 ml	
Rp2	デキサメタゾン(デカドロン，デキサートなど) グラニセトロン(カイトリルなど) 生理食塩水	6.6 mg 1 mg 50 ml	15分
Rp3	シスプラチン(ブリプラチン，ランダなど) 生理食塩水	25 mg/m^2 10 ml	1時間
Rp4	ゲムシタビン塩酸塩(ジェムザール)＋ 生理食塩水	1,000 mg/m^2 100 ml	30分
Rp5	生理食塩水	50 ml	15分

ジメンを示す．

今後の展望

進行胆道癌に対してはGEM＋CDDPが標準治療だが，現在，至適血漿内濃度を保ちやすい速度(1,000 mg/m^2/100分)で静注する定速静注GEMにオキサリプラチンを併用する試験(GEMOX)が行われ，その結果が待たれる．

また，胆管癌においては約8割で過剰発現をしているといわれているWT-1蛋白を抗原として投与し，これに対する抗原特異的な細胞傷害性T細胞を誘導する，というWT-1ワクチン療法についても治療効果が期待され，現在臨床試験が行われている．

分子標的薬に関しても研究が進められている．ASCO2009では，GEMOXにcetuximabを併用する群と併用しない群の比較試験(BINGO)が行われ，中間解析では主要評価項目であった4ヵ月無増悪生存割合が，併用群で61％(95％信頼区間20～70％)，非併用群で44％(同36～83％)であり最終解析結果が待たれる．また，ABC-02試験を行ったグループで，GEM＋CDDPにVEGFRチロシンキナーゼ阻害薬のcediranibを併用する群と併用しない群を比較するABC-03試験が行われている．

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