厚生労働科学研究費補助金

がん臨床研究事業

切除不能胆道がんに対する治療法の確立に関する研究

平成22年度　総括研究報告書

研究者代表　奥坂　拓志

平成23（2011）年３月

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研究者代表者　奥坂　拓志　国立がん研究センター中央病院　副科長

研究要旨：胆道がんは我が国のがん死亡数の第6位を占めており、また切除不能胆道がんの予後はきわめて不良であるため、より有効な非手術療法の開発が求められている。新しい抗がん剤であるS-1は切除不能胆道がん患者に対する治療薬として期待されており、臨床試験を行いその治療成績を明らかにする必要がある。本研究班では「進行胆道がんを対象としたゲムシタビン＋S-1併用療法とS-1単剤療法のランダム化第II相試験」を進め、登録を完了した。さらに「切除不能・再発胆道癌を対象としたゲムシタビン+CDDP+WT1ペプチドワクチン併用化学免疫療法とゲムシタビン+CDDP治療の第I/II相試験」の登録を開始した。

A．研究目的

切除不能胆道がん患者の予後はきわめて不良であり、その生存期間を向上するためには新しい有効な治療法の確立が必要である。S-1は本邦で開発された新しい抗がん剤であり、切除不能胆道がんに対しても高い奏効率が報告されている。本研究班では、まずS-1の二次治療薬としての有効性と安全性を評価するために、「ゲムシタビン耐性胆道がんに対するS-1の第Ⅱ相試験」を実施した。さらにS-1の一次治療薬としての有用性を検討するために、「進行胆道がんを対象としたゲムシタビン＋S-1併用療法とS-1単剤療法のランダム化第II相試験」を開始した。この試験により有用性が期待できるレジメンを慎重に選択したのちに第Ⅲ相試験を実施して、切除不能胆道がんに対する標準治療法を確立する。また、本研究班では国内外で開発が期待されているWT1ペプチドワクチンを用いた臨床試験も開始し、本疾患に対する有効性と安全性を評価する。

B．研究方法

（1）「進行胆道がんを対象としたゲムシタビン＋S-1併用療法とS-1単剤療法のランダム化第II相試験」について：

［研究形式］多施設共同のランダム化第Ⅱ相試験、プライマリーエンドポイントは1年生存割合。

［対象症例］切除不能胆道がんの未治療例、PS 0または1、骨髄・肝・腎などの主要臓器機能が保持され、十分な説明後に本人より文書で同意の得られた症例。

［症例の登録］JCOGデータセンターによる中央登録方式とする。

［治療内容］S-1単独療法群ではS-1をday 1-28に連日経口投与する。これを６週毎に原疾患の悪化または毒性のため中止するまで継続する。S-1とゲムシタビンの併用療法群ではゲムシタビンをday 1，8に静注投与し、S-1はday 1-14に連日経口投与する。これを３週毎に原疾患の悪化ま

たは毒性のため中止するまで継続する。
［予定症例数］症例数100例、症例集積期間2年を予定。
［研究の第三者的監視］JCOGに所属する研究班は共同で、Peer reviewと外部委員審査を併用した第三者的監視機構としての各種委員会を組織し、科学性と倫理性の確保に努めている。本研究も、JCOGのプロトコール審査委員会、効果・安全性評価委員会、監査委員会、などによる第三者的監視を受けることを通じて、科学性と倫理性の確保に努める。
(2)「切除不能・再発胆道癌を対象としたゲムシタビン+CDDP+WT1ペプチドワクチン併用化学免疫療法とゲムシタビン+CDDP治療の第I/II相試験」について：
［研究形式］多施設共同の第Ⅰ相/ランダム化第Ⅱ相試験、プライマリーエンドポイントは1年生存割合。
［対象症例］切除不能胆道がんの未治療例、PS 0または1、骨髄・肝・腎などの主要臓器機能が保持され、十分な説明後に本人より文書で同意の得られた症例。
［症例の登録］NPO日本臨床研究支援ユニットによる中央登録方式とする。
［治療内容］3週1コースとしてゲムシタビン、CDDPをday1，day8に投与し，day15は休薬する。WT1ペプチドワクチン群はWT1ペプチドワクチンをゲムシタビン、CDDPと同日に投与する。なお，CDDPは治療開始から最大24週まで、ゲムシタビンとWT1ペプチドワクチンはプロトコール治療中止基準に該当するまで治療を継続する。
［予定症例数］106例（第I相6例、第II相100例）、症例集積期間2年を予定。
倫理面への配慮
参加患者の安全性確保については、適格条件やプロトコール治療の中止変更規準を厳しく設けており、試験参加による不利益は最小化される。また、「臨床研究に関する倫理指針」およびヘルシンキ宣言などの国際的倫理原則を遵守する。

C．研究結果
（1）「S-1単独療法とS-1とゲムシタビンの併用療法とのランダム化第Ⅱ相試験」は、登録期間2年を予定したが、1年3ヶ月で登録を完了した。これまでのところ試験中止とすべき重篤な有害反応の報告は得られていない。現在追跡調査期間中であり最終解析後、次期第Ⅲ相試験の試験治療群を決定する予定である。
（2）「ゲムシタビン+CDDP+WT1ペプチドワクチン併用化学免疫療法とゲムシタビン+CDDP治療の第I/II相試験」は、平成23年1月にIRB承認を受け、2月より症例登録を開始した。3月7日現在、同意が5例より得られ、うちHLAの適合した3例で治療が開始されている。

D．考察
我が国における胆道がん死亡数は増加傾向にあり、悪性腫瘍死亡数の第６位となっている。切除不能胆道がんに対しては、ゲムシタビンを中心とする化学療法が行われているが、その治療成績は生存期間中央値が8か月前後ときわめて不良であり、より有効な治療法の開発が切望されている。最近、本邦で開発された経口抗がん剤であるS-1が切除不能胆道がんに対し優れた抗腫瘍効果を示すことが明らかにされ、胆道がんへの適応拡大が承認された。
本研究班ではS-1の切除不能胆道がんに対する位置づけを明らかにするため、最初に「ゲムシタビン耐性胆道がんに対するS-1の第Ⅱ相試験」を実施したが、期待奏効割合を下回り、本剤の一次治療薬としての位置づけを明らかにする臨床試

験が必要と考えられた。そこでこの試験に引き続き、「進行胆道がんを対象としたゲムシタビン＋S-1併用療法とS-1単剤療法のランダム化第II相試験」を開始した。この試験は一次治療薬としてS-1を用いる場合にゲムシタビンと併用して用いるのがよいのか、あるいはS-1単独で用いて、二次治療としてゲムシタビンを用いるのがよいのかを慎重に判断することを目的としている。このランダム化第II相試験で選択されたレジメンを用いて第III相試験を実施する計画である。最近、ゲムシタビンとシスプラチン併用療法の延命効果が報告されており、来るべき第III相試験ではこのゲムシタビンとシスプラチン併用療法がコントロールレジメンとなるものと考えられている。

胆道がんは依然予後不良な疾患であり、新しい視点からの治療開発戦略も必要と考えられる。我々は別の研究班でWT1ペプチドワクチンの臨床試験を行ってきており、その知見をいかして本疾患に対する本免疫療法の有効性と安全性を検討することとした。胆道がんは我が国には患者が多いにも関わらず新薬開発が遅れており、このような研究を実施することにより本疾患への関心が高まり、新薬治験の導入が促進することも期待したい。

E．結論

「進行胆道がんを対象としたゲムシタビン＋S-1併用療法とS-1単剤療法のランダム化第II相試験（JCOG 0805）」の登録が終了し現在追跡調査中である。「切除不能・再発胆道癌を対象としたゲムシタビン+CDDP+WT1ペプチドワクチン併用化学免疫療法とゲムシタビン+CDDP治療の第I/II相試験」を開始し、これまでのところ登録が順調に進められている。

F．健康危険情報

なし。

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H．知的財産権の出願・登録状況

1．特許取得

なし

2．実用新案登録

なし

3．その他

なし

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
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切除不能胆道がんに対する治療法の確立に関する研究

平成２２年度　研究成果の刊行物・別刷

研究代表者　奥坂　拓志
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中森　正二
井岡　達也
井口　東郎
船越　顕博

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Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan

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BACKGROUND: A British randomised study of gemcitabine plus cisplatin (GC) combination showed promising results in biliary tract cancer (BTC) patients. In our study, we evaluated the efficacy and safety of this combination compared with gemcitabine alone (G) in Japanese BTC patients.

METHODS: Overall, 84 advanced BTC patients were randomised to either cisplatin 25 mg m^{-2} plus gemcitabine 1000 mg m^{-2} on days 1, 8 of a 21-day cycle (GC-arm), or single-agent gemcitabine 1000 mg m^{-2} on days 1, 8 and 15 of a 28-day cycle (G-arm). Treatments were repeated for at least 12 weeks until disease progression or unacceptable toxicity occurred, up to a maximum of 48 weeks.

RESULTS: A total of 83 patients were included in the analysis. For the GC and G-arms, respectively, the 1-year survival rate was 39.0 *vs* 31.0%, median survival time 11.2 *vs* 7.7 months, median progression-free survival time 5.8 *vs* 3.7 months and overall response rate 19.5 *vs* 11.9%. The most common grade 3 or 4 toxicities (GC-arm/G-arm) were neutropenia (56.1%/38.1%), thrombocytopenia (39.0%/7.1%), leukopenia (29.3%/19.0%), haemoglobin decrease (36.6%/16.7%) and γ-GTP increase (29.3%/35.7%).

CONCLUSIONS: Gemcitabine plus cisplatin combination therapy was found to be effective and well tolerated, suggesting that it could also be a standard regimen for Japanese patients.

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Although biliary tract cancer (BTC) is a rare type of cancer throughout the world, it is more prevalent in East Asia and Latin America than in other countries (Matsuda and Marugame, 2007; Randi *et al*, 2009). According to 'Demographic Statistics in Japan (2009)' (compiled by the Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour, and Welfare (MHLW)), the number of deaths due to BTC was 17 311 in 2007, making this cancer the sixth leading cause of cancer death in Japan.

Despite great progress in diagnostic imaging, most cases of BTC are diagnosed as advanced and inoperable. Even if the tumour is not locally advanced, the primary tumour site is often contiguous with vital organs such as the liver, pancreas, or duodenum, or with major vessels such as the portal vein or hepatic artery. This anatomical peculiarity precludes resection of tumours in many cases. Furthermore, even if curative-intent surgical resection is performed, the cancer often relapses due to its invasive nature and its anatomical characteristics.

Systemic chemotherapy is usually indicated for patients with unresectable, advanced BTC or for those who have relapsed after operation; however, no standard treatment has yet been established for such patients. Gemcitabine hydrochloride is a deoxycytidine derivative that inhibits DNA elongation through intracellular phosphorylation of ribonucleotide reductase. In Japan, a single-arm Phase II study in patients with unresectable BTC confirmed that gemcitabine monotherapy had moderate efficacy and manageable toxicity, both of which were comparable with approved treatments for other cancers (Okusaka *et al*, 2006).

As gemcitabine had also been found to exhibit synergistic effects on cytotoxic activity *in vitro* and *in vivo* when combined with cisplatin (Peters *et al*, 1995; Bergman *et al*, 1996), clinical studies were conducted in various cancers with this combination. Results from these studies eventually led to use of the gemcitabine plus cisplatin (GC) combination as one of the standard treatments for non-small cell lung cancer and bladder cancer.

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The combination of GC has also been studied by many researchers for the treatment of BTC (Park *et al*, 2006; Eckel and Schmid, 2007; Pasetto *et al*, 2007; Lee *et al*, 2008). So far, the largest randomised Phase III study has been the recent UK ABC-02 study, in which the efficacy and safety of gemcitabine 1000 mg m^{-2} alone *vs* the combination of gemcitabine 1000 mg m^{-2} plus cisplatin 25 mg m^{-2} was evaluated by British research groups (Cancer Research UK and University College London). That study was initiated as a randomised phase II study with gemcitabine alone *vs* GC (UK ABC-01 study) and then was expanded to a phase III study (ABC-02 study) (Valle *et al*, 2009a, b).

Our study was planned to follow-up on an earlier study of gemcitabine monotherapy conducted in Japanese BTC patients (Okusaka *et al*, 2006). Given the encouraging results from the UK ABC-01 study, we conducted this study to (1) evaluate both gemcitabine monotherapy and the GC combination in Japanese BTC patients, and (2) determine whether benefits similar to those observed in the UK study could be obtained for the combination regimen.

The primary objective of the study was to compare the 1-year survival rate in patients with BTC who received one of these two therapies. The secondary objectives included response rate, progression-free survival (PFS) and assessment of safety.

MATERIALS AND METHODS

Study design

This was a multicentre, randomised phase II study to evaluate the efficacy and safety of GC combination compared with single-agent gemcitabine in chemotherapy-naive patients with locally advanced or metastatic BTC. Patients were randomised to either single-agent gemcitabine 1000 mg m^{-2} on days 1, 8 and 15 of a 28-day cycle (G-arm) or cisplatin 25 mg m^{-2} followed by gemcitabine 1000 mg m^{-2} on days 1, 8 of a 21-day cycle (GC-arm). Randomisation was stratified by primary site (gallbladder cancer or other BTC) and the presence or absence of primary tumour.

Eligibility criteria

Eligible patients met the following criteria: histologically confirmed unresectable locally advanced or metastatic cancer of the biliary tract; no history of earlier chemotherapy; performance status of 0 or 1; a life expectancy of at least 3 months; at least 20 years of age at the time of study entry; adequate function of major organs (haemoglobin $\geqslant$10 g per 100 ml, white blood cells $\geqslant$3000/mm^3, neutrophils $\geqslant$1500/mm^3, platelets $\geqslant$100 000/mm3, AST/ALT/ALP $\leqslant$3 times upper limit of normal (ULN), total bilirubin $\leqslant$2 times ULN, $\leqslant$3 times ULN for patients with obstructive jaundice or metastases to the liver, serum creatinine $\leqslant$1.5 times ULN, creatinine clearance or 24-h creatinine clearance $\geqslant$45 ml min^{-1}).

This study followed the ethical principles that have their origins in the Declaration of Helsinki, and was conducted in accordance with the protocol, the 'ordinance on Good Clinical Practice' and related regulations. Written informed consent was obtained from all patients who were considered eligible for participation in this study before enrolment. The Efficacy and Safety Evaluation Committee, an independent review board, was consulted if any efficacy and safety issues arose in the study.

Study treatment

The assigned treatment was given for a minimum of 12 weeks (at least four cycles in the GC-arm and three cycles in the G-arm) and continued to a maximum of 48 weeks (up to 16 cycles in the GC-arm and up to 12 cycles in the G-arm), unless disease progression (PD) was evident, an intolerable adverse event occurred or the patient was required to withdraw from the study.

Efficacy and safety assessment

All patients who received at least 1 dose of the study drug were included in the efficacy and safety assessment. Response rate was evaluated according to the Response Evaluation Criteria in Solid Tumors. Evaluation of tumours after patient randomisation was performed every 6 weeks until PD. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0).

Statistical design and analysis

The sample size was calculated by the selection method of Simon (Simon *et al*, 1985), which is based on the proposition that GC combination therapy is selected if the 1-year survival rate for the GC-arm is higher than that for the gemcitabine arm. We assumed a 1-year survival rate of 25% for the G-arm and 35% for GC-arm (Okusaka *et al*, 2006; Park *et al*, 2006). With these assumptions, 30 patients per arm were needed to appropriately select the combination therapy with a probability of $\geqslant$80%. To optimise safety and efficacy information, the sample size was set to 42 patients per arm.

The Kaplan–Meier method was used to estimate 1-year survival (primary outcome), PFS and 6-month PFS rates (secondary outcomes) for each treatment arm; 95% confidence intervals (CIs) were calculated. A Cox proportional hazards model was used to calculate the hazard ratio, 95% CI and its two-tailed *P*-value. Fisher's exact test was used to compare the patient characteristics, response and disease control rates, and toxicities between the two treatment arms. The exact CIs were calculated based on binomial distributions.

RESULTS

Patients

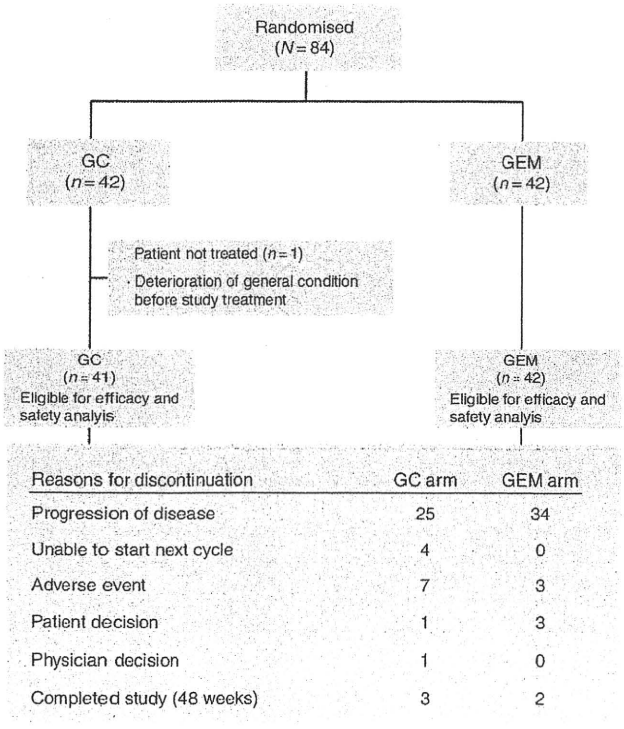
This study was carried out from September 2006 to October 2008 at nine study centres in Japan. Eighty-four patients were randomised to either gemcitabine monotherapy (G-arm) or GC combination (GC-arm). One patient assigned to the GC-arm was not treated because the general condition of the patient deteriorated before study treatment. All of the remaining 83 patients, 41 in the GC-arm and 42 in the G-arm, received at least 1 dose of study treatment. Efficacy and safety were evaluated for each of these 83 patients (Figure 1). Demographic variables (Table 1) were well balanced between the two treatment arms, except for patients with ampullary carcinoma (4 in GC-arm, 0 in G-arm).

Drug exposure and duration of the treatments

A total of 247 (median 6.0) and 203 (median 4.0) cycles were administered in the GC-arm and G-arm, respectively. Relative dose intensities were 78.9% for gemcitabine and 79.0% for cisplatin in the GC-arm, and 87.4% for gemcitabine in the G-arm. Three patients in the GC-arm and two patients in the G-arm completed 48 weeks treatment.

Efficacy

A total of 83 patients were evaluable for tumour response according to the protocol, 41 in the GC-arm and 42 in the G-arm. No complete tumour responses were observed. In total, eight patients in the GC-arm had a partial response (PR) compared with five patients in the G-arm (PR 19.5 *vs* 11.9%). In addition,



Reasons for discontinuation	GC arm	GEM arm
Progression of disease	25	34
Unable to start next cycle	4	0
Adverse event	7	3
Patient decision	1	3
Physician decision	1	0
Completed study (48 weeks)	3	2

Figure 1 CONSORT diagram. Disposition of patients. GC = gemcitabine–cisplatin combination; GEM = gemcitabine alone.

20 patients had stable disease in the GC-arm *vs* 16 patients in the G-arm (SD 48.8 *vs* 38.1%). The disease control rate (CR + PR + SD) was 68.3% (95% CI: 51.9, 81.9) *vs* 50.0% (95% CI: 34.2, 65.8) in favour of the combination therapy. The 1-year survival rate (39.0 *vs* 31.0%), median survival time (11.2 months *vs* 7.7 months) and median PFS (5.8 months *vs* 3.7 months) were better for the GC-arm *vs* G-arm (Figure 2). The hazard ratio between the GC and G-arms was 0.69 (95% CI: 0.42, 1.13) for overall survival (OS) and 0.66 (95% CI: 0.41, 1.05) for PFS (Table 2).

As shown in Table 3, the prognosis for patients with gallbladder cancer was worse than that for patients with non-gallbladder cancer; however, the median survival times were longer with the GC combination in gallbladder cancer patients (9.1 months *vs* 6.7 months), as well as in patients with non-gallbladder cancer (13.0 months *vs* 8.0 months). The prognosis for patients with primary tumours was worse than that for patients without primary tumours; however, the GC therapy showed longer median survival time in both patient subgroups (9.4 months *vs* 7.4 months in the patients with primary tumours, 16.1 months *vs* 12.7 months in the patients without primary tumours).

Safety

All adverse events observed in this study were predictable and manageable based on the safety profile of GC. As shown in Table 4, the most common grade 3 or higher adverse events (≥25%) were neutropenia (56.1%), thrombocytopenia (39.0%), haemoglobin decrease (36.6%), RBC decrease (34.1%), leukopenia (29.3%) and γ-GTP increase (29.3%) in the GC-arm, and neutropenia (38.1%) and γ-GTP increase (35.7%) in the G-arm. The incidence of haematotoxicity was higher in the GC-arm; grade 3 or more serious C-reactive protein increase was detected only in the monotherapy arm.

Table 1 Patient characteristics

Characteristic	GC (*N* = 41) *n* (%)	GEM (*N* = 42) *n* (%)	*P*-value
Gender			
Male	18 (43.9)	21 (50.0)	0.662
Female	23 (56.1)	21 (50.0)	
Age (year)			
Median	65.0	66.5	0.0812[a]
Range	43–80	49–78	
PS			
0	34 (82.9)	28 (66.7)	0.129
1	7 (17.1)	14 (33.3)	
Primary tumour sites			
Extrahepatic bile duct	8 (19.5)	11 (26.2)	0.239
Intrahepatic bile duct	14 (34.1)	14 (33.3)	
Gallbladder	15 (36.6)	17 (40.5)	
Ampulla	4 (9.8)	0 (0.0)	
Metastatic sites			
Liver	22 (53.7)	20 (47.6)	0.663
Regional lymph nodes	23 (56.1)	28 (66.7)	0.372
Distant lymph nodes	19 (46.3)	18 (42.9)	0.827
Lung	8 (19.5)	7 (16.7)	0.782
Peritoneum	7 (17.1)	7 (16.7)	1.000
Bone	0 (0.0)	1 (2.4)	1.000
Others	3 (7.3)	3 (7.1)	1.000
Initial onset or recurrence			
Initial onset	30 (73.2)	32 (76.2)	0.804
Recurrence after surgery	11 (26.8)	10 (23.8)	
Histological type			
Adenocarcinoma	39 (95.1)	41 (97.6)	0.616
Adenosquamous cancer	2 (4.9)	1 (2.4)	
Disease stage (gallbladder cancer, extrahepatic bile duct cancer, ampulla cancer)			
IIA	0 (0.0)	0 (0.0)	1.000
IIB	3 (7.3)[b]	2 (4.8)[b]	
III	2 (4.9)	2 (4.8)	
IV	16 (39.0)	17 (40.5)	
Recurrence after surgery	6 (14.6)	7 (16.7)	
Disease stage (intrahepatic bile duct cancer)			
II	0 (0.0)	1 (2.4)[b]	0.389
IIIA	0 (0.0)	1 (2.4)	
IIIB	0 (0.0)	0 (0.0)	
IIIC	0 (0.0)	2 (4.8)	
IV	9 (22.0)	7 (16.7)	
Recurrence after surgery	5 (12.2)	3 (7.1)	
Biliary drainage			
No	25 (61.0)	24 (57.1)	0.824
Yes	16 (39.0)	18 (42.9)	
Previous therapy			
No	30 (73.2)	28 (66.7)	0.855
Surgery	11 (26.8)	12 (28.6)	
Radiotherapy	0 (0.0)	1 (2.4)	
Surgery and radiotherapy	0 (0.0)	1 (2.4)	

Abbreviations: GC = gemcitabine and cisplatin; GEM = gemcitabine; PS = performance status. [a]*t*-test. [b]Patients were diagnosed as having unresectable disease with marked regional node metastases involving the proper hepatic artery and/or main portal vein.

There were no treatment related deaths. Most of the patients recovered from the above adverse events by reducing or discontinuing the study treatment.

Post-study chemotherapy

Thirty patients in the GC-arm received post-study chemotherapy including S-1, tegaful/gimeracil/oteracil potassium (19 patients), gemcitabine (10 patients) and tegaful/uracil (1 patient). In the G-arm, 33 patients received post-study chemotherapy including S-1 (20 patients), gemcitabine (11 patients), cisplatin/fluorouracil (1 patient) and doxorubicin/tegaful/uracil (1 patient).

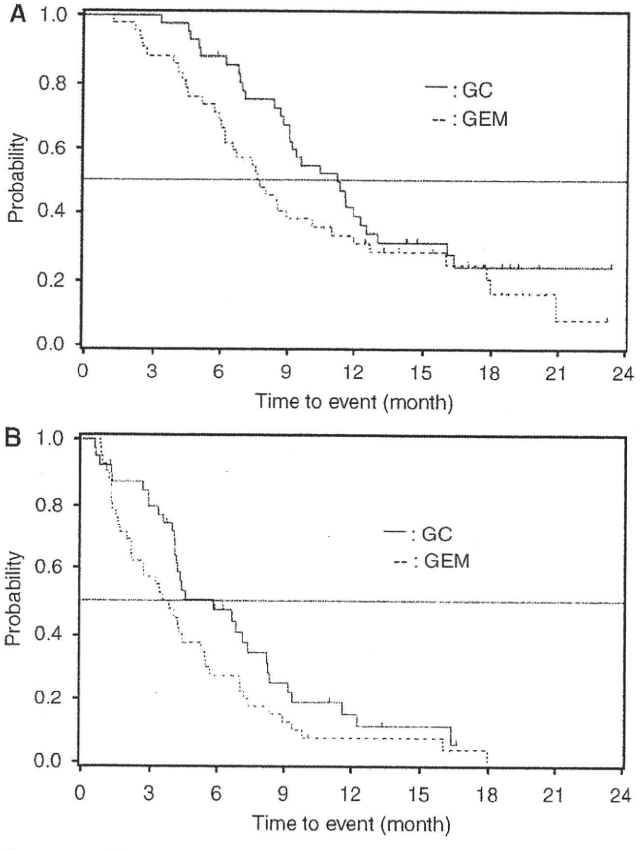


Figure 2 Kaplan–Meier curve of overall survival and progression-free survival. (**A**) Overall survival. (**B**) Progression-free survival. GC = gemcitabine–cisplatin combination; GEM = gemcitabine alone; CI = confidence interval.

DISCUSSION

Although this study (BT22 study) showed that gemcitabine monotherapy and the GC combination were both active in Japanese patients with advanced BTC, a superior benefit was obtained with the combination treatment. In the GC/G-arms, the 1-year survival rate was 39.0%/31.0%, median survival time was 11.2/7.7 months and median PFS time was 5.8/3.7 months (Table 2).

The UK ABC-02 study, which was conducted with the same dose and regimen as this study (Valle *et al*, 2009b), showed a similar benefit for the GC combination. The respective median survival/PFS times in that study were 11.7/8.5 months in their GC-arm, and 8.2/6.5 months in their G-arm.

The hazard ratios reported in the ABC-02 study for OS (0.68, 95% CI: 0.53, 0.86) and PFS (0.70, 95% CI: 0.56, 0.88) compared well with the respective values from our study: 0.69 (95% CI: 0.42, 1.13) and 0.66 (95% CI: 0.41, 1.05). As the number of patients was based on Simon's selection method (Simon *et al*, 1985), this study was not designed to compare and identify statistical significant differences between the two treatment arms. These hazard ratios

Table 3 Overall survival time by stratification factor

Median survival time (months) (95% CI)	GC (*N* = 41)	GEM (*N* = 42)	*P*-value
Tumour site			
Gallbladder	9.1 (6.9, 11.6)	6.7 (4.2, 11.0)	0.675
Non-gallbladder	13.0 (9.2, ***)	8.0 (6.1, 16.0)	0.110
Primary tumour			
Presence of primary tumour	9.4 (8.7, 11.6)	7.4 (5.9, 8.5)	0.253
Absence of primary tumour	16.1 (12.3, ***)	12.7 (6.5, ***)	0.389

Abbreviations: GC = gemcitabine and cisplatin; GEM = gemcitabine; CI = confidence interval. ***denotes upper limits are not available.

Table 2 Summary of time-to-event end points: overall response and survival

	GC (*N* = 41) *n* (%)	GEM (*N* = 42) *n* (%)	*P*-value
Overall response rate			
Complete response (CR)	0 (0.0)	0 (0.0)	
Partial response (PR)	8 (19.5)	5 (11.9)	
Stable disease (SD)	20 (48.8)	16 (38.1)	
Progressive disease (PD)	9 (22.0)	17 (40.5)	
Not evaluable (NE)	4 (9.8)	4 (9.5)	
Response rate (95% CI)	19.5% (8.8, 34.9)	11.9% (4.0, 25.6)	0.380
Disease control rate (CR+PR+SD) (95% CI)	68.3% (51.9, 81.9)	50.0% (34.2, 65.8)	0.119
Overall survival			
1-year survival rate (95% CI)	39.0% (23.7, 54.4)	31.0% (17.0, 44.9)	
Median survival time (95% CI)	11.2 months (9.1, 12.5)	7.7 months (6.1, 11.0)	
Hazard ratio (95% CI)	0.69 (95% CI: 0.42, 1.13)		0.139
Progression-free survival (PFS)			
Median PFS (95% CI)	5.8 months (4.1, 8.2)	3.7 months (2.1, 5.3)	
Hazard ratio (95% CI)	0.66 (95%CI: 0.41, 1.05)		0.077
6-Months PFS rate (95% CI)	47.4% (31.4, 63.4)	27.7% (14.0, 41.5)	

Abbreviations: GC = gemcitabine and cisplatin; GEM = gemcitabine; CI = confidence interval.

Table 4 Summary of maximum toxicity grades[a] (incidence ⩾30%)

	GC (*N*=41)			GEM (*N*=42)			
	Maximum toxicity grade			Maximum toxicity grade			
Events	**Grade 3 (%)**	**Grade 4 (%)**	**All grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All grades (%)**	***P*-value**
Haematological							
WBC count decreased	29.3	0	87.8	19.0	0	69.0	0.061
Haemoglobin decreased	26.8	9.8	85.4	9.5	7.1	85.7	1.000
Neutrophil count decreased	39.0	17.1	82.9	28.6	9.5	69.0	0.200
Platelet count decreased	26.8	12.2	80.5	4.8	2.4	76.2	0.791
RBC decreased	34.1	0	75.6	14.3	0	78.6	0.798
Haematocrit decreased	4.9	0	58.5	0	0	54.8	0.826
Non-haematological							
Anorexia	0	0	80.5	4.8	0	61.9	0.090
Nausea	0	0	68.3	0	0	42.9	0.027
Fatigue	0	0	58.5	2.4	0	50.0	0.511
AST increased	17.1	0	53.7	14.3	2.4	52.4	1.000
ALT increased	24.4	0	51.2	16.7	0	52.4	1.000
Vomiting	0	0	48.8	0	0	23.8	0.023
GGT increased	29.3	0	46.3	31.0	4.8	50.0	0.827
Pyrexia	0	0	43.9	4.8	0	57.1	0.190
LDH increased	0	0	36.6	0	0	35.7	1.000
Constipation	0	0	36.6	0	0	33.3	0.820
ALP increased	7.3	0	31.7	16.7	0	40.5	0.495
Weight decreased	0	0	31.7	0	0	31.0	1.000
Diarrhoea	2.4	0	31.7	0	0	26.2	0.634
Blood sodium decreased	17.1	0	31.7	9.5	0	19.0	0.214
C-reactive protein increased	0	0	26.8	7.1	0	52.4	0.025

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GC = gemcitabine and cisplatin; GEM = gemcitabine; GGT = γ-glutamyltransferase; LDH = lactate dehydrogenase; RBC = red blood cell; WBC = white blood cell. [a]Events were graded according to CTCAE v3.0.

strongly suggest that the GC combination has superior benefit compared with single-agent gemcitabine, even though there were no statistical significant differences in survival and PFS between the two arms in our study.

Although there have been many single-arm Phase II studies of the GC combination for BTC (Thongprasert *et al*, 2005; Kim *et al*, 2006; Charoentum *et al*, 2007; Meyerhardt *et al*, 2008; Valle *et al*, 2009a), these results have never been distilled to one fixed dose and regimen of GC. Many previous studies of GC combination reported relatively higher response rates, but with more serious treatment-related adverse events (Thongprasert *et al*, 2005; Kim *et al*, 2006; Charoentum *et al*, 2007; Meyerhardt *et al*, 2008). In the phase II study conducted by Thongprasert *et al* (2005), 17.85% of the patients who were treated with the GC combination required dose reduction, and in another Phase II study recently conducted by Meyerhardt *et al* (2008), dose reductions and study withdrawals were required for 50% of the patients who received the combination therapy. In our study, we also observed more frequent adverse events with the doublet (Table 4). However, as shown in Figure 1, only seven patients (17%) discontinued from the study because of adverse events and four patients (9.7%) required dose adjustments in the GC-arm.

Overall, the toxicity observed in this study was manageable. Although interstitial pneumonia was detected in one patient from each of the arms, both patients recovered with appropriate treatment. One grade 3 renal failure and one grade 2 peripheral neuropathy were observed in GC-arm, in line with similar events seen in previous studies of the GC combination (Thongprasert *et al*, 2005; Kim *et al*, 2006; Charoentum *et al*, 2007; Meyerhardt *et al*, 2008; Valle *et al*, 2009a). It is to be noted that despite the higher incidence of haematotoxicity in patients receiving the combination therapy, drug-caused myelosuppression did not result in febrile neutropenia or bleeding. Grade 3 or greater increases in C-reactive protein were observed only in the gemcitabine monotherapy-arm, also suggesting that the combination therapy did not increase neutropenic infections.

In this study, we stratified patients into those with gallbladder cancer and those with other BTCs. Gallbladder cancer has been reported to have a different biological behaviour (Kim *et al*, 2006; Doval *et al*, 2004; Jarnagin *et al*, 2006); furthermore, a pooled analysis by Eckel and Schmid (2007) revealed a higher response rate to chemotherapy and shorter OS for gallbladder cancer compared with other BTCs. As shown in Table 3, patients with gallbladder cancer showed worse survival than patients with other BTCs, this being consistent with previous reports (Eckel and Schmid, 2007; Wagner *et al*, 2009). It is important to note that median survival times were longer with the GC combination in patients with gallbladder cancer (9.1 months *vs* 6.7 months), as well as in patients with non-gallbladder cancer (13.0 months *vs* 8.0 months), suggesting that the combination therapy has greater benefit than monotherapy in gallbladder cancer and other BTC patients.

Another stratification factor used for this study was the presence or absence of a primary tumour, not a commonly used stratification factor in clinical trials for advanced BTC. Locally advanced or metastatic cancer, the stratification factor used in the UK ABC-01 and UK ABC-02 studies, is more commonly used, as both of these have been shown to affect OS in advanced BTC (Park *et al*, 2009). However, considering the importance of surgical resection of the primary tumour, we decided to use this as a stratification factor for patients in this study. As shown in Table 3, patients with primary tumours showed remarkably worse survival than patients without primary tumours. However, because of the limited number of patients in our subanalyses, the results should be viewed with caution, and the usefulness of this prognostic factor should be evaluated in future studies. We will continue our efforts

in collaboration with the UK ABC-02 study group to identify prognostic factors in a larger population, which may significantly affect clinical studies in BTC.

Despite the heterogeneous nature of BTC and the ethnic differences reported for this tumour type (Goodman and Yamamoto, 2007; Aljiffry *et al*, 2009), the outcomes from this study showed striking similarity with the large-scale phase III study (UK ABC-02) results. This suggests that cisplatin 25 mg m^{-2} plus gemcitabine 1000 mg m^{-2} on days 1 and 8 of a 21-day cycle would be beneficial in the treatment of advanced BTC.

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Conflict of interest

TO, KN, NM, SO, SK and JF have received honoraria, and YN, MK, JF and SN are employed by Eli Lilly Japan.

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