in plasma and plasma ultrafiltrate taken from Western patients administered 2-h oxaliplatin infusion of 130 mg/m^2 were previously reported, and the values were measured by ICP-MS (Inductively Coupled Plasma Mass Spectrometry), which we used in our study. These values of the C_{max}, AUC, terminal $t_{1/2}$ and CL were very similar to our data in the patients given the 130 mg/m^2 dose (10).

The elimination of platinum occurs mainly in urine rather than in feces (10). In this study, mean urinary excretion of oxaliplatin for 24 h was 33.9% of the level 2 administered dose (130 mg/m^2). This value was almost identical to the value of 35.9% in Western patients given a dose of 135–150 mg/m^2 (11).

Graham et al. (10) reported that limited platinum accumulation was observed in plasma and blood cells, but not in plasma ultrafiltrate. Our data on the platinum accumulation in Japanese patients was the same as that in Western patients, except for the data on the plasma ultrafiltrate. However, the degree of accumulation was less than 2-fold in both studies.

In conclusion, the worldwide standard dose of 130 mg/m^2/q3w for oxaliplatin monotherapy is also acceptable for treating

Table 3. Pharmacokinetic parameters of oxaliplatin

	90 mg/m^2 (n = 3)	130 mg/m^2 (n = 6)	Graham et al. (13)
Plasma platinum			
C_{max} (ng/ml)	2263.3 ± 145.7	3220.0 ± 177.9	3200 ± 340
PK model	2-CBM*	2-CBM*	-
$t_{1/2}\alpha$(h)**	7.6 ± 4.8	7.8 ± 3.3	-
$t_{1/2}\beta$(h)**	308.2 ± 29.6	259.8 ± 26.9	239 ± 54.4
CL (l/h/m^2)	0.37 ± 0.03	0.52 ± 0.13	-
V_{ss} (l/m^2)	110.3 ± 13.7	127.2 ± 19.4	-
AUC (μg.h/ml)	244.3 ± 19.7	258.3 ± 58.3	207 ± 60.9
Plasma ultrafilterable platinum			
C_{max} (ng/ml)	963.3 ± 101.3	1450.0 ± 166.5	1210 ± 100
PK model	3-CBM***	3-CBM***	3-CBM***
$t_{1/2}\alpha$(h)**	0.18 ± 0.01	0.17 ± 0.02	0.28 ± 0.06
$t_{1/2}\beta$(h)**	14.0 ± 1.0	14.5 ± 1.0	16.3 ± 2.90
$t_{1/2}\gamma$(h)**	246.7 ± 32.2	258.9 ± 61.4	273 ± 19.0
CL (l/h/m^2)	11.6 ± 1.4	11.7 ± 1.4	10.1 ± 3.07
V_{ss} (l/m^2)	1433.4 ± 196.3	1612.7 ± 360.5	582 ± 261
AUC (μg.h/m/l)	7.9 ± 0.9	11.3 ± 1.5	11.9 ± 4.60

Mean ± SD.
*Two-compartment Baysian model.
**Half-life.
***Three-compartment Baysian model.
CL, clearance; V_{ss}, volume of distribution at steady state; AUC, area under the plasma concentration–time curve

Table 4. The trough values of oxaliplatin

	90 mg/m^2 (n = 3)	130 mg/m^2 (n = 3)
Plasma platinum (ng/ml)		
1st cycle	131.7 ± 21.5	158.0 ± 14.2
2nd cycle	184.7 ± 19.9	235.3 ± 47.6
Plasma ultrafilterable platinum (ng/ml)		
1st cycle	1.5 ± 0.2	2.3 ± 0.2
2nd cycle	2.1 ± 0.2	3.2 ± 0.3
Blood cell platinum (ng/ml)		
1st cycle	483.7 ± 94.2	606.3 ± 73.3
2nd cycle	742 ± 46.2	951.0 ± 83.6

Mean ± SD.

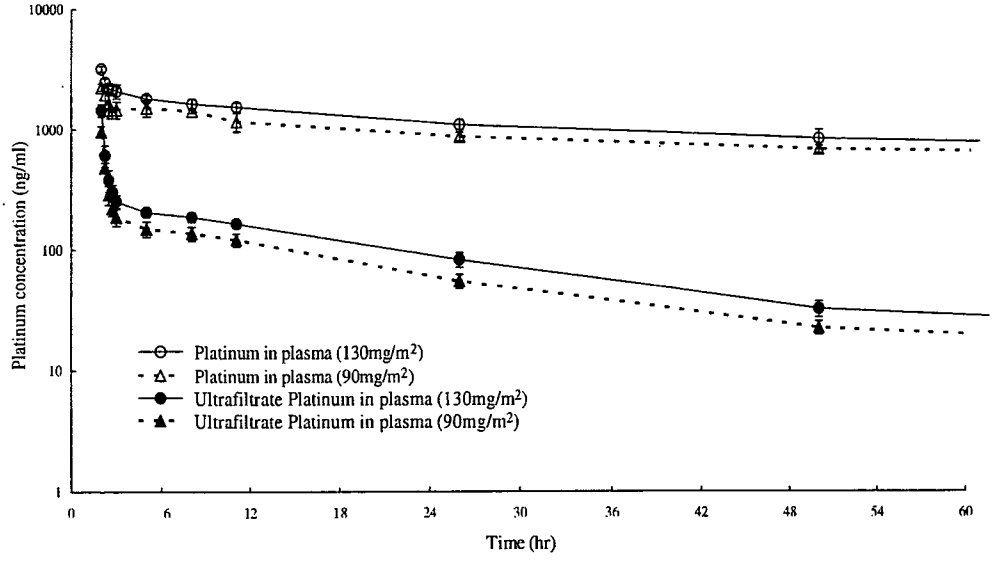

Figure 1. Mean plasma concentration–time curve for oxaliplatin.

Japanese patients, with only mild myelosuppression, neurotoxicity and gastrointestinal toxicities. No racial difference was suggested in the pharmacokinetics of oxaliplatin. A phase II study of oxaliplatin monotherapy and a phase I/II study of the combination of oxaliplatin with fluorouracil plus leucovorin have finished in Japanese patients with metastatic colorectal cancer. Further large clinical trials on oxaliplatin are warranted to evaluate the toxicity profiles and the clinical antitumor activity in Japanese patients.

Acknowledgments

We are grateful to Drs Y. Sakata, Y. Sasaki, I. Hyodo and T. Yamao for their kind advice, and many other participants of this study. We also thank S. Sugimoto, M. Matsuo, N. Sekine and H. Ogawa for their assistance in data management. This study was supported by the Yakult Honsha Co., Ltd., Tokyo, Japan.

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S-1の基礎と臨床
胃癌

胃癌に対するCPT-11+S-1併用（IRIS）療法
—S-1 2週投薬法—

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〔*Jpn J Cancer Chemother* 33(*Suppl* I): 75-78, *June*, 2006〕

Irinotecan Plus Oral S-1 in Patients with Advanced Gastric Cancer—Biweekly IRIS Regimen: Yoshito Komatsu[*1,3], Satoshi Yuki[*1,3], Takuto Miyagishima[*2,3] and Masahiro Asaka[*1,3] (*[1]*Third Dept. of Internal Medicine, Hokkaido University School of Medicine, *[2]*Dept. of Internal Medicine, Kushiro Rosai Hospital, *[3]*Hokkaido Gastrointestinal Cancer Study Group (HGCSG))*

Summary

We reported the results of phase I study with CPT-11 and S-1 (IRIS) in advanced gastric cancer (AGC) patients at ASCO 2002. Now I present an outline of this phase I/II trial. A combined treatment of IRIS (CPT-11+S-1) was given to the AGC patients who had not received prior chemotherapy. S-1 was orally administered twice a day for 14 days, and CPT-11 was administered as a 90-minute intravenous infusion on days 1 and 15. This schedule was repeated every 4 weeks. Fifteen patients were registered in this phase I study and 9 patients were added in this phase II study. Non-hematological toxicities were almost classified as grade 2 or lower, except for grade 3 nausea and grade 3 dermatitis of level 2.

These adverse events were manageable by administering anti-emetic drugs and a drug rest. As for hematological toxicities, grade 4 neutropenia occurred with one patient at level 1 and level 2 in phase I. And grade 4 neutropenia occurred with four patients at level 2 in phase II. However, they recovered after the drug rest, and we could continue the administration based on the standard dose modifications. These side effects were tolerable, and the overall response rate was 54.2%. MST of this regimen is 581 days. The IRIS treatment is effective and tolerable for outpatient treatments. **Key words**: Advanced gastric cancer, CPT-11, S-1, IRIS, HGCSG, **Corresponding author**: Yoshito Komatsu, Third Department of Internal Medicine, Hokkaido University School of Medicine, 7 West, 15 North, Kita-ku, Sapporo 060-8638, Japan

要旨 はじめに: われわれはHokkaido Gastrointestinal Cancer Study Group (HGCSG) において，手術不能または術後再発胃癌に対し，外来でも投与可能で有効な併用療法の開発のために2001年初めよりCPT-11+S-1併用(IRIS)療法(S-1 2週・CPT-11のbiweekly投与法)の臨床第I/II相試験を計画し実施した。対象・方法: この併用療法の適切な投与量を決定するための臨床第I相試験ではCPT-11は100 mg/m²から25 mg/m²ずつ150 mg/m²まで増量する3段階のレベルを設定し，day 1, 15に90分で点滴静注するものとした。S-1はカプセル剤であるため，体表面積ごとの通常投与法(80, 100, 120 mg/2×)で固定し，day 1, 14までの2週間の内服とした。結果: 臨床第I相試験の結果よりCPT-11の推奨投与量はレベル2の125 mg/m²に決定した。この推奨投与量にて早期臨床第II相試験へ移行し，さらに9例を追加して効果と安全性を確認した。臨床第I/II相試験としての奏効率は54.2%，全24例のMSTは581日と良好な結果であった。考察: IRIS療法(2週間法)は，進行胃癌に対する第一選択療法として外来でも安全に投与可能であり，将来の標準的化学療法の候補の一つとなり得るものと思われる。

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0385-0684/06/¥500/論文/JCLS

はじめに

手術不能または術後再発胃癌患者に対する化学療法は多岐を極め，様々な研究がなされてきたにもかかわらず，いまだ標準的治療といえる治療は報告されていない。胃癌患者に対する化学療法の有効性はいくつかの研究によってその生存期間の延長への寄与が証明されてはいるが十分なものではなく，必ずしも胃癌患者の quality of life (QOL) へ貢献できているとはいい難い。したがって胃癌に対する化学療法の進歩には有効な新薬の開発や併用療法の開発が必須であった。そんななかで，本邦では新しいフッ化ピリミジン系経口抗癌剤 S-1 が登場した。臨床成績も臨床第II相試験結果が報告[1]され奏効率は49%と単剤の抗癌剤としては驚くべき効果であった。また irinotecan (CPT-11) も日本で開発された薬剤であり大腸癌に有効な薬剤であることが報告されていた。また胃癌に対しても単剤で 20%[2]，併用療法では CDDP との組み合わせで約 50%の奏効率が報告[3]され，胃癌に対しても有用な薬剤として知られていた。当時，欧米を中心に大腸癌の初回治療例に対する CPT-11+5-FU+Leucovorin (IFL) の有用性が確認され[4]，本邦においても進行大腸癌に対して CPT-11+5-FU 併用療法の臨床試験が終了しており[5]，CPT-11 と 5-FU 併用での有効性は確認されていた。したがって S-1 と CPT-11 の併用療法は消化器癌に対して非常に有効であることが予想された。また S-1 が経口剤であるという点からも，外来での効果的な化学療法が可能となることも予想された。そこでわれわれは手術不能または術後再発胃癌に対し，外来でも投与可能でかつ有効な併用療法の開発のために 2001 年初めより CPT-11+S-1 (IRIS) 併用療法の臨床試験を計画し開始した。

I. 対象・方法

対象は組織学的に胃癌が証明された転移を伴う手術不能または術後再発胃癌患者で，年齢は 20～75 歳，PS が良好で，前治療歴のない書面による同意の得られた患者を対象とした。当時この併用療法の報告は皆無であり，われわれが最初の実施グループであったため，この併用療法の適切な投与量を決定するために臨床第 I/II相試験を計画した。本来新規薬剤である S-1 を増量するべきであったが，S-1 はカプセル剤であり体表面積から算出した量の投与は困難であるため，現在の投与法である体表面積ごとで固定した。また先発薬剤である CPT-11 は，単剤における 100 mg/m²の毎週投与，150 mg/m²の 2 週間ごとの安全性が証明されているため[6,7]，100 mg/m²から 25 mg/m²ずつ 150 mg/m²まで増量する 3 段階のレベルを設定し，2 週間おきに 90 分で点滴静注するものとした。当初 S-1 の投与期間について熟考したが，副作用の強いとされる CPT-11 との併用療法であることや，外来化学療法であることを考慮し，単剤であれば強い副作用が生じない 2 週間の内服とした (Fig. 1)。

II. 結　果

2001 年 2 月から 2002 年 12 月の間に，当科を中心に組織された Hokkaido Gastrointestinal Cancer Study Group (HGCSG) の参加施設において 24 例が登録された。全投与サイクル数は 91 サイクル，平均は 5.9 サイクルであった。また 2 コース以上の完遂率は 92%であった。臨床第 I 相試験ではレベル 1(6 例)，レベル 2(6 例)，レベル 3 (3 例) がエントリーした。非血液毒性に関しては grade 2 の下痢がレベル 2 で 1 例発現した。血液毒性では grade 4 の好中球減少がレベル 1 で 1 例，レベル 2 で 2 例に出現した。レベル 1 で CR 1 例を含む 3 例，レベル 2 で 3 例，レベル 3 で 2 例が PR となり全体では奏効率 53% (8/15) であった[8]。結果としてレベル 3 でも DLT に到達しなかったが，効果安全委員会での相談によりそれ以上のレベルアップはしないこととなった。したがって本併用療法の推奨投与量は規定により CPT-11 が 150

Body surface area (BSA: m²)	Initial dosage of S-1 (mg/day, as the tegafur dose)	Level	CPT-11 (mg/m²)
<1.25	40×2	1	100
1.25-<1.50	50×2	2	125
1.50≦	60×2	3	150

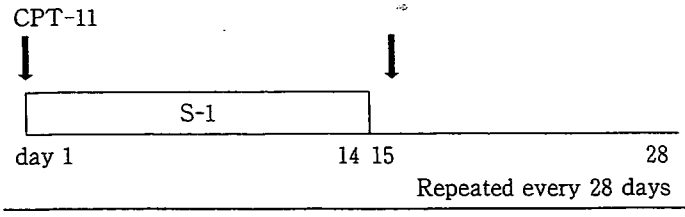

Fig. 1 Treatment schedule of S-1+CPT-11

Table 1 Toxicities

Level	1				2				3			
CPT-11	100 mg/m²				125 mg/m²				150 mg/m²			
No	6				15				3			
grade	1	2	3	4	1	2	3	4	1	2	3	4
Neutrocyte	1	2	2	1	3	1	3	6	1	1	1	0
Platelets	0	0	0	0	3	1	0	0	1	0	0	0
Hemoglobin	1	2	1	0	5	4	1	0	1	0	0	0
Diarrhea	1	0	0	0	5	2	1	0	2	0	0	0
Nausea/vomiting	1	1	1	0	4	1	4	0	1	0	0	0
Dermatitis	0	0	0	0	1	0	1	0	1	0	0	0
Alopecia	0	0	0	0	0	1	0	0	0	0	0	0

Table 2 Response

	No	CR	PR	NC	PD	RR (%)
Overall	24	1	12	10	1	54.2

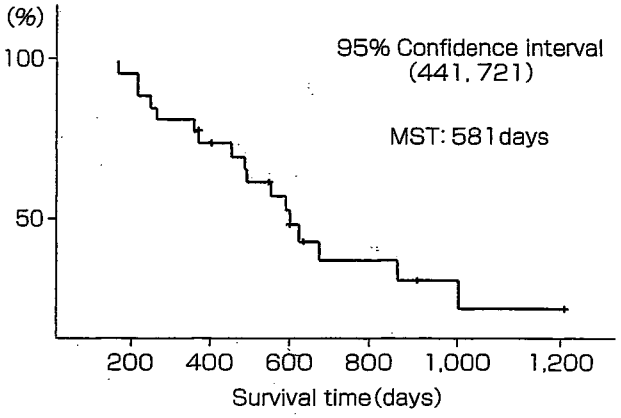

Fig. 2 Overall survival

mg/m²となるところであったが，日本におけるCPT-11単剤での隔週投与の推奨投与量が150 mg/m²であり，レベル1でも非常に重篤な骨髄抑制が1例出現したことを十分に考慮し，その後の臨床第II相試験に参加する施設の医師の意見を取り入れ，効果安全委員会との相談の上，レベル2の125 mg/m²に決定した。この推奨投与量にて早期臨床第II相試験へ移行し，さらに9例を追加して効果と安全性を確認した。全部でgrade 4の好中球減少患者が4例となったが，いずれも減量休薬基準に従って治療を継続することができた(Table 1)。臨床第I/II相試験としての奏効率は54.2% (13/24) と良好な結果であった(Table 2)。本治療で注目すべきは臨床第I/II相試験とはいえ，全24例のMSTは581日 (Fig. 2) と非常に素晴らしい結果であった[9]。

III. 考　察

このIRIS療法の組み合わせが優れていることの理論的背景としては以下の報告がある。S-1はDPD阻害剤CDHPを含有しており，DPD高発現症例に有効であることが報告されている[10]。しかし高TS発現症例には，5-FU系製剤は効果が低いことも以前から報告されており，S-1単剤ではあまり効果が期待できない可能性がある。しかし，高TS発現症例はI型DNA topoisomerase (topo-I) の発現量も高く相関性があることが報告されているため[11]，TS高発現症例に対してtopo-I阻害剤であるCPT-11を使用するとTSが下がることも報告されており，その有効性が期待されている。したがってCPT-11とS-1は，両薬剤の弱点を補い合うことが期待されるため，併用療法として最適な組み合わせであると考えている。S-1の投与日数が違うレジメンも報告されているが，単剤のdose intensityを越えてしまうようなものは，CPT-11との併用でさらに毒性が増強する可能性があり，一般に広く普及するには危険であると思われる。また投与間隔もわれわれのものはbiweeklyであり2週ごとの来院で治療が可能であるが，この間隔は日本の保険制度や日常の通院回数からいっても，1週ごとあるいは3週ごとといったものよりも受け入れやすい間隔であるものと考えられる。また他の併用療法も多数報告されているが，S-1+CDDPそしてCPT-11+CDDPの併用療法などは高い奏効率が報告されてはいるが，CDDPの投与に伴いハイドレーションが必要であり毎コースごとに入院を必要とする。しかし，われわれの併用療法は入院を必要としないため，すべて通院で治療を継続できるという意味でQOLの改善にも寄与できると考えられる。また奏効率自体は54%であるが，本療法のもう一つの注目点としては腫瘍制御率 (CR+PR+SD) が95.8%と非常に有効であることが予想される。以上より，副作用が耐用可能であり外来治療が可能でQOLの改善に寄与し高い奏効率を示し，そして臨床第I/II相試験ではあるがMST 581日という素晴らしい生存（サバイバルベネフィット）を得たことから，このわれわれの

CPT-11＋S-1併用療法（2週間法）は，進行胃癌に対する第一選択療法として，将来の標準的化学療法の候補の一つとなり得るものと思われる。2005年JCOG消化器内科グループにて実施されていた5-FU単独療法とS-1単独療法，CPT-11＋CDDP併用療法の臨床第III相比較試験（JCOG 9912）への最終登録も終了し現在フォローアップ期間となっているが，2006年末あるいは2007年早々にはその結果が報告され，本邦における進行胃癌治療に対する新標準的治療が決定する。それ以外にもS-1を標準的治療と想定した企業主導の大きな臨床第III相試験（S-1＋CPT-11，S-1＋CDDPなど）もすでに登録が終了していることから，2007年には本邦の胃癌の新標準的治療法が決定しそうであり，その報告が待たれる。

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Gastric Cancer (2006) 9: 36–43
DOI 10.1007/s10120-005-0355-2

Original article

Phase I-II study of biweekly paclitaxel administration with fixed-dose-rate cisplatin in advanced gastric cancer

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Abstract

Background. **Both paclitaxel (TXL) and cisplatin (CDDP) show efficacy against gastric cancer. The aim of this phase I-II study was to determine the maximum tolerated dose (MTD) and to evaluate the toxicity and efficacy of combination chemotherapy with these two agents.**

Methods. **Nineteen patients entered the phase I part of the study, and 21 patients entered the phase II part. TXL infusions were administered on days 1 and 15, with a fixed 30 mg/m² dose of CDDP.**

Results. **In the phase I part of the study, we determined dose level 5, which represented a TXL dose of 180 mg/m², with CDDP 30 mg/m², to be the MTD. The recommended dose (RD) was level 4, with a TXL dose of 160 mg/m² with CDDP, 30 mg/m². In the phase II part of the study, the response rate was 25.0%; five patients had a partial response, seven had stable disease, 6 had progressive disease, and 2 were not evaluable. Grade 3 or 4 neutropenia was the most common adverse event and occurred in 65% of the patients. During treatment, 25% of the patients received granulocyte colony-stimulating factor, but febrile neutropenia was not shown in any of the patients. Major nonhematological toxicities were nausea/vomiting, anorexia, fatigue, alopecia, and sensory neuropathy. Adverse reactions of grade 3 or 4 were shown by two patients, one with anorexia (5%) and the other with sensory neuropathy (5%).**

Conclusion. **The RD was determined to be TXL 140 mg/m², with CDDP 30 mg/m².**

Key words Paclitaxel · Cisplatin · Gastric cancer

Offprint requests to: K. Yamaguchi
Received: August 3, 2005 / Accepted: December 8, 2005

Introduction

Although various chemotherapy regimens have been reported for use in patients with gastric cancer, the median prognosis for survival in patients with chemotherapy for advanced gastric cancer remains less than 9–12 months [1]. Given these conditions, we sought to develop a new active combination therapy regimen to prolong median survival, while also seeking a regimen that would be suitable for outpatient clinical use, in order to decrease time of hospitalization.

Paclitaxel (TXL) is thought to be an effective drug for gastric cancer, with reported response rates ranging from 20% to 28% in single-agent phase II studies [2–4]. In two of these studies, median survival times were 234 and 340 days, respectively, although more than 50% of the patients had previously received chemotherapy [3,4]. Thus, it appears that TXL may prolong survival in gastric cancer patients.

Cisplatin (CDDP) is an active chemotherapeutic agent against gastric cancer. Treatment regimens including CDDP have shown high response rates [5–7]. CDDP has demonstrated synergism with variety of cytotoxic drugs, and synergism between TXL and CDDP has been established and reported [8,9].

Therapy combining CDDP and TXL has been reported in various regimens [10–14]. Most of these regimens consisted of administering 60 to 80 mg/m² of CDDP. However, patients receiving more than 50 mg/m² of CDDP may suffer nausea and vomiting [15], and they would then need hydration to prevent CDDP renal toxicity. Thus, more than 50 mg/m² of CDDP is not suitable for outpatient clinical use.

We sought to confirm the efficacy and toxicity of combination therapy with TXL and a fixed-dose administration of 30 mg/m² CDDP.

A biweekly regimen has been proposed to increase the dose intensity of TXL and to improve the ease of adoption for outpatient use. For this reason, we planned to evaluate biweekly TXL with a 30 mg/m² fixed-dose CDDP regimen.

Table 1. Dose levels (phase I)

Level	Paclitaxel (mg/m²)	Cisplatin (mg/m²)	No. of patients
1	100	30	3
2	120	30	4
3	140	30	3
4	160	30	6
5	180	30	3

Patients and methods

Patients

The objectives of this study were to determine the maximum tolerated dose (MTD) and to evaluate the toxicity and the preliminary activity of the above combination.

The criteria for eligibility included the following: (1) prior chemotherapy regimen completed 4 weeks before entry; (2) adequate bone marrow function (white blood cell [WBC] count ≥ 4000/mm³, platelet count ≥ 100 000/mm³, hemoglobin ≥ 9.0 g/dl), adequate liver function (serum bilirubin level ≤ 1.5 mg/dl and serum transaminase level ≤ twice the upper limit of the normal range; if hepatic metastasis had been documented, then serum transaminase level ≤ three times normal range) and adequate renal function (serum creatinine level ≤ 1.5 mg/dl, 24-h creatinine clearance ≥ 60 ml/min), normal electrocardiogram (ECG); (3) Eastern Clinical Oncology Group (ECOG) performance status (PS) of 2 or less; (4) age between 20 and 79 years; (5) absence of any other serious medical conditions; (6) absence of any other active malignancy; (7) life expectancy greater than 2 months.

Written informed consent was obtained from all patients prior to study entry. This study was approved by the Ethics Committees at the participating sites.

Treatment regimens

TXL infusions were administered on days 1 and 15, with a fixed 30 mg/m² dose of CDDP. To prevent hypersensitivity reactions, all patients were premedicated with 20 mg of dexamethasone intravenously, 50 mg of diphenhydramine orally, and 50 mg of ranitidine intravenously 1 h before TXL infusion. The starting dose of TXL was 100 mg/m², and it was intravenously infused within 1 to 3 h before 1- to 3-h infusion of CDDP. The TXL dose then consisted of increments of 20 mg/m² until severe or life-threatening toxicities were observed. Patients were administered this regimen once every 2 weeks unless disease progress or intolerable toxicity was observed. If WBC counts fell below 3000/mm³ or platelet counts fell below 75 000/mm³; or if grade 3 or 4 nonhematological toxicity occurred; or if body temperature rose over 38 °C or PS was over 3 immediately before administration, treatment was postponed.

For the first cycle of this therapy, the dose-limiting toxicity (DLT) was defined as National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3 or 4 neutropenia with infection or fever; or thrombocytopenia of 25 000/mm³ or less; or NCI-CTC grade 3 or 4 nonhematological toxicity, except for anorexia, nausea/vomiting, and alopecia. Treatment delay DLT was defined as treatment delay of 1 to 2 weeks for reasons of toxicity. The treatment dose at each level is summarized in Table 1.

At least three patients were treated at each dose level. If none of the first three patients experienced DLT, escalation to the next TXL level was permitted. If one of three patients experienced a DLT, three other patients were enrolled at this level. Among the resulting six patients, if one or two experienced DLT, escalation was permitted; if more than two patients experienced DLT, that level was deemed the MTD. If two or three of three patients experienced DLT, that level was also considered the MTD. After confirmation of the MTD, the recommended dose (RD) for a phase II study was defined as one level below the MTD.

In the phase II part of the study, patients were not eligible if they had received chemotherapy that involved more than one regimen or contained platinum derivatives and/or taxane derivatives, or if they had suffered more than grade 2 peripheral neuropathy in prior chemotherapy. If the following adverse events had been observed during the previous treatment, the dose for the following treatment would be reduced by one level: hematological toxicity of at least grade 4; nonhematological toxicity of at least grade 3; peripheral neuropathy of at least grade 2. For other inclusion and exclusion criteria, treatment schedules were the same as for the phase I part of the study.

Response evaluation and toxicity

Patients were evaluated before entry into this study, to determine the extent of disease, by physical examination, chest X-ray, computed tomographic (CT) scan of

Table 2. Patient characteristics

	Phase I (n = 19)	Phase II (n = 20)
Median age, years (range)	62 (50–78)	60 (45–76)
Male/Female	17/2	16/4
EOCG PS		
0	6	11
1	13	8
2	0	1
Histological type		
Intestinal type	11	7
Diffuse type	8	13
Primary surgical resection	8	12
Prior chemotherapy (including adjuvant)		
Yes	14	16
No	5	4
Prior chemotherapy regimen		
S-1	13	11
S-1 + CDDP	1	1
S1 + CPT-11	0	1
MTX + 5FU	0	1
MMC (i.a.)	0	1
UFT	0	1

chest and abdomen, and endoscopic examination of the upper gastrointestinal tract. Complete blood cell counts, liver function test, renal function test, and urinalysis were assessed at least once every 2 weeks during treatment. CT scans were repeated as necessary to evaluate measurable lesions.

NCI-CTC version 2 was applied to evaluate adverse drug reactions during the first and second cycles of treatment. The response criteria of the Japanese Research Society for Gastric Cancer [16] and the Response Evaluation Criteria in Solid Tumors Group criteria [17] were used to evaluate objective tumor response. In brief, the response criteria of the Japanese Research Society for Gastric Cancer define complete response (CR) as the complete disappearance of all measurable and evaluable lesions for a minimum of 4 weeks. A partial response (PR) is defined as a 50% or greater reduction in the sum of the products of the longest diameters of measurable lesions for a minimum of 4 weeks. Stable disease (SD) is defined as failure to observe a PR or CR and progressive disease for at least 4 weeks. Progressive disease (PD) is defined as a 25% or greater increase in the sum of the products of the longest perpendicular diameters of measurable lesions, or the appearance of new lesions. The response to primary tumors was assessed by the same Japanese criteria, based on roentgenographic and endoscopic findings.

Statistical considerations

The phase II part of this study was designed to test the null hypothesis that the true response probability is less than the not clinically significant level of 20%. The response rate was expected to be 40%. The probability of accepting the treatment with response probability (20%) is $P = 0.05$. The probability of rejecting the treatment with response probability (40%) is $P = 0.10$. Therefore, the sample size was 50 patients with $P = 0.05$; $P = 0.1$. After the enrollment of 20 patients, we planned to evaluate the toxicity, with the main point of the evaluation being suitability for an outpatient setting.

In the phase II part of the study, survival was calculated, from the date of treatment initiation, by the Kaplan-Meier method.

Results

Patient characteristics

In the phase I part of the study, 19 patients entered this trial between September 2001 and May 2003. Patient characteristics are summarized in Table 2. All 19 patients were evaluated for toxicity, and 13 patients exhibited measurable lesions evaluable for response. The median age of the patients was 62 years (range, 50 to 78 years). Ten patients had gastric cancer as a primary lesion, while 8 patients had undergone surgical resection for primary gastric cancer. Six patients had an

ECOG PS of 0, and 13 patients had an ECOG PS of 1. Histologically, 11 patients had intestinal-type adenocarcinoma, and 8 patients had the diffuse type. All patients had metastatic lesions. The metastatic sites were the lung in 1 patient, the liver in 6, the lymph nodes in 7, and the peritoneum in 8. Fourteen patients had received prior chemotherapy; 13 patients had received S-1 alone, and 1 had received S-1 plus CDDP. All prior chemotherapy was completed 4 or more weeks before entry: 5 patients were prior chemotherapy-naïve.

In the phase II part of the study, 21 patients entered between July 2003 and May 2004. One patient refused to receive the treatment regimen after the first administration, and this patient was excluded from analysis. Characteristics of the phase II patients are summarized in Table 2. In an interim analysis of safety, our group decided to cease continuing this part of the study because of the high proportion of dose reductions and treatments delays within the first cycle.

The median age of the patients was 60 years (range, 45 to 76 years). Eight patients had gastric cancer as a primary lesion, and 12 patients had undergone surgical resection for primary gastric cancer. Eleven patients had an ECOG PS of 0, 8 had an ECOG PS of 1, and 1 had an ECOG PS of 2. Histologically, 7 patients had intestinal-type adenocarcinoma, and 13 had the diffuse type. All patients had metastatic lesions. The metastatic sites were the lymph node in 15 patients; liver in 15; peritoneum in 4; and bone, ovary, and esophagus in 1 patient each. Sixteen patients had received chemotherapy; 11 had received T-S1 alone, 1 had received S-1 plus irinotecan (CPT-11), 1 had received T-S1 plus CDDP, 1 had received methotrexate plus 5-fluorouracil (5FU), 1 had received uracil/tegafur (UFT), and 1 had received mitomycin C as intraarterial chemotherapy for liver metastasis. All prior chemotherapy was completed 4 or more weeks before entry: 4 patients were chemotherapy-naive (3 had had adjuvant chemotherapy only).

Determination of MTD in the phase I part of the study

In the phase I part of the study, all patients were evaluable for adverse reactions, and 18 patients completed one or more cycles of treatment. At levels 1 and 2, one patient exhibited grade 4 neutropenia during the first cycle. At level 4, one of the first three patients exhibited grade 4 febrile neutropenia, while three other patients were enrolled to this level. At level 5, one patient exhibited grade 3 motor neuropathy, while one exhibited grade 3 myalgia with grade 3 dyspnea. We therefore determined dose level 5, which represented a TXL dose of 180 mg/m^2, with CDDP 30 mg/m^2, to be the MTD, and the RD to be level 4, with a TXL dose of 160 mg/m^2 plus CDDP 30 mg/m^2. The most common adverse reactions in the phase I part of the study are summarized in Table 3.

Safety

All 20 patients enrolled in the phase II part of the study were assessable for safety, and received a total of 48.5 cycles. The median number of cycles was 2. In these 20 patients, treatment delay, dose reduction, or both, occurred in 6, 2, and 3 patients, respectively, within 1 cycle (a total of 11 patients could not be administered the RD) and all of the dose reductions and treatment delays were due to a decrease in the WBC count or delay in recovery of neutropenia.

For the phase II part of the study, the overall numbers of hematological and nonhematological toxicities are listed in Table 3. Grade 3 or 4 neutropenia was the most common adverse event and occurred in 65% of the patients. During treatment, 25% of the patients received granulocyte colony-stimulating factor (G-CSF), but no patients had febrile neutropenia. Major nonhematological toxicities were nausea/vomiting, anorexia, fatigue, alopecia, and sensory neuropathy. Two patients showed adverse reactions of grade 3 or 4. One patient had anorexia (5%) and other had sensory neuropathy (5%). None of the patients had an increase of serum creatinine of more than grade 3 within two cycles.

Efficacy

In the phase I part of the study, 4 of the 19 patients showed no measurable lesions, while 2 patients discontinued the protocol due to DLT, all 6 being determined as not evaluable (NE). The remaining 13 patients were evaluable for efficacy. This group included 6 patients with a PR, 4 with SD, and 3 with PD, yielding a response rate of 46.1% in the evaluable patients (6 of 13 patients). The response rates in the evaluable patients with intestinal-type adenocarcinoma and diffuse-type adenocarcinoma were 50% (4/8) and 40% (2/5), respectively. The response rate of the evaluable patients with prior chemotherapy was 55.5% (5/9). The response rate of the evaluable patients without prior chemotherapy was 25% (1/4). (Table 4).

In the phase II part of the study, a total of 20 patients were evaluated to determine the response rate at the RD. The overall response rate was 25.0%; 5 patients had PR as the best response, 7 had SD, 6 had PD, and 2 were defined as not evaluable (NE). Subgroup analysis by pathological type for the 20 patients showed that the response rates were 28.6% (2/7) for those with intestinal-type adenocarcinoma who were evaluable and 23.1% (3/13) for evaluable patients with the diffuse type. Subgroup analysis by prior chemotherapy for the 20 patients showed that the response rate was 25.0%

Table 3. Adverse reactions

Toxic effects	Grade (no. of patients) 1	2	3	4	Grades 3 and 4 (%)
Phase I					
Hematological					
Leucopenia	3	6	4	0	21.1
Neutropenia	4	1	4	5	47.4
Anemia	6	8	0	0	0
Thrombocytopenia	1	0	0	0	0
Nonhematological					
Fever (noninfection)	2	1	0	0	0
Nausea/Vomiting	4	1	0	0	0
Constipation	0	2	0	0	0
Anorexia	4	2	0	0	0
Fatigue	1	2	0	0	0
Rash	1	0	0	0	0
Alopecia	2	1	—	—	0
Dyspnea	0	0	1	0	5.3
Neuropathy — motor	1	0	1	0	5.3
Neuropathy — sensory	2	0	0	0	0
Myalgia	2	0	1	0	5.3
Arthralgia	2	0	0	0	0
Earache	1	0	0	0	0
Heartburn	1	0	0	0	0
Phase II					
Hematological					
Leucopenia	4	5	5	1	30.0
Neutropenia	1	1	6	7	65.0
Anemia	3	7	3	0	15.0
Thrombocytopenia	0	0	1	0	5.0
Nonhematological					
Fever (noninfection)	2	0	0	0	0
Nausea/Vomiting	4	4	0	0	0
Diarrhea	3	0	0	0	0
Constipation	0	1	0	0	0
Stomatitis	2	0	0	0	0
Anorexia	3	2	1	0	5.0
Fatigue	4	3	0	0	0
Rash	1	1	0	0	0
Alopecia	8	3	—	—	0
Neuropathy — motor	3	0	0	0	0
Neuropathy — sensory	5	1	1	0	5.0
Myalgia	4	0	0	0	0
Arthralgia	4	0	0	0	0
Hypotension	1	0	0	0	0
Creatinine	1	1	0	0	0

(4/16) for the evaluable patients with prior chemotherapy and 25.0% (1/4) for those without prior chemotherapy (Table 4).

The median survival time was 272 days and the 1-year survival rate was 30% (Fig. 1).

Determination of MTD in the phase II part of the study

As mentioned above, 11 of the 20 patients (55% of the study subjects) could not be administered the RD on a biweekly schedule, so we decided on a new RD, as one level under the previous RD, which represented a TXL dose of 140 mg/m^2 with CDDP 30 mg/m^2. At this new RD, we are now performing a new phase II study to check the efficacy and feasibility of the regimen.

Discussion

This study determined the MTD and RD, and also evaluated the preliminary toxicity and activity of TXL with fixed doses of CDDP for advanced gastric cancer. TXL is a promising drug for use in combination with

Table 4. Overall response to treatment

Patients	*n*	CR	PR	SD	PD	NE	RR (%)[a]
Phase I							
Overall	19	0	6	4	3	6	46.1
Level							
1	3	0	2	1	0	0	66.6
2	4	0	2	2	0	0	50.0
3	3	0	1	0	1	1	50.0
4	6	0	1	1	2	2	25.0
5	3	0	0	0	0	3	0.0
Histological type							
Intestinal	11	0	4	2	2	3	50.0
Diffuse	7	0	2	2	1	2	40.0
Prior chemotherapy							
No	4	0	1	2	1	0	25.0
Yes	15	0	5	2	2	6	55.5
Phase II							
Overall	20	0	5	7	6	2	25.0
Histological type							
Intestinal	7	0	2	2	3	0	28.6
Diffuse	13	0	3	5	3	2	23.1
Prior chemotherapy							
No	4	0	1	1	2	0	25.0
Yes	16	0	4	7	4	2	25.0

[a]Response rate (RR) was estimated in evaluable patients only

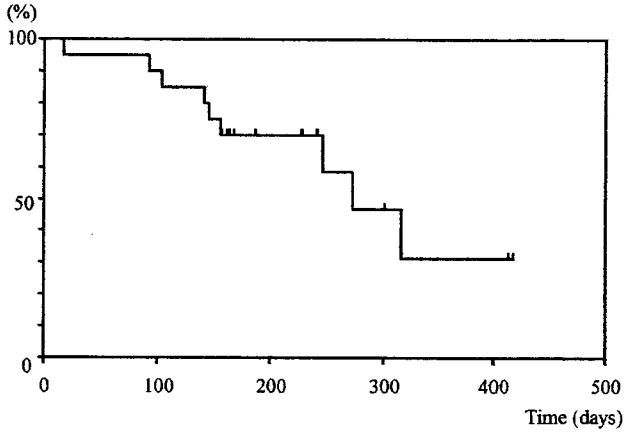

Fig. 1. Overall survival in the phase II part of the study

CDDP, and there are several phase I reports of combination chemotherapy involving TXL and CDDP. These two drugs have different mechanisms of action and fewer overlapping toxicities than other combinations, without neurotoxicity. When TXL was administered in combination with CDDP, treatment was sometimes delayed by the resulting neurotoxicity. When TXL administered every 3 weeks was compared to weekly TXL, the toxicity profile was better tolerated (particularly with respect to myelosuppression and peripheral neuropathy) at the weekly schedule, while efficacy remained almost unchanged [18]. This result shows that divided administrations of TXL may reduce myelosuppression and neuropathy. Before increasing dose-intensity, we conducted a phase I-II study of a biweekly regimen, because a biweekly schedule is suitable for outpatient clinical use.

Although high doses of CDDP are often used in combination regimens for gastric cancer, the efficacy of high doses is still open for debate. We set the CDDP dose at 30 mg/m^2 (because high doses of CDDP add to toxicity and require intense intravenous hydration to protect against renal toxicity) to develop a well-tolerated regimen ideal for the outpatient setting.

Compared with the results of a phase II study of a TXL-containing regimen for gastric cancer, our regimen was less toxic than the triweekly administration of TXL in that study [2–4], with especially notable reduced risks of grade 3 or 4 neutropenia and neuropathy. Kornek et al. [19] reported a phase II study of a biweekly schedule of combination therapy with 160 mg/m^2 TXL and 60 mg/m^2 CDDP in gastric cancer patients, with the regimen being based on a phase I study reported by van der Gaast et al. [14]. In the report of Kornek et al. [19], the regimen offered promising therapeutic activity, with a response rate of 44% among patients who had not undergone previous chemotherapy. However, 73% of their patients received G-CSF, 49% suffered peripheral neuropathy, and 11% developed documented infections though G-CSF support. An important issue in patients with gastric cancer is toxicity. The elderly or poor-performance-status patient population cannot tolerate aggressive regimens such as those with high doses of CDDP. Because treatment regimens with G-CSF support are still under consideration [20],

we should confirm the safety and the absence of need for G-CSF support treatment.

In the present study, we developed a treatment regimen without fluoropyrimidine for advanced gastric cancer. As most of the regimens that are expected to be first-line therapy contain fluoropyrimidines to prolong survival, treatments for fluoropyrimidine-resistant gastric cancer are necessary as second-line therapy. TXL is a good candidate for this situation because of its lack of cross-resistance to fluoropyrimidine. In the phase II part of the present study, about 75% of the patients had received a fluoropyrimidine-based regimen as first-line therapy. We found a response rate of 25.0% in the phase II part of the study, although more than 50% of the patients could not receive the RD on the biweekly schedule.

In our determination of the new RD, we discussed a dose reduction of the RD in the interim analysis, in which treatment delay and dose reduction had occurred in a total of 11 patients within one cycle on the enrollment of 20 patients in the phase II part of the study. Based on the phase I part of the study, we discussed that we should reduce the dose of TXL and start a new phase II study at the TXL dose of 140 mg/m^2. The outcome will depend on the point of whether efficacy can be observed at dose level one or dose level two (level 1 showed two PRs and one SD, while level 2 showed two PRs and two SDs) and whether these treatments could be continued until disease progression (data not shown) in the phase I part. Our initial concept was to develop a new treatment option which has good feasibility within the outpatient setting.

To determine the optimal RD is sometimes very difficult in a phase I study. The IFL regimen (irinotecan, 5FU, and leucovorin combination regimen) is a good example of such a difficulty. A phase I study of the IFL regimen was first reported by Saltz et al. [21], and after a phase III study [22], this regimen showed a high mortality rate within 60 days, and a new RD was decided upon as a modified IFL regimen. In the light of this example, we decided to decrease the TXL dose to one level below that in the phase I part of the present study.

Finally, we decided to reduce the dose of TXL from 160 mg/m^2 to 140 mg/m^2. We are now conducting a phase II study at the new RD to evaluate the efficacy and long-term feasibility of the regimen, particularly with respect to peripheral neuropathy, a characteristic side effect of TXL administration.

In conclusion, with regard to the TXL-plus-CDDP combination in our study: (1) the recommended dose was determined to be TXL 140 mg/m^2 with CDDP 30 mg/m^2; and (2) we found that this regimen showed modest efficacy and a safe toxicity profile so that it could be offered as a candidate component of standard regimens for treating gastric cancer. We are now performing another phase II study, with the Korea-Japan Collaborative Study Group, to confirm the efficacy and feasibility of TXL 140 mg/m^2 with CDDP 30 mg/m^2.

Acknowledgments We would like to thank Dr. Ryunosuke Kanemaru for his contributions as a committee member of the East Japan Gastric Cancer Treatment Study Group in Japan for evaluating the efficacy and safety of this treatment.

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Cancer Chemother Pharmacol (2006) 57: 647–653
DOI 10.1007/s00280-005-0095-3

ORIGINAL ARTICLE

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Phase II study of single-agent gemcitabine in patients with advanced biliary tract cancer

Received: 11 April 2005 / Accepted: 2 August 2005 / Published online: 2 September 2005

Abstract *Purpose*: This phase II study was conducted to evaluate the efficacy and toxicity of single-agent gemcitabine in patients with advanced or metastatic biliary tract cancer. *Patients and methods*: Gemcitabine 1,000 mg/m^2 was administered as an intravenous 30-min infusion on days 1, 8, and 15 for every 28 days. *Results*: Forty chemonaive patients with a median age of 61 (range 33–73) were enrolled, and all 40 patients were involved in efficacy and safety analyses. Seven (17.5%) achieved partial response; 15 (37.5%) had stable disease; 17 (42.5%) had progressive disease; and 1 (2.5%) was not evaluated. The median survival time was 7.6 months, and the 1-year survival rate was 25.0%. Grade 3/4 neutropenia occurred in 12 patients (30.0%), leukopenia in five patients (12.5%), and anemia in four patients (10.0%). The most common grade 3/4 nonhematologic toxicities were elevated ALT (15.0%) and elevated γ-GTP (12.5%). One patient had grade 4 hemolytic uremic syndrome and recovered after discontinuation of gemcitabine. *Conclusions*: In single-agent therapy, gemcitabine demonstrated moderate efficacy with manageable toxicity in patients with advanced or metastatic biliary tract cancer. Further evaluations are warranted, including the exact impact of gemcitabine on the management of advanced or metastatic biliary tract cancer.

Keywords Biliary tract cancer · Chemotherapy · Clinical trial · Gallbladder cancer · Gemcitabine

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Introduction

The incidence of biliary tract cancer has increased markedly in Japan over the past several decades. In 2002, biliary tract cancer was the sixth leading cause of cancer death in Japan with approximately 16,000 deaths and a mortality rate of 12.5 per 100,000. A continued sharp increase in age-adjusted mortality is predicted over the next 10 years [22, 25, 30].

Of all the treatment modalities for biliary tract cancer, only resection offers the opportunity for cure. However, because of metastases or invasion of the tumor directly into the adjacent liver or the hepatic artery, only a small minority of biliary tract cancer patients are candidates for resection with curative intent. The prognosis for these patients is dismal, and the impact of existing chemotherapy is virtually negligible. Therefore, there is a clear need for new, effective, chemotherapeutic regimens in the management of biliary tract cancer.

Gemcitabine is a novel nucleoside analogue, which requires to be phosphorylated to its active metabolite, gemcitabine triphosphate. Gemcitabine triphosphate competes with deoxycytidine triphosphate for incorporation into DNA, inhibiting DNA synthesis [16]. Gemcitabine has shown broad activity in a variety of tumors and is currently approved for use in non-small-cell lung

cancer and pancreatic cancer in Japan. Based on the results obtained in early phase studies in other locales and the established safety profile of the agent [3, 7, 8, 12, 24, 34, 35, 40], our group has conducted a multicenter, phase II trial of single-agent gemcitabine to investigate the response rate, toxicity, and time-to-event variables (progression-free survival, duration of tumor response, and survival time) in patients with advanced or metastatic biliary tract cancer.

Patients and methods

Eligibility criteria

Enrolled patients had histologically or cytologically confirmed adenocarcinoma of biliary tract, extrahepatic bile duct, gallbladder, or ampulla of Vater. Each patient was required to meet the following eligibility criteria: unresectable biliary tract cancer with at least one bidimensionally measurable tumor; no history of prior chemotherapy; no history of prior antitumor treatment for biliary tract cancer except resection and intraoperative or postoperative adjuvant radiotherapy; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; 20–74 years of age; estimated life expectancy ≥2 months; adequate renal function (creatinine ≤ upper limit of normal [ULN]); adequate liver function (bilirubin ≤ 2 times ULN and aspartate/alanine transaminases [AST/ALT] ≤ 2.5 times ULN); adequate bone marrow reserve (white blood cells ≤ 4,000/mm^3, neutrophils ≥2,000/mm^3, platelets ≥100,000/mm^3, and hemoglobin ≥10 g/dl); and written informed consent. Patients with pre-existing obstructive jaundice were also eligible after their bilirubin levels met the criteria by biliary stent insertion or percutaneous biliary drainage.

Patients were excluded from the study if they had pulmonary fibrosis, interstitial pneumonia, New York Heart Association class III or IV congestive heart failure, myocardial infarction within the preceding 6 months, diabetes mellitus with severe complications, marked pleural or pericardial effusion, marked peripheral edema, or active infection. Additional exclusion criteria included pregnant or lactating females, patients of reproductive potential who did not use effective contraception, severe drug hypersensitivity, central nervous system metastases, active concomitant malignancy, other serious medical conditions, or patients receiving any investigational drug within 30 days before enrollment.

The study was conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represented the greater protection of the individual. In addition, the study design was approved by the appropriate ethical review boards.

Study treatment

Gemcitabine (supplied by Eli Lilly, Japan) 1,000 mg/m^2 was administered as an intravenous 30-min infusion on days 1, 8, and 15 for every 28 days. The treatment was continued until evidence of disease progression or unacceptable toxicity.

For white blood cells < 2,000/mm^3, neutrophils < 1,000/mm^3, platelets < 70,000/mm^3, bilirubin > 3 times ULN, or AST/ALT > 5 times ULN, gemcitabine was omitted on that day and postponed to the next scheduled treatment day.

In subsequent cycles, gemcitabine was reduced to 800 mg/m^2 if neutrophils < 500/mm^3 for 4 days, white blood cells < 1,000/mm^3 for 4 days, platelets < 25,000/mm^3, bilirubin > 3 times ULN, or AST/ALT > 5 times ULN. Gemcitabine was also reduced to 800 mg/m^2 if a platelet transfusion was performed due to thrombocytopenia or if gemcitabine was omitted twice in succession due to toxicity. No dose adjustment was allowed during the same cycle. The treatment was discontinued if a second dose reduction was needed, if bilirubin > 5.0 times ULN, AST/ALT > 20 times ULN, or tumor progression was observed. The use of granulocyte colony-stimulating factor (G-CSF) was permitted for any grade 4 leukopenia or neutropenia or grade 3 neutropenia with high fever (38.0°C). Prophylactic administration of antiemetics was allowed.

Baseline and treatment assessments

Pretreatment evaluation included complete history and physical examination. In addition, complete blood count, biochemistry tests, urinalysis, and chest X-ray were performed. Performance status and laboratory tests, except for urinalysis, were assessed weekly. Urinalysis was performed during days 15–28 in each cycle. Tumor size was measured by CT scan or MRI during days 22–28 in each cycle. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19–9) were quantified every 4 weeks. All 40 patients who received at least one dose of gemcitabine were involved in the efficacy analyses.Objective tumor response was assessed every 4 weeks using WHO criteria [41]. The duration of response was calculated from the first day of treatment until documentation of disease progression. Survival was measured from the first day of treatment.

Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria version 2.0 [27]. A monitoring committee independently evaluated the efficacy and safety of the study.

Statistical analysis

Considering the results of previous trials using gemcitabine for advanced or metastatic biliary tract cancer, we expected an overall response rate of 15–20% in this

study. With this population, response rates typically have not exceeded 10% in patients treated with 5-fluorouracil (5-FU); therefore, a response rate of at least 15% in our study would suggest a potential benefit.

Our goal was to enroll 40 eligible patients. If no response occurred in the first 18 patients, accrual was terminated because the chance of a 15% response rate was only 5.3%. If the response rate was 15%, the statistical power (the probability of a 5% response rate) would be 73% with type I error of 5% (one-sided). For a response rate of 17.5%, the statistical power would be 85%, and the statistical power would be 92% for a response rate of 20%.

All time-to-event measures were calculated using the Kaplan–Meier method.

Results

Patient characteristics and disposition

From October 2001 to September 2003, 21 males and 19 females, with a median age of 61 years (range 33–73 years), were enrolled. Table 1 shows the baseline patient characteristics. Twenty-three patients (57.5%) had no prior therapy, and 17 (42.5%) relapsed after resection for primary lesion. The major metastatic lesions were the abdominal lymph nodes (67.5%) and liver (55.0%). Prior to the initiation of study treatment, obstructive jaundice was palliated with percutaneous transhepatic catheter placement (11 patients) or endobiliary stent placement (3 patients).

The reasons for the treatment discontinuation included progressive disease (34 patients), elevated blood pressure associated with worsening of renal function (one patient), hemolytic uremic syndrome (one patient), blood bilirubin increased with progressive disease (one patient), relapse of pre-existing schizophrenia (one patient), patient's refusal due to nausea/vomiting (one patient), and general fatigue (one patient).

Table 1 Baseline patient characteristics ($n=40$)

Characteristic	
Gender, *n* (%)	
Male	21 (52.5)
Female	19 (47.5)
Age, years	
Median (range)	61 (33–73)
ECOG performance status	
0	24 (60.0)
1	16 (40.0)
Primary lesion	
Extrahepatic bile duct	12 (30.0)
Gallbladder	22 (55.0)
Ampulla of Vater	6 (15.0)
CA19–9, *n* (U/ml)	
Median (range)	448.6 (1–77,820)
CEA, *n* (ng/ml)	
Median (range)	10.9 (0.5–1,790)
Metastatic sites, *n* (%)	
Abdominal lymph nodes	27 (67.5)
Liver	22 (55.0)
Peritoneum	4 (10.0)
Lung	2 (5.0)
Bone	1 (2.5)

ECOG Eastern Cooperative Oncology Group; *CA19–9* carbohydrate antigen 19–9; *CEA* carcinoembryonic antigen

Efficacy

All 40 patients were evaluated for efficacy and according to WHO criteria, seven patients achieved a partial response for an overall response rate of 17.5% (95% CI, 7.3–32.8%). The median duration of the response was 9.4 months (range, 2.6–9.4 months). Fifteen patients (37.5%) had stable disease, and 17 patients (42.5%) had progressive disease. Tumor response was not determined in one patient because she was transferred to another hospital before response evaluation. The serum CA 19–9 level was reduced by less than half in 11 (33%) of 33 patients who had a pretreatment level of above upper normal limit, and the CEA level was reduced by less than half in 6 (24%) of 25 patients. Of the 11 patients whose CA 19–9 level was reduced, 4 (36%) showed a partial response. Five (83%) of the six patients with the CEA response achieved a partial response.

At the time of analysis, 35 of 40 patients had died of cancer and two of five patients lived longer than 24 months after the initial administration of gemcitabine. The median progression-free interval was 2.6 months (95% CI, 1.7–3.8 months), and the median survival time was 7.6 months (95% CI, 5.4–9.3 months) (Fig. 1). The 1-year survival rate was 25.0%.

Toxicity

All 40 patients were evaluable for toxicity (Table 2). No toxic deaths occurred. Hematologic toxicity was reversible and manageable. Patients reported grade 3/4 neutropenia (30.0%), leukopenia (12.5%), and anemia (10.0%). Three patients had red blood cell transfusions due to hemolytic uremic syndrome, hemorrhagic shock, and anemia. No grade 3/4 thrombocytopenia was reported. Although two patients were treated with G-CSFs, there was no febrile neutropenia.

The most common nonhematologic toxicities, grades 1–4 were nausea (52.5%) and anorexia (52.5%), but only four patients (10%) required intravenous infusion due to these toxicities. The most common grade 3/4 nonhematologic toxicities were elevated ALT (15.0%) and elevated γ-glutamyltransferase (γ-GTP) (12.5%). Grade 4 elevated γ-GTP was observed in one patient, which was considered to be gemcitabine-related because the level returned to normal after treatment discontinuation. The patient, who had grade 3 uremia, grade 2 serum creatinine elevation, and grade 2 thrombocytopenia, was diagnosed with grade 4 hemolytic uremic syndrome and also recovered from these toxicities by

transfusion without dialysis after discontinuing gemcitabine. In another patient on day 25 of cycle 1, hemorrhagic shock occurred following unexpected hematemesis, which was unlikely to be gemcitabine related. Endoscopic examination showed acute gastric mucosal lesions, and prescribed nonsteroidal anti-inflammatory drugs to control abdominal pain were suspected to be the cause of hemorrhagic shock.

Dose intensity

A median of three cycles was administered (range, 1–14). Eleven patients (27.5%) completed one cycle; eight patients (20.0%) completed two cycles; and five patients (12.5%) completed three cycles. The planned mean dose intensity of gemcitabine was 750 mg/m^2; however, the actual mean dose intensity of gemcitabine was 688.7 mg/m^2. Thus, the dose intensity was 91.8% for gemcitabine. Of the 476 planned infusions, 37 dose omissions (7.8%) occurred, mainly due to neutropenia. There were no dose reductions.

Discussion

The vast majority of patients with biliary tract cancer are candidates for chemotherapy; however, chemotherapy for biliary tract cancer currently has only limited value in clinical practice. 5-FU is the mainstay of palliative chemotherapy, although response rates range from 0 to 13% in phase II trials [6, 11, 39]. It is generally accepted that combinations with 5-FU have little superiority over single-agent 5-FU, and the considerable toxicity often outweighs the benefit for the patients [11, 39]. Except for gemcitabine, no individual agent has shown a reproducible response rate over 15% [1, 12, 19, 29, 31, 33, 37]. Therefore, new agents need to be developed for truly effective chemotherapeutic regimens against this disease.

In a prospective randomized trial [4], gemcitabine is the only agent showing significant efficacy in respect to survival prolongation and symptom relief for patients with advanced pancreatic cancer; these results prompted trials for biliary tract cancer, which, to some extent, shares embryological and clinical features with pancreatic cancer. Several early-phase studies of single-agent gemcitabine at doses of 1,000–2,200 mg/m^2 have reported response rates of 8–60%, and median survival durations ranging from 6.5 to 11.5 months. [3, 7, 8, 14, 21, 24, 34, 35].

In our trial, gemcitabine 1,000 mg/m^2 was administered for 3 weeks with 1 week of rest; this schedule is currently approved in Japan for non-small-cell lung cancer and pancreatic cancer and is considered to be a standard regimen worldwide. Our overall response rate of 17.5% appeared to be comparable to previous trials with gemcitabine or other combination regimens and appeared near the highest results in single-agent therapy. In recent phase II trials of various single agents, responses were 8% in a study with cisplatin [29], 0% in paclitaxel [19], 0–25% in docetaxel [2, 31, 33], 11% in irinotecan [12], and 19% in capecitabine [23]. Our median overall survival of 7.6 months was also comparable to other trials of single-agent therapy, which ranged from 4.5 to 8.0 months [2, 12, 19, 23, 29, 31, 33, 37], and for combination therapies, which ranged from 5.0 to 14.0 months [5, 9, 10, 15, 18, 20, 26, 28, 32, 35, 36, 38]. However, it seemed to be longer when compared with other phase II trials for Japanese patients with advanced or metastatic biliary tract cancer, which was 5.3 months in uracil/tegafur, 5.9 months in cisplatin/

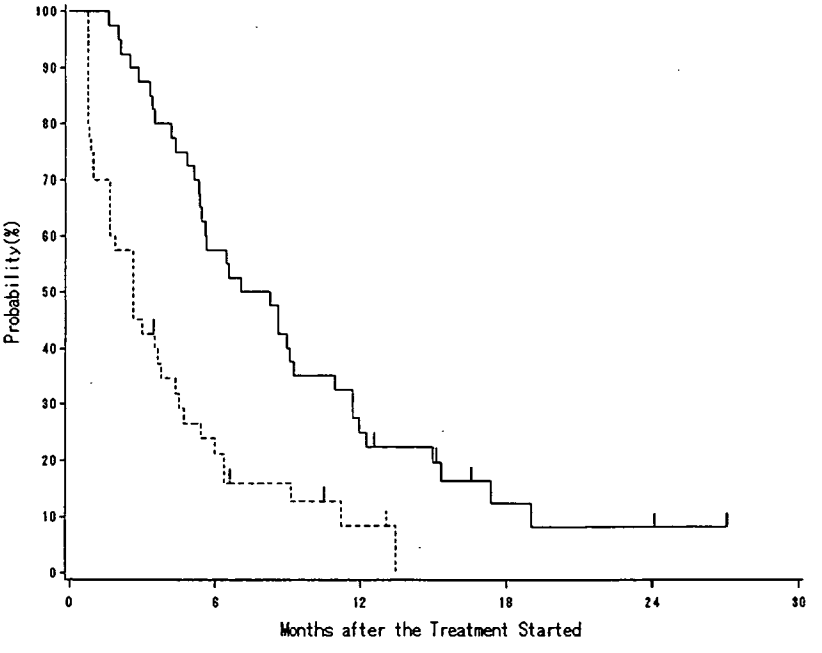

Fig. 1 Progression-free survival (*dashed line*) and overall survival (*solid line*) curves of patients with advanced biliary tract cancer receiving systemic chemotherapy with gemcitabine

Table 2 Adverse drug reaction

Adverse drug reaction	Grade 3		Grade 4	
	n	(%)	*n*	(%)
Hematologic toxicities				
Neutropenia	10	25.0	2	5.0
Leukopenia	5	12.5	0	0.0
Anemia	3	7.5	1	2.5
Thrombocytopenia	0	0.0	0	0.0
Nonhematologic toxicities				
Elevated ALT	6	15.0	0	0.0
Elevated γ-GTP	4	10.0	1	2.5
Elevated AST	2	5.0	0	0.0
Decreased serum sodium	2	5.0	0	0.0
Increased serum ALP	2	5.0	0	0.0
Urinary occult blood positive	1	2.5	0	0.0
Increased serum bilirubin increased	0	0.0	0	0.0
Increased serum creatinine	0	0.0	0	0.0
Proteinuria	0	0.0	0	0.0
Hematuria	0	0.0	0	0.0
Hemolytic uremic syndrome	0	0.0	1	2.5
Constipation	3	7.5	0	0.0
Vomiting	3	7.5	0	0.0
Nausea	2	5.0	0	0.0
Hematemesis	0	0.0	1	2.5
Diarrhoea	0	0.0	0	0.0
Stomatitis	0	0.0	0	0.0
Fatigue	0	0.0	0	0.0
Edema	0	0.0	0	0.0
Pyrexia	0	0.0	0	0.0
Biliary tract infection	1	2.5	0	0.0
Anorexia/Appetite impared	3	7.5	1	2.5
Rash	1	2.5	0	0.0
Alopecia	0	0.0	0	0.0
Hypertension	1	2.5	0	0.0
Hemorrhagic shock	0	0.0	1	2.5

ALT Alanine aminotransferase, *γ-GTP* γ-glutamyltransferase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase

epirubicin/5-FU, and 5.5 months in a study with cisplatin [18, 26, 29].

The toxicity profile in our study was generally acceptable. The major toxicities were myelosuppression; the incidences of grade 3/4 toxicities were 30.0% in neutropenia, 12.5% in leukopenia, and 10.0% in anemia. However, grade 4 toxicities were infrequent, and neither febrile neutropenia nor treatment-related deaths were observed. The toxicity profile in our study was consistent with past studies using gemcitabine in other tumors. For patients treated with cisplatin, epirubicin, and 5-FU [26], high incidences of grade 3/4 neutropenia (76.0%), leukopenia (59.0%), and death due to treatment-related sepsis 5.0% occurred despite a response rate (19%) similar to that in our study. There was only one episode of cholangitis in this study, although patients with biliary tract cancer are at high-risk for cholangitis, and sometimes severe sepsis occurs, which is derived from cholangitis during chemotherapy [26]. Transient elevations of hepatic enzymes have been reported in gemcitabine therapy for both pancreatic and biliary tract cancer; liver function may be easily affected by cholestasis due to existence of primary and/or metastatic tumors.

One patient developed hemolytic uremic syndrome, which was considered to be a manifestation of thrombotic microangiopathy, although gemcitabine-associated thrombotic microangiopathy is believed to be very rare, with estimated incidences of 0.008–0.31% [13, 17]. The event in this patient seemed to be a treatment-related adverse reaction; however, the patient recovered from hemolytic uremic syndrome without hemodialysis after discontinuation of gemcitabine. Grade 4 anemia was observed in one patient, who suffered grade 4 hematemesis and hemorrhagic shock. This was unlikely to be related to gemcitabine because no thrombocytopenia was observed in this patient. Also, upper gastrointestinal endoscopy revealed acute gastric mucosal lesions as the origin of the bleeding, which seemed to be related to prescribed non-steroidal anti-inflammatory drugs.

Our study was conducted among the largest group of patients with biliary tract cancer to date. In our study, gemcitabine was administered to patients who had biliary stent insertion or percutaneous biliary drainage, and no particular drug-related toxicity was observed in these patients. The result of our study is promising for patients with biliary tract cancer.

In conclusion, chemotherapy with single-agent gemcitabine was feasible and appeared to show efficacy in advanced or metastatic biliary tract cancer. Gemcitabine may provide a more favorable prognosis in patients with this disease compared to other chemotherapeutic regimes or best supportive care.

Acknowledgements This study was supported by Eli Lilly Japan who also supplied gemcitabine. We thank Ms. Keiko Kondo for her great help in manuscript preparation.

Appendix

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