

## Gemcitabine Combined with 5-Fluorouracil and Cisplatin (GFP) in Patients with Advanced Biliary Tree Cancers: A Pilot Study

YO-ICHI YAMASHITA<sup>1,2</sup>, AKINOBU TAKETOMI<sup>1</sup>, KENGO FUKUZAWA<sup>2</sup>,  
TOMOHARU YOSHIZUMI<sup>1</sup>, HIDEAKI UCHIYAMA<sup>1</sup>, MITSUO SIMADA<sup>3</sup>,  
KEN SHIRABE<sup>1</sup>, KENZO WAKASUGI<sup>2</sup> and YOSHIHIKO MAEHARA<sup>1</sup>

<sup>1</sup>Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582;

<sup>2</sup>Department of Surgery, Oita Red Cross Hospital, 3-2-37 Chiyo-machi, Oita 870-0033;

<sup>3</sup>Department of Digestive and Pediatric Surgery, Institute of Health Biosciences,

The University of Tokushima Graduate School, 3-18-15 Kuramoto-machi, Tokushima, 770-8503, Japan

**Abstract.** *Background:* Advanced biliary tree cancers have poor prognosis and chemotherapy has been shown to have little impact. To date, no standard chemotherapy regimens have been established. A pilot study to evaluate gemcitabine/5-Fluorouracil(5-FU)/cisplatin(CDDP) (GFP) chemotherapy in patients with advanced biliary tree cancers was performed. *Patients and Methods:* Eight patients with advanced intrahepatic cholangiocarcinoma and gallbladder carcinoma with no prior chemotherapy were treated with a 4-week cycle GFP chemotherapy consisting of gemcitabine at 1000 mg/m<sup>2</sup> on days 1, 8, and 15, and of 5-FU at 250 mg/patient and CDDP at 5 mg/patient on days 1 to 5, 8 to 12 and 22 to 26. *Results:* Of these 8 patients, no complete responses (CR) were observed, but 3 patients (37.5%) demonstrated partial responses (PR) with an additional 3 patients (37.5%) having stable diseases (SD), as assessed by RECIST. Two patients with PR and 1 patient with SD were treated by curative operation after GFP chemotherapy and all of them survived with no recurrence. The median overall survival time was 23.5 months, and median time to progression was 14.5 months. Grade 3/4 side-effects, such as leukopenia, thrombocytopenia and anemia were found in 4 patients (50%), but no patients dropped out because of toxicity. *Conclusion:* This GFP chemotherapy has promising antitumor activity and is well tolerated in patients with advanced biliary tree cancers. This regimen warrants further evaluation in a phase II study including larger numbers of patients.

Biliary tree cancer is an uncommon malignancy although its incidence appears to be increasing worldwide (1-3). Surgery remains the only potentially curative intervention; however, the majority of patients present with advanced unresectable disease and have a poor prognosis. Several phase II studies of chemotherapy (both monotherapy and combinative regimens) for biliary tree cancer have been conducted, with response rates ranging from 9.5-41.0% (4-8). Gemcitabine (2', 2' difluorodeoxycytidine), a deoxycytidine analog, has broad activity in a variety of solid tumors, including biliary tree cancers (4, 5). The addition of cisplatin (CDDP), oxaliplatin, docetaxel, or 5-Fluorouracil (5-FU) may increase the therapeutic effect, although at the expense of increased toxicity (6, 7, 9, 10). A pilot study was performed to evaluate gemcitabine/5-fluorouracil(5-FU)/CDDP (GFP) chemotherapy in previously untreated patients with advanced biliary tree cancers.

### Patients and Methods

**Patient selection.** Patients were eligible if they had pathologically proven, measurable and unresectable locally-advanced or metastatic adenocarcinoma arising from intrahepatic biliary ducts or the gallbladder. No prior chemotherapy was allowed. Additional inclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status <2 and adequate organ function (neutrophils >1.5x10<sup>3</sup>/µL, platelets >1.0x10<sup>5</sup>/µL, serum creatinine <160 µmol/L or actual or calculated creatinine clearance >60 mL/min, ALT<5X upper limit of normal (ULN), and total bilirubin <3xULN and stable for 2 weeks ). Written informed consent was obtained from each patient. The protocol was approved by the ethics committees of both institutes.

**Treatment.** The patients were treated on a 4-week cycle. Gemcitabine 1000 mg/m<sup>2</sup> was administered intravenously as a 30-min infusion weekly for 3 weeks every 4 weeks. 5-FU and CDDP were injected intravenously for 20 days every 4 weeks from

*Correspondence to:* Yo-ichi Yamashita, MD, Ph.D., Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. Tel: 81-92-642-5469, Fax: 81-92-642-5482, e-mail: yamashi@surg2.med.kyushu-u.ac.jp

**Key Words:** Gemcitabine, 5-Fluorouracil, cisplatin, biliary tree cancers.

**Table I.** Patient's characteristics.

Patient	Age	Sex	Disease	TNM Classification	Cause for inoperability
Case 1	72	M	GBCa	T3N1M1 : Stage IV	Liver meta, multiple
Case 2	78	F	GBCa	T3N1M1 : Stage IV	Liver meta, multiple
Case 3	74	M	IHCC	T4N1M1 : Stage IV	Liver meta, multiple
Case 4	56	M	GBCa	T3N1M0 : Stage III	Doudenal invasion
Case 5	62	M	IHCC	T4N1M0 : Stage III	Pera-aorta LN <sup>d</sup> meta
Case 6	47	M	GBCa	T3N1M0 : Stage III	Doudenal invasion
Case 7	687	M	GBCa	T3N1M1 : Stage IV	Peritoneal dissemination
Case 8	52	F	GBCa	T3N1M0 : Stage III	Doudenal invasion

Abbreviations: M, male; F, female; GBCa, gallbladder carcinoma; IHCC, intrahepatic cholangiocarcinoma; Meta, metastasis; LN<sup>d</sup>, lymphnode.

days 1 through 5, days 8 through 12 and days 22 through 26 at a dose of 250 mg/patient and 5 mg/patient, respectively. After 2 cycles, during outpatient treatment, Gemcitabine 1000 mg/m<sup>2</sup> was administered intravenously as a 30-min infusion on days 1 and 15 for 4 weeks, combined with 5-FU and CDDP injected intravenously on days 1 and 15 for 4 weeks at a dose of 750 mg/patient and 10 mg/patient, respectively. Treatment was continued until tumor progression, remission to be treated by curative operation, or unacceptable and uncontrollable toxicity occurred. The adverse events were recorded according to the National Cancer Institute of Canada Common Toxicity Criteria (version 2).

**Assessment.** Tumor response was assessed using the Response Evaluation Criteria in Solid tumors (RECIST) (11), with computer tomography scans at baseline and every 2 cycles or 8 weeks' treatment. Responses were confirmed by computed tomography at least 4 weeks later. The primary investigation of interest was overall response rate, with secondary investigations including overall survival, time to progression and safety and tolerability of the treatment.

## Results

Between April 2002 and March 2005, 8 patients were enrolled in this study at 2 centers. Patient characteristics are summarized in Table I. Six patients (75%) had gallbladder cancers. Three patients (37.5%) were locally advanced and 5 patients (62.5%) had distant metastasis, such as liver and lymph node metastases; all were judged as inoperable cases. Three patients (37.5%) underwent an additional curative operation after 2 cycles of GFP chemotherapy. Cases 6 and 8 were locally advanced gallbladder cancers with duodenal invasion, but tumor remission over 50% caused apparent duodenal stenosis after GFP chemotherapy. Case 7 was suspected of having peritoneal dissemination because of slight ascites at the Winslow foramen and the thickness of the omentum, but these symptoms disappeared after GFP chemotherapy. In addition, 3 patients (37.5%) were treated by GFP chemotherapy as outpatients and continued to be treated until progression (6, 13, and 30 cycles, respectively). No patient was removed from the study because of severe toxicity.

**Table II.** Clinical outcome of treatment.

Patient	Response	Operation	TTP (months)	Survival (months)	Status
Case 1	SD	-	5.1	6.2	Deceased
Case 2	PD	-	1.0	6.0	Deceased
Case 3	PD	-	1.0	8.2	Deceased
Case 4	SD	-	9.0	20.0	Deceased
Case 5	PR	-	20.0	27.0	Deceased
Case 6	PR	+	39.8	39.8	Alive
Case 7	SD	+	34.3	34.3	Alive
Case 8	PR	+	29.4	39.4	Alive

Abbreviations: SD, stable disease; PD, progressive disease; PR, partial response; TTP, time to progression.

**Table III.** Toxicity profile.

	Grade 1	Grade 2	Grade 3	Grade 4
<b>Hematological</b>				
Anemia	0	6	1	0
Leukopenia	0	3	4	0
Thrombocytopenia	0	3	1	0
<b>Non-hematological</b>				
Nausea	2	0	0	0
Vomiting	1	0	0	0
Appetite loss	4	2	0	0
Diarrhea	1	0	0	0

**Response and survival.** Response and survival are summarized in Table II. No complete responses were noted. Three patients achieved partial responses; the overall response rate was 37.5%. In addition, 3 patients (37.5%) had stabilization of their disease. The median time to progression (TTP) was 14.5 months and the median overall



Figure 1. CT imaging advanced gallbladder cancer in patient 6. Before GFP chemotherapy, the size of tumor was estimated at 8.2 x 7.3 cm (A). After 2 cycles of GFP chemotherapy, the size had decreased to 4.3 x 3.4 cm (B). His remission rate reached 50.3% and the effect of GFP chemotherapy was judged as "partial response" according to RECIST guideline. Arrows indicate the tumor. Combined pancreaticoduodenectomy and hepatectomy was performed. Gross appearance of resected specimen is presented (C). Arrows indicate the tumor. Microscopically, massive necrosis was found and the remnant viable region was diagnosed as poorly-differentiated adenocarcinoma (D).

survival (OS) 23.5 months. Three patients (37.5%) undergoing curative operation after GFP chemotherapy were alive without tumor recurrence beyond 24 months.

**Toxicities.** All patients were evaluable for toxicity. The hematological toxicity was significant and is described in Table III. Grade 3/4 leukopenia developed in 4 patients (50%), anemia in 1 patient (12.5%) and thrombocytopenia in 1 patient (12.5%). No grade 3/4 non-hematological toxicities, such as nausea, vomiting, appetite loss or diarrhea were found. Four patients (50%) required dose reductions because of toxicities.

**Presentation of a case with partial response (Case 6).** A 49-year-old male patient with advanced gall bladder cancer is presented. Duodenal invasion and peri-pancreatic lymph node metastasis were suspected. A partial response (remission rate 50.3%) was reached after 2 cycles of GFP chemotherapy (Figure 1 A, B) and duodenal invasion and peri-pancreatic

lymph node metastasis disappeared after GFP chemotherapy. A curative operation was feasible and, therefore, a combined pancreaticoduodenectomy and hepatectomy was performed and lymph node metastasis was found at the hepatoduodenal ligament (Figure 1C). The pathological diagnosis was poorly-differentiated adenocarcinoma with massive necrosis (Figure 1D). This patient has been alive for 39.8 months without tumor recurrence.

## Discussion

In this study, we observed impressive responses of locally advanced or metastatic biliary tree cancers to our GFP chemotherapy. These are some of the best results obtained so far in the management of advanced biliary tree cancers, including those of the various recent phase II studies summarized in Table IV (4-10, 12-19). There is no current standard chemotherapy for advanced biliary tree cancers.

Table IV. Summary of recent trials in biliary tree cancers.

Study	Regimen	No of patients	RR (%)	Toxicity*	Median survival (months)
Gallard <i>et al.</i> (4)	GEM (1000 mg/m <sup>2</sup> )	26	35.0	+	7.5
Lin <i>et al.</i> (12)	GEM (1000 mg/m <sup>2</sup> )	24	12.5	+	7.2
Kubicka <i>et al.</i> (13)	GEM (1000 mg/m <sup>2</sup> )	23	30.0	+	9.3
Penz <i>et al.</i> (5)	GEM (2200 mg/m <sup>2</sup> )	32	22.0	+	11.5
Alberts <i>et al.</i> (6)	GEM/FA/5-FU	42	9.5	++	9.7
Doval <i>et al.</i> (7)	GEM/CDDP	30	36.9	++	5.0
Andre <i>et al.</i> (9)	GEM/oxaliplatin	29	21.0	++	9.5
Kuhn <i>et al.</i> (10)	GEM/docetaxel	43	11.6	+++	11.0
Knox <i>et al.</i> (14)	GEM/capecitabine	45	31.0	++	14.0
Kornek <i>et al.</i> (16)	GEM/MMC	26	20.0	++	6.7
Patt <i>et al.</i> (8)	CDDP/Doxo/5-FU/IFN	21	41.0	+++	14.0
Kornek <i>et al.</i> (16)	MMC/capecitabine	25	31.0	++	9.3
Taieb <i>et al.</i> (18)	5-FU/CDDP	29	34.0	+	9.5
Raderer <i>et al.</i> (19)	5-FU/FA/MMC	20	16.0	++	9.5
Kim <i>et al.</i> (20)	capecitabine/CDDP	42	21.4	++	9.1
Current study	GEM/5-FU/CDDP	8	37.5	+++	23.5

Abbreviations: RR, response rate; GEM, gemcitabine; CDDP, cisplatin; MMC, mitomycin; FA, folid acid; 5-FU, 5-Fluorouracil; Doxo, doxolubicine.

\*Toxicity: reported > grade 3 nonhematological or significant hematological toxicity: +, mild, <20%, ++, moderate, 20% to 40%, +++, severe, >40%.

Clinical trials in advanced biliary tree cancers have suffered from the relative rarity of these tumors and the generally morbid patient population. The recent surge of new phase II trials in this disease reflects, not only the lack of consensus on the best treatment, but also the strong research interest in how to manage this challenging disease. In particular, 5 out of 8 patients (62.5%) in our study survived more than 20 months and 3 among these who underwent curative operation after GFP chemotherapy have survived more than 2 years without tumor recurrence. The pathological diagnosis of these 3 patients was poorly-differentiated adenocarcinoma with massive necrosis. However, the number of patients is too small in our pilot study to definitely establish this therapy.

The combination of Gemcitabine, 5-FU and CDDP has been considered synergistic based on laboratory data. By its direct inhibition of ribonucleotide reductase, Gemcitabine potentially augments the activity of 5-FU. Administered after 5-FU, it should further delay dUMP production, potentiating and prolonging the inhibition by 5dUMP (20). In addition, the synergism between Gemcitabine and CDDP appears to be mainly due to increased platinum-DNA adduct formation, possibly related to changes in DNA due to Gemcitabine incorporation into DNA (21). The results of our pilot study on TTP and OS, while only preliminary, were superior to those of phase II studies of Gemcitabine/5-FU/Leukoboline (6) or Gemcitabine/CDDP (7). The synergism should be schedule-dependent (20, 22) and the order of administration should be 5-FU,

Gemcitabine and CDDP. We maintained the above order during outpatient treatment, while Gemcitabine with continuous 5-FU/CDDP was administered for inpatients. This regimen of GFP chemotherapy, with slightly different drug doses, administration orders and time schedules, should be examined in further clinical trials.

Grade 3/4 hematological toxicity was found 4 patients (50%), but overall this chemotherapy was relatively well tolerated. Therefore, we consider that GFP chemotherapy is justified and worth further phase II study including large numbers as a multi-center trial. Locally advanced gallbladder cancers curatively resected had relatively good prognosis (3-year and 5-year survival of stage IV (M0) disease, 24 and 17%, respectively) (23); therefore, this study raises the possibility of using GFP chemotherapy for neoadjuvant chemotherapy against locally advanced biliary tree cancers.

## References

- Patel T: Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. *Hepatology* 33: 1353-1357, 2001.
- Taylor-Robinson SD, Toledano MB, Arora S, Keegan TJ, Hargreaves S, Beck A, Khan SA, Elliott P and Thomas HC: Increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales. *Gut* 48: 816-820, 2001.
- Davila JA and El Serag HB: Cholangiocarcinoma: the 'other' liver cancer on rise. *Am J Gastroenterol* 97: 3199-3200, 2002.
- Gallardo JO, Rubio B, Fodor M, Orlandi L, Yanez M, Gamargo C and Ahumada M: A phase II study of gemcitabine in gallbladder carcinoma. *Ann Oncol* 12: 1403-1406, 2001.

- 5 Penz M, Kornek GV, Raderer M, Ulrich-Pur H, Fiebiger W, Lenauer A, Depisch D, Krauss G, Schneeweiss B and Scheithauer W: Phase II trial of two-weekly gemcitabine in patients with advanced biliary tract cancer. *Ann Oncol* 12: 183-186, 2001.
- 6 Alberts SR, Al-Khatib H, Mahoney MR, Burgart L, Cera PJ, Flynn PJ, Finch TR, Levitt R, Windschitl HE, Knost JA and Tschetter LK: Gemcitabine, 5-fluorouracil, and leucovorin in advanced biliary tract and gallbladder carcinoma: a North Central Cancer Treatment Group phase II trial. *Cancer* 103: 111-118, 2005.
- 7 Doval DC, Sekhon JS, Gupta SK, Fuloria J, Shukla VK, Gupta S and Awasthy BS: A phase II study of gemcitabine and CDDP in chemotherapy-naïve, unresectable gall bladder cancer. *Br J Cancer* 90: 1516-1520, 2004.
- 8 Patt YZ, Hassan MM, Lozano RD, Waugh KA, Hoque AM, Frome AI, Lahoti S, Ellis L, Vauthey JN, Curley SA, Schnirer II and Rajzman I: Phase II trial of CDDP, interferon alpha-2b, doxorubicin, and 5-fluorouracil for biliary tract cancer. *Clin Cancer Res* 7: 3375-3380, 2001.
- 9 Andre T, Tournigand C, Rosmorduc O, Provent S, Maindrault-Goebel F, Avenir D, Selle F, Paye F, Hannoun L, Houry S, Gayet B, Lotz JP, de Gramont A and Louvet C: GERCOR Group. Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. *Ann Oncol* 15: 1339-1343, 2004.
- 10 Kuhn R, Hribaschek A, Eichelmann K, Rudolph S, Fahlke J and Ridwelski K: Outpatient therapy with gemcitabine and docetaxel for gallbladder, biliary, and cholangio-carcinomas. *Invest New Drugs* 20: 351-356, 2002.
- 11 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Glabbeke MV, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors (RECIST) guidelines. *J Natl Cancer Inst* 92: 205-216, 2000.
- 12 Lin MH, Chen JS, Chen HH and Su WC: A phase II trial of gemcitabine in the treatment of advanced bile duct and periampullary carcinomas. *Chemotherapy* 49: 154-158, 2003.
- 13 Kubicka S, Rudolph KL, Tietze MK, Lorenz M and Manns M: Phase II study of systemic gemcitabine chemotherapy for advanced unresectable hepatobiliary carcinomas. *Hepatogastroenterology* 48: 783-789, 2001.
- 14 Knox JJ, Hedley D, Oza A, Feld R, Siu LL, Chen E, Nematollahi M, Pond GR, Zhang J and Moore MJ: Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. *J Clin Oncol* 23: 2332-2338, 2005.
- 15 Duenas-Gonzalez A, Lopez-Graniel C, Gonzalez A, Reyes M, Mota A, Munoz D, Solorza G, Hinojosa LM, Guadarrama R, Florentino R, Mohar A, Melendez J, Maldonado V, Chanona J, Robles E and De la Garza J: A phase II study of gemcitabine and CDDP combination as induction chemotherapy for untreated locally advanced cervical carcinoma. *Ann Oncol* 12: 541-547, 2001.
- 16 Kornek GV, Schuell B, Laengle F, Gruenberger T, Penz M, Karall K, Depisch D, Lang F and Scheithauer W: Mitomycin C in combination with capecitabine or biweekly high-dose gemcitabine in patients with advanced biliary tract cancer: a randomised phase II trial. *Ann Oncol* 15: 478-483, 2004.
- 17 Taieb J, Mitry E, Boige V, Artru P, Ezenfis J, Lecomte T, Clavero-Fabri MC, Vaillant JN, Rougier P and Ducreux M: Optimization of 5-fluorouracil (5-FU)/cisplatin combination chemotherapy with a new schedule of leucovorin, 5-FU and cisplatin. *Ann Oncol* 13: 1192-1196, 2002.
- 18 Raderer M, Hejna MH, Valencak JB, Kornek GV, Weinlander GS, Bareck E, Lenauer J, Brodowicz T, Lang F and Scheithauer W: Two consecutive phase II studies of 5-fluorouracil/leucovorin/mitomycin C and of gemcitabine in patients with advanced biliary cancer. *Oncology* 56: 177-180, 1999.
- 19 Kim TW, Chang HM, Kang HJ, Lee JR, Ryu MH, Ahn JH, Kim JH, Lee JS and Kang YK: Phase II study of capecitabine plus cisplatin as first-line chemotherapy in advanced biliary cancer. *Ann Oncol* 14: 1115-1120, 2003.
- 20 Ren Q-F and Grem JL: Synergistic cytotoxicity and induction of parental DNA fragmentation with sequential gemcitabine and 5-fluoro-2' deoxyuridine in HT29 colon cancer cells. National Cancer Institute-Navy Center, Bethesda, MD AACR, Vol 36: 2421, 1995.
- 21 van Moorsel CJ, Pinedo HM, Veerman G, Bergman AM, Kuiper CM, Vermorken JB, van der Vijgh WJ and Peters GJ: Mechanisms of synergism between cisplatin and gemcitabine in ovarian and non-small-cell lung cancer cell lines. *Br J Cancer* 80: 981-990, 1999.
- 22 van Moorsel CJ, Veerman G, Bergman AM, Guechev A, Vermorken JB, Postmus PE and Peters GJ: Combination chemotherapy studies with gemcitabine. *Semin Oncol* 24(2 Suppl 7): S7-17-S7-23, 1997.
- 23 Kondo S, Nimura Y, Hayakawa N, Kamiya J, Nagino M and Uesaka K: Extensive surgery for carcinoma of the gallbladder. *Br J Surg* 89: 179-184, 2002.

*Received October 3, 2005**Accepted November 24, 2005*