Chemotherapy with Gemcitabine plus Cisplatin in Patients with Advanced Biliary Tract Carcinoma at Chang Gung Memorial Hospital: A Retrospective Analysis

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Background: A gemcitabine-cisplatin combination is a standard treatment option for patients with advanced biliary tract carcinoma (BTC). We assessed the efficacy and safety of this regimen at Chang Gung Memorial Hospital.

Methods: Between April 2009 and December 2010, 30 chemotherapy-naïve patients (13 men and 17 women; median age: 61.5 years) with advanced BTC were retrospectively analyzed. Treatment consisted of gemcitabine (Gemmis®; TTY, Taipei, Taiwan) 1000 mg/m^2, followed by cisplatin 30 mg/m^2 on days 1 and 8 every 3 weeks. Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria every 2–3 cycles. The toxicity was assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.

Results: At the end of July, 2011, 27 patients were evaluated using the RECIST criteria. According to the intent to treat analysis of response, 5 patients (16.7%) had a partial response, 10 patients (33.3%) had stable disease and 12 patients (40.0%) had progressive disease. The median time to progression (TTP) and median overall survival (OS) of the 30 patients were 4.8 months and 13.4 months, respectively. The patients with biliary obstruction requiring drainage before treatment had a significantly shorter OS than those without biliary obstruction (p = 0.02) even though the TTP showed no statistically significant difference (p = 0.69) between groups. The major grade III/IV adverse events in the 30 patients included infection (n = 8, 26.7%), anemia (n = 5, 16.7%), neutropenia (n = 4, 13.3%), and elevated alanine aminotransferase (n = 2, 6.7%). There were no treatment-related deaths.

Conclusions: Gemcitabine plus cisplatin is a feasible chemotherapy regimen with manageable toxicity in patients with advanced BTC. Maintaining good biliary drainage is essential for these patients.

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Key words: biliary tract carcinoma, cholangiocarcinoma, chemotherapy, gemcitabine, cisplatin, biliary drainage

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Biliary tract carcinomas (BTC) are heterogeneous malignancies originating from the epithelium of the biliary tract and include cancers of the gallbladder and ampulla of Vater and cholangiocarcinoma (intrahepatic, perihilar and extrahepatic).[1] BTCs are classified into early (resectable), locally advanced (unresectable but not metastatic), and metastatic disease according to the extent of cancer, with the latter two collectively called advanced BTC. Surgical resection is the only curative strategy for patients with early BTC, but more than half of patients are diagnosed with advanced BTC, including those with relapses after curative surgery.[2-4] Advanced BTC has a grave prognosis and the median survival is less than one year in most studies.

Palliative chemotherapy was established by Glimelius et al. in 1996 to improve both survival and quality of life.[5] Subsequently, chemotherapy with fluoropyrimidine (5-fluorouracil (5-FU), capecitabine), and gemcitabine, with or without platinum (cisplatin or oxaliplatin) has been studied, but the optimal chemotherapy regimen has been debated for more than a decade. In Taiwan, the 5-FU-based regimen has been most widely used, with a response rate of around 20% (Table 1).[6-11]

In 2007, Eckel et al. analyzed pooled phase II studies and concluded that gemcitabine combined with platinum compounds represented the provisional standard for chemotherapy.[12] An ABC-02 trial in 2010, the first phase III study for advanced BTC, indicated that the gemcitabine/cisplatin (GEM-CDDP) combination should be considered a standard treatment option for these patients.[3] Therefore, we retrospectively assessed the efficacy and safety of this regimen on patients with advanced BTC at Linkou Chang Gung Memorial Hospital (CGMH) in Taiwan.

METHODS

Patients

We retrospectively reviewed the medical records of all the patients with BTC consecutively treated between April 2009 and December 2010 at Linkou CGMH. Patients were required to have a histological confirmation of BTC with an inoperable state either because of locally advanced disease or evidence of distant metastasis. All patients had at least one measurable site of disease, an Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2, an absolute neutrophil count ≥ 1,500/μl, a platelet count ≥ 100,000/μl, a serum bilirubin level ≤ 2.0 mg/dl, and a serum creatinine level ≤ 1.5 times the upper limit of normal. No prior cytotoxic chemotherapy was allowed. Patients were excluded if they had a history of any other malignancies except for curative treated non-melanoma skin cancer or a cervical intra-epithelium neoplasm within 5 years. Our analysis was approved by the scientific and research ethics committees of CGMH.

Treatment plan

All chemotherapy-naïve patients with advanced BTC were treated using first-line chemotherapy with a GEM-CDDP regimen. The treatment consisted of gemcitabine (Gemmis®; TTY, Taipei, Taiwan) 1000

Table 1. Previous Phase II Studies of Advanced BTC in Taiwan

Authors	Regimen, dose (mg/m^2), days	No. of patients	RR/SD (%)	TTP (m)	OS (m)
Chen, 1998[6]	Weekly 24-h high-dose of F 2600 mg/m^2 and LV 150 mg	19	33/39	4	7
Chen, 2001[7]	MMC 10 mg/m^2 + weekly 24-h F 2600 mg/m^2 and LV 150 mg	25	26/42	3	6
Lin, 2003[8]	G 1000 mg/m^2 D1, 8, 15 every 4 weeks	24	12.5/33.3	2.5	7.2
Chen, 2003[9]	UFT 300 mg/m^2 + LV 60 mg D1-28 every 5 weeks	16	0/12.5	2.2	5.1
Hsu, 2004[10]	G 800 mg/m^2 + weekly 24-h F 2000 mg/m^2 + LV 300 mg/m^2 on D1, 8, 15 every 4 weeks	30	21.4/46.4	3.7	4.7
Chen, 2009[11]	Biweekly 2-day F 3000 mg/m^2 and LV 100 mg/m^2 infusion + Oxa 85 mg/m^2	32	18.8/31.3	3.7	7

Abbreviations: BTC: Biliary tract carcinoma; RR: response rate; SD: stable disease; TTP: time to progression; OS: overall survival; F: 5-FU; LV: Leucovorin; G: Gemcitabine; MMC: mitomycin C; Oxa: Oxaliplatin; UFT (Tegafur + Uracil); D: Day; h: hour; m: months.

mg/m² followed by cisplatin 30 mg/m² on days 1 and 8 every 3 weeks. The treatment was continued until disease progression, unacceptable toxicity or patient refusal. Second-line chemotherapy was allowed and the regimen was determined by physician assessment.

Study evaluation

Tumor response was evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines every 2–3 cycles. Toxicities were assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 3).

Statistical analysis

All analyses were performed on an intention to treat basis. The description of the cohort used median and extreme values for categorical variables and percentages with 95% confidence intervals (95% CI) for categorical variables. The overall survival (OS) time was defined as the date from the first treatment to death, last follow-up or data cut-off. Time to progression (TTP) was defined as the date from the first treatment to the earliest date of disease progression, death, last follow-up or data cut-off. Both the OS and TTP were analyzed using Kaplan-Meier curves and the log-rank test.

RESULTS

Patient characteristics

There were 32 consecutive patients with advanced BTC screened for this study between April 2009 and December 2010. Two of these patients were excluded because of a history of other primary malignancies, leaving a total of 30 subjects. There were 13 men and 17 women with a median age of 61.5 (range: 38-85). Most (n = 26, 86.7%) patients had an ECOG performance status of 0-1. The primary site of BTC included intrahepatic (n = 15, 50.0%), extrahepatic (n = 3, 10.0%), perihilar (n = 2, 6.7%) sites, the gallbladder (n = 4, 13.3%), and the ampulla of Vater (n = 6, 20.0%). A total of 12 patients (40.0%) had obstructive jaundice that required biliary drainage before chemotherapy: 7 had percutaneous transhepatic biliary drainage, 4 had internal biliary stents, and one had both external and internal drainage. The detailed patient characteristics are provided in Table 2.

Efficacy

By the end of July 2011, 27 patients were evaluated for responses by the RECIST criteria. One patient who refused treatment after the first cycle of chemotherapy and two patients who were lost to follow-up during the first two cycles of chemotherapy were not assessed. According to the intent-to-treat analysis of the responses, none had a complete response (CR), 5 (16.7%) patients had a partial

Table 2. Patient Characteristics (n = 30)

Characteristic	No. of patients (%)
Gender	
Male	13 (43.3)
Female	17 (56.7)
Age, years	
Median (range)	61.5 (38-85)
ECOG performance status	
0-1	26 (86.7)
2	4 (13.3)
Number of cycles	
Median (range)	3 (0.5-12)
Primary site	
Intrahepatic	15 (50.0)
Perihilar	2 (6.7)
Extrahepatic	3 (10.0)
Gallbladder	4 (13.3)
Periampullary	6 (20.0)
Extent of disease	
Locally advanced	9 (30.0)
Metastatic	21 (70.0)
Previous treatment	
Curative surgery	8 (26.7)
Nil	22 (73.3)
Drainage history	
No drainage	18 (60.0)
External drainage	7 (23.4)
Internal drainage	4 (13.3)
External and internal drainage	1 (3.3)
History of biliary tract stones	6 (20.0)
Tumor marker	
Elevated CA19-9 (> 37U/mL)	23/29 (79.3)
Elevated CEA (> 5 ng/mL)	11/27 (40.7)

Abbreviations: ECOG: Eastern Cooperative Oncology Group; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen.

response (PR), and 10 (33.3%) patients had stable disease (SD), resulting in a response rate ([RR], CR + PR) of 16.7% and a tumor control rate ([TCR], CR + PR + SD) of 50.0%. The other 12 (40.0%) patients showed progressive disease (PD). The median time to progression was 4.8 months (95% CI: 3.9–5.7) and the median overall survival was 13.4 months (95% CI: 8.9–17.9). The RR, TCR, TTP and OS were, respectively, 22.2%, 66.7%, 4.9 months, and 14.5 months in the patients without biliary obstruction and 8.3%, 25%, 3.2 months, and 8.9 months in the patients with biliary obstruction requiring drainage. There was no statistically significant difference in the TTP (log-rank, $p = 0.69$) between groups, but patients requiring biliary drainage had a significantly shorter OS (log-rank, $p = 0.02$) (Figure). The efficacy evaluation is shown in Table 3.

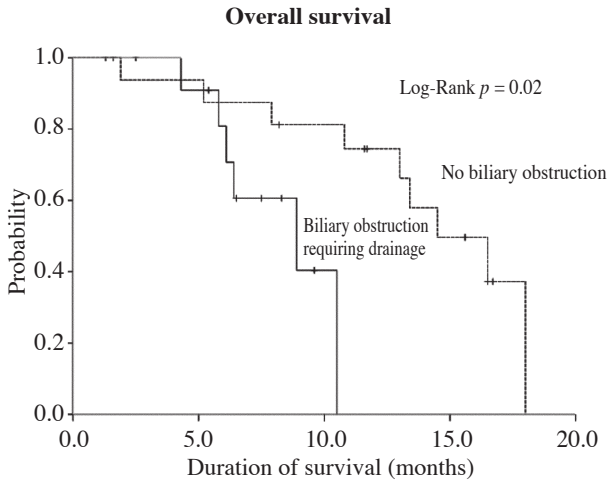

Figure Kaplan-Meier curve of overall survival in patients with biliary obstruction requiring drainage and patients without biliary obstruction.

Toxicity

The toxicity was assessed in all 30 patients by NCI-CTCAE (Table 4). Hematological side effects were commonly observed, but they were generally mild or moderate. The most common grade 3 or 4 toxicity was infection, which occurred in eight patients (26.7%). Among them, 7 patients had biliary tract infections (BTIs) and 6 of them had pre-existing biliary tract obstructions that required biliary drainage before protocol treatment. In addition, 2 patients developed liver abscesses. The other grade 3 or 4 adverse effects included anemia (n = 5, 16.7%), neutropenia (n = 4, 13.3%), and elevated alanine aminotransferase (n = 2, 6.7%).

DISCUSSION

We retrospectively analyzed the efficacy and safety of chemotherapy with GEM-CDDP, which achieved a TCR of 50.0%, median TTP of 4.9 months, and median OS of 13.4 months. The results on consecutive patients had comparable efficacy with prospective studies of GEM-CDDP including several phase II studies[2,13-23] and one phase III study[3] in selected patients (Table 5). Furthermore, we noted that GEM-CDDP also has a comparable TCR, TTP, longer OS, and less toxicity than has been seen in previous studies involving other regimens for

Table 3. Efficacy Evaluation (intention to treat)

	All patients (n = 30)	No biliary obstruction (n = 18)	Biliary obstruction requiring drainage (n = 12)
Objective overall response			
CR	0	0	0
PR	5 (16.7%)	4 (22.2%)	1 (8.3%)
SD	10 (33.3%)	8 (44.4%)	2 (16.7%)
PD	12 (40.0)	5 (27.8%)	7 (58.3%)
No assessment	3	1	2
TCR (CR + PR + SD)	50.0%	66.7%	25%
Median TTP (months, 95% CI)	4.8 (3.9-5.7)	4.9 (2.1-7.7)	3.2 (0.4-6.0)
Median OS (months, 95% CI)	13.4 (8.9-17.9)	14.5 (10.4-18.6)	8.9 (4.2-13.6)

Abbreviations: CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; TCR: tumor control rate; TTP: time to progression; OS: overall survival; CI: confidence interval.

advanced BTC in Taiwan (Table 1). The longer OS resulted from not only the efficacy of the GEM-CDDP treatment, but also advances in providing the best supportive care including carefully managing adverse events from chemotherapy and the complications of BTC itself. Therefore, chemotherapy using the GEM-CDDP combination offers a feasible, less toxic regimen in clinical practice.

Table 4. Adverse Events in the 30 Patients (NCI CTCAE version 3.0, 2001)

	All (%)	Grade 3 or 4 (%)
Hematologic		
Leukopenia	7 (23.3)	0
Neutropenia	6 (20.0)	4 (13.3)
Anemia	29 (96.7)	5 (16.7)
Thrombocytopenia	7 (23.3)	0
Nonhematologic		
Nausea	5 (16.7)	0
Vomiting	2 (6.7)	0
Diarrhea	2 (6.7)	0
Fatigue	4 (13.3)	0
Infection	8 (26.7)	8 (26.7)
ALT	13 (43.3)	2 (6.7)

Abbreviations: NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; ALT: alanine aminotransferase.

The most common adverse effect was hematologic toxicity including neutropenia, anemia and thrombocytopenia, but most of these effects were mild and manageable. In addition to myelosuppression, infection, especially in the biliary tract, was a frequent complication, since some of these patients had biliary tract obstructions and required good internal or external biliary drainage. These episodes of infection could delay upcoming anticancer treatment, and make the patient hesitant about chemotherapy, which could then affect the efficacy of chemotherapy.

The risk of BTI is high during chemotherapy even for patients who have adequate biliary drainage for obstructive jaundice before chemotherapy. In one of our previous reports,[7] four patients had treatment-related deaths, and 3 of them had percutaneous transhepatic drainage and died of neutropenic sepsis. Hsu et al. evaluated gemcitabine plus a 24-h infusion of high-dose 5-FU /leucovorin and reported 6 of 14 patients with drainage had BTIs.[10] In our present

Table 5. Prospective Studies of Gemcitabine/Cisplatin in Advanced BTC

Authors	Regimen, dose (mg/m^2), days	No. of patients	RR (%)/SD (%)	TTP (m)	OS (m)
Phase II studies in advanced BTC					
Thongprasert 2005[13]	G 1250 D1, 8 + C 75 D1	43	27.5/32.5	4.7	8.3
Lee 2006[14]	G 1000 D1, 8 + C 70 D1	24	20.8/50	5.0	9.3
Giuliani 2006[15]	G 1000 D1, 8 + C 75-80 D1	38	32/21	4	8+
Kim 2006[16]	G 1250 D1, 8 + C 60 D1	29	34.5/13.8	3	11
Park 2006[17]	G 1000 D1, 8, 15 + C 75 D1	27	33.3/25.9	5.6	10
Meyerhardt 2008[18]	G 1000 D1, 8 + C 30 D1, 8	33	21/36	6.3	9.7
Lee 2008[19]	G 1250 D1, 8 + C 70 D1	35	17.1/28.6	3.2	8.6
Valle 2009[2]	G 1000 D1, 8, 15	44	22.6/35.5	4.0	NR
	G 1000 D1, 8 + C 25 D1, 8	42	27.8/47.1	8.0	NR
Okusaka 2010[20]	G 1000 D1, 8, 15	42	11.9/38.1	3.7	7.7
	G 1000 D1, 8 + C 25 D1, 8	41	19.5/48.8	5.8	11.2
Phase II studies in advanced gallbladder cancer					
Malik 2003[21]	G 1000 D1, 8 + C 70 D1	11	64/18	6.4	9.7
Doval 2004[22]	G 1000 D1, 8 + C 70 D1	30	36.6/23.3	3.2	3.5
Misra 2005[23]	G 1000 D1, 8, 15 + C 40 D16, 17	40	52.5/17.5	5.5	7.4
Phase III studies in advanced BTC					
Valle 2010[3]	G 1000 D1, 8, 15	206	14.8/56.3	5.0	8.1
	G 1000 D1, 8 + C 25 D1, 8	204	25.5/55.3	8.0	11.7

Abbreviations: BTC: Biliary tract carcinoma; G: Gemcitabine; C: Cisplatin; RR: response rate; SD: stable disease; TTP: time to progression; OS: overall survival; D: Day; m: months; w: weeks; NR: not reported.

study, half of the 12 patients with biliary drainage had BTIs during treatment. The BTIs occurred more frequently in patients requiring biliary drainage during chemotherapy, so biliary drainage requires additional attention in the treatment plan.

We further analyzed the impact of biliary obstruction in patients with advanced BTC receiving palliative chemotherapy. The patients with biliary obstruction requiring drainage had a significantly shorter OS than those without biliary obstruction ($p = 0.02$), even though the TTP showed no statistically significant difference between groups. In other words, the patients with biliary obstruction indeed had a poorer prognosis even when drainage was adequate before chemotherapy. Patients with biliary drainage have a high risk of dysfunctional biliary drainage and BTI. To the best of our knowledge, no previous studies have reported that biliary obstruction is a prognostic factor in patients with advanced BTC receiving palliative chemotherapy, so further analysis of prognostic factors in advanced BTC is warranted.

It should be noted that mutation of the epidermal growth factor receptor (EGFR) and overexpression of tyrosine kinase growth factor receptors such as ErbB-2 and EGFR have been identified in a subgroup of patients with BTC.[24-26] Based on these molecular features, targeted monotherapy with erlotinib, cetuximab, lapatinib, and bevacizumab has been studied in BTC. Phase II studies of biochemotherapy combining gemcitabine-oxaliplatin (GEMOX) with cetuximab[27] or bevacizumab[28] showed much higher response rates of 63% and 40% which resulted in longer median overall survival times of 15.2 and 14.2 months, respectively. However, the correlation between molecular features and targeted therapy is still unclear and further studies should be conducted to achieve individualized treatment. In fact, a randomized phase II study of GEMOX with or without cetuximab in advanced BTC is ongoing in Taiwan (ClinicalTrials.gov, number NCT01267344), and biomarker prediction will be tested.

This current study has several limitations. First, since this is a retrospective single-institution analysis, we could only evaluate the feasibility of GEM-CDDP in our daily practice rather than the efficacy of the GEM-CDDP regimen. Second, treatment with gemcitabine is not reimbursed in patients with advanced BTC by National Health Insurance in Taiwan. Patients receiving GEM-CDDP as first-line chemotherapy comprised only a small proportion of the entire group, and some of these patients could not maintain chemotherapy until the disease progressed because of economic concerns. Third, we analyzed the impact of biliary obstruction in a single GEM-CDDP regimen which cannot represent all palliative chemotherapy. Some confounding factors should have been considered but the number of patients was too small for further univariate and multivariate analysis. Further analysis should be conducted to examine whether biliary obstruction is a prognostic factor in these patients with advanced BTC receiving chemotherapy.

In conclusion, GEM-CDDP is a feasible regimen with manageable toxicity for patients with advanced BTC. With this regimen, patients requiring biliary drainage had a significantly poorer prognosis than those without biliary drainage. Biliary drainage is an important issue in patients whose condition is complicated by biliary obstruction.

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使用化療吉西他濱 (Gemcitabine) 合併順鉑 (Cisplatin) 在長庚紀念醫院晚期膽道癌患者的經驗：回顧性分析

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背 景： 吉西他濱 (gemcitabine) 合併順鉑 (cisplatin) 在晚期膽道癌是一個標準的化學治療選擇，本研究於長庚紀念醫院評估此化學治療處方的療效和安全性

方 法： 於 2009 年 4 月至 2010 年 12 月期間，回顧性分析共 30 例未接受過化學治療的晚期膽道癌患者（13 名男性和 17 名女性，年齡中位數：61.5 歲）。化學治療處方包括第 1、8 天使用吉西他濱（健仕®；台灣東洋製藥）1000 mg/m^2 及順鉑 30 mg/m^2，每 3 週爲一個週期的治療。每 2–3 個週期使用實體腫瘤反應評估標準 (RECIST) 評估腫瘤反應，使用美國國家癌症研究院常見毒性標準 (NCI CTCAE) 3.0 版評估毒性。

結 果： 至 2011 年 7 月月底，共 27 例患者使用 RECIST 評估腫瘤反應。根據治療意向分析，5 例 (16.7%) 有部分反應，10 例 (33.3%) 疾病穩定，12 例 (40.0%) 疾病惡化。30 例患者腫瘤惡化時間及存活時間的中位數分別爲 4.8 個月和 13.4 個月。接受化療前因膽管阻塞需要引流的患者比沒有膽管阻塞的患者有顯著較短的存活時間 (p = 0.02)，即使兩組在腫瘤惡化時間無統計學顯著性差異 (p = 0.69)。在 30 例患者主要第三、四級不良事件包括感染 (26.7%)，貧血 (16.7%)，中性顆粒細胞低下 (13.3%)，以及丙氨酸轉氨酶(ALT) 升高 (6.7%)，並沒有治療相關死亡。

結 論： 治療晚期膽道癌的患者，吉西他濱合併順鉑使用是一個合適的化學治療處方，其毒性反應是可以處理的。維持良好膽管引流對這些患者是基本必要的。
(長庚醫誌 2012;35:420-7)

關鍵詞： 膽道癌，膽管癌，化學治療，吉西他濱，順鉑，膽道引流

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