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ORIGINAL ARTICLE

A phase II trial of biweekly oxaliplatin with simplified schedule of 48-h infusion of high-dose 5-fluorouracil and leucorvin for advanced biliary tract carcinoma

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Abstract
Purpose Advanced biliary tract carcinoma (BTC) is a dismal disease with no standard chemotherapy. We investigated efficacy and toxicity of biweekly oxaliplatin with 48-h infusion of 5-FU/LV in advanced BTC.
Methods All patients had histologic confirmation of BTC, at least one measurable site of disease, and had received no prior chemotherapy. Patients were older than 20 years with ECOG performance scores (PS) of 0–2. Treatment involved 2-h infusion of oxaliplatin (85 mg/m^2) diluted in D5W 500 ml followed by 48-h infusion of 5-FU (3,000 mg/m^2) and LV (100 mg/m^2) biweekly. Response evaluation was based on RECIST criteria and was carried out every two courses of treatment; toxicity evaluation was based on NCI common toxicity criteria version 3.0.
Results From August 2005 to December 2006, 34 chemotherapy-naive patients with advanced BTC were enrolled and 32 intention-to-treat patients were evaluated. Partial response was 18.8%, stable disease was 31.3%, resulting in a disease control rate of 50.0%. Median time to progression and survival was 3.7 and 7 months, respectively. The most common grade 3/4 toxicities were neutropenia 15.6% (5/32), stomatitis 9.4% (3/32), thrombocytopenia 6.3% (2/32), diarrhea 6.3% (2/32) and neuropathy 3.1% (1/32). No treatment-related deaths occurred.
Conclusions The biweekly OXA and 48-h infusion of 5-FU/LV in patients with advanced BTC showed tolerable and efficacy equivalent to other combination regimens treatment.

Keywords Biliary tract cancer · Chemotherapy · Oxaliplatin · 5-Fluorouracil · Leucovorin

Introduction

The results of treatment of locally unresectable or disseminated biliary tract carcinomas (BTC) to date have been discouraging, possibly due to its rarity. The most common extensively studied single agents for systemic application in BTC were 5-fluorouracil (5-FU) [1, 2]. 5-FU has been used as a single agent and in combination chemotherapy trials for the treatment of BTC; its impact on survival and response has been limited [3–5]. A randomized trial comparing FAM with 5-FU alone did not demonstrate any benefit in terms of response rate and survival [6]. Therefore, single agent treatment with either 5-FU is one of the recommended chemotherapeutic agents for patients with advanced BTC. The modulation of 5-FU with leucovorin (LV) has been widely documented for a better response

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than 5-FU alone in colorectal cancer [7]. We reported that a weekly 24-h infusion of high-dose 5-FU (HDFU) and LV for patients with BTC yielded acceptable results with mild toxicity in comparison to the conventional dose schedule of 5-FU/LV combination [8]. Subsequently, we added mitomycin to the weekly 24-h infusion of HDFU and LV [9]. The response rate and survival did not improve and the incidence of toxicity was higher than with HDFU/LV. A biweekly 48-h infusion of HDFU/LV with Cisplatin (CDDP) achieved a 34% response rate with a median survival of 9.5 months [10]. The major toxicity was acceptable and only one patient had a grade 4 thrombocytopenia. Obviously, the weekly 24-h or biweekly 48-h infusion of HDFU/LV for BTC is an acceptable schedule with a higher response and less toxicity. There is a need to explore other combination chemotherapy regimens in order to provide substantial disease control, low toxicity, and a convenient regimen for patients with BTC (Table 1).

Oxaliplatin (OXA), a cytotoxic agent from the diaminocyclohexane platinum family, has a mechanism similar to that of other platinum derivatives, but its spectrum of antitumor activity differs from those of CDDP and carboplatin [11]. Activity against CDDP-resistant colon carcinoma cell lines and the synergistic activity of the OXA and 5-FU combination have been shown experimentally [12]. Clinical toxicity of OXA-based therapy is distinct from that of other platinum drugs. It has no renal toxicity and minimal hematotoxicity, and causes both a reversible acute, cold-related dysesthesia and a dose-limiting cumulative peripheral sensory neuropathy [13]. At present, OXA with HDFU/LV is one of the standard care first-line therapies for metastatic colorectal cancer [14]. Nehls et al. [15] reported that 16 patients with advanced bile duct cancer received FOLFOX-3. The combination chemotherapy regimen achieved a disease control rate of 56% (partial response 19% and stable disease 37.5%) and median survival was 9.5 months among 19 patients. The author concluded that this regimen might be important in BTC treatment. We initiated the current phase II study to assess OXA combining a simplified schedule of biweekly 48-h infusion of HDFU and LV. The primary objective was to evaluate the response rate. The secondary objective was to determine time to progression, overall survival, feasibility and tolerance.

Patients and methods

Eligibility criteria

Patients were required to have histological confirmation of carcinoma of intrahepatic, perihilar, distal common bile duct, and gallbladder or periampular Vater areas with metastatic disease or inoperable state and at least one measurable site of disease [16]. Patients had no prior chemotherapy for advanced disease, but chemotherapy for a radio-sensitizer for an adjuvant setting was allowed. Prior local radiotherapy was allowed (at least 4 weeks after chemo-radiotherapy or radiotherapy). Patients were older than 20 years and recruited if they met the following criteria: ECOG performance status score $\leq$2; ANC $\geq$1,500 cells/L, platelet count $\geq$100,000/L, serum bilirubin level $\leq$3.0 mg/dL, and serum creatinine level $\leq$1.5 times the upper limit unit. Every patient was aware of the nature of his/her disease process and gave written informed consent. This study was approved by the scientific and research ethics committees of the participating institutions.

Table 1 Summary of phase II studies of 5U-based in BTC

Authors	No. of patients	Regimen	Response rate (%)	Time to progression	Over median survival
Hall et al. [3]	7	ADR, BCNU, Ftorafur	CR 29%, PR 14%	NA	11 months in responders
Harvey et al. [4]	17	ADR, mitomycin, 5-FU	PR 31%	NA	11 months
Falkson et al. [5]	53	1, 5-FU oral	1, 1/12 (8%)	NA	5.5 months
		2, 5-FU oral + STZ	2, 0		
		3, 5-FU oral + MeCCNU	3, 2/12 (16%)		
Chen et al. [8]	19	Weekly 24-h high-dose of 5-FU 2,600 mg/m^2 and LV 150 mg	33%	4 months	7 months
Chen et al. [9]	25	Mitomycin + weekly 24-h high-dose of 5-FU 2,600 mg/m^2 and LV 150 mg	26%	3 months	6 months
Taieb et al. [10]	29	Biweekly 2-day LV and 5-FU infusion and CDDP (LV5FU2-P)	34%	6.5 months	9.5 months

ADR adrimycin, *NA* no analysis, *STZ* streptozotozcin, *MeCCNU* methyl-CCNU

Exclusion criteria

Exclusions from this study included patients with hypersensitivity to any component of this chemotherapeutic regimen, patients with the history of other malignancy except curative treated non-melanoma skin cancer or CIN (cervical intra-epithelium neoplasm) carcinoma in situ within 5 years, patients who had serious concomitant illness that might be aggravated by chemotherapy, female patients who were pregnant or breast-feeding, patients who were receiving other concomitant chemotherapy, radiotherapy or any other anticancer treatment, patients whose mental states were not fit for clinical trials, and patients with CNS metastasis.

Treatment plan

Oxaliplatin (Oxalip, TTY Biopharm Company, Taipei, Taiwan) was administered at 85 mg/m^2 diluted in 500 ml 5% dextrose as a 2-h infusion, followed by 48-h continuous infusion of 5-FU 3,000 mg/m^2 and LV 100 mg/m^2 in Infusor (Baxter, USA). The study regimen was administered repeatedly every 2 weeks. The treatment was continued until disease progression and the occurrence of unacceptable toxicity or patient refusal.

Study evaluation

Tumor responses were evaluated after every two courses according to Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines. Toxicities were recorded based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC, Version 3, 2001).

Statistical considerations

The primary end point of this phase II study was response rate. Secondary end points were time to progression, overall survival time and safety. Time to progression was defined as the period from the first day of drug treatment to the date when progressive disease or relapse was clearly observed. Overall survival was the period from the first day of drug treatment to the date of death from any cause. Safety variables included toxicity grading, adverse events and laboratory values. According to the previous literature and the poor treatment outcome of this disease, we designed an optimal Simon's two-stage model to evaluate the first ten patients. Had no patients responded, the study was to be terminated and we would conclude that the response rate was 5%. Otherwise, an additional 19 patients were to be enrolled. Our design would yield 80% power to detect a response rate between 5 versus 20% with a significance level of 0.05. It would yield a 90% probability of detecting negative results if the true response rate was 5%, with 60% of early conclusion. The sample size was determined for complete evaluation of 29 patients.

Results

Patient characteristics

There were 34 patients screened for this study between August 2005 and December 2006 from four sites. The number of eligible patients for this study was 32 out of 34 since one patient violated inclusion criteria and one patient did not receive any dose of chemotherapy treatment. There were 13 females and 19 males patients with a median age of 62 (range: 41–82). Patient characteristics are provided in Table 2.

Efficacy

All the treatments were completed by the end of June 2007. Three patients among 32 cases had no tumor assessment due to the following reasons: the first patient had alcoholic hepatitis with poor liver function after first course of chemotherapy; the second patient had prolonged fever after an episode of

Table 2 Patient's characteristics

	N = 32
ECOG	
0	19
1	11
2	2
Gender: M/F	19/13
Age (median)	62 (Range: 41–82)
Median # of cycles	6 (Range: 1–20)
Primary site	
Peripheral type	7
Hilar type	1
Distal common bile duct	5
Gallbladder	10
Periampullary	8
Unclassified	1
Disease involvement sites	
Liver	23
Peritoneum	9
Intra-abdominal lymph nodes	16
Other	13
Drainage history	
No drainage	25
External drainage	3
Internal drainage	3
External and internal drainage	1

pneumonia without neutropenia; the third patient had prolonged fever without unknown etiology after first course of chemotherapy. According to intent-to-treat analysis of response, six patients out of 32 had a partial response 18.8% (95% CI: 7.2–36.4%), 10 had stable disease (31.3%), resulting in disease control rate of 50.0% (95% CI: 31.9–68.1%). Thirteen patients showed disease progression (44.8%). The median time to progression was 3.7 months (95% CI, 1.5–5.9 months) and the overall median survival time was 7.0 months (95% CI, 4.8–9.2 months) Table 3 summarized the efficacy results.

Toxicity

Toxicity was assessed in all 32 patients as summarized in Table 4. A total of 220 cycles of chemotherapy with a median of 6 were administrated to the 32 patients (range: 1–20). The most common hematologic toxicities in terms of per patient were thrombocytopenia (21/32, 65.6%) and neutropenia (12/32, 37.5%). The most common non-hematologic toxicities were abnormal liver function (20/32, 62.5%) and neuropathy (18/32, 56.3%). These adverse events were manageable. The major grade 3/4 toxicities of more than 5% were neutropenia 5/32 (15.6%), stomatitis 3/32 (9.4%), thrombocytopenia 2/32 (6.3%), and diarrhea 2/32 (6.3%). There were no treatment-related deaths. In addition, the toxicity by cycle was also presented in Table 4, which showed that the most common grade 3/4 toxicity of more than 5% was neutropenia (8.2%). The major reasons for withdrawal from the treatment were progression of disease in 21 patients, refusal in one patient, protocol violation in one patient and toxicities in nine patients. There were four allergic reactions due to OXA infusion among the nine patients who stopped the therapy due to toxicity.

Table 3 Efficacy evaluations (intention-to-treat)

Parameter	$N = 32$
Objective overall response	
Complete response	0
Partial response	6 (18.8%) (95% CI: 7.2–36.4%)
Stable disease	10 (31.4%)
Progression	13 (44.8%)
No assessment	3
Disease control rate (PR + SD)	50.0% (95% CI: 31.9–68.1%)
Time to progression (months)	3.7 (95% CI: 1.5–5.8)
Overall survival (months)	7.0 (95% CI: 4.8–9.2)

Discussion

The biweekly regimen of OXA and 48-h HDFU/LV achieved a disease control rate (PR and SD) of 50.0%, time to progression of 3.7 months, and overall median survival of 7 months. The adverse events were manageable. The major grade 3/4 toxicity among 32 patients was less than 10% except for neutropenia at 5/32 (15.6%). This result was similar to that of the FOLFOX-3 regimen [15]. However, our HDFU/LV infusion schedule was simpler than the FOLFOX-3 regimen; 24 or 48-h infusion HDFU/LV schedule used in treating BTC had been reported previously. This infusion schedule may result in higher dose-intensity and lower toxicity than conventional infusion or bolus schedule of 5-FU/LV [8]. CDDP with 48-h infusion of HDFU/LV

Table 4 Adverse events (CTC version III, 2001)

	By patient ($n = 32$)			By cycle ($n = 220$)		
	All (%)	Grade 3 (%)	Grade 4 (%)	All (%)	Grade 3 (%)	Grade 4 (%)
Hematologic						
Leukopenia	37.5	3.1	0.0	12.7	0.5	0.0
Neutropenia	37.5	9.4	6.3	26.4	6.8	1.4
Thrombocytopenia	65.6	6.3	0.0	22.7	0.9	0.0
Anemia	31.3	0.0	0.0	8.6	0.0	0.0
Non-hematologic						
Liver	62.5	0.0	0.0	11.8	0.0	0.0
Nausea	34.4	3.1	0.0	10.9	0.5	0.0
Vomiting	40.6	3.1	0.0	12.7	0.5	0.0
Mucositis	50.0	9.4	0.0	3.6	0.0	0.0
Diarrhea	34.4	6.3	0.0	5.0	0.9	0.0
Neuropathy	56.3	3.1	0.0	4.5	0.5	0.0
Allergy reaction	12.5	3.1	0.0	0.9	0.5	0.0
Fatigue	18.8	0.0	0.0	1.8	0.0	0.0
Hand–foot syndrome	6.3	0.0	0.0	0.9	0.0	0.0

(LV5FU2-P regimen) had demonstrated a PR in 34% and SD in 38% with 9.5 months of overall survival [10]. A randomized phase II study of 24-h infusion HDFU with or without CCDP was reported [17]. The objective response rates of 24-h HDFU and CDDP with HDFU/LV were 7.1 and 18.15%, respectively. The survival was better in CDDP combining HDFU/LV arm than the HDFU arm (8 vs. 5 months). But, the toxicity of CDDP combining HDFU/LV was higher than with HDFU. The author did not propose a phase III study because of higher toxicity even though the response and survival of the study arm was superior to that of the HDFU arm. Nevertheless, the author suggested that new drug combinations such as 5-FU and OXA should be evaluated for this disease. Recently, Nehls reported a phase II study of OXA and oral Capecitabine (CAPAX study) [18]. The results showed the response rate in 47 patients with GBC/ECC was 27% (4% complete responses), and in 23 patients (49%) stable disease (SD) was encountered. The most common grade 3/4 toxicity was peripheral sensory neuropathy (11 patients). From our results and those of two Nehl's studies, we conclude that OXA combining with HDFU/LV or oral fluoropyridime could have a nearly 20% response rate and survival close to 9 months. The major grade 3/4 toxicity was lower than with CDDP with HDFU/LV. OXA may potentially replace CDDP in order to reduce the toxicity and maintain or improve efficacy in future studies of BTC. Surprisingly, there were four patients who had acute allergic reactions during infusion of OXA. This adverse reaction has been reported only rarely in the literature [19]. Hence, one must keep in mind that there is the possibility of allergic reactions to OXA.

In addition to OXA with 5-FU/LV, the results of the studies on OXA combining with Gemcitabine (GEM) in treating biliary tract cancer was attractive [20, 21]. Harder et al. [20] reported that the combination of OXA and GEM had a tumor control rate (TCR) (CR + PR + SD) of 71% (PR 26% and SD 45%), time to progression (TTP) of 6.5 months and overall survival (OS) of 11 months in treating BTC. The major grade 3/4 toxicities were thrombocytopenia (23%), peripheral sensory neuropathy (19%), leucopenia (16%) and anemia (10%), which were higher than the grade 3/4 toxicities in this study. A recent another similar phase II study involving the combination of OXA and GEM was reported by Andre et al. [21], that showed the objective response rate was 20.5% in patients with non-gallbladder cancers (9/44 patients) and 4.3% in patients with gallbladder cancers (1/23). Median overall survival for the intention-to-treat population was 8.8 months and progression free survival was 3.4 months. A phase II study of GEM and 24-h HDFU/LV conducted in Taiwan showed a 21% response rate with similar toxicity but with TTP and OS of only 3.7 and 4.7 months, respectively [22].

Table 5 Summary of recent phase II studies of chemotherapy in BTC

Author	No. of patients	Regimen	Response rate (%)	Time to progression	Over median survival
Nehls et al. [15]	16	FOLFOX-3	PR 19% and SD 37.5% (Disease control rate 56%)	4.1 months	9.5 months
Hsu et al. [22]	30	GEM and weekly high-dose of 5-FU 2,000 mg/m^2 and LV	21.4%	3.7 months	4.7 months
Ducreux et al. [17]	58	Arm A: weekly 5-FU 3.0 gm/m^2 24-h infusion	Arm A: 7%	Arm A: 3.3 months	Arm A: 5.5 months
		Arm B: weekly 5-FU 2.0 gm/m^2 24-h infusion with LV 500 mg/m^2 and biweekly CDDP 50 mg/m^2	Arm B: 15%	Arm B: 3.3 months	Arm B: 8.5 months
Harder et al. [20]	31	GEM weekly for 3 weeks of 4-week with biweekly OXA	PR 26% and SD 45% (Disease control rate 71%)	6.5 months	11 months
Andre et al. [21]	70	GEM and OXA biweekly	PR 14.9% and SD 35.8%	3.4 months	8.8 months
Nehls et al. [18]	65	OXA 130 mg/m^2 day 1 and Xeloda 1,000 mg/m^2 bid for 2 weeks every 21-day	ICC: 38% SD GBC/ECC: PR 27%, SD 47%	ICC: 2.2 months GBC: 4.7 months ECC: 11.3 months	ICC: 5.2 months GBC: 8.2 months ECC: 16.8 months

GEM Gemcitabine, *OXA* Oxaliapltin

A pooled analysis of chemotherapy for 2,810 patients with BTC was published [23]. The response rate (CR + PR), TCR, time to tumor progression and over survival for 112 trials were 22.6, 57.3%, 4.1 and 8.2 months, respectively. Among the combination therapies utilized in the 112 trials, the subgroup analysis showed that those containing platinum or GEM showed higher response rates and tumor control rates. The combination of GEM and Platinum drugs appear to have better efficacy in terms of response rate and tumor control rate of 35 and 65%, respectively from this pooled analysis. The subgroup analysis of the pooled analysis also showed that 5-FU and platinum combination achieved an overall response rate and tumor control rates of 25 and 60%, respectively. Further phase III studies involving the comparison between regimen of OXA combining GEM or 5-FU in the treatment of BTC seem worthy. Recently, it was reported that seven of 52 patients (17%) on oral Erlotinib were progression-free at 6 months and three patients had PR [24]. Further studies of chemotherapy combining target therapy for BTC should also be considered (Table 5: summary of recent chemotherapy studies).

In conclusion, the efficacy of combination regimen of OXA and simplified biweekly 48-h infusion regimen of HDFU/LV in treating unresectable biliary tract cancer was similar to that of previous studies and the toxicities were manageable with lower incidence of myelosuppression. According to the results of this study, further studies to investigate more efficacious regimens for treating unresectable BTC should be encouraged.

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