A Phase II Study of Outpatient Biweekly Gemcitabine–Oxaliplatin in Advanced Biliary Tract Carcinomas

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Objective: Biliary tract carcinomas are uncommon but highly fatal malignancies. Unfortunately, most cases are ineligible for surgery at diagnosis with chemotherapy being the mainstay of treatment. The aim of this Phase II study was to evaluate the efficacy and safety of a biweekly outpatient regimen of gemcitabine plus oxaliplatin in cases of advanced biliary tract carcinomas.

Methods: Forty patients with advanced, chemotherapy-naïve biliary tract carcinomas were enrolled in the study between December 2005 and November 2009. All patients received the gemcitabine plus oxaliplatin treatment protocol as follows: gemcitabine 1000 mg/m² (30 min infusion) followed by oxaliplatin 85 mg/m² (2 h infusion) on days 1 and 15 of a 28-day cycle. The primary endpoint was the tumor control rate. Efficacy and safety analyses were done by intention to treat.

Results: The objective response rate was 27.5% and the tumor control rate was 65%. The median progression-free survival was 4 months and the median overall survival was 12 months. The tumor control was translated into a significant prolongation in overall survival. The regimen was generally well tolerated; Grade 3–4 toxicities were recorded in 25% of the patients with neutropenia being the most common (17.5%); Grade 3 sensory neuropathy was uncommon (2.5%).

Conclusions: The study provides further evidence for the activity of gemcitabine plus oxaliplatin combination as a first-line treatment for advanced biliary tract carcinomas. This combination can be given safely as a convenient biweekly outpatient regimen.

Key words: biliary – Phase II – gemcitabine – oxaliplatin

INTRODUCTION

Biliary tract carcinomas (BTCs) are invasive carcinomas that originate from the epithelial lining of the gallbladder and bile ducts. BTCs include cholangiocarcinomas (CCs) and gallbladder carcinoma (GBC). The anatomic location of CC can be described as intrahepatic, distal extrahepatic or hilar. Lesions can be described as mass-forming, periductal or intraductal, or as mixed mass-forming and periductal (1). The incidence and mortality rates of intrahepatic CC are rising, whereas GBC and extrahepatic CC incidences are slightly declining (2,3). Surgery is the only curative treatment option for BTCs. However, <25% of the patients are resectable at presentation with high relapse rates after surgery (4). Patients with unresectable BTCs can be considered for palliative chemotherapy, which is reported to improve overall survival (OS) and quality of life over best supportive care (5,6).

5-Fluorouracil (5-FU) is the most extensively studied single agent used in the treatment of BTCs; however, the efficacy of 5-FU-based regimens has been disappointing, with a response rate (RR) of <20% (7–9). Older non-platinum combination chemotherapy, with 5-FU, has not demonstrated a clear superiority over single-agent fluorouracil but has resulted in added toxicity (6,10).

Gemcitabine, a pyrimidine analogue, has been shown to be the most active single-agent therapy in BTCs (11). As a single-agent objective, response has been reported between 8
and 60% (12–15). Chemotherapy combinations based on gemcitabine have been evaluated with several agents, among them were 5-FU, mitomycin, docetaxel, irinotecan, capecitabine and cisplatin, and the objective response seen: 9–64% and stable disease 9.3–53% (11). The combination of gemcitabine with platinum compounds increased RRs and tumor control rates (TCRs) compared with gemcitabine alone (16).

The third-generation platinum analogue oxaliplatin was used as monootherapy in one Phase II study in patients with advanced BTCs. An objective RR of 20.6% was observed with an OS of 7 months (17).

Pre-clinical studies of the gemcitabine–oxaliplatin combination have demonstrated that gemcitabine synergistically interacts with oxaliplatin in terms of anti-tumor activity in vitro (18,19). Moreover, Mavroudis et al. (20) demonstrated the feasibility and safety of gemcitabine–oxaliplatin combination chemotherapy in a Phase I study involving patients with advanced solid tumors: the maximum tolerated dose was not reached and the combination was well tolerated with a manageable toxicity of doses up to 1400 mg/m² of gemcitabine on days 1 and 8 and doses up to 120 mg/m² of oxaliplatin. Some Phase II studies on BTCs with the gemcitabine–oxaliplatin combination have reported variable results and suggested clinical benefits that need to be confirmed (21–23).

The aim of this Phase II study was to evaluate the efficacy and toxicity of a biweekly regimen of gemcitabine plus oxaliplatin (GEMOX) in cases of advanced BTCs of our locality.

**PATIENTS AND METHODS**

**Eligibility Criteria**

Patients aged ≥18 years with histologically proven, locally advanced or metastatic, chemotherapy-naïve BTC (GBC and CC) were enrolled in the study. Other eligibility criteria included: Eastern Cooperative Oncology Group performance status ≤2; at least one unidimensionally measurable lesion; no prior chemotherapy for advanced disease; and adequate hematological (neutrophils ≥1500/mm³, platelets ≥100 000/mm³), renal [creatinine <1.5 × the upper limit of normal (ULN)] and hepatic function (alanine aminotransferase <5 × ULN, bilirubin <2.5 × ULN). Patients with jaundice or evidence of bile duct obstruction and in whom the biliary tree could be decompressed by endoscopic percutaneous endoprosthesi, with a subsequent reduction in bilirubin to <2.5 × ULN, were also eligible. Patients with prior malignancy or prior chemotherapy for advanced disease, central nervous system metastases or peripheral neuropathy grade ≥2 were excluded from the study. Prior radiation therapy within 4 weeks of the first gemcitabine administration was not permitted. Women of childbearing potential were required to be neither pregnant nor breastfeeding and to be under active contraception.

The protocol was approved by the institutional review board. Informed consent was obtained from each patient.

**Treatment Schedule and Toxicity Assessment**

All patients received the GEMOX treatment protocol as follows: gemcitabine 1000 mg/m² intravenous infusion over 30 min, followed by oxaliplatin 85 mg/m² intravenously over 2 h. Both drugs were given on days 1 and 15 of a 28-day cycle. Treatment was continued until progression, unacceptable toxicity or withdrawal of patient consent. Adverse events were recorded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0. Gemcitabine doses were reduced by 25% in all subsequent cycles for febrile neutropenia, Grade 4 hematologic toxicity lasting for more than 7 days or bleeding-associated thrombocytopenia. Oxaliplatin doses were reduced by 25% in the case of cumulative sensory peripheral neuropathy adverse event grade 2 persisting over 7 days. In the case of Grade 3 or 4 peripheral sensory neuropathy, oxaliplatin was stopped and treatment was subsequently continued according to the same schedule, but with gemcitabine alone. For patients who progressed, and still in a good performance status, palliative 5-FU-based single-agent chemotherapy was planned as the second-line chemotherapy.

**Treatment Evaluation and Statistics**

This Phase II study was designed with an 80% power to exclude a true TCR of <50% and detect a true TCR of ≥70%. The primary endpoint was the objective RR and TCR; secondary endpoints were time to progression, OS and toxicity. According to the Fleming one-stage design (24), the study requires 37 subjects to decide whether the proportion achieving tumor control, \( P \), is ≤0.5 or ≥0.7. If the number of patients achieving tumor control is 24 or more, the hypothesis that \( P \leq 0.5 \) is rejected with a target error rate of 0.05 and an actual error rate of 0.049. If the number of patients achieving tumor control is 23 or less, then the hypothesis that \( P \geq 0.7 \) is rejected with a target error rate of 0.2 and an actual error rate of 0.193. Estimating a dropout rate of 10%, a total of 40 patients were planned to be accrued for this study.

Tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) (25) with computer tomography (CT) scans performed at baseline and every two cycles of treatment. Responses were confirmed by CT scan at least 4 weeks later. Progression-free survival (PFS) was calculated from the date of entry to the study to the date of objective disease progression assessed by CT scan or death. OS was measured from the date of entry to the study to the date of last follow-up or death.

Data were analyzed on a personal computer running SPSS Release 15. All tests are considered significant if \( P < 0.05 \). For descriptive statistics of qualitative variables, the frequency distribution procedure was run with the calculation of the number of cases and percentages. For descriptive statistics of quantitative variables, the mean, range and standard deviation were used to describe central tendency and dispersion.
Association between categorical variables was tested by the $\chi^2$ test. The median follow-up was calculated by the use of the reverse Kaplan–Meier method (26). Survival and PFS analyses were calculated by the Kaplan–Meier product–limit estimator. The log rank test was used for comparison of the survival curves in subgroup analysis. The study outcomes were assessed according to the intention-to-treat principle. All statistical tests were two-sided.

**RESULTS**

**PATIENT CHARACTERISTICS**

Forty patients with advanced, chemotherapy-naïve BTCs were enrolled in the study between December 2005 and November 2009. The study was conducted in the Clinical Oncology and Nuclear Medicine Department and the Oncology Center of the University of Mansoura, Egypt. The cut-off date for data analysis was 31 May 2010. The diagnosis of advanced BTCs was based on radiological findings in 31 cases, whereas in 9 cases, the diagnosis of locally advanced disease was established during exploratory laparotomy. The primary cancer site has been the gallbladder in 14 (35%), intrahepatic bile ducts in 14 (35%) and extrahepatic bile ducts in 12 (30%) cases. The mean age of studied cases was 59 years with a slight female predominance and baseline characteristics are summarized in Table 1.

**TREATMENT RECEIVED**

A total of 129 cycles of chemotherapy were administered (median 4 cycles per patient, range 3–20 cycles). The most common reason for treatment discontinuation was disease progression (33 patients; 82.5%). In three patients (7.5%), the treatment was discontinued at the physician’s discretion because of poor PS. In four patients (10%), the treatment was discontinued before completing two cycles of treatment (one patient lost follow-up after receiving day 1 of the second cycle, one patient died of intestinal perforation owing to tumor infiltration after receiving the first cycle, and in the remaining two patients, chemotherapy was stopped early because of malignant biliary obstruction with failure of drainage). Treatment delays primarily due to hematologic toxicity were necessary in seven patients (17.5%). In two patients (5%), dose reductions had to be performed, due to hematologic toxicity. In one patient (2.5%), the dose of oxaliplatin had to be reduced and later on discontinued due to peripheral neuropathy, and the patient continued the treatment with gemcitabine alone.

**TOXICITY**

Toxicities according to the NCI-CTC version 3 are summarized in Table 2. Most of the studied patients suffered one or more adverse event of any grade. Overall, Grade 3–4 toxicities were recorded in 10 patients (25%). Grade 3–4 hematologic toxicities were recorded in nine patients (22.5%) including: neutropenia (17.5%) with three febrile episodes (7.5%), anemia in two patients (5%) and thrombocytopenia in two patients (5%). Grade 3–4 non-hematologic toxicities were recorded in three patients (7.5%). One-third of the patients developed peripheral neuropathy; of them one patient (2.5%) suffered Grade 3 neuropathy (after receiving eight cycles) that improved rapidly upon discontinuation of oxaliplatin. There was no difference in toxicity between patients with GBC and patients with CC. No treatment-related mortality was encountered in the study.

**EFFICACY**

Objective tumor response was observed in 11 patients (27.5%), 1 patient of them (2.5%) achieved complete response (CR) and 10 patients (25%) achieved partial response. Fifteen patients (37.5%) achieved stable disease. Thus, TCR was achieved in 65% of the cases (Table 3). No significant difference was observed between GBC and CC, as determined by criteria for RR (Table 4).

The median follow-up period of studied patients was 11 months (95% CI, 7.6–14.4 months). The median PFS for all patients was 4 months (95% CI, 2.7–5.4 months)

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
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<th>No. (%)</th>
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<tr>
<td><strong>Sex</strong></td>
<td></td>
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<tr>
<td>Male</td>
<td>17 (42.5)</td>
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<tr>
<td>Female</td>
<td>23 (57.5)</td>
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<tr>
<td><strong>Age</strong></td>
<td></td>
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<tr>
<td>Mean</td>
<td>59</td>
</tr>
<tr>
<td>Range</td>
<td>31–73</td>
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<tr>
<td><strong>Performance status (ECOG)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>1</td>
<td>26 (65.0)</td>
</tr>
<tr>
<td>2</td>
<td>10 (25.0)</td>
</tr>
<tr>
<td><strong>Primary cancer site</strong></td>
<td></td>
</tr>
<tr>
<td>GBC</td>
<td>14 (35.0)</td>
</tr>
<tr>
<td>CC</td>
<td>26 (65.0)</td>
</tr>
<tr>
<td><strong>Disease at presentation</strong></td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>9 (22.5)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>31 (77.5)</td>
</tr>
<tr>
<td>Biliary stent</td>
<td>8 (20.0)</td>
</tr>
<tr>
<td><strong>Metastasis</strong></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>17 (42.5)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>10 (25.0)</td>
</tr>
<tr>
<td>Lung</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>1 (2.5)</td>
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</tbody>
</table>
The median PFS was equal in both the gallbladder and CC (Fig. 2). Overall, 36 deaths were recorded during the study period. The median OS for all patients was 12 months (95% CI, 10.1–13.8 months) (Fig. 3). The median OS was higher in patients with CC (13 months; 95% CI, 11.4–14.7) than GBC (10 months; 95% CI, 4.6–15.4) and the difference was not statistically significant (log rank 2.8, *P* = 0.094) (Fig. 4). The median OS for patients who responded to treatment was 13 months (95% CI, 11.9–14 months), whereas the median OS for non-responders was 10 months (95% CI, 1–18.9 months) and the difference was of borderline significance (log rank 3.6, *P* = 0.057) (Fig. 5). A pronounced difference in the OS was found after subgroup analysis for tumor control, and the median OS for patients who achieved tumor control was 13 months (95% CI, 11.9–14.1 months) versus 3 months (95% CI, 2.8–3.2 months) for patients who suffered progressive disease (log rank 43, *P* < 0.0001) (Fig. 6).

**DISCUSSION**

BTCs are uncommon but highly fatal malignancies (1). Unfortunately, most BTCs are ineligible for surgery at
diagnosis due to advanced stage of the disease or associated liver function impairment. Median survival of patients with advanced disease is in the range of only a few months (16). Even in patients undergoing aggressive surgery, the general outcome of patients with BTCs has been disappointing and the reported 5-year survival rates are generally from 8 to 44% (27).

BTCs are known to be notoriously difficult to evaluate for response or progression. Although some patients have parenchymal lesions that lend themselves to objective measurement, many patients have malignant sclerosing disease along bile ducts, which, even in the presence of a response, may show little change on conventional imaging (28). In addition, recent Phase II studies of chemotherapy in advanced BTCs found that the TCR rather than the RR is a significant surrogate marker for survival in this setting (29,30). These findings validate the TCR as the primary endpoint chosen for the current study.

In a pooled analysis of 112 studies (including 2810 patients) of systemic chemotherapy in advanced BTCs, a comparison of regimens containing one or two drugs showed a significant superiority of two-drug combinations compared with monotherapy concerning RR (pooled RR 28 vs. 15%, \( P < 0.001 \)) and TCR (pooled TCR 61 vs. 50%, \( P < 0.001 \)) with a trend for OS (median 9.3 vs. 7.5 months, \( P = 0.061 \)). Three or more drug regimens resulted in a lower RR.
compared with two-drug combinations. The two-drug combination of gemcitabine with platinum compounds increased RR and TCR compared with gemcitabine alone (16).

Although the combination of gemcitabine and cisplatin showed favorable RR (36.6%), the regimen was associated with a high frequency of Grade 3 and 4 toxicities (28,31). The replacement of cisplatin by the third-generation platinum analogue oxaliplatin could help to reduce the emetic and potential renal toxicity of cisplatin without loss of treatment efficacy (32). In addition, the combination of gemcitabine and oxaliplatin has the advantage of being relatively safe in comparison to other cytotoxic drugs in patients with impaired liver function (33).

The GEMOX regimen every 2 weeks used in the current study reached the goal of achieving a TCR > 50%, with an overall response rate (ORR) of 27.5% (including 2.5% CR), an overall TCR of 65%, a median PFS of 4 months and a median OS of 12 months. The results of the current study emphasize the value of GEMOX regimen in the management of advanced BTCs. BTCs are a heterogeneous group of malignancies; therefore, a direct comparison of Phase II results is subject to selection bias. With this limitation in mind, however, the current results compare favorably with Phase II data for GEMOX in advanced BTCs. The reported overall objective RR ranged from 15 to 50%, TCR of 50–70% and median OS of 8.8–12 months (21–23,29,34).

Phase III data of chemotherapy regimens in advanced BTCs were limited until a recent report by Valle et al. (35). This study of 410 patients showed that the addition of cisplatin to gemcitabine compared with gemcitabine alone led to a significant improvement in progression-free survival (median 8.4 vs. 6.5 months; \( P = 0.003 \)) and a benefit in OS (median 11.7 vs. 8.3 months; \( P = 0.002 \)). Another study of 83 evaluable patients confirmed these results in Japanese patients (36). These data help to establish the combination of gemcitabine–cisplatin as a new standard of systemic treatment for patients with advanced BTCs. The GEMOX regimen used in the current study achieved a 12-month median survival, which is equivalent to that achieved by the gemcitabine–cisplatin combination. Future studies on GEMOX should be in comparison to the new standard gemcitabine–cisplatin combination as regard: TCR, survival data, safety and cost/benefit issues.

Previous studies reported conflicting results about the differential outcome between the gallbladder compared with other cancers of the biliary tree (16,21,34,37). In the current study, we found no significant differences in the RR, PFS or OS between GBC and CC subgroups. The differences reported by previous trials might be influenced by the small number of patients accrued to these trials, a center effect or the inclusion of unconfirmed responses. Our findings are supported by the absence of difference in the ORR between GBC and CC when subgroup analysis was performed in a large Phase III trial (35).

It is known that small improvements in bile duct lumen size will have a significant effect on biliary drainage, as determined by Poiseuille’s law (38) which holds that for a fixed-pressure difference, flow is related to tube diameter to the fourth power. The maintenance of biliary drainage is critical in patients with advanced BTCs because it enables systemic chemotherapy to continue and avoids potentially life-threatening biliary sepsis. A small response in tumor bulk of BTCs less than that considered by conventional response criteria may therefore have a greater effect on survival than would be the case for other cancers. This explains the highly significant prolongation in the OS associated with tumor control in the current study, which is consistent with that of other published data (29,30).

Previous Phase II studies used variable schedules of gemcitabine–oxaliplatin combination. Gemcitabine has been evaluated in a 30 min infusion (22), 1 h infusion (29) or as a fixed rate infusion (10 mg/m²/min) (21,30). Oxaliplatin was administered on the same day of gemcitabine administration (22,23,29) or on day 2 (21,30,34). Clinical data are mixed regarding the therapeutic benefit of the infusion rate of gemcitabine in terms of the RR and survival advantage (39–41). The administration sequence of the two drugs did not affect the results significantly in pharmacokinetics studies (42,43). We used a different schedule from other Phase II studies. Gemcitabine was administered as a short infusion followed by oxaliplatin in the same day. This allowed the GEMOX combination here to be delivered as a convenient outpatient regimen that requires two monthly visits. In addition, the dose of oxaliplatin was modified to 85 mg/m² biweekly, unlike previous studies that used 100 mg/m² (21–23,34). This may have contributed to the high tolerability of the GEMOX combination used in the current study; there were no treatment-related deaths, Grade 3–4 toxicities were recorded in 25% of the patients with neutropenia being the most common (17.5%) and Grade 3 sensory neuropathy was uncommon (2.5%). In a German study by Harder et al. (22), patients were treated with gemcitabine 1000 mg/m² (30 min infusion) on days 1, 8 and 15 and oxaliplatin 100 mg/m² (2 h infusion) on days 1 and 15, and the treatment protocol was repeated every 4 weeks. Treatment delays were necessary in 87% of the patients mainly due to bone marrow toxicity, especially thrombocytopenia, and infections. In 42% of the patients, dose reductions had to be performed. In 19% of the patients, oxaliplatin had to be reduced and later discontinued owing to peripheral sensory neuropathy. In a subsequent international study by Andre et al. (34), the GEMOX regimen consisted of gemcitabine 1000 mg/m² (100 min infusion) on day 1 and oxaliplatin 100 mg/m² (2 h infusion) on day 2 every 2 weeks; overall, Grade 3/4 toxicity occurred in 70% of the patients, and the sponsor could not rule out a relationship between study treatment and three deaths (4.5%).

In conclusion, this study provides further evidence for the activity of GEMOX combination as a first-line treatment for advanced BTCs. This combination can be given safely as a convenient biweekly outpatient regimen to palliate patients with advanced BTCs. Tumor control achieved with GEMOX...
treatment translates into a clinical benefit in OS. These promising results now need to be verified in Phase III trials comparing the GEMOX regimen to the new standard gemcitabine–cisplatin combination.

Conflict of interest statement
None declared.

References

