Phase II study of capecitabine plus cisplatin as first-line chemotherapy in advanced biliary cancer

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Background: A phase II study was conducted to assess the efficacy and tolerability of substituting capecitabine for 5-fluorouracil in combination with cisplatin in patients with advanced biliary cancer.

Patients and methods: Patients with previously untreated metastatic or unresectable measurable biliary adenocarcinoma received oral capecitabine 1250 mg/m2 twice daily on days 1–14, and intravenous cisplatin 60 mg/m2 on day 1. This cycle was repeated every 21 days.

Results: Forty-two patients were enrolled in this study. Of these, 38 were assessable for efficacy and 41 were assessable for safety. A median of three cycles of treatment (range one to eight) were administered. One patient achieved a complete response, and eight had partial responses, giving an overall response rate of 21.4% in the intention-to-treat population (95% confidence interval 9.1% to 33.9%). The median response duration was 5.1 months. The median time to progression and median overall survival were 3.7 and 9.1 months, respectively. The most common grade 3/4 adverse events were neutropenia (20% of patients), vomiting (12%), diarrhea (7%) and stomatitis (5%). There were no treatment-related deaths.

Conclusions: The combination of capecitabine and cisplatin has promising antitumor activity and is well tolerated in patients with advanced biliary cancer.

Key words: biliary tract neoplasms, capecitabine, chemotherapy, cholangiocarcinoma, cisplatin, gall-bladder neoplasms

Introduction

Adenocarcinomas of the gall-bladder and bile ducts are relatively uncommon tumors in Western countries [1]. However, they account for ~4.8% of all malignant neoplasms and are estimated to be the seventh most common form of cancer in South Korea [2]. Biliary cancer is one of the most aggressive human malignancies. The prognosis for patients with advanced or metastatic disease is dismal, with median survival usually being <4 months in patients not treated with chemotherapy [3, 4]. Surgical resection remains the only potentially curative treatment, although ~80% of patients are not eligible for surgery. Findings from one randomized trial suggested that combination chemotherapy may improve survival and have symptomatic benefits in patients with advanced biliary cancer when compared with best supportive care, although this study had relatively small numbers of patients [3]. The most extensively studied single agent in biliary cancer to date has been 5-fluorouracil (5-FU), although response rates following first-line treatment of advanced disease have tended to be low (10–13%) [5, 6]. Response rates following single-agent cisplatin in advanced biliary cancer have been similarly disappointing (8%) [7].

The apparent synergy between 5-FU and cisplatin has led to the widespread use of regimens combining these agents in the treatment of various tumor types. In phase II studies, a regimen of 5-day continuous infusion 5-FU and cisplatin has demonstrated a response rate of 24% in patients with advanced biliary cancer [8]. Several phase II studies demonstrated superior response rates (29–40%) with the ECF regimen, which combines protracted infusion of 5-FU plus epirubicin and cisplatin [9–11]. In the majority of these regimens, 5-FU has been administered as a continuous infusion. However, catheters and pumps are necessary for the administration of protracted 5-FU infusion, requiring frequent outpatient visits or admission when a schedule of short infusions is administered. These factors add to the cost, morbidity and the inconvenience of treatment.

Capecitabine (Xeloda®, Hoffmann-La Roche) is a novel fluoropyrimidine carbamate designed to mimic continuous infusion of 5-FU and deliver 5-FU to target tumor cells. The drug is rapidly and extensively absorbed as an intact molecule, thereby avoiding gastrointestinal toxicity, and is then metabolized to 5-FU in three steps. In the final step, 5′-deoxy-5-fluorouridine is converted to 5-FU by thymidine phosphorylase (TP), which is significantly more active in tumor tissue than in adjacent healthy tissue. TP
expression has been detected by immunohistochemistry in 39–63% of biliary cancer specimens [12, 13]. A pilot study showed that capecitabine (1000 mg/m² twice daily for 14 days every 21 days) achieved a response rate of 19% in patients with advanced biliary cancer [14]. Capecitabine has also produced antitumor activity with tolerable safety profiles when given in combination with cisplatin in patients with various other solid tumor types [15–17]. The current phase II study was conducted to evaluate the response rate, time to progression (TTP), overall survival and safety of a combination regimen of capecitabine/cisplatin in patients with advanced biliary cancer.

Patients and methods

Patient selection

Eligible patients had histologically confirmed unresectable advanced or metastatic adenocarcinoma of the gall-bladder or biliary tree with at least one unidimensionally measurable lesion (diameter ≥ 2 cm, as assessed by physical or X-ray examination including chest X-ray or computed tomography scan). Other eligibility criteria were age 18–75 years and Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients had received no prior chemotherapy or radiation therapy. Adequate hematological (hemoglobin ≥ 9 g/dl, absolute neutrophil count ≥ 2.0 × 10⁹/l, platelet count ≥ 100 × 10⁹/l), hepatic (total bilirubin ≤ 1.5 mg/dl, serum transaminases ≤ 3 × upper normal limit or ≤ 5 × upper normal limit in cases of hepatic metastases), and renal (serum creatinine ≤ 1.5 mg/dl) functions were required. The protocol was approved by the institutional review board, and all patients gave written informed consent before enrolment.

Treatment schedule

Capecitabine was administered orally at a dose of 1250 mg/m² twice daily according to the standard intermittent schedule (14 days of treatment followed by a 7-day rest period). Cisplatin was administered intravenously at a dose of 60 mg/m² for 1 h with a standard hydration method on day 1. Treatment was repeated every 21 days. Treatment was continued until progressive disease (PD) or the development of unacceptable toxicity, or if the patient chose to discontinue treatment.

Dose modification for adverse events

Toxicity was evaluated before each treatment cycle according to the National Cancer Institute of Canada Common Toxicity Criteria, version 2.0. Dose adjustments for each drug were made according to the previous guidelines [15]. Patients were required to meet all of the following criteria to begin the next cycle of treatment: platelet count ≥ 75 × 10⁹/l; neutrophil count ≥ 1.0 × 10⁹/l; and resolution or improvement of clinically significant non-hematological adverse events to grade 1 or 0. If treatment was delayed for 21 days, patients were excluded from the study.

Assessment of compliance and dose intensity

Compliance to capecitabine therapy was monitored by questioning patients and counting their remaining pills at each outpatient visit. The ratio of the actual administered dose to the scheduled dose was calculated. Dose intensity was defined as the total amount of drug given (mg/m²) divided by the number of weeks.

Pretreatment, follow-up studies and response evaluation

Physical examination and chest X-rays were carried out before each cycle of therapy. Complete blood counts and biochemical tests were performed before and on day 15 of each cycle. Tumors were measured every three cycles until tumor progression. Tumor response was classified based on the Response Evaluation Criteria in Solid Tumors Guidelines [18]. Patients with complete response (CR) or partial response (PR) required a confirmatory disease assessment at least 4 weeks later. Patients with no confirmed tumor response were not regarded as responders.

Statistical analysis

All enrolled patients were included in the intention-to-treat analysis of efficacy. The trial was conducted according to the two-stage Gehan design [19] with overall response rate as the primary end point. Assuming a true response rate of at least 15%, initially 19 patients were accrued. Because the probability of obtaining no response in 19 patients was <0.05, the trial was to be closed if no responses were observed. The decision was made to continue the study if at least one treatment response was observed and six additional patients were to be included according to the rules, to obtain an accuracy of 0.10 for the final response rate. According to this design, the probability of completing the trial was >95% if the true response rate was at least 15%. However, accrual was continued to a total of 42 patients so that the proportion of patients responding could be better defined.

Duration of response, TTP and survival were estimated as secondary end points by the Kaplan–Meier method. The duration of response was defined as the interval from the onset of CR or PR (whichever status was recorded first) until evidence of PD was found; TTP was calculated from the date of entry to the date of PD; overall survival was measured from the date of entry to the date of death.

Results

Patient characteristics

A total of 42 patients were enrolled between September 2000 and May 2002. Table 1 lists the characteristics of the patients. The median age was 55 years, and most of the patients (74%) had a good performance status (0 or 1 on the ECOG scale). Nineteen patients (45%) had primary gall-bladder cancer; in the remaining patients, the primary tumor had arisen in the biliary tree. Six patients had undergone palliative surgery for biliary decompression, and three patients had received endoscopic stents or percutaneous biliary drainage for the relief of obstructive jaundice before study entry. The liver and abdominal lymph nodes were the most common sites of metastases. Baseline serum CA 19-9 levels were recorded in all patients and were found to be elevated in 27 (64%).

Efficacy and survival

A total of 38 patients were evaluable for response. The remaining four patients were not assessable for response because of loss to follow-up. The overall response rate in the intention-to-treat population (all patients) was 21.4% [95% confidence interval (CI) 9.1% to 33.9%], including one confirmed CR and eight confirmed PRs (Table 2). Taking into account the 12 patients who had SD, responses according to the primary disease sites were noted in the gall-bladder (six of 19, 32%), intrahepatic cholangiocarcinoma (two of 14, 14%), and extrahepatic cholangiocarcinoma (one of nine, 11%). The median duration of response in the nine responding patients was 5.1 months. The median TTP for all patients was...
3.7 months (95% CI 2.3–5.2) (Figure 1) and the median overall survival was 9.1 months (95% CI 6.7–11.3) (Figure 2).

**Adverse events and treatment delays/reductions**

A total of 157 treatment cycles (median three; range one to eight) were administered, of which 151 cycles were assessable for safety. The remaining six cycles in six patients were not assessable for safety. The frequencies of hematological and non-hematological adverse events are shown in Tables 3 and 4, respectively. The most common grade 3/4 hematological adverse event was neutropenia, which occurred in 20% of the patients (all grade 3). However, no patients experienced febrile neutropenia. The most common grade 3 non-hematological adverse events were vomiting (12%), nausea (7%), diarrhea (7%) and stomatitis (5%). Grade 3 hand–foot syndrome occurred in only 2% of the patients. There were no treatment-related deaths during the study.
Treatment was delayed in 56 cycles and the dose was reduced in five cycles. Treatment doses were modified for the following reasons: hematological toxicity (36%); nausea/vomiting (19%); diarrhea (11%); stomatitis (10%); and hand–foot syndrome (5%). There was a higher incidence of dose reduction with capecitabine compared with cisplatin. The median dose intensity for capecitabine and cisplatin during the first six cycles is depicted in Figure 3.

Table 5 lists the proportion of patients taking chemotherapy at full dose in respective treatment cycles. The median dose intensity for capecitabine over all treatment cycles was 0.9816 mg/m²/week (range 7839–11792) and 18.8 mg/m²/week (range 17.2–20.4) for cisplatin; these figures correspond to 84.1% and 94.0% of the planned dose intensities, respectively. Compliance to the treatment regimen was good, with 94% compliance to capecitabine during the first three cycles of treatment.

**Discussion**

The results of the present study indicate that the combination of capecitabine and cisplatin is active and well tolerated as first-line chemotherapy for advanced biliary cancer. The overall response rate (21%), median TTP (3.7 months) and median overall survival (9.1 months) following treatment with the capecitabine/cisplatin regimen are comparable with results reported previously with...
5-FU/cisplatin combinations. A 5-day continuous infusional 5-FU/cisplatin regimen was reported to achieve a response rate of 24% and median overall survival of 10 months [8], and response rates and overall survival with the ECF regimen have been reported to be 29–40% and 6.4–11 months, respectively [9–11]. A recent phase II study combining fractionated cisplatin and de Gramont 5-FU plus leucovorin regimen suggested improvement compared with classical 5-FU/cisplatin combination [9–11], in terms of efficacy and safety [20].

In addition to antitumor efficacy, toxicity and convenience are critically important issues for the choice of new treatment combinations. The current capecitabine/cisplatin regimen has the advantage over infusional 5-FU/cisplatin regimens of convenience and practicability, and has clear potential to reduce health-care resource expenditure. Toxicity has been a significant problem with different schedules of 5-FU/cisplatin regimens, and needs to be improved. In one study, a 5-day continuous infusional 5-FU/cisplatin regimen was associated with high rates of grade 3/4 hematological toxicities (40%), including febrile neutropenia in 17% of patients, and also emesis (25%), although a relatively high dose of cisplatin was used in this study [8]. Furthermore, severe (grade 4) hematological toxicity including febrile neutropenia (16%) was observed in 32% of patients receiving ECF; severe alopecia was also frequently observed with this combination [9]. In our experience, the main grade 3/4 adverse event associated with the capecitabine/cisplatin regimen was neutropenia. Nevertheless, neutropenia was an isolated event and was not associated with fever or infection. The incidence of adverse events other than neutropenia was rather low; the most common grade 3 non-hematological adverse events were vomiting (12%), nausea (7%), diarrhea (7%) and stomatitis (5%). Furthermore, hand–foot syndrome occurred rarely with this combination, despite using the full dose of standard, intermittent capecitabine as a single agent (1250 mg/m² twice daily for 14 days every 21 days). This lower incidence of hand–foot syndrome in the present study might be related to frequent dose reduction, due mainly to neutropenia.

The feasibility and activity of combining capecitabine and cisplatin with or without epirubicin has also been demonstrated in advanced gastric and esophageal cancer [15, 21]. In the present study, we combined cisplatin with the standard, intermittent capecitabine regimen every 21 days, because the safety profile of capecitabine differs from that of cisplatin with little overlap of key side-effects. However, the dose intensities of capecitabine and cisplatin were 84% and 94%, respectively. Dose intensity for capecitabine fell after the second cycle of treatment, and frequent dose reduction for capecitabine was necessary due to neutropenia. Therefore, we recommend reducing the starting dose of capecitabine to 1000 mg/m² twice daily on days 1–14 every 21 days in further evaluations of this combination. This suggestion is supported by the recent publication of results from a phase I study using capecitabine plus cisplatin in head and neck cancer, the authors of which recommended a regimen of capecitabine 1000 mg/m² twice daily on days 1–14, combined with intravenous cisplatin 100 mg/m² on day 1 every 21 days for future phase II studies [17].

Biliary tumors can occur anywhere in the hepatobiliary system and are often classified according to location. In the present study, gall-bladder cancer appeared to respond more readily to capecitabine/cisplatin treatment than cholangiocarcinoma, although response rates were not statistically significantly different, perhaps because of the relative small number of patients included in the study. The response rates according to primary sites in the present study are in line with the results obtained with single-agent capecitabine treatment [14] and with a 5-FU/cisplatin/interferon/doxorubicin regimen [22]. However, it is important to note that patients with cholangiocarcinoma in the present study had more extensive disease than those with gall-bladder cancer. Consequently, further study may be needed to clarify response to chemotherapy according to primary tumor sites before firm conclusions can be made regarding the benefits of individual treatment regimens in patients with advanced biliary cancer.

In conclusion, capecitabine plus cisplatin is well tolerated and has promising antitumor activity when administered as first-line treatment for patients with advanced biliary cancer. Importantly, replacing 5-FU with oral capecitabine means that this regimen can be administered on an outpatient basis and is more convenient for patients than regimens combining infusional 5-FU with cisplatin.

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References


