A phase II trial of S-1 and cisplatin in patients with metastatic or relapsed biliary tract cancer

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Background: Optimal chemotherapy for advanced biliary tract cancer (BTC) is yet to be defined. We carried out this study to evaluate the efficacy and toxicity of combination chemotherapy with S-1 and cisplatin in metastatic or relapsed BTC.

Patients and methods: Patients with pathologically proven BTC were eligible. The chemotherapy regimen consisted of S-1 (40 mg/m² p.o. b.i.d. from D1–14) and cisplatin (60 mg/m² on D1), repeated every 3 weeks.

Results: Fifty-one BTC patients (metastatic:relapsed = 37:14, Gall-bladder:intrahepatic bile ducts:extrahepatic bile ducts = 16:25:10) were enrolled from January 2005 to December 2006. Median age was 57 years (range, 31–71) and most patients had a good performance status. The overall response rate was 30% [95% confidence interval (CI), 17.3–42.7] and complete response was observed in two patients (4%), partial response in 13 (26%), stable disease in 21 (42%), and progressive disease in 9 (18%). With a median follow-up of 12.4 months, the median time to progression was 4.8 months (95% CI, 3.3–6.3) and median overall survival was 8.7 months (95% CI, 6.0–11.4). Major toxic effects were grade 3/4 neutropenia (8.9% of all cycles) and febrile neutropenia was observed in six cycles (2.7% of all cycles).

Conclusion: Combination chemotherapy with S-1 and cisplatin was a moderately effective outpatient-based regimen in BTC patients. Toxic effects were moderate but manageable.

Key words: Biliary tract cancer, Cisplatin, S-1

introduction

Biliary tract cancers (BTC), including cancer of the Gall-bladder, intrahepatic, and extrhepatic bile duct, account for <2% of malignancies in Western countries [1]. In Korea, BTC seem to be more common, accounting for 4% of all malignancies [2]. BTC are often diagnosed at a locally advanced unresectable or metastatic stage. Although chemotherapy is reported to have significant benefit over best supportive care [3], no standard chemotherapy has yet been identified.

5-fluorouracil (5-FU), the most extensively studied agent, yields response rates of 0%–10% as a single agent and 20%–30% with combination chemotherapy. However, 5-FU-based combination regimens have considerable toxic effects and entail the inconvenience of continuous i.v. infusions [4–7]. Recently, several phase II studies have been carried out with various combinations of newer agents, such as gemcitabine, capecitabine, and oxaliplatin with response rates ranging from 20% to 40% [8–13].

S-1 is a novel oral fluoropyrimidine agent, which contains tegafur, gimeracil (5-chloro-2,4-dihydroxypyridine), and oteracil potassium. Gimeracil is a competitive inhibitor of dihydroxyridinm dehydrogenase and achieves higher concentrations of 5-FU in plasma and tumor tissues. The antitumor effects of S-1 have already been demonstrated in various solid tumors, and in a phase II study of S-1 monotherapy in patients with advanced BTC, the response rate was 21.1% and median overall survival (OS) was 8.3 months, which is comparable to other studies with newer agents [14]. Fluoropyrimidines are known to have synergistic effects with cisplatin [15, 16], and combinations of S-1 and cisplatin are reported to have high response rates with tolerable toxicity profiles in solid tumors other than BTC [17–21]. We therefore carried out this phase II trial to evaluate the efficacy and toxicity of combination chemotherapy with S-1 and cisplatin in metastatic or relapsed BTC.

patients and methods

eligibility criteria

Patients with pathologically proven locally advanced unresectable, metastatic, or relapsed biliary tract adenocarcinoma were eligible for this
study. At least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) [22] was required. Other eligibility criteria included age between 18 and 75 years, Eastern Cooperative Oncology Group performance status (PS) of 0 to 2, no prior chemotherapy or radiotherapy, and adequate bone marrow, hepatic, and renal function (absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$, total bilirubin $\leq 2 \times$ upper limit of normal (ULN), serum transaminases $\leq 2.5 \times$ ULN, alkaline phosphatase $\leq 5 \times$ ULN, serum creatinine $\leq 1.5 \times$ ULN or actual or calculated creatinine clearance $\geq 60$ ml/min). Written informed consent was obtained from each patient before enrollment and the protocol was approved by the institutional review board of the Seoul National University Hospital, Seoul, Korea.

treatment and dose modification
Most patients were treated on an outpatient basis. S-1 was administered orally at a dose of 40 mg/m² twice daily for 14 days, followed by a 7-day rest period. Cisplatin was given as a 90-minute infusion on day 1 of each cycle at a dose of 60 mg/m². Treatment was repeated every 3 weeks until disease progression, unacceptable toxicity, or withdrawal of patient consent.

Drug administration was delayed until ANC $\geq 1.5 \times 10^9/L$, platelet count $\geq 75 \times 10^9/L$, and recovery from non-hematologic toxicity to baseline or less than or equal to grade 1. S-1 was reduced by 25% on all subsequent cycles for febrile neutropenia, grade 4 neutropenia, grade 3/4 thrombocytopenia, greater than or equal to grade 3 non-hematologic toxic effects. Cisplatin was reduced by 25% for febrile neutropenia and greater than or equal to grade 3 non-hematologic toxic effects.

assessment
The primary end point of this study was response rate and secondary end points were toxicity, duration of response, time to progression (TTP) and OS. Tumor response was assessed using RECIST criteria [22], with computed tomography scans at baseline and every two cycles (6 weeks). Any responses were confirmed 4 weeks later. Toxicity was evaluated at each cycle according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

statistical analysis
According to Simon’s two-stage phase II optimal design [23], a sample size of 43 was required to accept the hypothesis that the true response rate is $\geq 25\%$ with 80% power, and to reject the hypothesis that the response rate is $\leq 10\%$ with 5% significance. In the initial stage, 18 assessable patients were to be entered into the study and if responses were $\leq 2$, accrual was to be terminated. If three or more responses were observed, then 25 additional patients were to be entered in the second stage to achieve a target sample size of 43 assessable patients. Estimating a dropout rate of 10%, at least a total of 47 patients were planned to be accrued for this study.

Duration of response, TTP, and OS were estimated by the Kaplan–Meier method. The SPSS version 13.0 statistical software program (SPSS, Chicago, IL) was used for all statistical analyses.

results
patient characteristics
We enrolled 51 patients with advanced BTC from January 2005 to December 2006 (Table 1). The median age of the patients was 57 years (range, 31–71) and most patients had a good PS. There were 26 men (51.0%) and 25 women (49.0%). All patients had metastatic or relapsed disease, and there were 16 cases of Gall-bladder cancer (31.4%), 25 cases of intrahepatic bile duct cancer (49.0%), and 10 cases of extrahepatic bile duct cancer (19.6%). None of the patient had received prior systemic chemotherapy for BTC.

drug delivery
Patients received a total of 225 cycles of treatment, with a median of five cycles (range, 1–10) per patient. The average relative dose intensities were 85.5% for S-1 and 85.6% for cisplatin (Table 2). S-1 was administered with a reduced dose in 29 cycles (12.9%), and cisplatin in 15 cycles (6.7%). The chemotherapy schedule was delayed in 70 cycles (31.1%).

efficacy and survival
In the first stage, 18 assessable patients had entered into the study and six patients showed complete response (CR) or partial response (PR). Consequently, we proceeded to second stage according to Simon’s two-stage design. Of the 51 patients, 45 were assessable for responses. Of the six non-assessable, two were referred to other hospitals for the second opinions during second cycle of chemotherapy without evidence of disease progression, two refused further chemotherapy due to toxicity, and one patient was dropped out from the study because he had cholangiohepatitis with microabscess on day 3 of the first cycle. The last patient was lost to follow-up after the first cycle of chemotherapy, and later was found to have stopped S-1 on day 5 without any apparent toxic effects or evidence of

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Number of patients accrued</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>57 (37–71)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26</td>
<td>51</td>
</tr>
<tr>
<td>Female</td>
<td>25</td>
<td>49</td>
</tr>
<tr>
<td>PS (ECOG scale)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>50</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Presentation of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initially metastatic</td>
<td>37</td>
<td>72.5</td>
</tr>
<tr>
<td>Relapsed after surgery</td>
<td>14</td>
<td>27.5</td>
</tr>
<tr>
<td>Biliary stent</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Primary sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gall-bladder</td>
<td>16</td>
<td>31.4</td>
</tr>
<tr>
<td>Intrahepatic bile duct</td>
<td>25</td>
<td>49</td>
</tr>
<tr>
<td>Extrahepatic bile duct</td>
<td>10</td>
<td>19.6</td>
</tr>
</tbody>
</table>

PS, performance status; ECOG, Eastern Cooperative Oncology Group

Table 2. Dose intensity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose intensity (mg/m² per week)</th>
<th>Relative dose intensity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Planned (range)</td>
<td>Median delivered dose (range)</td>
</tr>
<tr>
<td>S-1</td>
<td>373.3 (194.6–373.3)</td>
<td>318.6 (194.6–373.3)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>20.0 (12.0–20.0)</td>
<td>17.3 (12.0–20.0)</td>
</tr>
</tbody>
</table>
He had stopped chemotherapy due to personal belief on natural healing. Excluding the last patient, the overall response rate (ORR) was 30% (95% confidence interval [CI], 17.3–42.7) with two CRs (4%) and 13 PRs (26%) (Table 3). Twenty-one patients had stable disease (42%), and nine had progressive disease (18%) yielding a disease control rate of 72%. The median time to response was 5.7 weeks (range, 5.1–17.4) and median response duration was 8.3 months (range, 1.1–16.7).

With a median follow-up of 12.4 months, the median TTP was 4.8 months (95% CI, 3.3–6.3) (Figure 1) and the median OS was 8.7 months (95% CI, 6.0–11.4) (Figure 2) with a 1-year survival rate of 42.5%. The median OS in responders has not been reached, but the median TTP in responders was 9.6 months (95% CI, 3.4–15.8). The median OS in patients with disease stabilization was 12.8 months (95% CI, 7.4–18.2) and the median TTP in this group was 5.7 months (95% CI, 3.8–7.6). Gender, age, PS, initial presentation of disease, and primary site of disease were not related to the OS and TTP, but OS was significantly longer in relapsed disease compared with initially metastatic disease (17.1 versus 8.0 months, P = 0.041).

toxic effects
Fifty patients were assessable for toxic effects (Table 4). Adverse events occurring during treatment were predominantly of grade 1 or 2. The most common grade 3/4 hematologic toxicity was neutropenia, which occurred in 20 cycles (8.9%). Six patients experienced febrile neutropenia which required brief episodes of hospitalization and empirical administration of antibiotics. Grade 3/4 non-hematologic toxic effects were uncommon, and the most common such toxicity was grade 3/4 hyponatremia, which occurred in eight cycles (3.6%). One patient developed cholangiohepatitis with microabscess on day 3 of the first cycle without neutropenia. This event was considered to be related to underlying malignant strictures of intrahepatic ducts and multiple intrahepatic duct stones, and not clearly related to the study treatment, but was included in Table 4.

discussion
This phase II trial is apparently the first study to demonstrate the efficacy of combination chemotherapy with S-1 and cisplatin in metastatic or relapsed BTC. No current standard chemotherapy has been established for advanced BTC. Aside from modest efficacy of existing agents, clinical trials in BTC have suffered from the rarity of the disease and the general high morbidity of the patient population. Nevertheless there has been a recent review of phase II trials with newer combinations and newer agents for BTC [8–14, 24, 25].

In the current study, the ORR was 30% (95% CI, 17.3–42.7), and overall disease control rate was 72%. The median TTP was 4.8 months and the median OS was 8.7 months. The OS was shorter than some recent studies but this must be cautiously interpreted [9–13], since the validity of direct comparisons among small phase II studies with highly heterogeneous patient
groups is dubious. Nearly half of the patients had intrahepatic duct carcinoma in this study, which tended to have lower response rates and survival compared with gall-bladder cancer, as in other studies. Nevertheless, our study is one of the largest BTC series, and showed a high disease control rate with a high median number of cycles given to each patient. The median response duration was 8.3 months and the median TTP in responders was 9.6 months, suggesting maintained durable activity. The median OS in responders has not yet been reached.

The main grade 3/4 toxicity in this study was neutropenia, and febrile neutropenia had occurred in six patients (12%) but was easily managed without discontinuing the protocol. The incidence of adverse events other than neutropenia was rather low, with most common adverse events being grade 1/2 nausea and anorexia. Compared with other studies with capecitabine and cisplatin combination, which have shown high rates of hand-foot syndrome, only some grade 1 hyperpigmentations were noted in this study [10, 25].

In conclusion, this phase II study indicates that combination therapy with S-1 and cisplatin is moderately effective in patients with advanced BTCs. The toxicity was moderate, but manageable. Regarding its convenience as an outpatient based treatment, it seems to be a reasonable option as first-line chemotherapy for patients with BTC.

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