A Phase II Study of Docetaxel and Cisplatin in Patients with Gastric Cancer Recurring After or Progressing During 5-FU/Platinum Treatment

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Background: Docetaxel plus cisplatin (DP) is a combination chemotherapy regimen that is active against untreated advanced gastric cancer. We evaluated the feasibility of DP treatment in patients with recurring or metastatic gastric cancer who had been previously treated with other chemotherapy regimens.

Patients and methods: The DP regimen consisted of doxetaxel (75 mg/m2 i.v.) and cisplatin (60 mg/m2 i.v.) over 1 h on Day 1 every 4 weeks for a maximum of nine cycles.

Results: Thirty-seven patients (28 men, 9 women; median age, 53 years; range 28–71 years) received a total of 128 cycles of therapy (median, 3; range 1–9). Twenty-six patients had recurrent disease and 11 had metastatic tumors. The objective response rate was 32.4% (95% confidence interval = 16.6–48.3%), including 1 complete response and 11 partial responses. Eleven had stable disease, whereas 12 had progressive disease. The median duration of response was 70.5 days (range 30–392 days). Grade 3/4 toxicities included anemia (10.8%), leukopenia (27.0%), neutropenia (51.4%), thrombocytopenia (2.7%), nausea/vomiting (5.4%) and oral mucositis (13.5%). Median time to progression was 136 days and median overall survival was 235 days.

Conclusion: The DP combination was well tolerated and effective for patients with metastatic gastric cancer treated previously with 5-fluorouracil/platinum chemotherapy.

Key words: docetaxel – platinum – fluorouracil – gastric cancer

INTRODUCTION

Gastric cancer is a major health problem and the leading cause of cancer deaths in the world. Although the only proven curative modality is surgical resection, advanced, unresectable gastric cancer is incurable, with a median survival of only 6–9 months without treatment. Since palliative chemotherapy has improved survival benefits compared with best supportive care (1–3), many drug regimens have been tested to improve palliative chemotherapy. Docetaxel is a semisynthetic taxane, which is more potent than the natural taxane paclitaxel in promoting tubulin polymerization and in inhibiting microtubule depolymerization (4). Docetaxel has been tested as a single agent in gastric cancer patients treated with previous chemotherapy regimens (5,6), including cisplatin/fluorouracil-containing regimens commonly used to treat advanced gastric cancer (7,8). Because of the unsatisfactory results of front-line chemotherapy with cisplatin/fluorouracil, the need for salvage regimens has increased. In Phase II trials, docetaxel/cisplatin (DP) showed activity against advanced gastric cancer (9,10). Nevertheless, there have been few studies of DP combination chemotherapy for gastric cancer relapsed after 5-fluorouracil (5-FU)/platinum chemotherapy. We, therefore, performed a Phase II study to evaluate the efficacy and toxicity of DP in patients with recurrent or progressive gastric cancer who had been treated previously with 5-FU/platinum chemotherapy regimens.

PATIENTS AND METHODS

PATIENTS ELIGIBILITY

Patients with metastatic gastric cancer patients who showed recurrence after or progression during adjuvant or palliative chemotherapy with 5-FU/platinum were eligible for this study. The patient population was included for a purpose of salvage treatment. At least one unidirectional measurable lesion was required for response evaluation. Gastric cancer was confirmed pathologically. Other eligibility criteria included age 18 years or older, an ECOG performance status of 3 or lower; life expectancy >3 months; no history of immunosuppression.

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immunodeficiency or HIV infection; no previous or current history of invasive cancer; adequate bone marrow (WBC \( \geq 4000/\mu L \), platelets \( \geq 100,000/\mu L \)), kidney (creatinine \( \leq 1.5 \text{ mg/dL} \) or creatinine clearance \( \geq 60 \text{ mL/min} \)) and liver (bilirubin \( \leq 2.0 \text{ mg/dL} \), transaminases levels \( = 3 \) times the upper normal limit) function. Exclusion criteria included any coexisting serious medical illness, including severe infection, impaired renal function (creatinine clearance < 60 mL/min or serum creatinine > 2.0 g/dL) and age > 75 years. This protocol was approved by the institutional review board of Ulsan University Hospital, and all patients gave written informed consent.

**TREATMENT SCHEME**

Baseline evaluations included a chest X-ray, complete blood count, chemistries, routine urine examination and tests identifying extents of disease such as abdominal computed tomogram or bone scintigram.

The DP chemotherapy regimen consisted of docetaxel (75 mg/m² i.v. over 1 h) and cisplatin (60 mg/m² i.v. over 1 h) on Day 1 every 4 weeks. Patients received premedications with an H2-blocker and an antihistamine before the start of docetaxel infusion, and dexamethasone (20 mg) was infused for 30 min before docetaxel. One liter of hydration was given before and after cisplatin treatment. If grade 3/4 non-hematologic toxicities, grade 4 hematologic toxicities except for anemia, or febrile neutropenia were detected, the DP dose was reduced 25% during the next cycle. When treatment was delayed for more than 2 weeks, the next cycle was considered omitted. Since this was a study of salvage chemotherapy, dose omission was permitted for only one cycle. A total of nine cycles of DP was planned in cases of responsive or stable disease, unless chemotherapy could not be performed owing to other causes such as the deterioration of a patient’s general condition or a patient’s unwillingness to undergo further chemotherapy.

**END POINTS AND EVALUATION OF TREATMENT**

Primary end points were response rate and toxicities of DP chemotherapy. Secondary end points were time to progression (TTP) and overall survival (OS). Response was assessed every 2 cycles by standard Response Evaluation Criteria In Solid Tumors (RECIST) (11). Toxicities was evaluated and graded on Days 1 and 14 of each cycle by National Cancer Institute common toxicity criteria, version 2, using physical examination, complete blood count, chemistry and tests indicated. Intention-to-treat analysis was used to evaluate patients for response, toxicity and survival.

**STATISTICAL METHODS**

If over three patients among 17 patients have objective response, this study is regarded to be adequate to proceed further and to enroll more 20 patients up to 37 patients assuming P0 of 20%, P1 of 40%, alpha error of 0.1 and beta error of 0.1 based on Simon two-stage Phase II design. The final decision is made to be effective if over 10 out of 37 patients have objective response. Response and toxicities were shown by descriptive methods. For scale variables, data are given as medians (with range in parentheses), whereas for nominal variables, data are given as number of patients (with percentage in parentheses), if not specified otherwise. The starting point for various time intervals was the starting day of DP chemotherapy. The date of disease progression was used to calculate TTP, whereas time to death from any cause was used to calculate OS. The reference date was 31 August 2004. The Kaplan–Meier method was used to estimate survival.

**RESULTS**

From July 2001 to October 2003, a total of 37 patients were eligible for this study. As of 31 August 2004, the median follow-up was 17.4 months (range 3.8–36.3 months). Median time from first-line chemotherapy to DP was 8.7 months (range 0.26–42.8 months). Only one patient, who refused further chemotherapy after the second cycle of DP, was lost to follow-up. All patients were assessable for response and toxicities.

Of the 37 patients, 28 were male and 9 were female. Their median age was 55 years (range 28–71 years). Their baseline characteristics are shown in Table 1. All patients had metastatic disease at the time of enrollment. Sixteen (43.2%) patients showed tumor recurrence after adjuvant chemotherapy, whereas the remaining 21 patients (56.8%) were refractory to first-line treatment, 10 relapsing during adjuvant chemotherapy and 11 with primary refractory disease. Surgery was performed in 26 (60.3%) patients. All first therapies were fluorouracil–platinum combination treatments, 19 (51.4%) with 5-FU/cisplatin, 17 (45.9%) with 5-FU/hepatiplatin and 1 (2.7%) with 5-FU/carboplatin (Table 2), and the median number of first-line chemotherapy cycles was 6 (range 1–13). The most common metastatic sites were peritoneal mass (12 patients, 32.4%), lymph nodes (11 patients, 29.7%) and liver (10 patients, 27%).

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The 37 patients received a median of three DP cycles (range 1–9; total 128). Only nine patients (24.3%) completed the scheduled number of cycles (9); the remaining 28 patients (75.5%) patients terminated DP early on account of disease progression in 17 patients (60.7%), patient refusal of further chemotherapy in seven patients (25%), worsening of general condition in three patients (10.7%) and pneumonia in one patient (3.6%).

Owing to anorexia, chemotherapy was delayed for a week in one (0.8%) cycle and omitted in two (5.4%) cycles. The relative dose intensity during the cycles of both docetaxel and cisplatin was 1 (range 0.85–1). DP dose was reduced 25% during five (3.9%) cycles, two (1.6%) for leukopenia and three (2.3%) for anorexia. Grade 1 anemia was observed in 20 patients (54.1%) during 53 cycles (41.4%). Grade 1/2 leucopenia was noted in 19 patients
Elevation of transaminase was frequently found, but it was mostly mild, with 10 patients (27.0%) having grade 1 and 4 (14.8%) having grade 2, but none having grade 3/4. Only grade 1 neutropenia was found in 1 patient.

The most common grade 3/4 toxicity was neutropenia. Grade 3 neutropenia was observed in 6 patients (16.2%) during 25 cycles (19.5%), whereas grade 4 neutropenia was observed in 13 patients (46.4%) during 23 cycles (18.0%). Therefore, grade 3/4 neutropenia occurred in 19 patients (51.4%) and in 48 cycles (37.5%). Grade 3/4 oral mucositis was observed in 5 patients (13.5%) during five cycles (3.9%), and grade 3/4 nausea/vomiting was observed in 2 patients (5.4%) during two cycles (1.6%). The relationship between DP treatment and toxicity is shown in Table 3.

While on DP treatment, one patient (2.7%) experienced complete remission, 11 (29.7%) experienced partial remission, 11 (29.7%) had stable disease and 14 (37.8%) had progressive disease. The objective response rate (ORR) was 12/37 [32.4%; 95% confidence interval (CI) = 16.6–48.3%]. The median duration of response was 70.5 days (range 30–392 days). Median TTP was 136 days (95% CI = 103.7–168.3) (Fig. 1). All patients progressed during the follow-up period except for one patient who refused further chemotherapy after the second cycle and was lost to follow-up; this patient had a final response of stable disease. As of the reference date (31 August 2004), 19 patients (51.4%) are alive with progressive disease. Median OS from the onset of DP chemotherapy was 235 days (95% CI = 176–294 days) (Fig. 2). Median OS from diagnosis was 27.7 months.

### DISCUSSION

Docetaxel has been compared with cisplatin/fluorouracil, with or without epirubicin, in patients with advanced stomach cancer, as a single agent, in sequential schemes and in combination regimens, including docetaxel plus fluorouracil, irinotecan and/or cisplatin (9,10,12–17). The overall response rates of docetaxel containing regimens have been found to vary from 25 to 61.5%. Phase II trials of DP combination chemotherapy for patients with advanced gastric cancer reported ORR rates from 37 to 56%, TTP ranging from 6.1 to 6.6 months and OS ranging from 9 to 10.4 months (9,10). These findings suggested that DP may be useful as salvage therapy in the treatment of metastatic gastric cancer.

In view of the minimal impact of chemotherapy on patient survival, a considerable conclusion seems to be made for whether chemotherapy for patients with advanced gastric cancer have any advantages over best supportive care. The median survival of patients undergoing chemotherapy was longer than that of patients with best supportive care (1–3). In addition to the significant survival advantage obtained with chemotherapy, stabilization in quality-of-life was also seen in the treated patients. However, the clinical benefit of a salvage chemotherapy is not proven yet. No randomized-controlled trial data suggest a benefit of second-line chemotherapy compared...
with supportive care alone. Some studies suggest that patients who respond to second-line therapy consistently survive longer compared with non-responders and other studies showed that symptomatic benefit may be obtained from second-line therapy (18–21).

We evaluated the activity and toxicity of DP in patients with metastatic gastric cancer who had been treated formerly with 5-FU/platinum chemotherapy regimens. Although weekly docetaxel salvage therapy did not show significant antitumor activity in patients with advanced gastric cancer (5), the encouraging results with docetaxel as front-line therapy and the acceptable ORRs of sequential regimens in gastric cancer suggested to us that doetaxel may be effective as a salvage chemotherapy agent (9,10,22,23). In our study, ORR was 32.4%, indicating that, although it was salvage therapy, DP had significant activity in these patients which was comparable to that obtained when DP is used as front-line therapy. An additional 29.7% of patients achieved stable disease, suggesting that DP therapy has palliative and salvage roles. From the onset of DP chemotherapy, the median OS was 235 days, despite the short duration of TTP.

Table 3. Toxicities of docetaxel and cisplatin combination chemotherapy

<table>
<thead>
<tr>
<th>NCI toxicity</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients (%) / number of cycles (%)</td>
<td>Number of patients (%) / number of cycles (%)</td>
<td>Number of patients (%) / number of cycles (%)</td>
<td>Number of patients (%) / number of cycles (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (21.6)/40 (31.3)</td>
<td>20 (54.1)/35 (41.4)</td>
<td>3 (8.1)/7 (5.5)</td>
<td>1 (2.7)/1 (0.8)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>9 (24.3)/35 (27.3)</td>
<td>10 (27.0)/35 (27.3)</td>
<td>10 (27.0)/13 (10.2)</td>
<td>–</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 (8.1)/6 (4.7)</td>
<td>2 (5.4)/10 (7.8)</td>
<td>6 (16.2)/25 (19.5)</td>
<td>13 (35.1)/23 (18.0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (2.7)/2 (1.6)</td>
<td>–</td>
<td>1 (2.7)/1 (0.8)</td>
<td>–</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>1 (2.7)/1 (0.8)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Elevated AST/ALT</td>
<td>10 (27.0)/19 (14.8)</td>
<td>4 (10.8)/4 (3.1)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Elevated ALP</td>
<td>–</td>
<td>1 (2.7)/1 (0.8)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Azotemia</td>
<td>1 (2.7)/1 (0.8)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>4 (10.8)/8 (6.3)</td>
<td>4 (10.8)/4 (3.1)</td>
<td>2 (5.4)/2 (1.6)</td>
<td>–</td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>5 (13.5)/10 (7.8)</td>
<td>7 (18.9)/8 (6.3)</td>
<td>4 (10.8)/4 (3.1)</td>
<td>1 (2.7)/1 (0.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2.7)/1 (0.8)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

NCI, National Cancer Institute; –, 0 (0)/0 (0); AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase.

Figure 1. Time to progression (TTP). Days from the start of docetaxel/cisplatin chemotherapy to the date of proven progression. Median TTP was 136 days (95% CI = 103.7–168.3 days).

Figure 2. Overall survival (OS). Days from start date of docetaxel/cisplatin chemotherapy to date of death from any cause. Median OS was 235 days (95% CI = 176–294 days).
were not found. Only nine (24.3%) patients completed the number of cycles scheduled, with many having to terminate early owing to disease progression. Delay and omission of chemotherapy were rare.

A previous study of weekly docetaxel as salvage treatment found that asthenia was the most common toxicity, although it did not delay scheduled therapy (5). However, we were unable to assess asthenia in our study. Patient refusal of further chemotherapy may have been due, at least in part, to generally deteriorated conditions resulting from asthenia. The patients enrolled in this study were quite heterogeneous, with the time from first-line therapy to DP therapy varying widely and a mix of patients who recurred after and progressed during first-line therapy. This heterogeneity may have confused the interpretation of our results. Most of the patients treated with platinum derivatives had received cisplatin or heptaplatin. In a previous study, however, we found that heptaplatin was less active as a first-line therapy (24), suggesting that our salvage DP therapy was active in patients pretreated with heptaplatin. However, of the patients who experienced a complete or partial response, more had been treated with cisplatin than with heptaplatin (data not shown). While there were some limitations, this study showed that DP chemotherapy had the reasonable activity for advanced gastric cancer patients who had been exposed to 5-FU/platinum chemotherapy and had the possible role for salvage or second-line chemotherapy.

Giuliani et al. (6) evaluated docetaxel single therapy in 30 patients with advanced gastric carcinoma refractory to first-line chemotherapy. They observed five partial responses for the first group patients. Because docetaxel seems to be effective in second-line or salvage setting, we will study docetaxel with other active agents such as irinotecan as a second-line or salvage therapy instead of repeated platinum exposure (25,26).

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References


