RAPID COMMUNICATION

Phase II study of protracted irinotecan infusion and a low-dose cisplatin for metastatic gastric cancer

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AIM: To test protracted irinotecan infusion plus a low-dose cisplatin in this Phase II trial to decrease its toxicity.

METHODS: The eligibility criteria were: (1) histologically proven measurable gastric cancer; (2) performance status of 0 or 1; (3) no prior chemotherapy or completion of prior therapy at least 4 wk before enrollment; (4) adequate function of major organs; (5) no other active malignancy; and (6) written informed consent. The regimen consisted of irinotecan (60 mg/m²) on d 1 and 15 for metastatic gastric cancer and treatment regimen of irinotecan (70 mg/m²), d 1, 2, 3, 15, 16, and 17. Treatment was repeated every 4 wk.

RESULTS: Thirty-one patients were registered between April 2000 and January 2001. The response rate for all 31 patients, 20 patients without prior chemotherapy, and 11 patients with prior chemotherapy was 52% (16/31), 60% (12/20), and 36% (4/11), respectively. The median survival time was 378 d. The median number of courses given to all patients was 2. Grade 4 neutropenia occurred in 11 (35%) patients, while grade 3 to 4 diarrhea or nausea occurred in 1 (3%) and 3 (10%) patients, respectively. Fatigue was minimal as grade 1 fatigue was found only in 3 (10%) patients. Other adverse events were mild and no treatment-related deaths occurred.

CONCLUSION: This regimen showed a high level of activity and acceptable toxicity in patients with metastatic gastric cancer.

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Key words: Gastric cancer; CPT-11; CDDP; Protracted Irinotecan; Chemotherapy

Imamura H, Ikeda M, Furukawa H, Tsujinaka T, Fujitani K, Kobayashi K, Narahara H, Kato M, Imamoto H, Takabayashi A, Tsukuma H. Phase II study of protracted irinotecan infusion and a low-dose cisplatin for metastatic gastric cancer. World J Gastroenterol 2006; 12(40): 6522-6526

http://www.wjgnet.com/1007-9327/12/6522.asp

INTRODUCTION

In Japan, for advanced gastric cancer, surgery is still the most effective treatment and good survival can be achieved if the tumor is resectable. On the contrary, unresectable advanced or recurrent gastric cancer still has a poor prognosis and chemotherapy is the most important treatment for survival prolongation. To date, combination chemotherapy with 5-fluorouracil (5-FU) and cisplatin has been used most widely. This two-drug regimen showed superior response rate in comparison with single-agent 5FU regimen, however, failed to demonstrate survival prolongation. This regimen has response rates ranging from 10% to 35%, and the median survival time (MST) from 6 to 8 mo with around 10% in a 2-year survival. Advent of new active agents is awaited.

Among new drugs, irinotecan, a derivative of camptothecin, has strong antitumor activity through inhibition of DNA topoisomerase I. It has a single agent activity with a response rate of 23.3%. As the response rate is not satisfactory, irinotecan was first investigated in combination with cisplatin. Phase I study was conducted for metastatic gastric cancer and treatment regimen of irinotecan (70 mg/m², d 1 and 15) and cisplatin (80 mg/m², d 1), every 4 wk, was recommended. Boku's group tested this regimen for metastatic gastric cancer. The overall response rate was 48% and the median survival time was 272 d. Although no treatment-related deaths occurred, adverse events were severe, including grade 4 neutropenia in
57% of the patients and grade 3 or 4 diarrhea in 20%. As for renal toxicity, they found a total of 34% (grade 1: 23%, grade 2: 11%) serum creatinine increase. This combination study was followed with modification of weekly schedule to reduce toxicity in western countries. Ajani et al. conducted phase II study with irinotecan (65 mg/m²) with cisplatin (30 mg/m²), both administered intravenously 1 d per week for 4 consecutive weeks, followed by two weeks recovery period. Of the 36 patients registered, 21 achieved complete or partial response with response rate of 58%. They had one treatment-related death of neutropenic sepsis with multiple organ failure. Major toxic effects were diarrhea, neutropenia, and fatigue. The incidence of grade 3 or 4 neutropenia was 37%, however, grade 3 or 4 diarrhea was still found in 22% of patients. Surprisingly, grade 3 or 4 fatigue was 41%, a cause of delays or cancellation of drugs. To decrease adverse events, Fujitani et al. conducted a pharmacokinetic study of continuous infusion of irinotecan for 24 h combined with infusion of cisplatin over 90 min, and demonstrated only mild hematological and nonhematological adverse reactions, while protracted infusion of irinotecan increased the area under the concentration time curve (AUC) of SN-38.

Accordingly, we further investigated the safety and efficacy of this combined protracted infusion of irinotecan (to maintain a high AUC of SN-38) with a low-dose cisplatin to determine whether this regimen can improve response rate and reduce toxicity.

MATERIALS AND METHODS

Eligibility criteria
Patients were required to satisfy the following eligibility criteria; (1) histologically proven gastric cancer; (2) measurable metastatic lesions; (3) Eastern Clinical Oncology Group scale performance status of 0 or 1; (4) no prior chemotherapy or completion of therapy at least 4 wk before entry; (5) adequate function of the bone marrow (WBC count ≥ 4 × 10⁹ and ≤ 12 × 10⁹, platelet count ≥ 100 × 10⁹, and hemoglobin ≥ 95 g/L), liver (serum bilirubin ≤ 25.6 µmol/L and serum transaminases ≤ 1667 nkat/L), and kidneys (serum creatinine ≤ 133 µmol/L); (6) normal cardiac function; (7) no other severe medical conditions; (8) no other active malignancy; and (9) ability to give written informed consent. This study was approved by the institutional review boards of all participating hospitals.

Treatment schedule
On d 1, irinotecan (60 mg/m²) was administered as a 24-h infusion; the drug was diluted in 500 mL of saline or 50 g/L glucose and was protected from the light. Cisplatin (10 mg/m²) was administered as a 60-min intravenous infusion with adequate hydration on d 1, 2, and 3. The same doses of irinotecan and cisplatin were repeated on d 15 and 15-17, respectively, to complete one course. Treatment was repeated every 4 wk until the occurrence of disease progression, patient refusal, or unacceptable adverse reactions. On d 15, if the patient had leucopenia or thrombocytopenia of grade 2 or higher, diarrhea of grade 1 or higher, or fever (a temperature > 38°C) due to infection, administration of the second dose of irinotecan was delayed for one week. If recovery from the adverse reaction did not occur after one week, the second dose was skipped. If a grade 4 hematologic adverse event, grade 3 or 4 diarrhea, fever associated with infection, or omission of the second dose occurred, the dose of irinotecan for the second course was reduced to 50 mg/m². The antiemetic granisetron was given before cisplatin administration. Granulocyte colony-stimulating factor (G-CSF) was used when grade 4 leucopenia and/or neutropenia occurred. If the patient stopped treatment due to toxicity or tumor progression, other chemotherapy or surgery was offered.

Evaluation
The National Cancer Institute Common Toxicity Criteria (Version 2.0) were applied for the assessment of adverse events. The objective response of measurable lesions was evaluated by standard World Health Organization criteria. Both patient eligibility and the response to treatment were reviewed extramurally.

Statistical analysis
The expected efficacy rate of this regimen was hypothesized to be 50%, so the required number of patients was 25 when the 95% confidence interval was set at ± 20%. Because some patients might be excluded from analysis, the target number of patients for this study was set at 30. Analysis was performed on an intent-to-treat basis. The percentage of patients with complete remission (CR) plus partial remission (PR) among all treated patients was defined as the response rate. The 95% confidence interval (CI) of the response rate was calculated using the normal approximation and precision method. The Kaplan-Meier method was used to calculate the survival period.

RESULTS

Patients characteristics
Thirty-one patients were enrolled from April 2000 to January 2001. One patient was found to be ineligible because the performance status was 2. As analysis was performed on an intent-to-treat basis, this patient was also analyzed for efficacy and safety, so all 31 patients were assessed for efficacy and safety. Their clinical characteristics are shown in Table 1. The median age was 60.5 (range: 26-75 years) and 21 patients (68%) had performance status of 0. Sixteen patients (52%) had intestinal type adenocarcinoma and 14 patients had diffuse tumors. The measurable metastatic lesions were located in the lymph nodes in 20 patients (26 lesions), liver in 13 patients, peritoneum in 3 patients, ovary in 2 patients, and the skin, lung, and rectum in one patient each, respectively. Twenty patients (65%) had not received prior chemotherapy, while the other 11 patients had undergone chemotherapy with 5-FU, cisplatin plus 5-FU, or other drugs. All of the patients who had received prior therapy showed progressive disease before enrollment. The total number of treatment courses was 84 with a median number of 2 cycles per patient (range 1-5). A total of 149 of 168 planned CPT-11 administration was carried out. While a total of 112 of 122 (92%) planned CPT-11 was administered in the first and second cycle, a
total of 37 of 46 (80%) planned CPT-11 administration in the third to fifth cycles. Dose reduction was not required in the first cycle, but it was needed in 8 patients in the second cycle and one patient in the third cycle. Causes of dose reduction were grade 4 neutropenia in 5 patients, grade 4 leukopenia in one patient, and second dose skip in 3 patients. Treatment was stopped due to tumor progression in 8 patients, refusal to continue in 9 patients, and insufficient recovery from adverse reactions in 3 patients. Median duration between the beginning and end of treatment was 75 d. The actual administered dose of CPT-11 in the all courses was 25.7 mg/m² per week and that of cisplatin was 13.0 mg/m² per week, which corresponded to 85.5% and 86.4% of the planned doses.

Response and survival
There were no complete remissions, but partial remission was achieved in 16 patients for a response rate of 52% (16/31 patients, 95% CI: 33% to 70%). The response rate was 60.0% for the 20 patients without prior chemotherapy (12/20 patients, 95% CI: 36% to 81%), while the rate for the 11 patients with prior chemotherapy was only 36% (4/11 patients, 95% CI: 11% to 69%). The response rate of patients with lymph node, liver, and peritoneal metastasis were 54% (14/26 patients), 54% (7/13 patients) and 33% (1/3 patients), respectively (Table 2). The median duration of response for all the patients was 218 d. The median survival time of all patients was 378 d, while the median survival time of the 20 patients without prior chemotherapy was 509 d. The 1-year and 2-year survival rates were 57% (95% CI: 37%-72%) and 9% (95% CI: 2%-23%), respectively (Figure 1).

Adverse reactions
Adverse reactions to this regimen are shown in Table 3. Grade 4 neutropenia, leukopenia, anemia, and thrombocytopenia were observed in 11 (35%), 3 (10%), 2 (6%), and 1 (3%) of the patients, respectively. The median nadir of the neutrophil count was seen on d 8 (range: d 2-19). G-CSF was administered to 15 patients (48%) during 28 courses. Non-hematologic adverse reactions (nausea, diarrhea, increased AST, and increased bilirubin) were all moderate, with grade 3 nausea (10%) and grade 3 diarrhea (3%) being the maximal reactions. Loperamide or other mild anti-diarrheal medicines were effective for diarrhea, while granisetron and other common anti-emetic medicines were effective for nausea without additional hydration. Renal
toxicity determined by the level of serum creatinine was also mild. We found 8 patients (26%) with only grade 1 abnormal creatinine level. Fatigue was found in only 3 patients and all grade 1. The non-hematologic reactions did not disrupt the treatment schedule and there were no treatment-related deaths.

**DISCUSSION**

The aim of this phase II study was to confirm the antitumor effects and safety of combined chemotherapy of protracted infusion of irinotecan and low-dose cisplatin[8]. Protracted infusion of irinotecan significantly increases the AUC of active metabolite, SN-38[10], suggesting it has the potential to maximize the effect of irinotecan. The response rate to irinotecan as a single agent for gastric cancer was reported to be 23.3%[8] and that for cisplatin was 20%[11]. The overall response rate of the 31 patients in the present series was 52% and that of 20 patients without any prior chemotherapy was 60%, with both rates being better than for single agent therapy. These data are consistent with a previous phase II study of cisplatin and irinotecan therapy[8], and confirms the activity of combined therapy of irinotecan and cisplatin.

Diarrhea is a serious toxicity of irinotecan therapy. The incidence of grade 3 or 4 diarrhea was reported to be 18.8% or 35.6% with irinotecan alone and 21.9% or 35.6% with bolus combined administration[12-15]. In the previous phase II studies of irinotecan and cisplatin, diarrhea was still one of the major cause that could affect treatment schedule and the incidence of grade 3 or 4 diarrhea was around 20%[8,9]. In the present study, grade 4 diarrhea did not occur and only one patient (3%) suffered from grade 3 diarrhea that did not necessitate a change of schedule.

The incidence of grade 3 or 4 neutropenia (77%) is still high in this study, and Boku et al[9] found the incidence of grade 3 or 4 neutropenia was 89%. Ajani et al[8] demonstrated that 37% grade 3 or 4 neutropenia by weekly administration. Sakaki et al[16] found a positive correlation between the AUC of irinotecan and the decrease of the white cell count, however, diarrhea has a stronger correlation with the AUC of SN-38 than with that of irinotecan. As this treatment regimen has greater AUC of active metabolite, SN-38 over irinotecan, we expected to find more hematological toxicities than diarrhea. To the contrary, we found significantly less common severe diarrhea, and high incidence of grade 3 or 4 neutropenia that was comparable to the previous Japanese trials[8]. The target dose of irinotecan for this study (60 mg/m² × 2) was lower than that used by Boku (70 mg/m² × 2)[9] or that used to treat lung cancer (60 mg/m² × 3)[17,18]. Actual dose of CPT-11 administered in the Boku’s study was 28.5 mg/m² per week, and that in our study was 25.7 mg/m² per week, so our regimen seemed to reduce the incidence and grade of diarrhea while achieving a similar response rate with a lower dose of irinotecan.

Nausea and renal toxicity is a common problem with cisplatin therapy, so we administered a low dose of 10 mg/m² on six occasions to achieve a total dose of 60 mg/m². Grade 3 nausea occurred in 3 patients (10%) and there was no grade 4 nausea. Low-dose, repeated administration has already been reported to decrease the incidence and grade of nausea due to cisplatin[19-22]. Some Japanese authors have reported that repeated cisplatin administration at a low dose reduces the incidence of nausea and allows outpatient treatment, and that this method achieves a high response rate and longer survival when combined with irinotecan without the need for 24-h infusion of the latter drug[20,21]. As for renal toxicity, Boku et al with high-dose cisplatin administration[8] found grade 1 or 2 serum creatinine increase in 23 and 11% of patients, respectively. We found only grade 1 abnormality, and the incidence of 26%, demonstrating that renal toxicity with this regimen is minimal. As hydration is not required to prevent renal toxicity with low-dose therapy[20-22], continuous infusions are not necessary after finishing irinotecan administration on d 2, 3, 16, and 17.

In order to complete this regimen, hospitalization is required to receive 24-h irinotecan infusions and 6 divided dose of cisplatin. Therefore, this regimen is not applicable for out-patient basis; however, as the incidence of fatigue of this regimen was 10% (only grade 1), severe diarrhea was rare, and hydration was not necessary, it is possible to treat patients on an out-patient basis between infusions. Ajani et al demonstrated very high incidence (41%) of grade 3 or 4 fatigue with weekly irinotecan and cisplatin administration, and they discussed cisplatin might contribute to excessive fatigue, thus either the dose of cisplatin might be reduced, or cisplatin might be replaced by other agents. Our results with 10% grade fatigue suggested that low dose cisplatin is a practical alternative for reducing the fatigue.

In conclusion, though hospitalization is required at this time, 24-h infusion of irinotecan combined with a low-dose, repeated administration of cisplatin achieved a high response rate and prolonged the survival of patients with metastatic gastric cancer. This regimen also reduces non-hematologic adverse reactions and thus shortens the time in hospital.

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