A Preliminary Study of Preoperative Chemotherapy Combining Irinotecan and Cisplatin in Patients with Gastric Cancer with Unresectable Para-aortic Lymph Node Metastases

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Background: A high response rate has been reported for chemotherapy combining irinotecan (CPT-11) and cisplatin (CDDP) against advanced gastric cancer. The strong anti-tumor activity of this regimen makes it very attractive as a preoperative chemotherapy. We conducted a preliminary study on preoperative chemotherapy with this regimen in patients with unresectable gastric cancer with para-aortic lymph node metastases to evaluate the feasibility of it as a treatment strategy.

Methods: Patients with unresectable para-aortic lymph node metastasis without distant hematogenous metastasis (H0, M0 and M1 LYM) and peritoneal dissemination (P0) were eligible for entry. The preoperative chemotherapy consisted of at least three cycles of CPT-11 (70 mg/m²) on days 1 and 15 and CDDP (80 mg/m²) on day 15, repeated every 4–6 weeks. Chemotherapy was followed by surgery with extended lymph node dissection in patients who achieved complete or partial responses and whose cancers were judged to be resectable.

Results: Six patients were entered into the study. In total, 18 cycles of chemotherapy were performed and five patients received at least three cycles. Objective partial responses were achieved in four patients. The major toxicities in the chemotherapy were neutropenia and diarrhea, but these were clinically acceptable. Four patients underwent surgery after the chemotherapy, and macroscopically complete resections with extended lymph node dissection were achieved in two patients. There were no therapy-related deaths. We found no pathological complete responses, but observed a definite histopathological effect caused by the chemotherapy in surgical specimens. The median survival time of all patients was 12 months. The longest survival without relapse is >6 years from the start of therapy.

Conclusions: We conclude that preoperative chemotherapy with CPT-11/CDDP therapy is feasible in patients with advanced gastric cancer and that the regimen is safe when followed by surgery. Further clinical studies with larger numbers of patients are warranted to evaluate the efficacy of this strategy.

Key words: gastric cancer – irinotecan (CPT-11) – cisplatin (CDDP) – neoadjuvant chemotherapy – preoperative chemotherapy

INTRODUCTION

Despite a declining incidence in many developed countries, gastric cancer remains the second most common cause of cancer-related deaths globally (1). Although gastric cancer is potentially curable when diagnosed at an early stage, the possibility of cure decreases according to the progression of clinical stage. To improve the treatment outcome of advanced gastric cancer, both medical and surgical therapeutic approaches have been aggressively investigated for many years. In the surgical approach, the mainstay against gastric cancer has been the complete resection of the primary tumor in combination with systemic lymph node dissection. To achieve higher curability, aggressive extended surgery, such as left upper abdominal evisceration (LUAE) or gastrectomy with para-aortic lymph node dissection, was introduced in the treatment of patients with advanced disease (2–4). However, patients with distant lymph node metastases have a high risk for relapse even when
they undergo aggressive extended surgery and the prognosis of these patients still remains poor (5). These facts suggest that gastric cancer with distant lymph node metastases should be regarded as a potential systemic disease which represents a limitation to the potential therapeutic impact of surgery alone against it. Although postoperative adjuvant chemotherapy in high-risk patients has been tested in numerous clinical trials, its effect has not been established beyond reasonable doubt (6). In the medical approach, various combinations of active drugs have been tested in many clinical trials to find an effective chemotherapy against unresectable and metastatic cases of the disease. At present, there is significant evidence that adding systemic chemotherapy to the best supportive care could provide benefits in survival and quality of life as compared with the best supportive care alone (7–9). In general, 5-fluorouracil (5FU)-based or cisplatin-based combinations are widely accepted as potential standard therapies with which the response rate is around 30–40% (10). However, effects of these chemotherapy regimens on survival prolongation still remain unsatisfactory, with a median survival time around 6–7 months in recent large-scale randomized trials (11–13). Therefore, there is a clear need for new chemotherapy regimens comprising new active drugs with novel mechanisms of action in order to improve the treatment outcome of this disease. Additionally, the investigation of the multimodality therapy, i.e. an appropriate combination of surgery, chemotherapy and radiation therapy, has been considered to be a high priority for clinical research in the treatment of advanced gastric cancer in recent years.

Preoperative chemotherapy is a promising strategy of multi-modality therapies. A strong rationale exists for using preoperative chemotherapy to improve the treatment outcome in advanced solid tumors, and therefore it is currently accepted as an effective treatment for ovarian, head and neck cancer and extremity tumors. Preoperative chemotherapy is considered to have a number of potential clinical advantages (14). In preoperative chemotherapy for potentially resectable cases, exposure to chemotherapy at the earliest time may prevent rapid growth of metastases after treatment of the primary sites and may also prevent the emergence of chemoresistant clones. Moreover, tumor reduction induced by preoperative chemotherapy may increase the chance for curative resection, and the response to chemotherapy may enhance local control or permit a more conservative resection by decreasing the size of the tumor or by down-staging. In preoperative chemotherapy for potentially unresectable cases, the major rationale is to render unresectable cases resectable by primary chemotherapy. Preoperative chemotherapy against advanced gastric cancer has been investigated in several clinical trials (14). A recent report suggested that the response to preoperative chemotherapy is the single most important predictor of overall survival in preoperative chemotherapy for locally advanced gastric cancer (15). However, a randomized controlled trial failed to demonstrate an advantage for preoperative FAMTX (5FU, doxorubicin and methotrexate) therapy, which is one of the standard regimens for 5FU-based chemotherapy against advanced gastric cancer, in comparison with surgery alone in terms of the down-staging effect and the curative resectability rate (16). Therefore, there is a strong rationale for investigating preoperative chemotherapy with stronger drug regimens for usage in a preoperative setting.

Boku et al. (17) reported a high response rate using a combination of CPT-11 and CDDP against advanced gastric cancer, with an overall response rate of 59% in chemotherapy-naive patients (one complete response and 17 partial responses among 29 patients). The objective of this study was to evaluate the feasibility of preoperative CPT-11/CDDP therapy and safety in surgery following this chemotherapy in order to determine whether this strategy is worthy of further investigation in a large scale clinical trial.

SUBJECTS AND METHODS

ELIGIBILITY

Patients enrolled in this study were required to fulfill the following criteria: histologically confirmed gastric adenocarcinoma; presence of para-aortic lymph node metastases (N4; detection of two or more enlarged lymph nodes, of size >10 mm by CT scan); absence of distant hematogenous metastasis (H0, M0; M1 LYM was regarded as eligible) and peritoneal dissemination (P0); performance status (PS) ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale; no prior chemotherapy or radiotherapy; age ≤70 years; acceptable bone marrow function (WBC ≥4000/mm3 and platelet ≥100 000/mm3); acceptable liver function (serum bilirubin level ≤1.5 mg/dl and serum transaminase level ≤3-fold the upper limit of normal); normal renal function (serum creatinine and blood urea nitrogen within the upper limit of normal and creatinine clearance ≥50 ml/min); normal cardiac function (normal ECG); and written informed consent. The study protocol was approved by the institutional review board of the Cancer Institute Hospital, Tokyo, Japan.

TREATMENT

The dose and schedule for CPT-11 and CDDP in the present study were chosen based on the report by Boku et al. (17). In the present study, CPT-11 (70 mg/m2) was administered over 90 min by intravenous infusion, which was followed by CDDP (80 mg/m2) administered over 120 min by intravenous infusion with adequate hydration on day 1. The same dose of CPT-11 as on day 1 was administered on day 15. At the time of the administration of CPT-11 on day 15, patients were required to fulfill the following criteria: leukocyte count ≥3000/mm3; platelet count ≥100 000/mm3; and no sign of diarrhea or infection. When the patients did not meet these criteria, the administration of CPT-11 was postponed until recovery with an allowance of 7 days. When the patients did not meet these criteria within 7 days, CPT-11 was skipped and the next cycle was restarted with a reduced dose of CPT-11 (60 mg/m2). Chemotherapy was repeated every 4–6 weeks, and at least three cycles...
were completed before surgery. In patients who exhibited hematological toxicity of grade 4 or diarrhea of grade 3, the dose of CPT-11 was also reduced to 60 mg/m² in subsequent administrations. Granisetron was administered to prevent nausea and vomiting. Tumor response was assessed by CT scan as well as endoscopy and upper gastrointestinal series of the target lesions before each cycle of chemotherapy and at the end of treatment.

For patients who achieved a partial or complete response after at least three cycles of chemotherapy, the resectability of the tumors was reassessed according to the findings of a CT scan of the whole abdomen and chest, endoscopy of the upper gastrointestinal tract, an upper gastrointestinal series and a barium enema. The absence of any enlarged lymph nodes of size >10 mm by CT scan was required to be judged as resectable. Patients who were judged to be candidates for curative resection underwent surgery with curative intent (gastrectomy with extended lymph node dissection; D4 lymph node dissection as described in the Japanese Classification of Gastric Carcinoma). Surgery with extended lymph node dissection was not performed in patients whose cancers had remained unresectable after chemotherapy but the palliative surgery was performed if clinically indicated. Surgery was performed at least 3 weeks after the last chemotherapy. In patients whose disease progressed during the chemotherapy period, the protocol CPT-11/CDDP therapy was terminated and subsequently adequate salvage therapies including chemotherapy with other regimens and/or possible palliative therapies were performed. When any unexpected incurable factors were identified during surgery, full surgical procedure with the extended lymph node dissection was not indicated, and adequate salvage therapies including chemotherapy with other regimens and/or possible palliative therapies were subsequently performed.

Patients who had undergone surgery were followed up every 3 months by medical and surgical oncologists. A CT scan of the whole abdomen, a chest X-ray and a blood examination including tumor markers were performed every 3 months and endoscopy of the upper gastrointestinal tract was performed once in the first postoperative year. In subsequent years, a CT scan of the whole abdomen, a chest X-ray and a blood examination including tumor markers were performed every 4 months and endoscopy of the upper gastrointestinal tract was performed once a year.

**EVALUATION OF RESPONSE AND TOXICITY AND HISTOPATHOLOGICAL EXAMINATION OF SURGICAL SPECIMENS**

The objective response to chemotherapy in measurable and primary lesions was evaluated according to the criteria of the Japanese Research Society for Gastric Cancer (18). Toxicity was assessed according to the Japan Clinical Oncology Group common toxicity criteria (19). The overall survival was calculated for the period from the date of registration to the date of death. Time to remission was calculated from the date of initiation of treatment to the onset of PR. Postoperative complications were

**Table 1. Patient characteristics and treatment outcomes**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>PS</th>
<th>Primary lesion Cycles of chemotherapy administered</th>
<th>Response</th>
<th>Time to PR (days)</th>
<th>Intervals between chemotherapy and surgery (days)</th>
<th>Curability by surgery</th>
<th>Survival after chemotherapy (months)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>59</td>
<td>M</td>
<td>0</td>
<td>A</td>
<td>Poor</td>
<td>3</td>
<td>39</td>
<td>Curative</td>
<td>23</td>
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<tr>
<td>2</td>
<td>37</td>
<td>M</td>
<td>1</td>
<td>A</td>
<td>Poor</td>
<td>4</td>
<td>35</td>
<td>Curative</td>
<td>182</td>
</tr>
<tr>
<td>3</td>
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<td>M</td>
<td>1</td>
<td>M-A</td>
<td>Poor</td>
<td>2</td>
<td>185</td>
<td>Curative</td>
<td>182</td>
</tr>
<tr>
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<td>46</td>
<td>F</td>
<td>1</td>
<td>C-M</td>
<td>Poor</td>
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<td>28</td>
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<td>28</td>
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<tr>
<td>5</td>
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<td>M</td>
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<td>119</td>
<td>Palliative</td>
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<td>3</td>
<td>137</td>
<td>Palliative</td>
<td>137</td>
</tr>
</tbody>
</table>

PS, ECOG performance status. aPS, ECOG performance status. bA, lower third of the stomach; M, middle third of the stomach; C, upper third of the stomach. cPoor, poorly differentiated adenocarcinoma; Sig, signet-ring cell carcinoma. Mod, moderately differentiated tubular adenocarcinoma. dPR, partial response; NC, no change; PD, progressive disease.
assessed to evaluate the safety of this preoperative chemotherapy. The formalin-fixed surgically resected specimens were examined by the pathologists and the histological change in tumors possibly effected by the chemotherapy was evaluated according to the criteria of the Japanese Research Society for Gastric Cancer (18).

RESULTS

Between December 1996 and March 1998, six patients were entered into the present study. The pretreatment baseline characteristics and treatment outcomes of all patients are listed in Table 1. Four male and two female patients were registered as the first line chemotherapy. The median age of the patients was 55 years (range, 37–68 years). One patient had a PS = 0 and the remaining five patients had PS = 1. Two patients had a macroscopically scirrhous type of advanced gastric cancer (type 4). Histologically, five patients had diffuse types of adenocarcinoma (three had poorly differentiated adenocarcinoma and two had signet-ring cell carcinoma), and one patient had an intestinal type of adenocarcinoma (moderately differentiated tubular adenocarcinoma).

CPT-11/CDDP CHEMOTHERAPY

In total, 18 cycles of chemotherapy were performed and five patients received at least three cycles of chemotherapy. Toxicity observed during the chemotherapy period is summarized in Table 2. Major adverse events were myelosuppression and gastrointestinal toxicity. Grade 4 neutropenia and grade 3 diarrhea occurred in three and two patients, respectively, and the dose of CPT-11 was reduced to 60 mg/m² in subsequent administrations to these patients. The GCSF was administered in two patients for the treatment of grade 4 neutropenia. Diarrhea was manageable with standard loperamide therapy. Grade 4 neutropenia and grade 3 diarrhea did not recur after the dose reduction of CPT-11 in subsequent cycles. Nausea and vomiting were mild or moderate. The transient elevation of ALT or AST was observed in five patients. Alopecia was experienced in all patients. There were no chemotherapy-related deaths. The overall toxicity was clinically acceptable. Objective partial responses were achieved in four of six patients (response rate, 66%; 95% confidence interval of 22.3–95.7%), consisting of responses of the lymph node metastases and primary gastric lesions in four and three patients, respectively. The median time to remission achieved was 37 days (range, 28–72 days).

SURGERY

Four patients underwent surgery after CPT-11/CDDP therapy including two curative and two palliative resections. The median interval between the initiation of chemotherapy and the surgery was 160 days (range, 119–185 days). Two patients (patients 1 and 2) underwent gastrectomy with para-aortic lymph node dissection (D4) and achieved a macroscopically complete resection (curability B) (Fig. 1). In patient 1, whose disease involved left supraclavicular nodes (M1 LYM), the lymphadenectomy of cervical and supraclavicular lymph nodes was added. The total operation time in patients 1 and 2 was 12 h and 13 h, respectively. In patient 5, the surgery did not result in a curative resection, in spite of the fact that a partial response was achieved. This patient underwent palliative gastrectomy, because peritoneal dissemination was found during surgery. In patient 4, the disease progressed during the chemotherapy and palliative gastrectomy was performed for the purpose of symptom relief. The surgery-related complications were overall manageable and there were no serious ones. The retention of left pleural effusion was observed postoperatively in two patients (patients 2 and 4), and diarrhea was observed in two patients who underwent para-aortic lymph node dissection (patients 1 and 2). The median admission period after surgery was 25 days with a range of 19–30 days.

Two patients did not undergo surgery. In patient 3, surgery was not performed in spite of the fact that tumors in both the primary lesion and lymph node metastasis responded to chemotherapy and were judged as being surgically resectable. Instead, chemotherapy was continued because the patient refused to undergo surgery. In patient 6, the tumor did not respond to chemotherapy (NC) and surgery was not performed.

SURVIVAL

The median survival time of all patients was 12 months (Table 1). In patient 1, who underwent curative surgery after four cycles of chemotherapy, recurrence in abdominal lymph nodes occurred 6 months after surgery and the patient died of systemic recurrence 23 months after the initiation of chemotherapy. One patient (patient 2) has been followed up with disease-free survival lasting 6 years without any postoperative anticancer therapies.
HISTOPATHOLOGICAL FINDINGS

Histological findings of surgically resected specimens are listed in Table 3. There were no pathological complete responses (pCRs). The grade of histological change was associated with the clinical response. The grades of the histological effect of chemotherapy in the responders were grade 1a (patient 1) and grade 1b (patient 2), whereas they were grade 0 in non-responders (patients 4 and 5). Histological examination of the specimens of resected lymph nodes revealed that viable cancer cells were detected in 70 out of 165 lymph nodes in patient 1. However, a histological examination of specimens from patient 2 revealed that viable cancer cells were found in only one out of 115 resected lymph nodes and most metastatic lymph nodes had become necrotic with fibrosis.

DISCUSSION

In the present study, we selected patients with advanced gastric cancer with unresectable para-aortic lymph node metastasis (N4) without distant or peritoneal metastasis (H0, M0, P0). We based this strategy on a trial reported by Nakajima et al. (20) in which long-term survivors were observed in similar groups of patients. Seike et al. (21) also observed favorable outcomes in some patients with a similar strategy. In this setting, appropriate selection of patients based on the accurate staging of disease is an important issue for clinical trials of this strategy. To exclude patients with hematogenous metastases such as lung or liver metastases, all patients were required to be examined with whole body CT scanning before entry, and MRI and skeletal scintigraphy were also performed according to individual necessity. Peritoneal dissemination was clinically evaluated based on the comprehensive findings of a CT scan, upper gastrointestinal series and barium enema examination. Laparos-
copy with cytological examination of peritoneal lavage should be useful for the accurate diagnosis of peritoneal dissemination in future studies, but was not attempted in the present preliminary study. To determine the indication for surgery of curative intent after CPT-11/CDDP therapy, these evaluation procedures were also performed at that point.

In the present study, toxicities of CPT-11/CDDP therapy were acceptable, however, occurrence of severe neutropenia was similar to the previous report. There were no serious surgery-related complications in a total of four operations including two palliative and two extended surgeries (D4) with curative intent. Therefore, preoperative chemotherapy with CPT-11/CDDP did not seem to increase operative risks significantly. The operation time of extended surgery was relatively longer than that of primary surgery without preceding chemotherapy. However, this is not associated specifically with the chemotherapy regimen performed in this study. Generally, the metastatic lymph nodes or former tumor area frequently presents as hard, fibrous tissue due to the effect of chemotherapy, which can make surgery more difficult and hence prolong operation time. Persistent diarrhea was observed as the sequela of the para-aortic lymph node dissection, which commonly occurs in patients who undergo such operations.

The results of the present study and previous reports give us an important clinical implication for the rationale of adding surgery after effective chemotherapy. In the present study, two patients underwent curative surgery after chemotherapy, among whom one achieved long-term survival of >6 years after therapy without relapse. Nakajima et al. (20) reported that the survival outcome of partial response patients with curative surgery was good, while for partial response patients who received non-curative surgery, it was as poor as that of non-responders. These findings suggest that complete eradication of cancer cells as a result both of chemotherapy and surgery is essential to achieve long-term survival. A review of previous trials of preoperative chemotherapy against advanced gastric cancer showed that pCR was achievable, however, it was quite rare as only six pCRs were observed in a total of 333 evaluated patients from 10 trials (14). In the present study, although significant shrinkage of tumors was observed in preoperative CPT-11/CDDP therapy, no pCRs were achieved. These results suggest that the risk of tumor regrowth is always substantial even when a good clinical response to chemotherapy is observed. They also support the rationale for adding surgery for the purpose of complete eradication of the residual cancer cells after chemotherapy. In such situations, we consider that extended surgery is essential regardless of the degree of tumor regression by preoperative chemotherapy to remove the former tumor area as completely as possible for curative intent. These clinical implications should be confirmed in future by well-designed clinical trials.

There have been several reports on the phase II trials of preoperative chemotherapy against unresectable gastric cancer with various chemotherapy regimens. The outcome of these studies showed that the response rates were 50–70% with a median survival of 6.5–18+ months and that this strategy was overall feasible (14,20,22–26). The high response rates were mainly contributed to by the patient selection in which eligible subjects were mainly those with locally advanced disease in these studies. Although it is difficult to compare the results of the present study with these historical data because of the small sample size of the present study and different patient populations between studies, the efficacy regarding results in this study seems to be similar to previous reports. Although early effects, such as increase in resectability, has been promising in previous reports, data of long-term survival has been very limited in patients treated with preoperative chemotherapy against unresectable disease. It is noteworthy that one patient enrolled in our study is still disease-free 6 years after the start of therapy.

We conclude that the combination chemotherapy of CPT-11 and CDDP is feasible as preoperative chemotherapy against unresectable gastric cancer and can be safely followed by surgery, including extended surgery, without increasing perioperative risk. Large-scale clinical trials are warranted to evaluate the efficacy and safety of this strategy. Based on the results of the present study, a multi-institutional phase II trial of preoperative chemotherapy is currently being carried out with this regimen in a patient population similar to the present study by the Japan Clinical Oncology Group (JCOG0001 study).

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References


