Neoadjuvant Chemotherapy in Scirrhous Cancer of the Stomach Using Uracil and Tegafur and Cisplatin

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We administered a mixture of uracil and tegafur (UFT)/cisplatin (CDDP) chemotherapy in 28 patients with scirrhous gastric cancer. In the regimen, UFT was orally administered at a dose of 200 mg/m² twice a day. The CDDP was administered at a dose of 90 mg/m² by 24-hour continuous infusion every 4 weeks. As a result, antitumor effects for primary gastric foci were achieved in 14 of the 28 patients (50%). Ascites from peritoneal dissemination disappeared completely in eight of 13 patients (62%). Total gastrectomy was performed in ten patients after 2 to 3 courses of chemotherapy. Histological response grades assessed on the resected specimen were Grade 2 in four, Grade 1b in three, Grade 1a in one and Grade 0 in two patients. Neoadjuvant chemotherapy is feasible against scirrhous gastric cancer and a subsequent prospective randomized trial should be prepared to clarify the survival benefit of the treatment.

Key words: survival time, histological changes, biochemical modulation

Introduction

According to the National Gastric Cancer Registration Survey Report of 1984, early gastric cancer accounts for 36% of all gastric cancer cases, suggesting remarkable progress in the diagnosis of this malignancy (1). Advanced gastric cancer represents the remaining 64%, and scirrhous gastric cancer accounts for about 15% of these cases. This type of cancer is well known to be rapidly growing and the early expression of its malignancy is still unclear even by the retrospective observation of radiological and endoscopic films recorded previously (2, 3), and the complication of cancerous peritonitis is often noted at the time of diagnosis (4). The affliction of this cancer in young women may not be infrequent, and the prognosis is extremely poor (5). Even if scirrhous gastric cancer is macroscopically resected, peritoneal metastasis may be present microscopically (with a high positivity rate in intraperitoneal free cancer cells and a high recurrence rate) (6). In this sense, it may be inevitable to consider many cases of scirrhous gastric cancer to be beyond the point of benefit from surgical treatment. Therefore, surgery combined with chemotherapy is necessary for the treatment of patients with scirrhous gastric cancer.

With regard to chemotherapy for advanced gastric cancer, as reviewed by Leichman and Berry in 1991 (7), cisplatin-based regimens have been widely adopted as the effective combinations, based on the experimental results of Schabel et al in which cisplatin combined chemotherapy has shown synergistic cytotoxicity against murine L1210 leukemia (8). Preusser et al reported etoposide/adriamycin/cisplatin (EAP) regimen in the treatment of gastric cancer and demonstrated overall responses in 64% (43/67) patients (9). This regimen was, however, considered to be not recommendable because of its toxicity (10). Lacave et al reported cisplatin 24-hour infusion combined with 5-fluorouracil 5-day continuous infusion in the treatment of advanced gastric cancer have demonstrated overall responses in 41% (22/53) patients (11). In 1994, Findlay et al reported a phase II trial, epirubicin and cisplatin combined with 5-fluorouracil 21-week continuous infusion (ECF) and demonstrated objective responses in 71% (91/128) patients (12). In 1994, Rougier et al reported on neoadjuvant chemotherapy with cisplatin and combined 5-fluorouracil continuous infusion and demonstrated overall responses in 56% (17/27) patients (13). They concluded that neoadjuvant chemotherapy is useful in locally advanced gastric cancer.

In this article, we report the result of the treatment of scirrhous gastric cancer with uracil and tegafur/cisplatin (UFT/CDDP) regimen. This treatment has been developed and adopted at our hospital since 1987 (14), on the basis of the biochemical
modulation mechanism which would be later described more in
detail (14, 15).

We also present surgical results in a case in which UFT/
CDDP was administered in advance as a neoadjuvant chemotherap,
y and examine the usefulness of this combined modality.

Patients and Methods

From November 1987 to February 1995, 28 patients with
cirrhous gastric cancer who presented to our hospital received
UFT/CDDP chemotherapy. All patients had histologic confir-
mation of adenocarcinoma of the stomach. Patients did not
receive prior chemotherapy. Patients were required to have
adequate hematological, renal, hepatic, cardiac function and a
life expectancy of at least 2 months. All patients or patients’
family gave informed consent prior to the study; ages of the
patients ranged between 32 and 73 years (mean: 55.5); M/F:
12/16 (16).

The stomach is divided into three segments; upper (C),
middle (M) and lower (A) third (17). According to this classi-
fication, cirrhous gastric cancer occupied only one segment (M
region) in one patient (4%), and she had the combination of
peritoneal dissemination accompanying ascites. The cancer
was located in two segments in seven patients (25%), including
four (14%) with cancer affecting C and M regions, and three
(11%) affecting M and A regions. All three regions were
affected in 20 patients (71%). Ascites was noted in 13 patients
(46%) at the first examination. They had no distant metastasis.
The histological type of the disease was signet ring cell carci-
noma in 16 patients (57%), poorly differentiated carcinoma in
seven (25%) and moderately differentiated tubular adenocarci-
noma in five (18%).

Chemotherapy (4, 18)

Initially, UFT at a daily dose of 400/m2 was orally adminis-
tered, divided into two doses before breakfast and supper for 8
weeks, then UFT 250/m2 was orally administered in the same
manner after the first 8 weeks. CDDP was administered 5 to 7
days after the start of UFT treatment. CDDP at a dose of 90 mg/
m2 was reconstituted and administered in a mixture of 1,400 ml
of 5% glucose solution and 1,400 of normal saline with 20
mEqKCL over 24 hours. CDDP treatment was followed by
reduced CDDP dose of 80 mg/m2/day for the second and third
courses.

Patients received a mixture of 700 ml 5%-glucose and 700
ml normal saline with 10 mEqKCL by 12 hours continuous
infusion given before and after each dose of CDDP (Figs. 1, 2).
To maximize the benefits of long-term exposure of cisplatin,
this drug was administered by 24-hour continuous intravenous
infusion. In patients with the complication of cancerous perito-
nitis, however, 100 mg/body of cisplatin was directly injected
into the peritoneum. Administration was performed at a fre-
quency of once in four weeks, and repeated (two or) three times.
Surgery was scheduled 3 to 4 weeks after the second (or third)
cisplatin administration. In patients who continued chemoth-
ery without surgery, additional administration of CDDP 80
mg/m2 was given at the time point at which re-exacerbation
of cancerous lesions was observed or anticipated. Maximum
number of courses was five.

Hydration and diuresis (4, 18)

To prevent nephrotoxicity induced by cisplatin, hydration
and diuresis were performed before and after cisplatin admin-
istration, as shown in Fig. 2. A mixture of 700 ml of 5% glucose
solution and 700 ml of physiological saline solution (with 10
mEq of KCl) was continuously infused for 12 hours starting
from 13 hours before cisplatin administration, and, immedi-
ately thereafter, 200 (to 300) ml of 20% D-mannitol was
intravenously infused over one hour (which was followed by
24-hour continuous intravenous infusion of cisplatin). For
hydration after cisplatin administration, the above glucose-
saline solution with added KCl was administered for one to
three days to facilitate diuresis. About 3,000 ml and 2,000 ml (or
more) of daily urine volume were secured on the day of cisplatin
administration, and the days before and after the administra-
tion, respectively. A 5HT3 receptor antagonist of serotonin (5-
Figure 2. Scheme of UFT/CDDP therapy. Cisplatin was dissolved in 2,800 ml of physiological saline – 5% glucose solution with 20 mEq KCl, and administered intravenously for 24 hours. Hydration and diuresis was also induced before and after cisplatin infusion, using 200 to 300 ml of 20% D-mannitol. Antiemetic drugs such as granisetron was also given once or twice a day to prevent nausea and vomiting.

hydroxytryptamine; 5HT) was used to prevent emesis in the morning and evening of the day of cisplatin administration, and whenever necessary thereafter.

Surgical treatment

After two or three courses of chemotherapy, secondary treatment with total gastrectomy was performed in patients who exhibited improvement of primary foci, after informed consent had been obtained. The resected stomach was sliced into 5-mm sections, and subjected to histological examination for the purpose of identifying antitumor effects of the chemotherapy. Survival times were compared with those of 25 scirrhous gastric cancer patients who were treated surgically at the Department of Surgery of our hospital during the same period of time.

Analysis

Tumor response rates were documented according to the revised criteria for evaluating the efficacy of chemotherapy/ radiation therapy in the treatment of gastric cancer (1993) (19).

Evaluation of chemotherapy

The revised criteria for evaluating the efficacy of chemotherapy/radiation therapy in the treatment of gastric cancer (1993) was used (19). First, cancer lesions were visualized by barium filling method in the upright frontal position, showing narrowness of the involved area, due to diffusely infiltrating disease. With regard to scirrhous gastric cancer (diffusely infiltrating tumors), assessment of efficacy of chemotherapy was as follows: Complete response (CR) was defined as the disappearance of all tumors on X-ray films for a minimum of four weeks. Partial response (PR) was defined as a minimum of 50% enlargement of the involved area on X-ray films persisting for more than four weeks. No change (NC) was defined as a less than 50% enlargement for a minimum of four weeks. Progressive disease (PD) was defined as tumor progression detected by X-ray examination (19).

Regarding the assessment of histological efficacy of chemotherapy, in brief, the criteria was as follows: Grade 3; the disappearance, necrosis, and/or degeneration of total cancer, Grade 2; those changes of more than two-thirds cancer, Grade 1b; those changes of one-third to two-thirds cancer, Grade 1a; those changes of less than one-third cancer, and Grade 0; almost no improvement of cancer (19).

Adverse reactions were recorded in compliance with the rules of the Japan Society for Cancer Therapy (20). The survival rate was calculated using the Kaplan-Meier method for the period from the initiation of treatment until February 1995.

Results

Overall response

A total of 28 patients were accrued to this study. There were fourteen partial responses against the primary foci with an overall response rate of 50%. Among the 13 patients with cancerous peritonitis, ascites disappeared completely in eight (62%). Eleven patients (39%) showed no changes (NC) and three patients (10%) showed progressive disease (PD). Total gastrectomy was performed in ten patients after evaluation of response, including 7 PR, 2 NC and 1 PD patients. Palliative total gastrectomy was performed in the patient with PD upon request of the patient and the family. The degree of histological improvement in the resected gastric specimen was evaluated as Grade 2 in four patients, as reported in a previous paper (21, 22), Grade 1b in three, Grade 1a in one and Grade 0 in two. On the basis of the
relationship with radiological findings before surgery, the histological effects were evaluated as Grade 2 in four of the seven PR patients, and as Grade 1b in the remaining three patients. Among the two NC patients, one was evaluated as Grade 1a and the other as Grade 0. Histological effects were not noted in the patient with PD (Grade 0).

**Survival**

Median survival time (MST) of all patients was 10.1 months. The MST of responders and non-responders was 15.1 months and 6.2 months, respectively. Figure 4 compares the survival of patients treated with UFT/CDDP/surgery and surgery alone. In the latter, the 25 patients with scirrhous gastric cancer had undergone surgical resection at the Department of Surgery of our hospital during the same period of time. MST was 20.2 months.
months in the patients treated with combined therapy and 7.0 months in those treated solely with surgery.

Adverse reactions

The most frequently reported toxicities were nausea and vomiting, anemia and leukopenia. There was no patient who experienced grade 4 toxicity. Grade 3 and Grade 2 leukopenia were shown in 3 and 9 patients, respectively. Grade 2 anemia were shown in 14 (50%) out of 28 patients. Renal and hepatic dysfunction were observed but reversible. However, patients with decreases in hemoglobin of Grade 2 (9.4–8.0 g/dl) and Grade 1 (10.9–9.5 g/dl) received concentrated erythrocyte transfusions.

Discussion

The scirrhous gastric cancer (Linitis plastica or Borrmann's type 4) we have discussed in this article was defined as a diffuse advanced cancer with scirrhous invasion, which occupies more than one-third of the entire stomach, centering around the gastric body (23). According to the definition of Nakamura et al, it would be evaluated as "problematic scirrhous gastric cancer" (24). It is not a merely histological scirrhous gastric cancer such as those subclassified into Borrmann’s type 3 or early cancer-like morphology. The depth of invasion was diagnosed as at least subserosal layer and/or exposure on the serosa (23). With respect to the results of surgical treatment of scirrhous gastric cancer, Ichikura and Tamakuma reported a two-year cumulative survival rate of about 30%, a three-year of 20% (as determined from the survival curve) and a five-year of 10% in patients whose primary lesion invaded into the subserosal or deeper layers and surgical treatment resulted in curability of A or B (25). According to the results of surgical treatment reported by Furukawa et al (26) and Iwanaga et al (27), two-, three- and five-year survival rates in patients treated with conventional total gastrectomy and pancreatico-duodenectomy resection were about 30%, 10–20% and 10%, respectively. Among the patients treated with left upper abdominal evisceration (LUAЕ) and the Appleby extended operation (n=17), the two- to four-year survival rate was about 50% (as determined from the survival curve) (26, 27). The results of surgical treatment, applied principally in our hospital with total gastrectomy and lymph node dissection, are not exactly as good as those of the above extended surgery (LUAЕ, etc.), even though the operation was limited to gastrectomy and lymph node dissection. In the present study, survival time and postoperative quality of life were also favorable, and therefore, preoperative, neoadjuvant chemotherapy was considered to have a significant value. With respect to preoperative chemotherapy for scirrhous gastric cancer, Mai et al applied sequential methotrexate 5-fluorouracil (MTX/5FU) therapy and other therapies, and reported their usefulness (28).

In this section, both experimental and clinical basis of UFT/CDDP combination chemotherapy must be given and the validity of the treatment would be assessed in relation to clinical results. First, UFT/CDDP therapy avoids myelotoxicity by omitting Adriamycin, mitomycin C, and epirubicin. Secondly, a long-term continuous intravenous infusion of 5-fluorouracil was replaced by an oral administration of UFT with benefit of practical use. In addition to antitumor activity of cisplatin by forming DNA interstrand crosslinks, the combination of UFT with cisplatin exerts synergistic inhibitory activity on DNA synthesis through dual biochemical modulation mechanism (15). In 1979, Fujii et al reported that coadministration of uracil increased the antitumor activity of 1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur) and level of 5-fluorouracil in rodents (29). Ikenaka et al demonstrated that such an increase in antitumor activity as well as an increased level of 5-fluorouracil especially in tumor tissues, was the result of the decreased activity of 5-fluorouracil degradation by uracil, i.e. uracil inhibits dihydrodruaryl dehydrogenase activity (30). Moreover, phosphorylation of 5-fluorouracil was not influenced with uracil. Clinically, it was also shown that with UFT (a combination of uracil and tegafur in a 4:1 molar ratio), a higher level of 5-fluorouracil was obtained in tumor tissues compared to those in normal tissues and plasma (31, 32). These results suggest the possibility of relatively tumor selective toxicity of UFT, in connection with the fact of an increased amount of fluoropyrimidine activating enzymes in tumor tissues (33). Concerning the plasma level of 5-fluorouracil it was shown that the concentration (area under curve; AUC) was similar between continuous i.v. infusion of 5-fluorouracil 250 mg/m² and UFT 400 mg/m² orally daily (34, 35).

In regard to the combination of UFT and cisplatin, cisplatin promotes inhibition of DNA synthesis by enhanced formation of reduced folate 5,10-methylentetrahydrofolate (CH2FH4), which makes a ternary complex with thymidylate synthase (TS) and 5-fluoro-2′,deoxyuridine-5′-monophosphate (FdUMP), as already described by Scanlon et al in 1986 (14), and confirmed by Shirasaka et al in 1993 (15). As for the administration schedule of cisplatin alone, Drewinko et al showed in a L-1210 in vitro experiment that long-term continuous administration over 8 hours was more beneficial than short-term administration (36). Posner et al reported that clinically, 5-day continuous intravenous administration has been assumed to be superior to bolus administration (37). Lacave et al also adopted a 24-hour continuous intravenous infusion (11). In 1987, Taoka et al reported the efficacy of 24-hour continuous intravenous infusion of cisplatin in the treatment of far-advanced and recurrent gastrointestinal cancer (38). Recently, Shirasaka et al showed greater antitumor activity of a combination of UFT (Day 1–7 postimplant) and cisplatin (once on Day 1) compared to either drug alone (15). We administered 80–100 mg/m² of cisplatin by continuous 24-hour intravenous infusion every 4 weeks along with the oral administration of UFT at a dose of 200 mg/m² twice a day (4, 18).

In a previous trial, UFT/CDDP therapy was indicated for 20 patients with bulky advanced gastric cancers, and resulted in the response rate of 80% (16/20) in primary lesions according to the revised efficacy criteria in 1993 (19). Ascites due to peritoneal dissemination completely disappeared in seven out of 8 patients (88%). Myelotoxicity was mild except anemia. As can be seen
Table 1. Toxicity of UFT/CDDP Chemotherapy

<table>
<thead>
<tr>
<th>Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>3.9-3.0</td>
<td>2.9-2.0</td>
<td>1.9-1.0</td>
<td>0.9≥</td>
</tr>
<tr>
<td>WBC (×10^3/μl)</td>
<td>5 (17.9%)</td>
<td>9 (32.1%)</td>
<td>3 (10.7%)</td>
<td>—</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>99-70</td>
<td>69-50</td>
<td>49-30</td>
<td>29≥</td>
</tr>
<tr>
<td>PL (×10^3/μl)</td>
<td>5 (17.9%)</td>
<td>1 (3.6%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Anemia</td>
<td>10.9-9.5</td>
<td>9.4-8.0</td>
<td>7.9-6.0</td>
<td>5.9≥</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>9 (32.1%)</td>
<td>14 (50.0%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>26-40</td>
<td>41-60</td>
<td>61-80</td>
<td>81≤</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>1.6-3.0</td>
<td>3.1-5.0</td>
<td>5.1-8.0</td>
<td>8.1≤</td>
</tr>
<tr>
<td>Nausea/ vomiting</td>
<td>nausea</td>
<td>vomiting at times</td>
<td>vomiting needs therapy</td>
<td>—</td>
</tr>
<tr>
<td>diarrhea</td>
<td>loose stool 2-3 days</td>
<td>watery stool 3-4 days</td>
<td>watery stool over 5 days</td>
<td>bloody stool dehydration and electrolyte imbalance</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (10.7%)</td>
<td>1 (3.6%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>GOT, GPT (U)</td>
<td>41-100</td>
<td>101-500</td>
<td>501-1,000</td>
<td>1,001≤</td>
</tr>
</tbody>
</table>


Initially, metoclopramide/dexamethasone/oralpredexamethasone combination was used in advance, to prevent nausea and vomiting. More recently, granisetron was used with better effects. Myelosuppression was mild except for a decrease in hemoglobin content.


from the results of the study by Akazawa and Yoshida (39), histological examination of our resected specimens suggests that chemotherapy is more effective in poorly differentiated cancer cells. The above ten patients of this study were not actually treated with postoperative adjuvant chemotherapy, or received no chemotherapy at all. Secondary treatment with adjuvant chemotherapy should be considered in the future. Moreover, more complete lymph node dissection during the operation is expected to prolong survival times.

Surgical treatment of patients with complicating peritoneal dissemination also remains as a future task (40). Most of all, development of chemotherapy with better efficacy is eagerly anticipated.

With regard to the conduction of chemotherapy, Yonemura et al demonstrated in 1993 that neoadjuvant chemotherapy using cisplatin/mitomycin C/UFT/etoposide (PMUE) achieved longer survival times than did postoperative adjuvant chemotherapy in the treatment of high-grade advanced gastric cancer (41). The results obtained from the present study should be confirmed by a randomized control study (phase III study) comparing preoperative UFT/CDDP and surgery alone.

Acknowledgements: The authors wish to express their thanks to Dr. Masanori Shimoyama, Director of the National Hospital of Nagoya, for his valuable advice especially at the beginning of this work.

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