The Role of the Outpatient Clinic in Chemotherapy for Patients with Unresectable or Recurrent Gastric Cancer

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Background: Recently, outpatient chemotherapy centers have become popular in Japan. To clarify the actual conditions of outpatient clinics, we surveyed entire clinical courses of chemotherapy in patients with unresectable or recurrent gastric cancer.

Methods: From the medical records of 64 patients with unresectable or recurrent gastric cancer with no prior chemotherapy, we obtained data on overall survival, non-hospitalized survival, the number of and reasons for attendance at the outpatient clinic and hospitalization, and medical conditions at discharge.

Results: The median follow-up time was 520 days, the median survival time was 353 days, and the median non-hospitalized survival time was 282 days. Patients attended the outpatient clinic 1917 times in total; 145 (8%) of these were unplanned visits for accidental disease, disease progression, or toxicity. Patients were hospitalized 291 times in total: 110 (38%) of hospitalizations were unplanned or emergencies because of disease progression or toxicity. Patients were discharged 290 times in total; in 56 of these discharges (19%) unresolved medical problems remained, such as toxicity, total parenteral nutrition, or symptoms related to cancer. Three patients (5%) died from treatment-related leucopenia and thrombocytopenia.

Conclusions: Patients with unresectable and recurrent gastric cancer were treated at outpatient clinics for periods up to 80% longer than the entire clinical course of chemotherapy. However, there were some unplanned or emergency hospitalizations and some patients still experienced medical problems at discharge. The role of the outpatient clinic is very important to chemotherapy for patients with unresectable or recurrent gastric cancer.

Key words: gastric cancer – chemotherapy – outpatient clinic

INTRODUCTION

Gastric cancer is one of the leading causes of death in Japan and throughout the world. Recent progress in diagnostic procedures and surgical treatment has improved the curability of gastric cancer in the resectable stages. However, the prognosis of unresectable or recurrent gastric cancer still remains poor. Randomized trials have demonstrated that fluorouracil (5-FU)-based chemotherapy can improve survival and quality of life (QOL) in patients with unresectable or recurrent gastric cancer compared with best supportive care (1). Although several phase III trials have been conducted for patients with advanced gastric cancer in recent decades, no standard treatment has been established.

However, various novel anti-tumor agents have been developed recently, including irinotecan (CPT-11), oral pyrimidines, taxanes and molecular target agents. Many phase I and II trials have reported on the activities of these new agents, which are used either as single agents or as combination therapy. For the patient, hospitalization deteriorates daily activity, and non-hospitalized survival can thus represent one substantial improvement to QOL. Many of these new drugs, especially oral anti-tumor drugs, can be used in an outpatient setting and may therefore contribute to prolonging the non-hospitalized survival of patients with gastric cancer treated with chemotherapy. While in Japan...
most patients for chemotherapy have received in-hospital treatment, many hospitals have recently been establishing chemotherapy centers, where efforts are made to treat patients on an outpatient basis. The Japan Clinical Oncology Group (JCOG) has adopted non-hospitalized survival time as a secondary endpoint in JCOG9912 (Randomized phase III study of 5-FU continuous infusion versus CPT-11 plus cisplatin versus S-1 in advanced gastric cancer).

In gastric cancer, conditions of patients may deteriorate suddenly as a result of various complications such as peritoneal dissemination, which is usually undetectable by radiological imaging and sometimes causes bowel obstruction, hydronephrosis and obstructive jaundice. It is suggested that management of gastric cancer by chemotherapy at outpatient clinics may be more difficult than other non-digestive malignancies.

Few reports have documented the clinical course from the initiation of treatment to death in patients with gastric cancer treated with chemotherapy, and actual problems in outpatient clinics have scarcely been reported in detail. For example, it is not even known how long the non-hospitalized survival is and what kind of problems are encountered at outpatient clinics during chemotherapy and therefore we are left to conclude that the provision of chemotherapy over a full clinical course for cancer patients is still in its infancy in Japan. In this retrospective study, we surveyed the entire clinical course of patients with unresectable and recurrent gastric cancer treated with chemotherapy to investigate the actual conditions of outpatient clinics during cancer treatment, in order to improve the system in the near future.

PATIENTS AND METHODS

PATIENT SELECTION

From 199 patients with unresectable and recurrent gastric cancer receiving chemotherapy at the Shizuoka Cancer Center between September 2002 and March 2004, we selected patients who fulfilled the following eligibility criteria listed in JCOG9912: (i) histologically proven unresectable or recurrent adenocarcinoma of the stomach, except for patients whose unresectable cancer was limited to class V by cytological examination of the abdominal cavity or with no visible tumor; (ii) no prior chemotherapy; (iii) adequate oral intake without nutritional support; (iv) no severe peritoneal dissemination associated with massive ascites or remarkable findings detected by barium enema; (v) age between 20 and 75 years; (vi) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or better; (vii) no massive pleural effusion; (viii) no other active malignancies; (ix) adequate bone marrow (white blood count 3000–12 000/μl, platelets ≥100 000/μl), renal (creatinine: ≤1.5 mg/dl), and hepatic functions (aspartate aminotransferase ≤99 IU/l, alanine aminotransferase ≤99 IU/l, bilirubin ≤2.0 mg/dl); (x) no other serious medical complications; (xi) no symptomatic brain metastasis; and (xii) written informed consent for chemotherapy.

TREATMENT SCHEDULE

All chemotherapy regimens were approved in clinical practice to treat patients with gastric cancer by the Clinical Practice Review Committee of the Shizuoka Cancer Center. All patients provided informed consent before chemotherapy was initiated and the chemotherapy continued until tumor progression, unacceptable toxicity, or patient’s refusal to continue. For each patient, the chemotherapy regimen was selected according to the patient and physician’s choice for the first-line treatment. Treatment was generally performed by the following schedule: (i) S-1 alone: S-1 (40 mg/m² per day, orally twice daily) on days 1–28 every 6 weeks (2,3); (ii) S-1 and cisplatin (CDDP): S-1 (40 mg/m² per day, orally twice daily) on days 1–21 and CDDP (70 mg/m², intravenously) on day 8 every 5 weeks (4); (iii) sequential methotrexate (MTX) and 5-fluorouracil (5-FU): weekly administration of MTX (100 mg/m², bolus) followed by 5-FU (600 mg/m², bolus) at 3-h intervals, calcium leucovorin (10 mg/m², orally or intravenously) administered six times every 6 h starting 24 h after MTX (5), (iv) CPT-11 and CDDP: CPT-11 (70 mg/m², intravenously) on days 1 and 15, and CDDP (80 mg/m², intravenously) on day 1 every 4 weeks (6); (v) 5-FU continuous infusion (5-FU c.i.): 5-FU (800 mg/m², continuous infusion) on days 1–5 every 4 weeks (7); (vi) weekly paclitaxel (w-PTX): weekly administration of PTX (80 mg/m², intravenously) for 3 weeks every 4 weeks (8); (vii) CPT-11 and mitomycin C (MMC): CPT-11 (150 mg/m², intravenously) and MMC (5 mg/m², bolus) every 2 weeks (9); (viii) 5-FU and isovorin (l-LV): weekly administration of 5-FU (600 mg/m², bolus) and l-LV (250 mg/m², 2-h infusion) for 6 weeks every 8 weeks (10); (ix) 5-FU and CDDP: 5-FU (800 mg/m², continuous infusion) on days 1–5 and CDDP (80 mg/m², intravenously) on day 1 every 4 weeks (7); (x) CDDP injected intraperitoneally (11); (xi) CPT-11 alone: CPT-11 (150 mg/m², intravenously) every 2 weeks (12,13); (xii) CDDP and etoposide (VP-16): CDDP (80 mg/m², intravenously) on day 1 and VP-16 (100 mg/m², intravenously) on day 1 every 3 weeks (14); (xiii) hepatic arterial infusion (HAI): 5-fluorouracil (333 mg/m² each week, epirubicin (30 mg/m²) once every 4 weeks and mitomycin-C (2.7 mg/m²) once every 2 weeks administered by HAI (15); (xiv) MMC alone: weekly administration of MMC (5 mg/m², bolus). Dose and schedule were modified according to each patient’s medical condition and any toxicities observed in the previous courses.

EVALUATION AND STATISTICAL ANALYSIS

The overall survival time was calculated from the date of the first administration of chemotherapy of the first-line treatment to the date of death by any causes, or to the last date of confirmed survival. The non-hospitalized survival time was
estimated by subtracting the period of hospitalization by any causes from the overall survival time. We checked the number of and reasons for attendance at outpatient clinics and recorded all treatments, including supportive care, performed at each attendance. We also assessed the number of times patients were hospitalized, the reasons for hospitalization and medical conditions at discharge. We accumulated early death observed within 30 days after the last administration of chemotherapy to investigate the cause of death. Survival analysis was performed using the methods of Kaplan and Meier, by adopting all deaths from any cause as events.

RESULTS

PATIENT CHARACTERISTICS

One hundred and ninety-nine patients received chemotherapy during the study period, of whom 135 patients were excluded from analysis and 64 patients fulfilled the eligibility criteria and were entered into the study. The reasons for exclusion were prior chemotherapy (70 patients), no visible tumor (13 patients), older than 76 years (13 patients), severe peritoneal dissemination (10 patients), inadequate oral intake (nine patients), other active malignancy (eight patients), serious medical complication (seven patients), PS 3 or 4 (four patients), and symptomatic brain metastasis (one patient).

Table 1 shows the characteristics of the patients. The median age was 64 years (range 32–75 years); 30 patients were PS 0, 27 patients were PS 1, and seven patients were PS 2. One patient had no metastatic sites, 34 patients had one metastatic site, 22 patients had two metastatic sites, eight patients had three or more metastatic sites.

TREATMENT

Table 2 lists the chemotherapy regimens received over the entire clinical courses of the patients. The median number of regimens was two (range, 1–6), 72% of patients received second-line chemotherapy, and 39% of patients had three or more chemotherapy regimens. In 31 patients (48%), the first-line chemotherapy was started at the outpatient clinic. Oral administration of S-1 was the most frequently used in first-line chemotherapy (35 patients, 55%), and 21 (33%) patients who were given CDDP-containing regimens or continuous infusion of 5-FU required hospitalization. The most frequently used forms of second-line chemotherapy were w-PTX (26 patients, 57%) and a combination of CPT-11 and CDDP (11 patients, 24%).

ATTENDANCE AT THE OUTPATIENT CLINIC

Table 3 lists the number of and reasons for attendance at the outpatient clinic. The median number of visits to outpatient clinics was 29 visits per patient (range, 0–84). The total number of visits was 1917, of which 145 (8%) were unplanned, which were caused by accidental disease (50 visits), disease progression (46 visits), toxicity (45 visits), or for prescription (four visits). Supportive care was performed in outpatient clinics at 142 visits (7%) such as hydration (88 visits), transfusion (28 visits), abdominal paracentesis (eight visits), insertion of a central venous line (seven visits), and administration of granulocyte colony-stimulating factor (two visits).

SURVIVAL AND HOSPITALIZATION

Although some patients were referred to other hospitals, we obtained the information concerning the reason and period

### Table 1. Patient characteristics

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PS, performance status.

### Table 2. Treatment

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*Repetition (+). S-1, tegafur-gimeracil-oteracil-potassium; CDDP, cisplatin; MTX, methotrexate; 5-FU, 5-fluorouracil; CPT11, irinotecan; ci, continuous infusion; PTX, paclitaxel; MMC, mitomycin; I-LV, I-leucovorin; ip, intra peritoneum; VP-16, etoposide.
of hospitalization, and the date and cause of death by making inquiries directly to these hospitals.

The median follow-up was 520 days (range, 309–871 days), and the median overall survival time was 353 days. The 1-year survival rate was 49%, while the 2-year survival rate was 26% (Fig. 1). The median non-hospitalized survival time was 282 days (range, 0–786 days) and the median total period of hospitalization for each patient was 59 days (range, 0–138 days) (Fig. 2). The median number of hospitalizations was four (range, 0–15) per patient and the median period of each hospitalization was six days (range, 1–96 days). The total number of hospitalizations was 291, of which 110 (38%) were unplanned and reasons for unplanned hospitalization were related to disease progression (85 hospitalizations), toxicity (14 hospitalizations), accidental disease (nine hospitalizations), or examination (two hospitalizations) (Table 4).

**MEDICAL CONDITION AT DISCHARGE**

Patients were discharged 290 times (Table 5), 56 (19%) of which were associated with an unresolved medical problem needing intensive care or follow-up to be managed at the outpatient clinic. These included toxicity (14 discharges), total parenteral nutrition (14 discharges), symptoms of cancer (17 discharges), percutaneous endoscopic gastrostomy (seven discharges), and other problems (four discharges).

**TREATMENT-RELATED DEATH**

Fifteen patients (23%) died within 30 days after the last administration of chemotherapy. Of these 15 patients, three died of treatment-related death (TRD), and the other 12 early deaths within 30 days after last administration of chemotherapy occurred after confirming tumor progression. Two of three TRDs were treated at the outpatient clinic. One patient with PS 2 and massive ascites caused by peritoneal dissemination received w-PTX regimen as the second line setting. Vomiting appeared on day four after the sixth administration of chemotherapy and he entered the hospital for septic shock on the same day. Despite intensive supportive care he died on day five. Another patient with PS 1 and chronic renal failure received w-PTX regime as the third line setting. Although the only complication he had was grade 1 (NCI-CTC ver.2) nausea till day four, he entered hospital for grade 4 leucopenia on day five after the eighth administration of chemotherapy agent. While he recovered from leucopenia on day 11, grade 3 thrombocytopenia persisted. Bleeding from primary tumor occurred after confirming disease progression and he died of hypovolemic shock on day 26. The last patient died of pneumocystis carini...
DISCUSSION

In the recent randomized studies investigating the effects of single agent 5-FU therapy or the combination therapy of 5-FU plus CDDP, docetaxel and 5-FU plus CDDP, 5-FU and doxorubicin plus MMC or etoposide and leucovorin plus 5FU, it was reported that the median survival time was 7–9 months, the 1-year survival rate was 28–40% and 2-year survival rate was 7–18% (7,16–19).

For the single agent therapy of S-1, a novel oral derivative of 5-FU, the median survival time of 207 days, and 1- and 2-year survival rates of 36 and 14%, respectively, were reported in a Japanese phase II study (2,3). Furthermore a Japanese phase I/II study of S-1 combined with CDDP reported a median survival time of 383 days, and 1- and 2-year survival rates of 52 and 10%, respectively (4).

However, a Japanese phase II study on CPT-11 combined with CDDP showed a median survival time of 322 days (6). In our study, the median survival time was 353 days, and 1- and 2-year survival rates were 49 and 26%, respectively. Although our survival data were obtained by retrospective analysis, our clinical outcomes seem to be equal or exceed those reported in previous studies.

In our study, the median non-hospitalized survival time was 282 days and median overall survival time was 352 days. We found no reports referring to non-hospitalized survival of patients with gastric cancer and it is difficult to compare our results with those of other researchers. In our hospital, we use various supportive systems to help patients remain at home and to care for patients from the initiation of chemotherapy to the terminal stage.

The incidence of TRD is 1–5% in some phase III studies (7,16). Three TRDs caused by leucopenia and thrombocytopenia occurred in our study (5%). Of two patients who were treated at the outpatient clinic, one patient entered hospital quickly after symptoms appeared. Another patient recovered from the leucopenia immediately after hospitalization so we do not consider that chemotherapy at the outpatient clinic caused delay of supportive care and that TRD might have been avoided if the patients had been treated in hospital. The number of early deaths within 30 days after the last administration of chemotherapy in our series seems high. The median number of chemotherapy regimens was two, and many patients received three or more chemotherapy regimens. Some of them were initiated despite poor medical conditions. We thus hypothesize that the risk of TRD increases according to the number of regimens received.

Moreover, the indications for chemotherapy, especially in the subsequent treatment lines, should be decided more carefully to promote the safety of chemotherapy.

Most patients undergoing chemotherapy visit the hospital usually once every week or two. The median number of visits to the outpatient clinic was 29 and the median survival time was about 1 year. However, because of toxicity or disease progression, the patients’ medical conditions sometimes changed between planned visits. We found that 8% of the total number of visits to the outpatient clinic were unplanned and that 7% of all visits required supportive care. We made an effort to prolong non-hospitalized survival by providing home nutrition and other supporting systems. This situation might make the incidence of unplanned attendance at the outpatient clinic look high, but we believe these are important in providing chemotherapy for patients with gastric cancer.

The incidence of unplanned or emergency hospitalization was 38% of the total number of hospitalizations. The main reason for hospitalization was worsening of patient’s medical conditions caused by disease progression. Gastric cancer sometimes causes impaired oral intake, ileus, ascites, hydronephrosis and other severe complications. These serious complications can not be managed at an outpatient hospital.
clinic, and therefore the median duration of emergency hospitalization (16 days) was longer than that of planned hospitalization (five days). These data suggest the importance of establishing a system by which patients are accepted quickly for unplanned or emergency hospitalization in order to ensure safety of chemotherapy.

As mentioned above, we made an effort to prolong non-hospitalized survival by providing various support systems and 19% of the total number of discharges had associated problems such as toxicity, total parenteral nutrition at home, symptoms of cancer and percutaneous endoscopic gastrostomy. Although we helped patients adapt to these problems before discharge, our data suggest that these problems could also be managed or resolved at an outpatient clinic.

In conclusion, chemotherapy for patients with unresectable recurrent gastric cancer can be performed safely with support in hospitals. Japanese hospitals should not only establish outpatient chemotherapy centers but also a system to quickly provide emergency care during chemotherapy. We expect that the support system for providing chemotherapy safely will become more popular in Japan, and contribute to patients’ QOL in the near future.

Conflict of interest statement
None declared.

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