—Report on Experiments and Clinical Cases—

Adjuvant Chemotherapy with S-1 Followed by Docetaxel for Gastric Cancer and CY1P0 Peritoneal Metastasis after Relatively Curative Surgery

Yoshikazu Kanazawa, Shunji Kato, Itsuo Fujita,
Hiroyuki Onodera and Eiji Uchida

Department of Surgery, Nippon Medical School

Abstract

Objective: The aim of this study was to assess the feasibility and safety of adjuvant chemotherapy with S-1 followed by docetaxel.

Patients and Method: Twenty-eight patients with advanced gastric cancer underwent gastrectomy without preoperative chemotherapy. These patients were divided into 3 groups on the basis of cytologic results of peritoneal lavage (CY) and the presence of local peritoneal metastatic nodules (P): CY1-P0, CY0-P1, and CY1-P1. Oral S-1 (80 mg/m^2/day) was administered for 3 consecutive weeks, followed by intravenous docetaxel (35 mg/m^2) on days 29 and 43 (1 cycle). This cycle was repeated every 8 weeks. The primary endpoint was the ability to complete 6 cycles of S-1 followed by docetaxel. The secondary endpoints were safety, progression-free survival, mean survival time (MST), and overall survival (OS).

Results: The subjects were 18 men and 10 women (39 to 78 years old, median age, 64 years). The extent of peritoneal metastasis was CY1-P0 in 8 patients, CY0-P1 in 14 patients, and CY1-P1 in 6 patients. Both hematologic and nonhematologic toxicities were generally mild. The completion rate of the planned 6 cycles of the protocol was 71.4% (20 of 28 patients). Median progression-free survival was 22.9 months, and the 2-year survival rate was 78.6%. The overall MST was 34.3 months, and the MST by group was 34.5 for CY1-P0, 34.3 for CY0-P1, and 19.3 months for CY1-P1. The OS in the CY1-P0 and CY0-P1 groups was significantly longer than that in the CY1-P1 group ($P<0.05$).

Conclusion: Adjuvant chemotherapy with S-1 followed by docetaxel is safe and well tolerated and has the potential to improve OS in patients with a status of CY1P0 following relatively curative resection.

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Key words: S-1, docetaxel, gastric cancer, peritoneal metastasis, CY1, adjuvant chemotherapy

Correspondence to Yoshikazu Kanazawa, MD, Department of Surgery, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: kanazawa-y@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

Introduction

Peritoneal metastasis generally arises from free cancer cells shed from the serosal surface of advanced gastric cancers. These free cancer cells can be detected through cytologic examination of peritoneal lavage fluid. Positive cytologic results, classified as CY1 by the Japanese Classification of Gastric Carcinoma[1], suggest a high risk of peritoneal carcinomatosis. Patients with a status of CY1 are considered to have stage IV disease, which is incurable, and surgery is ruled out[2]. However, there is no standard postsurgical treatment strategy for patients with a status of CY1. Moreover, recent developments in cancer chemotherapy have improved outcomes in a certain population of patients with a status of CY1.

Multimodal treatment strategies, including surgery and effective anticancer drugs, remain the only hope for cure in patients with minimal peritoneal metastasis. Indeed, administration of S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo), a mixture of tegafur, gimeracil, and potassium oxonate, decreased the incidence of peritoneal carcinomatosis after curative surgery in a phase III adjuvant trial[3]. On the other hand, Yoshida et al.[4] have reported that S-1 plus docetaxel shows activity against disseminated peritoneal metastases.

In the present study, we modified the S-1 plus docetaxel regimen reported by Yoshida et al[4] and administered this modified regimen to patients with a status of CY1 and local peritoneal metastasis (P1) following relatively curative surgery. The aim of the study was to assess the feasibility and safety of the modified protocol for adjuvant chemotherapy with S-1 followed by docetaxel.

Patients and Methods

1. Patients

Twenty-eight patients were enrolled in this study at our institution from April 2006 through March 2010. All patients underwent gastrectomy for advanced gastric cancer but received no preoperative chemotherapy. They had a performance status of 0 or 1 and a life expectancy of at least 3 months. According to the 12th edition of the Japanese Classification of Gastric Carcinoma[5], peritoneal metastasis is diagnosed on the basis of positive cytologic results for peritoneal lavage in a patient with a status of CY1 or local peritoneal metastatic nodules around the primary lesion only in a patient with P1 status. The patients were divided into 3 groups: CY1-P0, CY0-P1, and CY1-P1.

Written informed consent was obtained from each patient before enrollment, and the protocol was approved by the institutional ethics committees of the participating centers.

2. Study Design

Oral S-1 (80 mg/m^2/day) was administered for 3 consecutive weeks, after which intravenous docetaxel (35 mg/m^2) was administered on days 29 and 43 (1 cycle). This cycle was repeated every 8 weeks. Treatment was started within 8 weeks of surgery. If patients had hematologic or nonhematologic toxicity of grade 3 or 4, the dose of docetaxel was reduced from 35 to 30 mg/m^2. If the adverse event did not resolve, the dose of S-1 was reduced from 120 to 100 mg or from 100 to 80 mg. The minimum daily dose of S-1 was 80 mg.

3. Treatment Evaluation

The primary endpoint was the ability of the patient to complete 6 cycles of S-1 followed by docetaxel. The secondary endpoints were safety, progression-free survival (PFS), mean survival time (MST), and overall survival (OS). Adverse events were graded with the National Cancer Institute Common Toxicity Criteria, version 2.0[6].

4. Statistical Analysis

Survival was calculated with the Kaplan-Meier method. Statistical analysis was performed with the software program IBM SPSS Statistics, version 15.0 (IBM Corp., Armonk, NY, USA), according to the instructions given by medical statistics articles[7]. A value of $P<0.05$ was considered to indicate statistical significance.

Results

1. Patient Characteristics

Twenty-eight patients were enrolled in the study: 18 men and 10 women aged 39 and 78 years (median age, 64 years) (**Table 1**). Five patients had differentiated adenocarcinoma, and 23 had undifferentiated carcinoma. Ten patients underwent distal gastrectomy, and 18 underwent total gastrectomy. According to Eastern Cooperative Oncology Group criteria, the performance status was 0 in 26 patients and was 1 in 2 patients. The extent of peritoneal metastasis was graded as CY1-P0 in 8 patients, CY0-P1 in 14 patients, and CY1-P1 in 6 patients.

Table 1 Patient characteristics

Characteristics	No. of patients (n=28)
Age (years)	
median	64
range	39–78
Sex	
Male	18
Female	10
Histologic type	
differentiated	5
undifferentiated	23
Surgery	
Distal gastrectomy	10
Total gastrectomy	18
Performance status	
0	26
1	2
Peritoneal metastasis	
CY1-P0	8
CY0-P1	14
CY1-P1	6

2. Treatment-related Toxicity

Both the hematologic and nonhematologic toxicities that occurred were generally mild (**Table 2**). Grade 2 neutropenia occurred in 4 patients (14.3%), grade 1 to 2 appetite loss in 5 patients (17.8%), and grade 3 stomatitis and grade 3 exanthema in 1 patient each. No treatment-related deaths occurred after completion of this regimen.

3. Feasibility

The completion rate of the planned 6 cycles of the protocol was 71.4% (20 of 28 patients). In each case the reason for discontinuing treatment was adverse events. One patient required the reduction of the dose of docetaxel, and another patient required the reduction of the doses of both S-1 and docetaxel.

4. PFS and OS

After a median follow-up 40.3 months (range, 5.9–68.0 months), 9 of 28 patients (32.1%) were alive. Median PFS was 22.9 months (**Fig. 1**). The MST was 34.3 months, and the 2-year survival rate was 78.6% (**Fig. 2**). In addition, the MST by group was 34.5 months for CY1-P0, 34.3 months for CY0-P1, and 19.3 months for CY1-P1. The OSs in the CY1-P0 and CY0-P1 groups were significantly longer than that in the CY1-P1 group ($P<0.05$) (**Fig. 3**).

Table 2 Treatment-related toxicity

Toxicity*	No. of patients (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic				
Neutropenia	0	4 (14.3%)	1 (3.6%)	0
Anemia	0	0	0	0
Thrombocytopenia	0	0	0	0
Nonhematologic				
Appetite loss	3 (10.7%)	2 (7.1%)	0	0
Nausea, Vomiting	1 (3.6%)	0	0	0
Stomatitis	0	1 (3.6%)	1 (3.6%)	0
Exanthema	0	0	1 (3.6%)	0

*National Cancer Institute Common Toxicity Criteria, version 2.0

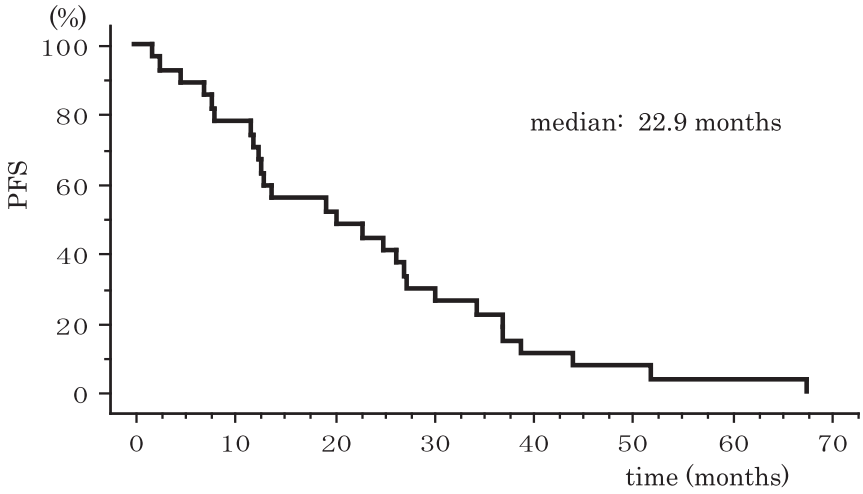

Fig. 1 Progression-free survival (PFS)

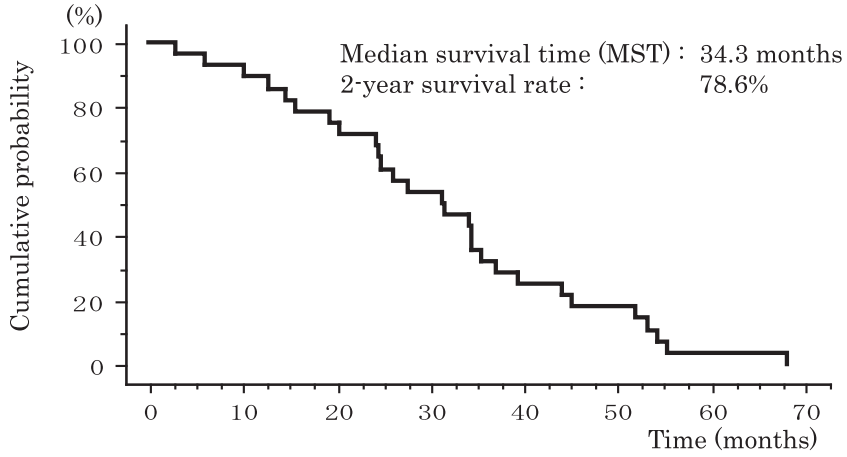

Fig. 2 Overall survival

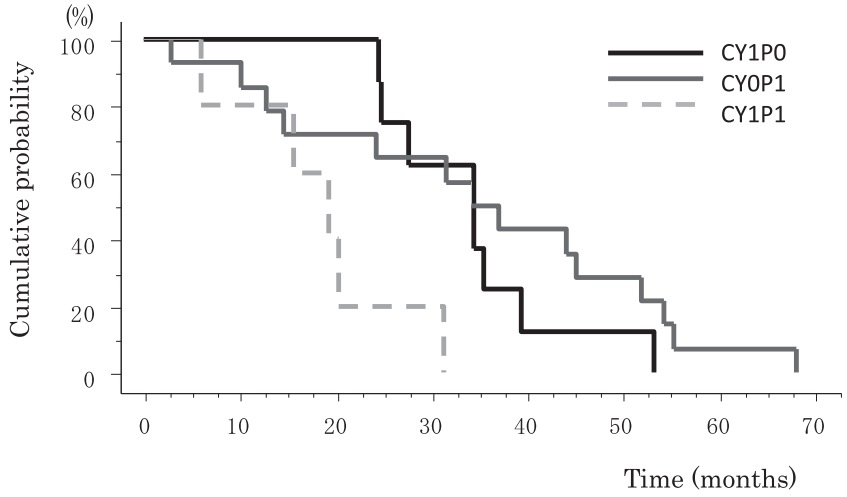

Fig. 3 Overall survival (subgroup analysis)

Discussion

The aim of this study was to assess the feasibility and safety of adjuvant chemotherapy with S-1 followed by docetaxel. In the present study, we modified the S-1 plus docetaxel regimen reported by Yoshida et al[4] because Yoshida's regimen had caused severe adverse events, and administered this modified regimen to patients with a status of CY1 and local peritoneal metastasis (P1) following relatively curative surgery. According to the results of this study, adjuvant chemotherapy with S-1 followed by docetaxel is safe and well tolerated and has the potential to improve OS in patients with a status of CY1P0 following relatively curative resection.

Adjuvant monotherapy with S-1 or taxane has been reported to be acceptable and efficient for preventing peritoneal recurrence. Sakuramoto et al.[3] have reported that S-1 orally administered as an adjuvant treatment is effective against stage II or III gastric cancer, achieving a lower incidence of peritoneal metastasis than does surgery alone. Moreover, Kodera et al.[8] have reported that S-1 monotherapy achieved survival surpassing historical controls in patients with a status of CY-1P0. We have previously reported[9], that this regimen achieved an MST of 14.8 months in patients with advanced gastric cancer and peritoneal metastasis. On the other hand, weekly intravenous administration of paclitaxel has been reported to be effective against extensive peritoneal metastasis[10–13]. Jo et al.[14] have administered docetaxel (75 mg/mm^2) monotherapy as a second-line treatment for patients with peritoneal metastasis and found that this regimen was active and well tolerated after the failure of treatment with a fluoropymidine and a platinum-based agent. In addition, combination treatment with S-1 and docetaxel is considered to have a greater inhibitory effect on thymidylate synthase activity, leading to enhanced antitumor effectiveness[15,16]. These findings led us to administer the combination of S-1 plus docetaxel as an adjuvant treatment for patients with minimal and local peritoneal metastasis after relatively curative gastrectomy. However, the treatment schedule needed to be modified to avoid a high incidence of severe adverse events. Thus, a modified S-1/docetaxel protocol was administered in the present study.

The regimen administered in this study produced low rates of grade 3 or 4 hematologic and nonhematologic toxicities. Yoshida et al.[4] have reported that simultaneous combination therapy with S-1 and docetaxel for advanced or recurrent gastric cancer was associated with grade 3 or higher neutropenia and appetite loss in 58.3% and 14.6% of patients, respectively. Tamura et al.[17] have reported that grade 4 neutropenia occurred in 28% of cases, febrile neutropenia in 9%, and grade 3 nonhematologic toxicities in 7.2%. In the present study, the rates of grade 3 neutropenia and appetite loss were only 3.6% and 0%, respectively. Although the reason why the rate of adverse events was lower with our regimen than with other regimens is unknown, the difference in the treatment schedule may be a factor. First, in our regimen docetaxel was administered on days 29 and 43, after S-1 had been administered, whereas in other studies both docetaxel and S-1 were administered on day 1. Second, the initial dose of docetaxel was 35 mg/m^2 in our study but was 40 mg/m^2 in other studies.

Adjuvant chemotherapy with S-1 followed by docetaxel is safe and well tolerated. Most patients were able to receive the planned 6 cycles of this protocol. Moreover, when patients were not able to be treated according to the protocol, they were still able to continue treatment for 1 year after surgery when dosages were reduced and the schedule was postponed. Both drugs have been widely used as monotherapies, and methods of dealing with adverse effects have been established. Therefore, we believe the protocol used in our study can easily be tolerated for a longer period of time.

Adjuvant chemotherapy with S-1 followed by docetaxel seems to improve the clinical outcomes of PFS, MST, and OS in patients with a status of CY1-P0 or CY0-P1. Kobayashi et al.[18] have shown that the MST in patients with a status of CY1-P0 is similar to that in patients with CY0-P1. Nashimoto et al.[19] have found that patients with a status of CY1-P0 or

CY0P1 have a better prognosis than do patients with a status of CY1P1; this finding suggests more effective treatment is needed for the latter group of patients. The results of these studies agree with the results of the present study, but the MST and OS of patients with a status of CY1-P0 or CY0-P1 in our study were longer than those in earlier studies. In our previous study, the MST of patients with peritoneal metastasis receiving S-1 as adjuvant monotherapy was 14.8 months. Therefore, the MST of patients with a status of CY1-P0 or CY0-P1 in the present study was longer than indicated by the results of our previous study.

Our present results suggest that adjuvant chemotherapy with S-1 followed by docetaxel has the following advantages: (1) enhanced anticancer effectiveness due to the different mechanisms of the 2 drugs; (2) a low incidence of adverse events. In conclusion, adjuvant chemotherapy with S-1 followed by docetaxel is safe and well tolerated, and this treatment has the potential to improve OS in patients with a status of CY1P0 after relatively curative resection.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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