Clinical Study

Oncology

Oncology 2011;80:296–300
DOI: 10.1159/000329090

Received: December 12, 2010
Accepted after revision: May 2, 2011
Published online: July 18, 2011

Phase II Feasibility Study of Adjuvant S-1 plus Docetaxel for Stage III Gastric Cancer Patients after Curative D2 Gastrectomy

Shigeyuki Tamura[a] Kazumasa Fujitani[b] Yutaka Kimura[c] Takeshi Tsuji[e] Jin Matsuyama[f] Shohei Iijima[g] Hiroshi Imamura[h] Kentaro Inoue[d] Kenji Kobayashi[i] Yukinori Kurokawa[b] Hiroshi Furukawa[h] the Osaka Gastrointestinal Cancer Chemotherapy Study Group

Department of Surgery, [a]Kansai Rosai Hospital, Amagasaki, [b]National Hospital Organization, Osaka National Hospital, [c]NTT West Osaka Hospital, and [d]Kansai Medical University, Osaka, [e]Wakayama Rosai Hospital, Wakayama, [f]Yao Municipal Hospital, Yao, [g]Minoh City Hospital, Minoh, [h]Sakai Municipal Hospital, Sakai, and [i]Kinki Central Hospital, Itami, Japan

Key Words

Gastric cancer · Adjuvant chemotherapy · S-1 · Docetaxel · Gastrectomy · D2 lymph node dissection

Abstract

Objective: The aim of this prospective study was to evaluate the feasibility and safety of adjuvant S-1 plus docetaxel in patients with stage III gastric cancer. ***Methods:*** We enrolled 53 patients with pathological stage III gastric cancer who underwent D2 gastrectomy. They received oral S-1 (80 mg/m^2/day) administration for 2 consecutive weeks and intravenous docetaxel (40 mg/m^2) on day 1, repeated every 3 weeks (1 cycle). The treatment was started within 45 days after surgery and repeated for 4 cycles, followed by S-1 monotherapy (4 weeks on, 2 weeks off) until 1 year after surgery. The feasibility of the 4 cycles of chemotherapy, followed by S-1 administration, was evaluated. ***Results:*** A total of 42 patients (79.2%, 95% CI 65.9–82.9) tolerated the planned 4 cycles of treatment with S-1 and docetaxel, and 34 patients (64.2%, 95% CI 49.8–76.9) completed subsequent S-1 monotherapy for 1 year. Grade 4 neutropenia was observed in 28% and grade 3 febrile neutropenia in 9% of the patients, while grade 3 nonhematological toxicities were relatively low. ***Conclusions:*** Adjuvant S-1 plus docetaxel therapy is feasible and has only moderate toxicity in stage III gastric cancer patients. We believe that this regimen will be a candidate for future phase III trials seeking the optimal adjuvant chemotherapy for stage III gastric cancer patients.

Introduction

The principal aims of adjuvant chemotherapy for curatively resected gastric cancer are to prevent distant or local recurrence and improve the survival of patients. In Japan, several studies concerning postoperative adjuvant chemotherapy for patients with gastric cancer have been performed since 1960, but none of these studies demonstrated therapeutic benefits of adjuvant chemotherapy [1–6].

The National Surgical Adjuvant Study Group for Gastric Cancer study evaluated postoperative chemotherapy for patients with T2, N1–2 gastric cancer from 1998 using uracil-tegafur (an oral fluoropyrimidine prodrug) for 18 months, excluding stage I gastric cancer, based on an analysis of previous studies. Although this study was interrupted because of the introduction of S-1 and the start

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0030–2414/11/0806–0296$38.00/0

Accessible online at:
www.karger.com/ocl

Shigeyuki Tamura
Department of Surgery
Kansai Rosai Hospital
Amagasaki, Hyogo 660-8511 (Japan)
E-Mail stamura@kanrou.net

of a new large-scale trial – the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) – using S-1 for stage II and III gastric cancer from 2001, the results of this study showed that adjuvant chemotherapy with uracil-tegafur was effective for T2, N1–2 gastric cancer [7].

In an ACTS-GC study, adjuvant chemotherapy using S-1 has been reported to be effective for Japanese stage II and III gastric cancer patients who have undergone a D2 dissection. This trial was stopped on the recommendation of the independent data and safety monitoring committee, because the first interim analysis, performed 1 year after completion of enrollment, showed that the 3-year overall survival (OS) rate of 80.1% in the S-1 group was higher than that of 70.1% in the surgery-only group. However, in stage III gastric cancer patients, the difference in the 3-year OS rate between the S-1 group and the surgery-alone group was less than that in stage II [8].

Therefore, to improve the prognosis for patients with advanced gastric cancer after curative resection, more effective chemotherapy is required for patients with stage III gastric cancer.

Recently, several combination chemotherapeutic regimens involving S-1 and other anticancer drugs such as cisplatin, taxanes and irinotecan (CPT-11) have been reported to yield and increased overall response rates and prolonged median survival time [9–12].

In these studies, in patients with advanced gastric cancer, S-1 plus docetaxel has shown that the response rate and median OS was 56% and 14.3 months, respectively. Moreover, gastrointestinal toxicities of this combination regimen were reported to be comparatively few and low grade: anorexia (6.3%), stomatitis (10.4%) and nausea (6.3%), which was considered to be advantageous for the postoperative patients [10].

Therefore, S-1 plus docetaxel may be a promising regimen for stage III advanced gastric cancer after curative resection, as well as being a candidate for an experimental arm in the next adjuvant chemotherapy trial.

The aim of this phase II study was to evaluate the feasibility and safety of adjuvant chemotherapy of S-1 plus docetaxel for stage III gastric cancer patients.

Patients and Methods

Eligibity Criteria

The eligibility criteria of this study were: (1) histologically proven gastric cancer of stage IIIA or IIIB after R0 surgery with D2 lymph node dissection; (2) age 20–80 years; (3) Eastern Cooperative Oncology Group performance status 0–1; (4) no previous treatment for cancer except for the initial gastric resection for the primary lesion; (5) adequate digestive function; (6) duration of the period from surgery <6 weeks, and (7) adequate organ function, including a leukocyte count between 4,000 and 12,000 mm^3, a neutrophil count >2,000 mm^3, a platelet count >100,000 mm^3, a hemoglobin count >9.0 g/dl, aspartate aminotranferase and alanine aminotransferase levels within 2.5 times the upper limit of the normal range, a serum bilirubin level <1.5 mg/dl, a serum creatinine level <1.2 mg/dl, and creatinine clearance of at least 60 ml/min. Moreover, absence of other severe medical conditions and an absence of synchronous or metachronous malignancy were needed for this study.

Exclusion criteria were as follows: infection or suspected infection with fever; congestive heart failure; uncontrolled diabetes or hypertension; interstitial pneumonia or lung fibrosis; symptomatic brain metastasis; liver cirrhosis or active hepatitis, and pregnancy. Patients with a history of prior chemotherapy were also excluded.

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

The eligibility criteria for stage classification was judged in accordance with the guidelines of the Japanese Gastric Cancer Association [13] and all patients were additionally staged using the 6th edition of UICC TNM staging system [14].

Study Design

In this feasibility study, oral S-1 (80 mg/m^2/day) was administered for 2 consecutive weeks and intravenous docetaxel (40 mg/m^2) on day 1, repeated every 3 weeks (1 cycle). The treatment was started within 45 days after surgery and repeated for 4 cycles. After 4 cycles of this treatment, S-1 was administered as daily monotherapy according to the schedule of the ACTS-GC study until 1 year after surgery. Namely, patients received 2 oral doses of 40 mg/m^2 of S-1 per day, for 4 weeks, followed by 2 weeks of no chemotherapy. If patients had hematological toxic effects of grade 3 or 4 or nonhematoligic toxic effects of grade >2, their dose of docetaxel was reduced from 40 to 35 mg/m^2, and at the same time, the dose of S-1 was reduced from 120 to 100 mg, or from 100 to 80 mg or from 80 to 50 mg per day.

The primary endpoint was the feasibility of completing 4 cycles of S-1 plus docetaxel; the secondary endpoints were safety, disease-free survival, OS and feasibility of S-1 administration until 1 year after surgery. The definition of feasibility of administration was 'treatment completion rate >75% at 4 cycles of S-1 plus docetaxel therapy' and the completion of treatment rate was defined as follows: (full analysis set – number of discontinued patients by adverse events)/number of all patients × 100.

We adopted the combination chemotherapy method reported by Yoshida et al. [10], using the same schedule. Although it is difficult to decide how many cycles of S-1 plus docetaxel should be performed in an adjuvant setting, we decided to carry out this study with 4 cycles of S-1 plus docetaxel based on the results of a study using an average of 4 courses reported by Yoshida et al. [10], which was performed for patients with advanced and recurrent gastric cancer.

Follow-Up

Patients underwent hematologic tests and assessments of clinical symptoms at least once during every course of chemotherapy. The presence of a relapse was determined by means of imaging

Table 1. Patient characteristics

		Patients (n = 53)
Age, years	Median	65
	Range	43–78
Gender	Male	42
	Female	11
ECOG PS	0	31
	1	22
Pathological type	Intestinal	23
	Diffuse	29
	Others	1
Stage[1]	IIIA	36
	IIIB	17
T stage[2]	pT2	21
	pT3	30
	pT4	2
N stage[2]	pN0	1
	pN1	22
	pN2	30
M stage[2]	M0	53
	M1	0
Stage[2]	IIIA	36
	IIIB	16
	IV (T4, N1)	1

ECOG PS = Eastern Cooperative Oncology Group performance status.
[1] Japanese classification. [2] TNM classification.

studies, including ultrasonograpy, computed tomography and gastrointestinal endoscopy. Patients underwent abdominal computed tomography at 6-month intervals during the first 2 years after surgery, at 1-year intervals thereafter until 5 years after surgery, and also underwent gastrointestinal endoscopy at 1-year intervals.

Statistical Analysis

The calculation of the sample size for the study was based on an expected feasibility rate of 75% and a threshold feasibility rate of 50%, using a 2-sided α error of 0.05 and a statistical power of 90%. The planned sample size was 50 patients, allowing for a 20% dropout rate. The feasibility rate was evaluated by exact binominal test. Statistical analysis was done using R software version 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

We enrolled 53 patients from 13 institutions for this study, 42 men and 11 women with a median age of 65 years (range 43–78), between May 2007 and August 2008. Thirty-six patients had stage IIIA disease and 17 patients had stage IIIB disease. The demographic and clinicopathological characteristics of these patients are listed in table 1.

Table 2. Adverse events of 4 cycles of chemotherapy with S-1 plus docetaxel (n = 53)

	G1	G2	G3	G4	≥G3, %
Hematologic					
Anemia	20	11	2	0	3.3
Leukopenia	7	17	7	3	18.9
Neutropenia	4	4	11	15	49.1
Thrombocytopenia	7	0	0	0	3.8
Febrile neutropenia	–	–	5	0	9.4
Nonhematologic					
AST/ALT	7	0	0	0	0
Total bilirubin	4	3	0	0	0
Nausea	9	3	3	0	5.7
Vomiting	2	2	0	0	0
Anorexia	16	7	5	0	9.4
Fatigue	12	8	3	0	5.7
Stomatitis	5	1	1	0	1.9
Diarrhea	6	3	0	0	0
Alopecia	5	3	–	–	0

National Cancer Institute Common Toxicity Criteria, version 3.0. AST = Aspartate aminotransferase; ALT = alanine aminoransferase.

Toxicity

The most frequent grade 3–4 hematological toxicity during 4 cycles of this regimen was neutropenia, which was observed in 26 of 53 patients (49.1%) (table 2). Grade 3 febrile neutropenia was observed in 5 patients (9%). Additional grade 3–4 hematological toxicities consisted of leukopenia in 10 patients (18.9%) and anemia in 2 patients (3.8%). Nonhematological toxicities of grade ≥3 involved nausea in 5.7%, anorexia in 9.4% and fatigue in 5.7%. There was no grade 4 nonhematological toxicity in any patient.

No treatment-related deaths occurred within 30 days after completion of this regimen.

Feasibility

The feasibility of the planned 4 cycles of treatment was 79.2% (95% CI 65.9–89.2; $p < 0.001$ under the null hypothesis) with 42 out of 53 patients (table 3). Reasons for discontinuation of this regimen were adverse events in 9 patients, by physician's decision in 1 patient, and 1 patient postponed the treatment schedule due to personal rea-

Table 3. Feasibility of protocol treatment

	S-1 plus docetaxel for 4 cycles	S-1 plus docetaxel and S-1 monotherapy for 1 year
Patients	53	53
Completed	42	34
Not completed	11	19
Treatment completing rate	79.2% (65.9–89.2)	64.2% (49.8–76.9)

Figures in parentheses are 95% CIs.

sons. A total of 42 patients completed 4 cycles of S-1 and docetaxel, but 8 patients did not follow the planned S-1 monotherapy: 3 due to recurrent cancer, 2 due to toxicity, 1 due to patient refusal, 1 due to the physician's decision, and 1 due to personal reasons.

The relative performance of S-1 and docetaxel for 4 cycles of chemotherapy was 79.6 and 87.8%, respectively. Moreover, the compliance rates of S-1 patients were 84.9, 73.6, 69.8 and 64.2% (95% CI 49.8–76.95) at 3, 6, 9 and 12 months after surgery, respectively.

Discussion

This phase II study demonstrated that postoperative adjuvant S-1 plus docetaxel therapy of 4 cycles is feasible, with a feasibility rate of 79.2%. Moreover, the compliance of S-1 treatment was similar to those of the ACTS-GC study up to 1 year after surgery: 84.9 versus 87.4% at 3 months, 73.6 versus 77.9% at 6 months, 69.8 versus 70.8% at 9 months and 64.2 versus 65.8% at 12 months, respectively [8].

Since there were few gastrointestinal toxicities during an additional 4 courses of docetaxel, this combination regimen seemed to be highly tolerable. These results may have important implications for future adjuvant treatment strategies for stage III gastric cancer.

In Japan, for metastatic or recurrent gastric cancer, S-1 plus cisplatin is now considered to be one of the standard regimens based on a phase III trial (SPIRITS study) [16].

The results of the SPIRITS study (S-1 vs. S-1 plus cisplatin) established the superiority of the S-1 plus cisplatin combination over S-1 monotherapy [15]. The rate of response to combination therapy versus monotherapy was 54 versus 31% ($p = 0.0018$), and the median survival time was 13.0 versus 11.0 months ($p = 0.0366$).

Therefore, S-1 plus cisplatin is considered to be a candidate for an experimental arm in the next adjuvant chemotherapy trial.

More recently, adjuvant chemotherapy studies using S-1 plus cisplatin have been reported for patients with resected gastric cancer [16, 17]. Five courses of S-1 plus cisplatin appear to be too toxic as postgastrectomy treatment for clinical stage II/III patients who underwent gastrectomy but turned out to be stage IV gastric cancer, so that the median relative dose intensities of S-1 and cisplatin were only 37 and 40%, respectively [16]. Moreover, a feasibility study of adjuvant chemotherapy with 3 courses of S-1 plus cisplatin followed by S-1 monotherapy until 1 year after surgery demonstrated that 3 courses of combined chemotherapy were not feasible because of the high incidence of grade 3–4 toxicities including neutropenia (40%), anorexia (28%) and nausea (8%) [17]. In this clinical trial, they suggested the modified protocol, the first chemotherapy cycle of which consisted of S-1 monotherapy; then, cisplatin was added to cycles 2, 3 and 4, followed by S-1 monotherapy up to 1 year after surgery. This amended protocol is more feasible than the original protocol, because of relatively few grade 3–4 toxicities including neutropenia (37%), anorexia (8%) and nausea (3%) and should be considered as a feasible experimental arm for the next postoperative adjuvant phase III trial [17].

Nausea and anorexia are commonly observed adverse reactions after the administration of cisplatin, and dehydration due to impaired oral food intake could increase the renal toxicity of cisplatin, especially in patients immediately after gastrectomy.

On the other hand, preclinical pharmacokinetic studies on docetaxel have shown that its hepatobiliary excretion is the major route of elimination, while renal excretion is minimal (<5%) [18–20]. Thus, it seems that docetaxel is a suitable anticancer agent for patients immediately after surgery. Moreover, S-1 plus docetaxel can be given in outpatient clinics, while S-1 plus cisplatin usually requires hospitalization to ensure hydration; thus, the former reduces the inconvenience to both patients and clinicians.

In both Japan and Korea, phase III studies of S-1 alone versus S-1 and docetaxel (JACCRO GC03 study) as chemotherapy for advanced gastric cancer are ongoing and the results should be reported soon [21].

If the results of the JACCRO GC03 study are favorable, it seems that the present regimen will become a promising candidate for adjuvant chemotherapy in stage III gastric cancer.

In conclusion, postoperative adjuvant chemotherapy with S-1 and docetaxel of 4 cycles and S-1 monotherapy afterwards until 1 year after surgery is considered to be feasible for patients who have undergone gastrectomy for gastric cancer.

This should be regarded as a potential experimental arm together with S-1 plus cisplatin for the next adjuvant phase III study comparing S-1 plus other drug combination chemotherapy and S-1 alone as adjuvant chemotherapy for patients who have undergone curative resection with D2 lymph node dissection for stage III gastric cancer.

Acknowledgements

We are indebted to the physicians and all of the clinical study teams at the participating institutions. We also thank Mr. Toshio Shimokawa for his scientific advice, and Ms. Akiko Hotta and Ms. Hiroko Maruyama for their excellent secretarial assistance at the Osaka Gastrointestinal Cancer Chemotherapy Study Group data center. The authors are also indebted to Prof. J. Patrick Barron of the Department of International Medical Communications of Tokyo Medical University for his review of the manuscript.

References

1 Nakajima T, Fukami A, Ohashi I, Kajitani T: Long-term follow-up study of gastric cancer patients treated with surgery and adjuvant chemotherapy with mitomycin C. Int J Clin Pharmacol Biopharm 1978;16:209–216.

2 Nakajima T, Fukami A, Takagi K, Kajitani T: Adjuvant chemotherapy with mitomycin C, and with a multi-drug combination of mitomycin C, 5-fluorouracil and cytosine arabinoside after curative resection of gastric cancer. Jpn J Clin Oncol 1980;10:187–194.

3 Nakajima T, Takahashi T, Takagi K, Kuno K, Kajitani T: Comparison of 5-fluorouracil with ftorafur in adjuvant chemotherapies with combined inductive and maintenance therapies for gastric cancer. J Clin Oncol 1984;2:1366–1371.

4 Nakajima T, Okabayashi K, Nakazato H, Iwanaga T, Ohta K, Kinoshita T, Kitou T, Yamamura Y, Furukawa H, Hiratsuka M: Adjuvant chemotherapy with MFC-related regimens for patients with gastric cancer after curative gastrectomy. Jpn J Soc Cancer Ther 1994;29:654–662.

5 Nakajima T, Nashimoto A, Kitamura M, Kito T, Iwanaga T, Okabayashi K, Goto M: Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomized trial. Lancet 1999;354:273–277.

6 Nashimoto A, Nakajima T, Furukawa H, Kitamura M, Kinoshita T, Yamamura Y, Sasako M, Kunii Y, Motohashi H, Yamamoto S, Gastric Cancer Surgical Study Group, Japan Clinical Oncology Group: Randomized trial of adjuvant chemotherapy with mitomycin, fluorouracil, and cytosine arabinoside followed by oral fluorouracil in serosa-negative gastric cancer: Japan Clinical Oncology Group 9206-1. J Clin Oncol 2003;21:2282–2287.

7 Nakajima T, Kinoshita T, Nashimoto A, Sairenji M, Yamaguchi T, Sakamoto J, Fujiya T, Inada T, Sasako M, Ohashi Y, National Surgical Adjuvant Study of Gastric Cancer Group: Randomized controlled trial of adjuvant uracil-tegafur versus surgery alone for serosa-negative, locally advanced gastric cancer. Br J Surg 2007;94:1468–1476

8 Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K, ACTS-GC Group: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007;357:1810–1820.

9 Koizumi W, Tanabe S, Saigenji K, Ohtsu A, Boku N, Nagashima F, Shirao K, Matsumura Y, Gotoh M: Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. Br J Cancer 2003;89:2207–2212.

10 Yoshida K, Ninomiya M, Takakura N, Hirabayashi N, Takiyama W, Sato Y, Todo S, Terashima M, Gotoh M, Sakamoto J, Nishiyama M: Phase II study of docetaxel and S-1 combination therapy for advanced or recurrent gastric cancer. Clin Cancer Res 2006;12:3402–3407.

11 Mochiki E, Ohno T, Kamiyama Y, Aihara R, Haga N, Ojima H, Nakamura J, Ohsawa H, Nakabayashi T, Takeuchi K, Asao T, Kuwano H, North Kanto Gastric Cancer Study Group: Phase I/II study of S-1 combined with paclitaxel in patients with unresectable and/or recurrent advanced gastric cancer. Br J Cancer 2006;95:1642–1647.

12 Inokuchi M, Yamashita T, Yamada H, Kojima K, Ichikawa W, Nihei Z, Kawano T, Sugihara K: Phase I/II study of S-1 combined with irinotecan for metastatic advanced gastric cancer. Br J Cancer 2006;94:1130–1135.

13 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma – 2nd English edition. Gastric Cancer 1998;1:10–24.

14 Sobin LH, Witteking C: International Union Against Cancer (UICC) TNM Classification of Malignant Tumours, ed 6. New York, Wiley, 2002.

15 Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M: S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 2008;9:215–221.

16 Kodera Y, Ishiyama A, Yoshikawa T, Kinoshita T, Ito S, Yokoyama H, Mochizuki Y, Ito H, Tsuburaya A, Sakamoto J, Nakao A, Chubu Clinical Cancer Group: A feasibility study of postoperative chemotherapy with S-1 and cisplatin (CDDP) for gastric carcinoma (CCOG0703). Gastric Cancer 2010;13:197–203.

17 Takahari D, Hamaguchi T, Yoshimura K, Katai H, Ito S, Fuse N, Kinoshita T, Yasui H, Terashima M, Goto M, Tanigawa N, Shirao K, Sano T, Sasako M: Feasibility study of adjuvant chemotherapy with S-1 plus cisplatin for gastric cancer. Cancer Chemother Pharmacol 2010, Epub ahead of print.

18 Mori K, Kamiyama Y, Kondo T, Kano Y, Kodama T: A phase II study of docetaxel and infusional cisplatin in advanced non-small cell lung cancer. Chemotherapy 2005;51:120–125.

19 Bruno R, Sanderink GJ: Pharmacokinetics and metabolism of taxotere (docetaxel). Cancer Surv 1993;17:305–313.

20 Clarke SJ, Rivory LP: Clinical pharmacokinetics of docetaxel. Clin Pharmacokinet 1999;36:99–114.

21 Fujii M: Chemotherapy for advanced gastric cancer: chemotherapy for advanced gastric cancer: ongoing phase III study of S-1 alone versus S-1 and docetaxel combination (JACCRO GC03 study). Int J Clin Oncol 2008;13:201–205.