A feasibility study of outpatient chemotherapy with S-1 + cisplatin in patients with advanced gastric cancer

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Abstract

Background Regimens of standard-dose cisplatin have usually been administered as inpatient chemotherapy in Japan. This prospective study evaluated the feasibility of outpatient chemotherapy with standard-dose cisplatin in Japanese patients with advanced gastric cancer.

Methods Advanced gastric cancer patients received an S-1 + cisplatin regimen (S-1: 80–120 mg days 1–21; cisplatin: 60 mg/m² day 8, every 4–5 weeks), either as outpatient chemotherapy with oral hydration on days 9–10, or as inpatient chemotherapy with intravenous hydration on days 9–10, based on the results of an oral hydration test

during days 1–7 of the first cycle. The primary endpoint was the completion rate of two cycles in the outpatient group.

Results A total of 36 patients were enrolled: 32 were allocated to the outpatient group and 4 to the inpatient group. The completion rate of two cycles in the outpatient group was 78% [90% confidence interval (CI): 63–89]. The median of the total number of treatment cycles of S-1 + cisplatin and the median progression-free survival in the outpatient group were 5 (range 1–11) and 10.6 months (95% CI 4.2–16.9), respectively. Although seven patients in the outpatient group discontinued treatment, mainly owing to gastrointestinal toxicity, most of them could continue S-1 + cisplatin by switching to inpatient chemotherapy from the next cycle.

Conclusion Outpatient chemotherapy with S-1 + cisplatin in advanced gastric cancer patients can be safely and effectively administered in Japan with appropriate patient selection and supportive treatment.

Keywords Cisplatin · Gastric cancer · Oral hydration · Outpatient chemotherapy · S-1

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Background

Gastric cancer is the most common cause of morbidity from cancer in Japan, and despite a decrease in recent years its mortality rate is still as high as 16% among all cancers [1]. Unresectable or recurrent gastric cancer has an extremely poor prognosis, so the establishment of a standard chemotherapy regimen is a high priority. Since the FAM-TX [5-fluorouracil (5-FU) + doxorubicin + methotrexate] regimen demonstrated a survival advantage over best

supportive care [2], various regimens have been developed around the world.

Although a 5-FU continuous infusion regimen had long been considered the standard in Japan for unresectable or recurrent gastric cancer, based on the results of the Japan Clinical Oncology Group (JCOG) 9205 trial [3], an S-1 (tegafur, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate) + cisplatin (CDDP) regimen recently replaced it, on the basis of the JCOG 9912 trial [4] and SPIRITS trial [5], and this regimen is now widely used. In China, as well as in Japan, S-1 + CDDP is regarded as one of the standard treatments for unresectable or recurrent gastric cancer, based on the results of a domestic randomized controlled trial [6]. The FLAGS trial was conducted in Western countries to prove the superiority of S-1 + CDDP over 5-FU + CDDP, and S-1 + CDDP demonstrated better overall survival (although without statistical significance) and a significantly better safety profile [7].

Outpatient chemotherapy has gradually become popular in Japan with the spread of outpatient chemotherapy units [8]. However, regimens containing standard-dose CDDP (≥ 50 mg/m²) have usually been administered as inpatient chemotherapy because the regimen is highly emetic and requires intensive hydration [9], although it is commonly administered as outpatient chemotherapy in Western countries. According to a recent conference presentation in Japan, only 3.7% of chemotherapy with standard-dose CDDP was administered on an outpatient basis in Japan. The drug lag of new-generation antiemetics, plus delays in the development of antiemetic guidelines and in the improvement of the infrastructure of outpatient chemotherapy units, are other reasons for the high proportion of inpatient treatment. This situation decreases the quality of life of patients and imposes a large financial burden due to the hospitalization cost.

In recent years, some encouraging reports have emerged from Japan. A report on the safety data of a retrospective study in lung cancer patients who received standard-dose CDDP with a “short hydration regimen [10]”, which was already common in Western countries, was presented at a recent meeting in Japan. However, it is assumed that oral hydration is unsuitable for advanced gastric cancer patients, due to their specific conditions, such as the stenosis caused by the primary lesion, anorexia in postgastrectomy patients, and potential bowel obstruction due to peritoneal dissemination. We performed a single-institute retrospective study in 45 advanced gastric cancer patients receiving S-1 + CDDP as the first-line treatment, and found that 15 patients (33%) with gastrointestinal toxicity of grade 1 or less for their entire treatment period could be potential candidates for safely receiving standard-dose CDDP as outpatient chemotherapy. This paper reports on a prospective study conducted to evaluate the feasibility of

outpatient chemotherapy with S-1 + CDDP in advanced gastric cancer patients in Japan.

Patients and methods

Patients

Eligibility criteria were as follows: unresectable or recurrent gastric cancer, or advanced gastric cancer which required neoadjuvant chemotherapy with S-1 + CDDP; histologically confirmed gastric adenocarcinoma; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; aged between 20 and 75 years; agreed to take oral hydration of ≥ 1.5 L/day; and adequate organ functions: neutrophil count $\geq 1200/\text{mm}^3$, hemoglobin level ≥ 8.0 g/dL, platelet count $\geq 75000/\text{mm}^3$, total bilirubin level ≤ 3.0 mg/dL, and aspartate aminotransferase and alanine aminotransferase levels ≤ 100 IU/L. In terms of renal function, either a serum creatinine level of ≤ 1.5 mg/dL or an estimated creatinine clearance of ≥ 50 mL/min was required. Prior chemotherapy was allowed except for a CDDP-containing regimen, and measurable lesions were not mandatory. Although the conditions of patients with and without prior chemotherapy might have been different, we considered it allowable to include patients with prior chemotherapy (except for those who had received CDDP previously), because this study did not actually aim to prove the efficacy and safety of S-1 + CDDP.

Written informed consent was obtained from all patients, and the study was approved by the institutional review boards of each of the two institutions involved. The study was monitored for the entire time by an independent data and safety monitoring committee, and kept within the Helsinki Declaration and Japanese Ethical Guidelines for Clinical Studies. This study is registered with University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), number 000002685.

Treatments

The study schema is shown in Fig. 1. S-1 was administered orally twice daily at a dose of 80–120 mg/day [80 mg/day for a body surface area (BSA) of <1.25 m², 100 mg/day for a BSA of 1.25 – 1.5 m², and 120 mg/day for a BSA of ≥ 1.5 m²] for 21 consecutive days, followed by a 14-day rest; and CDDP was administered intravenously at a dose of 60 mg/m² on day 8. The protocol treatment was defined as two cycles, and we recommended continuing S-1 + CDDP as a subsequent treatment when it was effective. When administered as neoadjuvant chemotherapy, the rest period could be shortened to a minimum of 7 days. Patients were given an oral hydration test during

Fig. 1 Flow chart of protocol treatment. CDDP cisplatin

days 1–7 of the first cycle. In the oral hydration test, patients were required to take oral hydration of ≥ 1.5 L/day in addition to food every day throughout days 1–7. Patients wrote down the self-reported amount of oral hydration every day throughout days 1–7, and the physicians checked it by the next morning. Chemotherapy in the first cycle was initiated after hospital admission in every patient, to enable an accurate check of the amount of oral hydration. Patients were allocated to the outpatient group (group A) if they passed the oral hydration test (or if they could take oral hydration of ≥ 1.5 L/day every day throughout days 1–7), and they were allocated to the inpatient group (group B) if they failed the test. Group A patients were administered intravenous hydration only on day 8, and were encouraged to take oral hydration of ≥ 1.5 L/day on days 9–10. They were then discharged, and continued to take S-1 until day 21. In the second cycle they were not given an oral hydration test, and CDDP was administered at the outpatient chemotherapy unit on day 8. Group B patients were administered intravenous hydration of the same amount as group A patients on day 8 and 2 L/day on days 9–10, and CDDP was administered in the hospital ward on day 8 in the second cycle.

The CDDP administration method in group A is shown in Table 1. In group A, a total of 2300 mL hydration was administered in 5 h and 15 min. Patients were orally administered antiemetics on days 9–11 and diuretics when

Table 1 Cisplatin administration method in group A

Day 8			
Normal saline	1000 mL	Drip infusion	2 hours
Dexamethasone	20 mg	Drip infusion	15 minutes
Granisetron	1 mg		
Normal saline	50 mL		
Cisplatin	60 mg/m ²	Drip infusion	1 hour
Normal saline	250 mL		
Normal saline	1000 mL	Drip infusion	2 hours
Days 9–10			
Oral hydration	≥ 1.5 L	Orally	
Days 9–11			
Dexamethasone	16 mg	Orally	
Granisetron	2 mg		
Furosemide	40 m	Orally (as needed)	

they gained weight by ≥ 1.5 kg in relation to their weight on day 8. Group B patients were administered these drugs intravenously. The regimen of antiemetics was in accordance with the 1999 American Society of Clinical Oncology (ASCO) guidelines [11], because newer agents such as aprepitant and palonosetron had not been approved in Japan when the study was being planned. Group A patients were required to contact their physicians immediately when they could not take adequate oral hydration on days

9–10, and they were administered intravenous hydration as needed, resulting in discontinuation of the protocol treatment. Even in these patients, S-1 + CDDP could be continued. The completion of treatment was defined as follows: had taken S-1 for ≥ 14 days per cycle, had been administered CDDP, and had not met the discontinuation criteria for S-1 + CDDP. Treatment discontinuation was required in any of the following cases: inadequate oral hydration despite a lack of major toxicity or intravenous hydration on days 9–10 (group A only), administration of second-cycle CDDP as inpatient chemotherapy at the physician's discretion (group A only), disease progression, unacceptable toxicity, patient's refusal, and physician's judgment.

Physical and blood examinations were required every week in the first cycle and every other week in the second cycle. The toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Imaging tests were performed after the completion of two cycles, and the response was evaluated with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 in those patients with measurable lesions.

Statistical analysis

The completion rates of two cycles in the SPIRITS trial and in our retrospective study were 70% (90% CI 63–76) and 78% (90% CI 65–87), respectively, as the first-line treatment in the hospital ward. Because the patients were recruited to this study regardless of their history of prior chemotherapy (except for those who had received CDDP previously), and CDDP was administered as outpatient chemotherapy in group A, a 50% completion rate of two cycles in group A was considered acceptable. Given that the point estimate was around 50%, and the 90% CI was between 30 and 70%, 20 patients were required in group A. Therefore, given that the proportion allocated to group A was around 60%, and in expectation of a few ineligible patients, the total sample size required was determined to be 35 patients.

The primary endpoint was the completion rate of two cycles in group A. The secondary endpoints were as follows: the completion rate of two cycles in group B, progression-free survival in each group, and adverse events in each group. Progression-free survival was defined as the period from the registration date to the earlier of the first radiological or clinical disease progression or death from any cause. In the event that neither disease progression nor death occurred, the case was censored at the last date confirmed as progression-free. When a patient in the neoadjuvant setting could subsequently receive curative surgery, the case was censored at the date of surgery.

A follow-up survey was scheduled 1 year from the date of the last registration. Progression-free survival was analyzed using the Kaplan–Meier method. All of the analyses were performed by an intention-to-treat method, using SAS version 9.2.

Results

A total of 36 patients were registered from two institutions in Japan between October 2008 and July 2009; 32 patients were allocated to group A and 4 to group B. Patient characteristics in each group are shown in Table 2. In terms of ECOG performance status, all the patients were either 0 or 1. In five patients the regimens were administered as neoadjuvant chemotherapy, and all five of these patients were allocated to group A. Seven patients (22%) in group A and one (25%) in group B had a history of prior chemotherapy (Table 3). The median follow-up period was 13.0 months (range 3.0–21.3).

The number of patients who completed the protocol treatment was 25 in group A, and 4 in group B. Therefore, the completion rate of two cycles was 78% (90% CI 63–89) in group A, and 100% (90% CI 47–100) in group B. Of the five patients who received S-1 + CDDP as neoadjuvant chemotherapy, two could receive curative surgery subsequently. Of the seven patients (22%) in group A who could not complete the protocol treatment, six could continue

Table 2 Patient characteristics

	Group A N = 32	Group B N = 4
Median age, years (range)	62 (34–75)	65 (59–75)
Sex		
Male	22	4
Female	10	0
ECOG performance status		
0	13	1
1	19	3
Treatment line		
Neoadjuvant chemotherapy	5	0
First line	20	3
Second line	4	1
Third line	3	0
Primary lesion		
Yes	27	2
No	5	2
Peritoneal metastasis		
Yes	20	3
No	12	1

ECOG Eastern Cooperative Oncology Group

S-1 + CDDP as inpatient chemotherapy from the next cycle, whereas one was forced to switch to S-1 monotherapy due to grade 3 anorexia, nausea, and diarrhea.

Adverse events in each group are shown in Table 4. In regard to the elevation of the serum creatinine level in group A, creatinine of all-grade and grade 3–4 was found in 14 patients (44%) and none (0%), respectively. All-grade creatinine promptly resolved in most patients: it was still found only in 5 patients (16%) at the completion of the second cycle, and in the same number at the completion of the S-1 + CDDP regimen. There were no treatment-related deaths or early deaths within 30 days after treatment discontinuation.

In group A, delay in initiation of the second cycle due to adverse events occurred in six patients (19%), dose reduction related to adverse events was required in five patients (16%), and treatment discontinuation was required in seven patients (22%) for the following reasons: six had severe gastrointestinal toxicity, and one had inadequate

oral hydration on days 9–10 despite a lack of major toxicity.

The median of the total number of treatment cycles of S-1 + CDDP, including subsequent treatment after the third cycle, was 5 (range 1–11) in group A, and 5 (range 2–7) in group B. Median progression-free survivals in group A and B were 10.6 months (95% CI 4.2–16.9) and 5.6 months (95% CI 1.7–9.5), respectively (Fig. 2).

Discussion

In the present study, the completion rate of two cycles in group A was 78% (90% CI 63–89), and this met the pre-defined threshold. In addition, all the other endpoints, as well as the median of the total number of treatment cycles of S-1 + CDDP, were equal to or better than those found in previous reports [5, 12].

Based on these positive results in both groups, we conclude that outpatient chemotherapy with standard-dose CDDP in advanced gastric cancer patients is feasible, and that an oral hydration test has the potential to be appropriate for patient selection into outpatient chemotherapy or inpatient chemotherapy. To our knowledge, this is the first prospective study in Japan to have proven that outpatient chemotherapy with standard-dose CDDP can be performed safely.

The major reason for treatment discontinuation in the seven patients in group A was severe gastrointestinal toxicity. We could not find major differences in patient characteristics between those who could and those who could

Table 3 Prior chemotherapy

	Group A <i>N</i> = 32	Group B <i>N</i> = 4
First line		
S-1 monotherapy	5	1
5-FU continuous infusion	1	0
5-FU + methotrexate	1	0
Second line		
NK105 (micelle product of paclitaxel)	3 ^a	0

5-FU 5-fluorouracil

^a All patients received S-1 monotherapy as first line

Table 4 Adverse events

	CTCAE v 3.0	Group A <i>N</i> = 32		Group B <i>N</i> = 4	
		All grades <i>N</i> (%)	Grades 3–4 <i>N</i> (%)	All grades <i>N</i> (%)	Grades 3–4 <i>N</i> (%)
Leukocytes		23 (72)	3 (9)	3 (75)	0 (0)
Neutrophils		14 (44)	7 (22)	3 (75)	0 (0)
Hemoglobin		32 (100)	2 (6)	3 (75)	0 (0)
Platelets		13 (41)	0 (0)	2 (50)	0 (0)
Febrile neutropenia		1 (3)	0 (0)	0 (0)	0 (0)
Infection with normal ANC		2 (6)	1 (3)	0 (0)	0 (0)
Creatinine		14 (44)	0 (0)	0 (0)	0 (0)
Fatigue		20 (63)	0 (0)	3 (75)	0 (0)
Anorexia		27 (84)	4 (13)	4 (100)	0 (0)
Nausea		22 (69)	2 (6)	3 (75)	0 (0)
Vomiting		7 (22)	1 (3)	1 (25)	0 (0)
Stomatitis		17 (53)	0 (0)	2 (50)	0 (0)
Diarrhea		17 (53)	3 (9)	2 (50)	0 (0)
Constipation		15 (47)	0 (0)	2 (50)	0 (0)

CTCAE Common Terminology Criteria for Adverse Events, v version, ANC absolute neutrophil count

Fig. 2 Progression-free survival in group A

not complete the protocol treatment, and it is difficult to predict such toxicities in advance. Six out of these seven patients in group A were able to continue S-1 + CDDP by switching to inpatient chemotherapy from the next cycle. In addition, another two patients who completed the protocol treatment could also continue it by switching to inpatient chemotherapy in their subsequent treatment. Of the 31 patients in group A who received not less than two cycles of S-1 + CDDP, 23 patients stayed in group A for the entire time and 8 moved to group B subsequently. The proportion of any toxicity of grade 3 or more was 13% in patients who stayed in group A, and 38% in patients who moved to group B, indicating a certain level of difference; however, almost all the patients who moved to group B experienced these severe toxicities during the treatments in group A, not after they moved to group B. In addition, all-grade creatinine (39 and 25%), median progression-free survival (7.0 and 8.0 months), and the median of the total number of treatment cycles of S-1 + CDDP (4 and 5) were all comparable in these two subgroups: patients who stayed in group A and those who moved to group B. This study therefore also proved that S-1 + CDDP can be safely continued even if it is initiated as outpatient chemotherapy and subsequently has to be switched to inpatient chemotherapy.

The present study has several limitations. Firstly, we prospectively examined only two cycles as the protocol treatment. This is because we included patients in the neoadjuvant setting in the target population, and we usually give such patients no more than two cycles of S-1 + CDDP. However, the median of the total number of treatment cycles of S-1 + CDDP was equal to or better than that found in previous reports [5, 12], so we do not consider this to be a major issue.

Secondly, there is insufficient evidence for the adequacy of the specified volume, 1.5 L/day, of oral hydration we used, both during the period of the oral hydration test and on days 9–10. To our knowledge, there has been no randomized controlled trial to determine an adequate infusion

volume on the day of CDDP administration, and there is far less evidence for the amount of oral hydration required before or after the day of CDDP administration. A report on the pharmacokinetics of CDDP showed that the blood level of free CDDP, which causes renal toxicity, diminished below the limit of detection sensitivity on the day after CDDP administration [13], and it is thought that hydration on the day after CDDP administration may not be indispensable.

Thirdly, the regimen of antiemetics we used was outdated because of the drug-lag of approval of new-generation antiemetics in Japan. Aprepitant was finally approved in Japan in October 2009 and palonosetron was approved in January of 2010.

Outpatient chemotherapy with standard-dose CDDP in Japan can also be justified from a cost standpoint. According to the estimate at our institution, the treatment cost per cycle was JPY 131,834 in group A (fee-for-service and drug cost for three visits) and JPY 317,860 in group B (fee-for-service for two visits and Diagnosis Procedure Combination cost for 6-day hospitalization). The cost of outpatient chemotherapy administration in group A was therefore as low as 42% of that of the inpatient administration in group B.

This finding does not mean we ought to force outpatient chemotherapy on those who do not want to accept oral hydration, or those who strongly desire to receive inpatient chemotherapy. However, we should keep in mind that many more patients prefer outpatient chemotherapy to inpatient chemotherapy [14, 15], even when the regimen contains standard to high-dose CDDP [16]. Also, it may be possible to give outpatient chemotherapy from the first cycle without an oral hydration test for patients who agree to take oral hydration of ≥ 1.5 L/day, because of improvements in antiemetics compared with those used before. One important point to note is that timely switching from outpatient chemotherapy to inpatient chemotherapy should be considered for patients with any severe gastrointestinal toxicity or inadequate oral hydration.

In conclusion, outpatient chemotherapy with S-1 + CDDP in advanced gastric cancer patients can be safely and effectively performed in Japan with appropriate patient selection and supportive treatment. However, the long period of infusion (more than 5 h) on the day of CDDP administration is a major issue. Further improvement in outpatient chemotherapy units is essential to allow the general use of outpatient chemotherapy with standard-dose CDDP in Japan.

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Conflict of interest None declared.

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