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Short Hydration in Chemotherapy with Cisplatin plus S-1 for Advanced or Recurrent Gastric Cancer: A Retrospective Study

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Abstract

Background: Despite there are a few reports that assessed the S-1 + CDDP regimen with short hydration regimen for unresectable or metastatic gastric cancer, there is no consensus on the best regimen for short hydration. The aim of study was to evaluate the safety and the efficacy of S-1 plus cisplatin doublet chemotherapy with short hydration. Methods: S-1 was administered orally (p.o.) twice daily for the first 3 weeks of a 5-week cycle. Dose of S-1 administered was calculated according to the body surface area. CDDP was given as an intravenous (i.v.) infusion of 60 mg/m^2 on day 8 of each cycle. Patients received the total of 1900 ml infusion containing 1000 ml of acetate Ringer's solution as pre- and post-hydraion. 300 ml of 20% mannitol was administered as a diuretic. Results: 35 patients with unresectable or recurrent gastric cancer were enrolled. The reasons for termination of S-1 + CDDP were as follows: 21 (63.6%) by progressive disease; 12 (31.4%) by toxicity. Even though 12 of 35 patients (34.2%) were discontinued S-1 + CDDP chemotherapy, only one patient was discontinued by Grade 2 of increased creatinine. TTF (time to progression) was 174 days (3 - 586 days), and the median of the total number of treatment cycles of S-1 + CDDP was 3.31. Median overall survival, as secondary endpoint, was 518 days. Conclusions: Our study suggested that the short hydration regimen is as safe and efficient as the continuous hydration regimen.

Keywords

Short Hydration, Cisplatin Plus S-1, Gastric Cancer

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1. Introduction

Gastric cancer is the most common form of cancer and the second leading cause of cancer death in Japan. Gastric cancer is a major disease not only in east Asian countries, but also in the world [1]. Since JCOG (Japan Clinically Oncology Group) 9912 trial revealed that S-1 monotherapy showed non-inferiority for the 5-FU continuous infusion regimen, S-1 monotherapy had been considered the standard first line regimen for unresectable or recurrent gastric cancer in Japan [2]. Since this trial, randomised controlled trials of various treatment regimens containing cisplatin (CDDP) have produced disappointing findings in patients with advanced gastric cancer. However, SPIRITS trial showed that S-1 + CDDP regimen was better survival compared to S-1 monotherapy; S-1 + CDDP has been regarded as the standard first line systemic therapy for unresectable or recurrent gastric cancer in Japan [3]. In turn, CDDP containing regimens, for example ECF (epirubicin, cisplatin, fluorouracil), DCF (docetaxel, cisplatin, fluorouracil), are also regarded as the standard first line regimen for unresectable or recurrent gastric cancer in US and Europe [4] (National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2015 Gastric Cancer).

Mor V. *et al*. reported that outpatient hospital care of medical oncology is clinically equivalent to inpatient care, which causes no negative psychosocial effects, and costs less than inpatient care. Moreover, they reported that most of patients hoped to receive outpatient chemotherapy if possible [5]. To avoid the nephrotoxicity, previous cisplatin containing regimens needs the 24-h/hydration. Because of this weak point, cisplatin containing regimen has not been applied to outpatient chemotherapy. Although it has been reported that short hydration chemotherapy containing cisplatin was safe and efficient in lung cancer, there were a few reports in gastric cancer. On the other hand, there is no consensus on the best regimen for hydration. In this study, we assessed the S-1 + CDDP regimen with short hydration based on the NCCN Guidelines Template for patients with unresectable metastatic gastric cancer.

The aim of study was to evaluate the safety and the efficacy of S-1 plus CDDP doublet chemotherapy with short hydration.

2. Patients and Treatment

2.1. Patients

Between March 2010 and September 2012, we retrospectively evaluated 35 patients with unresectable or recurrent gastric cancer who received chemotherapy containing S-1 and cisplatin in our institutes. Patients with histologically proven metastatic or recurrent gastric cancer were eligible for the study. Other patient's eligibility criteria were as follows: an Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 1; neutrophil count ≥ 1200 /mm^3, hemoglobin level ≥ 8.0 g/dL, platelet count ≥ 75,000/m^3. In terms of renal function, either a serum creatinine level of ≤1.5 mg/dL and an estimated creatinine clearance of ≥60 mL/min were required.

2.2. Treatments

S-1 was administered orally (p.o.) twice daily for the first 3 weeks of a 5-week cycle. Dose of S-1 administered was calculated according to the body surface area; less than 1.25 m^2, 40 mg; 1.25 - 1.5 m^2, 50 mg; and greater than 1.5 m^2, 60 mg. CDDP was given as an intravenous (i.v.) infusion of 60 mg/m^2 on day 8 of each cycle. Patients were received the total of 1900 ml infusion containing 1000 ml of acetate Ringer's solution as pre- and post-hydraion. 300 ml of 20% mannitol was administered as a diuretic. Palonosetron 0.75 mg i.v., dexamethasone 9.9 mg i.v. and aprepitant 125 mg p.o. were administered 1 hour before infusional chemotherapy (**Figure 1**). Aprepitant 80 mg p.o. and dexamethasone 4 mg p.o. were administered on days 2 and 3. This treatment schedule was repeated every 5 weeks according to SPIRITS trial [3].

We investigated patients who altered regimen to short hydration from conventional hydration. When physician confirmed the safety of CDDP short hydration in conference, patients were administered inpatient chemotherapy to outpatient chemotherapy.

2.3. Statistical Analysis

The primary endpoint was safety. Secondary endpoints were: overall survival (OS) and time to treatment failure (TTF). Treatment administration was regulated by evaluation of blood cell count before the start of the treatment

cycle. Every four to six weeks, lesions were evaluated and measured mainly on computed tomography (CT). Response was defined according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 4.0). We used Kaplan-Meier method and calculate survival curves, and log-rank test to make treatment comparisons. Statistical analysis was performed using IBM SPSS statistics version 22.0 (SPSS Inc., Chicago, IL).

This trial was conducted in accordance with the World Medical Association Declaration of Helsinki and Japanese Good Clinical Practice guidelines.

3. Results

3.1. Patient Characteristics

A total of 35 patients were enrolled. Patients characteristics were shown as follows: male/female 24/11; median age (range) 62.1 (33 - 79); Histological type intestinal/diffuse/AFP secreting adenocarcinoma/squamous cell carcinoma 15 (42.8%)/17 (48.6%)/1 (2.9%)/2 (5.7%) (**Table 1**). 32 patients were administered chemotherapy as inpatient chemotherapy, remaining 3 patients were induced chemotherapy as outpatient chemotherapy. 7 patients out of 35 were altered treatment regimen to short hydration from long hydration. All patients were induced chemotherapy with short hydration since March 2010.

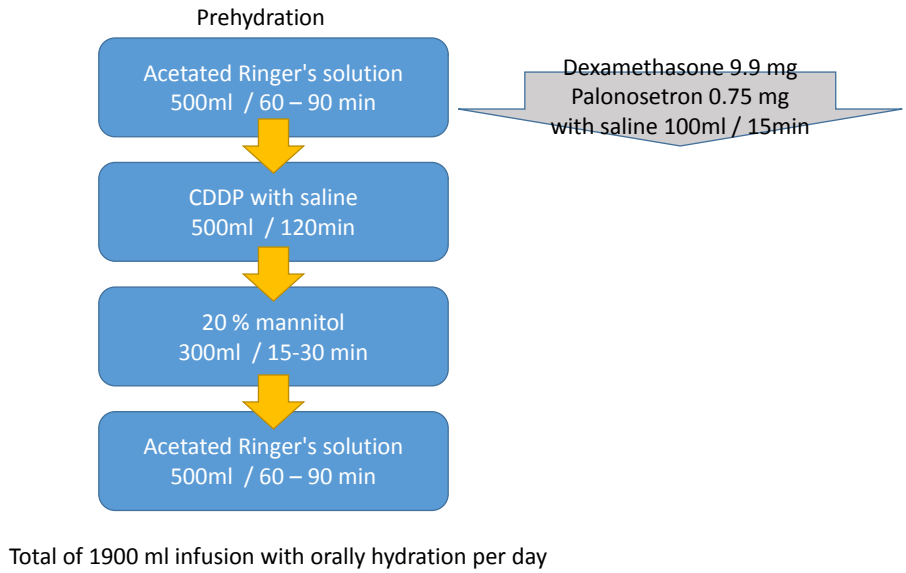


Figure 1. CDDP administration.

Table 1. Patient characteristics.

Age	62.1 (33 - 79)
Gender	
Male/Female	24/11
Histological type	
Intestinal type	15 (42.8%)
Diffuse type	17 (48.6%)
AFP secreting adenocarcinoma	1 (2.9%)
Squamous cell carcinoma	2 (5.7%)

3.2. Toxicity

Two patients were continuing S-1 + CDDP treatment at the end of observation period. In remaining 33 patients, the reasons for termination of S-1 + CDDP were as follows: 20 (60.6%) by progressive disease (PD); 10 (30.3%) by toxicity. Toxicity was consists of five anorexia, one nausea, one diarrhea, one neutropenia, one Alanine aminotransferase increased, and one creatinine increased (**Table 2(a)**, **Table 2(b)**). Even though 10 of 35 patients (28.6%) were discontinued S-1 + CDDP chemotherapy by toxicity, only one patient were discontinued by Grade 2 of increased creatinine. Maximum creatinine level of the patient was 1.48 mg/dL on day 8.

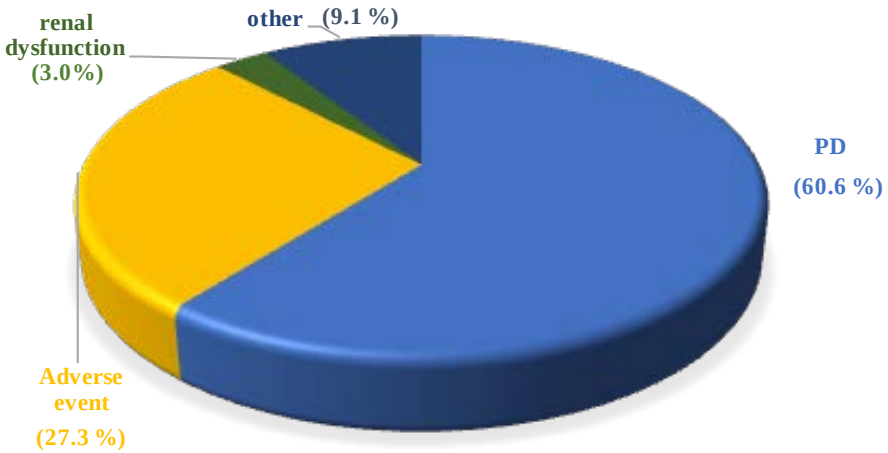
When we compared dose intensity of S-1 + CDDP between the reason of discontinuation by toxicity and progressive disease, the results were shown in **Table 3**. The mean age of toxicity group was 64.9 (47 - 74), and that of PD group was 60.3 (33 - 79). The mean dose of S-1 was 110.0 mg in toxicity group and 111.4 mg in PD groups. The mean dose of CDDP was 88.3 mg in toxicity group and 92.7 mg in PD group. Even if patients discontinued chemotherapy by toxicity, 5 of 10 patients (50.0%) were able to be administered S-1 monotherapy. TTF including S-1 monotherapy followed by S-1 + CDDP discontinuation was slightly longer than only S-1 + CDDP therapy (204 days versus 174 days, **Figure 2**). In summary, we did not observe a significant difference between two groups.

Table 2. (a) Treatment interruption; (b) Distribution of reasons for treatment discontinuation.

(a)

	n = 33
Progressive disease	20 (60.6%)
Adverse events	10 (30.3%)
Anorexia	5 (15.2%)
Nausea	1 (3.0%)
Diarrhea	1 (3.0%)
Neutropenia	1 (3.0%)
Alanine aminotransferase increased	1 (3.0%)
Creatinine increased	1 (3.0%)
Cognitive disturbance	2 (6.1%)
Ileus	1 (3.0%)

(b)



PD; progressive disease

Table 3. Comparison of treatment discontinuation by toxicity and PD.

	Toxicity	PD
Age	64.9 (47 - 74)	60.3 (33 - 79)
Gender Male/Female	8/2	12/8
Dose of S-1	110.0 mg/body	111.4 mg/body
Dose of CDDP	88.3 (76 - 103) mg/body	92.7 (60 - 113) mg/body
Secondary therapy (including S-1 monotherapy)	5 (50.0%)	3 (15.0%)

PD: Progressive disease.

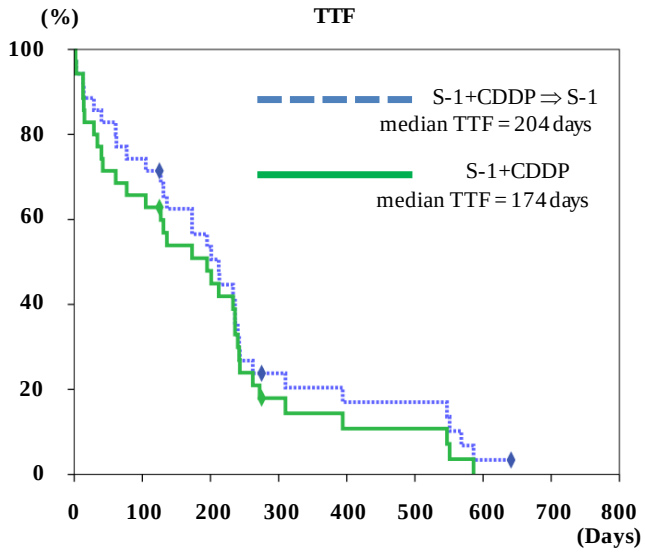


Figure 2. Kaplan-Meier curve of time to treatment failure (TTF) of S-1 monotherapy followed S-1 + CDDP discontinuation.

3.3. Efficacy

Duration of median follow up was 378 days (32 - 694 days). TTF as secondary endpoint was 174 days (3 - 586 days), and the median of the total number of treatment cycles of S-1 + CDDP were 3.31 (1 - 9) (**Figure 3**). Median overall survival, as secondary endpoint, was 518 days (32 - 683 days) (**Figure 4**).

4. Discussion

In the present study, we investigated the safety and efficacy of S-1 + CDDP short hydration for unresectable or recurrent gastric cancer.

Previous study validated short hydration containing CDDP (≥75 mg/m^2/cycle) in lung cancer. The study revealed the safety and efficacy antecedent to gastric cancer [6]. Another study compared 30 patients with gastric cancer, lung cancer, and the urothelial cancer who received outpatient chemotherapy containing CDDP (≥60 mg/m^2/cycle) with short hydration regimen to those who received hospital chemotherapy with continuous hydration. The study reported that there were no differences between two groups in creatinine level, and relative dose intensity in the short hydration group was higher than that in the continuous hydration group [7].

Okazaki *et al.* prospectively reported short hydration regimen of S-1 + CDDP for gastric cancer patients. Advanced gastric cancer patients received an S-1 + CDDP regimen, either as outpatient chemotherapy with oral hydration on day 9 to 10, or as inpatient chemotherapy with intravenous hydration on day 9 to 10, based on the results of an oral hydration test during day 1 to 7 of the first cycle. Patients were infused 1000 ml of normal saline before premedication and 1000 ml of normal saline after CDDP administration on day 8. Patients ingest

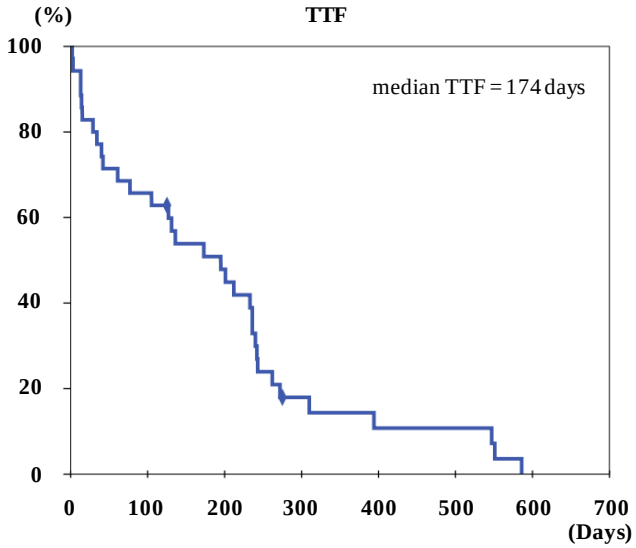


Figure 3. Kaplan-Meier curve of time to treatment failure (TTF).

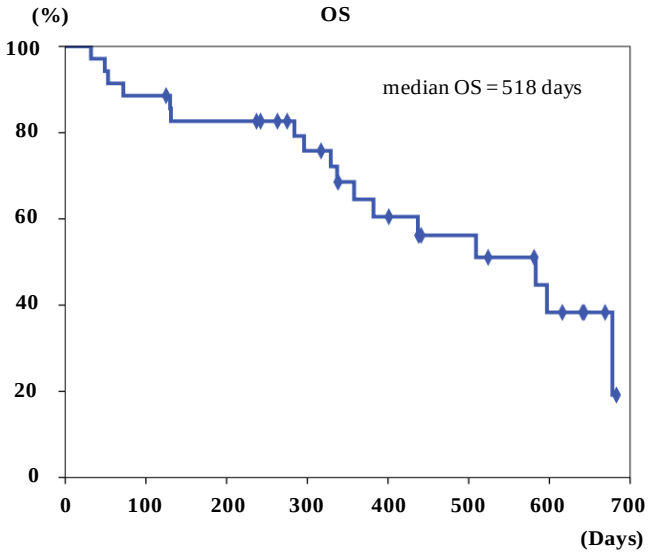


Figure 4. Kaplan-Meier curve of overall survival (OS).

orally 1500 ml of water on day 9 and 10 [8]. Satake *et al.* who is the author in the present study reported that patients were infused 1000 ml of 0.45% NaCl with Mg 2.5 mEq as prehydration and 500 ml of 0.45% NaCl with Mg 2.5 mEq as posthydration with 1000 ml of oral hydration. They administered total 2250 ml of hydration for four hours on day 8 [9].

Comparing our study and these previous studies, we did not identify the significant differentiation of patient characteristics, dose intensity, toxicity and survival. In this study, patients were administered hydration by only intravenous infusion without oral hydration. Despite less hydration, as a result, we considered that the nephrotoxicity of our regimen was similar as that of previous reports. Gastric cancer patients are relatively elder, and it is difficult especially for elder patients to apply the high dose oral hydration in outpatient chemotherapy. Therefore we considered that our hydration regimen was more feasible than previous two reports for outpatient chemotherapy.

In the SPIRITS trial, Grade 3 or 4 adverse events in the S-1 + CDDP arm were shown in **Table 4** [3]. In this study, the reason for treatment discontinuation were almost less toxicity than SPIRITS study. Despite S-1 + CDDP regimen is highly emetogenic chemotherapy, we did not observe the treatment discontinuation by nausea

Table 4. Comparison of Grade 3 - 4 adverse events between SPIRITS trial and our trial.

	Our results (n = 35)	SPIRITS trial (n = 148)
Anorexia	6 (17.1%)	45 (30%)
Nausea	1 (2.9%)	17 (11%)
Diarrhea	1 (2.9%)	6 (4%)
Neutropenia	1 (2.9%)	59 (40%)
Increased creatinine	1 (2.9%)	0

and vomiting in our study. This result was leaded according to the progression of anti-emetic therapy compared with SPIRITS era. Previous reports suggest that the triplet anti-emetic regimen comprising aprepitant, palonosetron, and dexamethasone was useful for cisplatin-based highly emetogenic chemotherapy [10] [11].

The present study has several limitations. Limitation was as follows: duration of follow up was short, small number of patients, retrospective study design.

Prospective phase 2 trial of Japan Southwest Research Support Organization Group (JSWOG)-G1 study to evaluate feasibility of S-1 + CDDP chemotherapy with short hydration is undergoing, there is further discussion expected in the future.

5. Conclusion

Our study suggested that the short hydration regimen was as safe and efficient as the continuous hydration regimen.

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