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Prospective Study of Triple Combination Chemotherapy Consisting of Paclitaxel, S-1, and 24-Hour Infusion of Cisplatin (PSC) for Inoperable Highly Advanced Gastric Cancer

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1. Introduction

Although the prognosis of unresectable gastric cancer remains poor (Hohenberger & Gretshel, 2003), recent advances in chemotherapy for this cancer have considerably improved the therapeutic effects. An oral fluoropyrimidine anticancer agent, S-1, developed in Japan, was designed to enhance the anticancer activity of 5-FU via combination with two modulating substances: gimeracil to inhibit dihydropyrimidine dehydrogenase and potassium oxonate to reduce gastrointestinal toxicities (Shirasaka, et al, 1996). The antitumor effects of fluoropyrimidine are known to be enhanced through biochemical modulation of folate metabolism modified by cisplatin (Scanlon, et al, 1986), and combination therapy using S-1 and cisplatin reportedly achieves high response rates (Koizumi, et al, 2008; Lenz, et al, 2007). Therefore, in Japan, S-1 with cisplatin is the standard therapy for advanced gastric cancer. However, disease progression is still observed in up to 40% of cases (Iwase, et al, 2005; Koizumi, et al, 2008) and further improvement of treatment is thus necessary.

Taxanes have shown encouraging anti-tumor activities against various malignancies, including gastric cancer (Ohtsu, et al, 1998; Sulkes, et al, 1994). Taxane derivatives, docetaxel and paclitaxel, have a unique mechanism of action that differs from those of fluoropyrimidines and platinum compounds. The docetaxel containing combination regimens are associated with severe neutropenia (Yamaguchi, et al, 2006). Just recently, a phase I/ II study of docetaxel combined with S-1 plus cisplatin (DSC triple therapy) was conducted for advanced gastric cancer, and a very high tumor response rate was achieved with febrile neutropenia developing in approximately 20 % of patients (Nakayama, et al, 2008; Sato, et al, 2010). Paclitaxel combined with other drugs reportedly has tolerable toxicity (Kang, et al, 2008). In addition, continuous infusion of cisplatin for 24 hours has

been used to minimize side effects including renal and hematological toxicity (Ina, et al, 2008; Iwase, et al, 2005) with anti-tumor effects the same as in previous reports (Koizumi, et al, 2008 ; Lenz, et al, 2007). Therefore, with the aim of improving the tumor response to S-1 plus cisplatin therapy, we combined paclitaxel with S-1 plus cisplatin (PSC triple therapy) for the treatment of advanced gastric cancer.

2. Patients and methods

Patients were eligible if they signed an informed consent document and met all of the following criteria; (1) pathologically proven inoperable gastric cancer and at least one measurable lesion; (2) age 20 to 75 years; (3) Eastern Cooperative Oncology Group performance status of 0 to 2; (4) white blood cell count between 4000 and 12,000 /mm³, platelet count > 100,000/mm³, haemoglobin > 8 g/ dl; serum bilirubin < 1.5 mg/ dl, aspartate aminotransferase and alanine aminotransferase < 3 times the upper limit of normal (ULN); and serum creatinin less than or equal to ULN; (5) no prior chemotherapy or one regimen that was completed > 4 weeks before entry. S-1 at a dose of 70 mg/m² was given orally twice daily for 2 weeks followed by 2 weeks rest. Paclitaxel at a dose of 120 mg/m² was administered by 2-hour infusion on day 1, cisplatin at a dose of 60 mg/m² by continuous infusion for 24 hours on day 14 (Figure 1). Patients received a maximum of 6 cycles. The objective response to chemotherapy was evaluated employing the criteria proposed by the Japanese Research Society for Gastric Cancer (Japanese Research Society for Gastric Cancer, 1995) for the primary lesion and according to RECIST (Response Evaluation Criteria in Solid Tumors) for metastatic lesions. A complete response (CR) was defined as the disappearance of all evidence of cancer for at least 4 weeks. According to RECIST, a partial response (PR) was defined as a greater than 50% tumor volume reduction. A new lesion or enlargement exceeding the original tumor size by 25% was defined as progressive disease (PD). All patients not in these categories were considered to have stable disease (SD). Progression-free survival (PFS) and overall survival (OS) were calculated from the start of PSC triple therapy until death or the most recent follow-up day. The Kaplan-Meier method was used to plot PFS and OS curves. The National Cancer Institute common toxicity criteria version 4.0 was applied to evaluate adverse effects. Doses were adjusted at the initiation of subsequent cycles, if severe toxicity (grade 3 - 4) was present; S-1 was discontinued and then resumed at a reduced dose (10 mg/m²/ day) and paclitaxel was reduced by 25% in the next cycle when toxicity resolved. Cisplatin was postponed until toxicity resolved; the maximum duration of postponement was no more than 2 weeks.

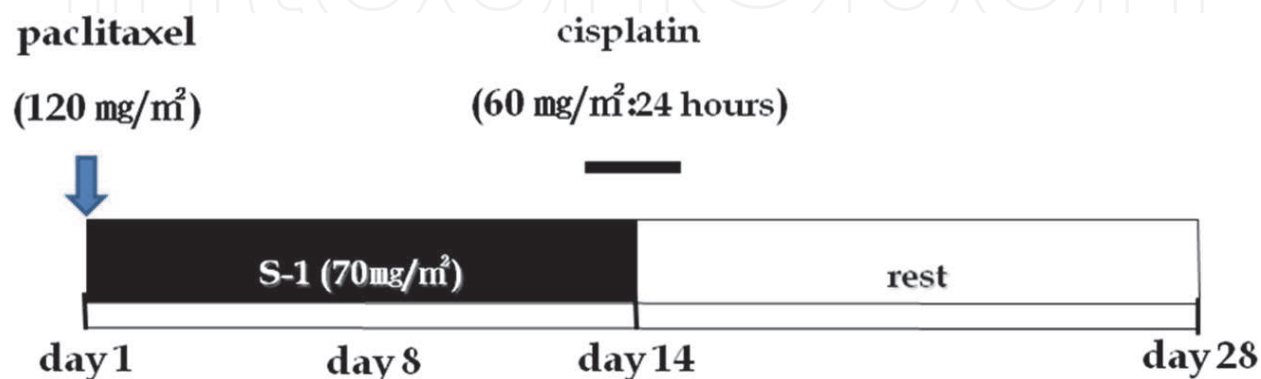


Fig. 1. PSC triple combination therapy

S-1 at a dose of 70 mg/m² was given orally twice daily for two weeks followed by two weeks rest. Paclitaxel at a dose of 120 mg/m² was administered by 2-hour infusion on day 1, cisplatin at a dose of 60 mg/m² by continuous infusion for 24 hours on day 15. Patients received a maximum of 6 cycles. Doses were adjusted at the initiation of subsequent cycles, if severe toxicity (grade 3-4) was present; S-1 was discontinued and then resumed at a reduced dose (10 mg/m²/day) and paclitaxel was reduced by 25% in the next cycle when toxicity resolved. Cisplatin was postponed until toxicity resolved; the maximum duration of postponement was no more than 2 weeks.

3. Results

3.1 Study population

Ten patients with metastatic or recurrent gastric cancer were enrolled from November, 2005 to October, 2010 in our hospital. Patient characteristics are summarized in Table 1. There were 8 men and 2 women, with a median age of 65 (range, 57-73) years. Performance status was 0 in 4 patients, 1 in 2, and 2 in 4. Metastases were identified in the liver in 3 patients, the lung in 2, lymph nodes in 6, and the peritoneum in 7. Prior chemotherapy was conducted in 4 patients (S-1/ paclitaxel in 3; S-1 alone in 1), while the other 6 were chemo-naïve. These patients were administered a total of 40 cycles, with the median being 5 cycles (range, 3-6).

Characteristics	No. of patients
Gender	
Male	8
Female	2
Age	57 - 73
Median	65
Performance Status	
0	4
1	2
2	4
Pathology	
Intestinal	4
Diffuse	6
Target Lesions	
Primary tumor	6
Liver	3
Lung	2
Lymph nodes	6
Peritoneum	7
(Ascites)	(3)
Total cycles	3 - 6
Median	5

Table 1. Patient backgrounds

3.2 Efficacy

The response rates according to site are shown in Table 2: primary lesion, 67% (4 of 6); lymph node metastases, 83% (5 of 6); liver metastases, 67% (2 of 3); and lung metastases, 100% (2 of 2). The overall response rate was 70% (7/10; CR 1, PR 6) and the disease control rate was 100%. Seven patients received subsequent chemotherapy: 3 S-1 alone, 3 S-1/irinotecan and, 1 paclitaxel alone. The median PFS was 373 days (95% CI: 160-573 days) (Figure 2). In this series, no patients underwent surgery after PSC, but the median OS was 747 days (95% CI: 488-1714 days) as shown in Figure 3.

	CR	PR	SD	PD	Response rate	CR rate
Overall	1	6	3	0	70 %	10 %
Primary lesion	1	3	2	0	67 %	10 %
Lymph node	1	4	1	0	83 %	10 %
Liver	0	2	1	0	67 %	0 %
Lung	1	1	0	0	100 %	50 %
Ascites	0	3	0	0	100 %	0 %

Table 2. Objective response rates

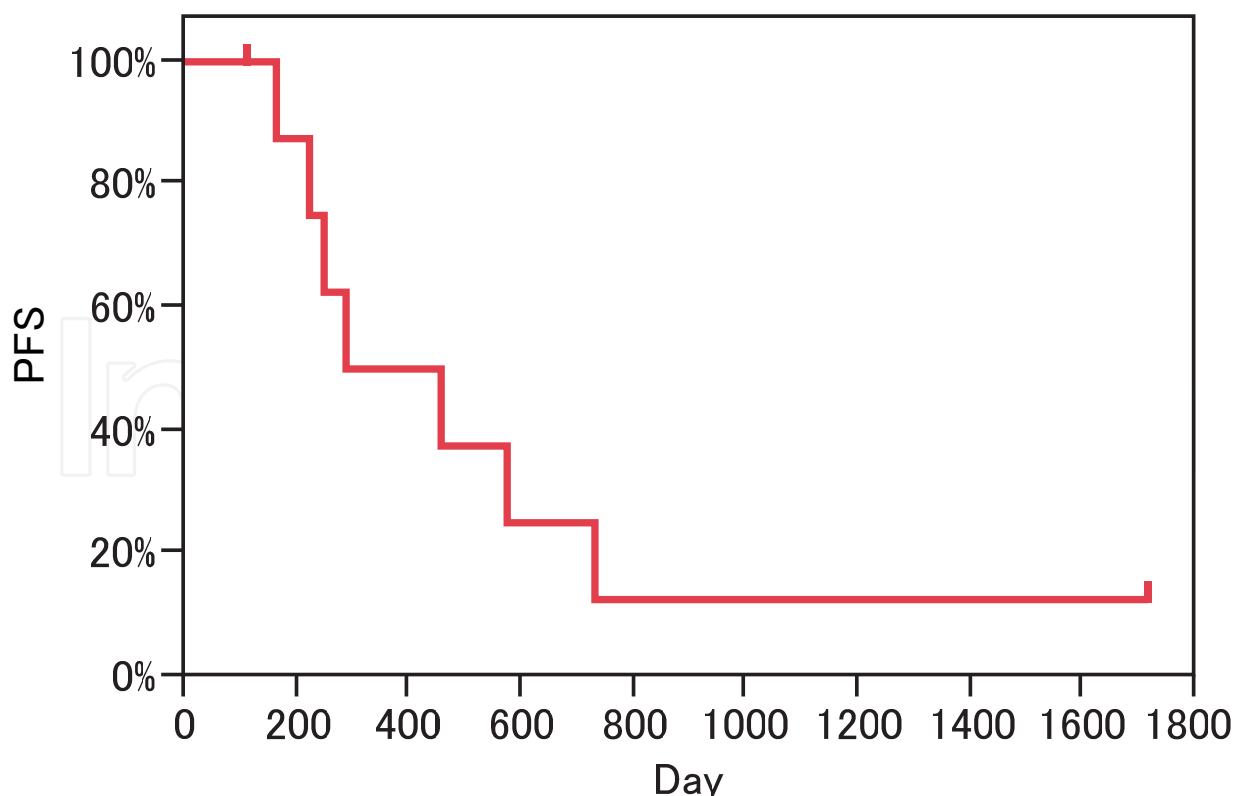


Fig. 2. Progression-free survival (PFS) in patients receiving PSC therapy
Kaplan-Meier analysis of PFS in 10 patients showed PFS to be 373 days (95% CI: 160-573 days).

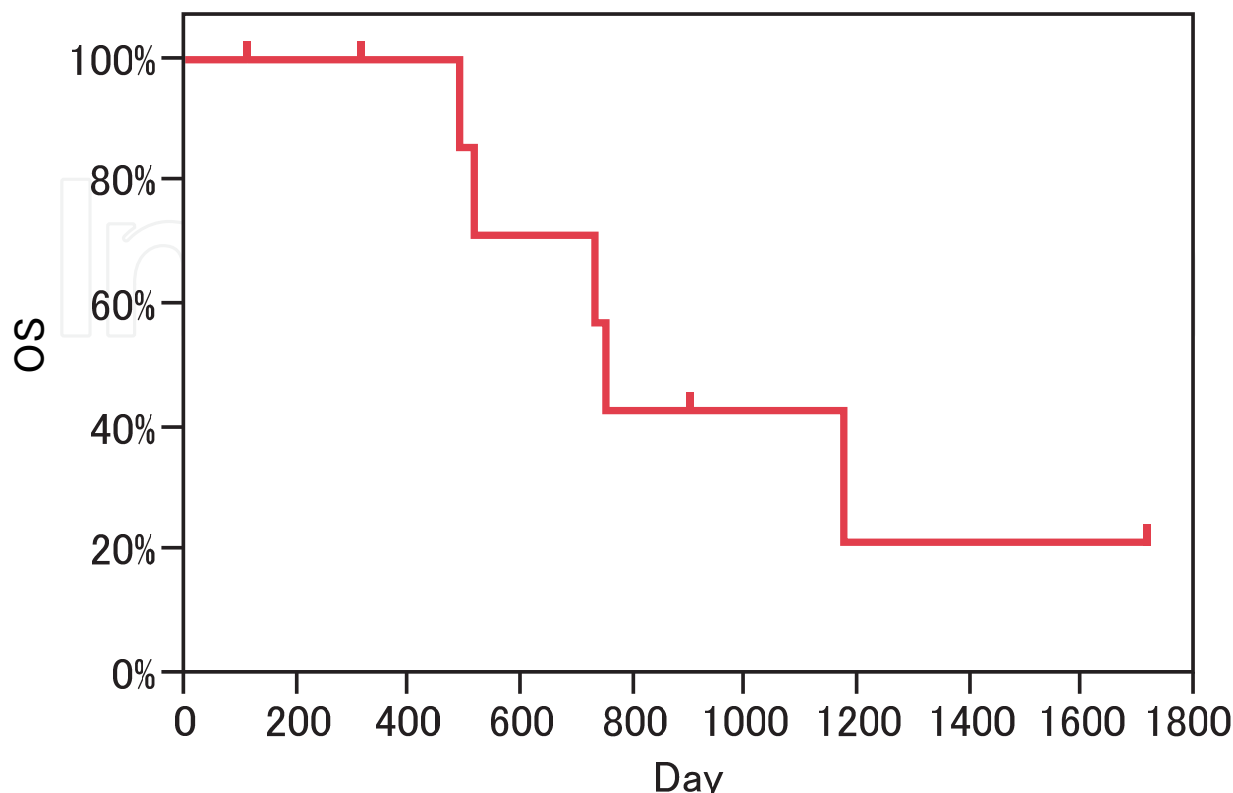


Fig. 3. Overall survival (OS) in patients receiving PSC therapy

Kaplan-Meier analysis of OS in 10 patients showed OS to be 747 days (95% CI: 488-1714 days).

3.3 Adverse effects

Adverse effects during PSC triple therapy were assessed in all 10 patients (Table 3). The most frequently observed severe (grades 3 and 4) toxicity was neutropenia (6 cases, 60%). Febrile neutropenia was observed in only one case (10%). As for non-hematological toxicities, severe anorexia and mucositis (grade 3) were observed in one case. Neither renal dysfunction nor hand-foot syndrome occurred in this study. There were essentially no differences in toxicity between patients with versus without prior chemotherapy.

4. Discussion

A prospective study of PSC triple therapy was conducted for metastatic or recurrent gastric cancer in our hospital. There have been few studies on the use of these three agents in unresectable gastric cancer. Iwase, et al. recommended the following doses: paclitaxel 120 mg/m², cisplatin 60 mg/m², and S-1 70 mg/m², based on the multicenter phase II study (Iwase, et al, 2010). Our patients were treated according to this regimen. This triple combination therapy yielded a high clinical response rate (70%) and a very high disease control rate (100%). In Japan, S-1/ cisplatin should be regarded as a reference regimen. In terms of survival effects, PSC triple therapy (median OS: 747 days [95% CI, 488-1714 days]) was apparently superior to S-1/ cisplatin, for which OS ranged from 10.4 to 13.0 months (Koizumi, et al, 2008 ; Lenz, et al, 2007). PSC appears to be more beneficial than other triple

Toxicity (n = 10)	Grade		
	2	3	4
Hematological toxicity			
Leucopenia	5	3	1
Neutropenia	3	4	2
Thrombocytopenia	3	1	0
Anemia	4	2	0
Non-hematological toxicity			
Skin rash	1	0	0
Mucositis	0	1	0
Diarrhea	0	1	0
Anorexia	3	1	0
Nausea	1	1	0
Vomiting	1	0	0
Liver dysfunction	1	0	0

Table 3. Toxicity incidence

Grade is based on the National Cancer Institute common toxicity criteria, version 4.0.

combination therapies (OS; DCF therapy 9.2 months, DSC therapy 687 days) (Sato, et. al, 2010; van Custem, et al, 2006).

In this trial, all toxicities were manageable and no patients died due to adverse effects. Neutropenia was the most common toxicity, but febrile neutropenia occurred in only one patient, who also had severe mucositis and diarrhea during the same (5th) course of PSC therapy. Continuous infusion of cisplatin for 24 hours induces nausea and vomiting, but the toxicity was milder than that associated with bolus injection of cisplatin. In addition, since June, 2010 we have routinely used aprepitant (Warr, et. al, 2005) to prevent gastrointestinal symptoms induced by cisplatin. Aprepitant remarkably reduces both the incidence and degree of vomiting, nausea, and anorexia.

Our prospective study further support the results of a phase II study (Iwase, et al, 2010) indicating that triple combination chemotherapy consisting of paclitaxel, S-1, and cisplatin had a favorable safety profile with encouraging efficacy against inoperable advanced gastric cancer. This PSC regimen is the major candidates for becoming the standard treatment for advanced gastric cancer. The results of controlled studies comparing PSC triple therapy with S-1/ cisplatin therapy are eagerly anticipated.

5. References

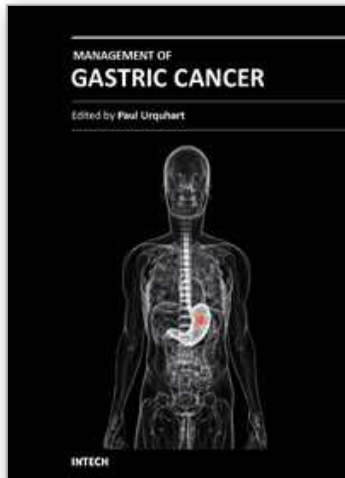
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Gastric cancer is the fifth most common cancer and the second most common cause of cancer death worldwide. More than 50% of the patients have advanced disease at diagnosis and in this case the disease has a poor outcome. The staging of gastric cancers is based on endoscopic ultrasound, computed tomography, magnetic resonance imaging, positron emission tomography, in addition to the laparoscopic staging. Many improvements in the surgical techniques have been seen in the last decade. Laparoscopic surgery is an emerging approach which offers important advantages: less blood loss, reduced postoperative pain, accelerated recovery, early return to normal bowel function and reduced hospital stay. D1 lymphadenectomy, with a goal of examining 15 or greater lymph nodes is a standard. D2 dissection is considered as a standard in several institutions especially in eastern Asia. Perioperative chemotherapy and adjuvant concurrent radiochemotherapy are recognized as standards treatments. Palliative chemotherapy is the mainstay treatment of advanced stages of the disease (metastatic and non-operable tumors). Despite these treatment advances, the prognosis of gastric cancer remains poor with a 5-year survival ranging from 10 to 15% in all stages combined.

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