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ORIGINAL ARTICLE

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A phase I combination chemotherapy study of biweekly paclitaxel and S-1 administration in patients with advanced gastric cancer

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Abstract The aim of the current study was to determine the maximum tolerated dose (MTD) and the dose limiting toxicity (DLT) of a combination of paclitaxel and S-1 in patients with advanced gastric cancer. Fifteen patients were enrolled. The dose for S-1 was set at 80 mg/m^2/day (days 1–14), while the dose for paclitaxel increased by 10 mg/m^2 for every three patients, with a starting dose of 100 mg/m^2 and was given biweekly on day 1 and 15. There was no severe toxicity (grade 4) recorded in patients receiving up to 120 mg/m^2 of paclitaxel. Leukopenia/neutrophilia with grade 1 to 3 occurred in six patients up to level 3. At 130 mg/m^2 of paclitaxel, grade 4 leukocytopenia and neutropenia events and grade 3 diarrhea developed in one out of three patients. One patient in another group of three patients that were enrolled at level 3, developed grade 4 granulocytopenia with fever (a body temperature higher than 38°C) and grade 3 leukocytopenia. Eight patients, out of a total of 15, showed a partial response, resulting in an objective response rate of 53%. Five patients received gastrectomy. Median survival time was 428 days and the 1 year survival rate was 53%. Biweekly paclitaxel/S-1 combination chemotherapy could be safely used for the treatment of advanced gastric cancer. The recommended doses for a phase II study with paclitaxel and S-1 are 120 mg/m^2 and 80 mg/m^2, respectively.

Keywords Gastric cancer · Chemotherapy · Paclitaxel · S-1

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Introduction

Metastatic or locally unresectable gastric carcinoma remains an incurable disease with a median survival of only 6–9 months. Although several new chemotherapeutic regimes have been shown to produce a high response rate early in the disease, they have not been successful in prolonging life and overall survival. However, recently new agents are being widely investigated in the treatment of advanced gastric cancer in North America and Europe [1]. Paclitaxel is an important antitumor compound, which acts as a toxic agent on mitotic spindle formation and induces mitotic arrest [2]. Anti-tumor activity of paclitaxel has been documented in several tumors. It has also been demonstrated that paclitaxel exerts a potent inhibitory effect on tumorigenesis in gastric carcinoma cell lines at concentrations similar to those used clinically [3]. Paclitaxel is an active agent against gastroesophageal cancer [4].

5-Fluorouracil (5-FU) has been used as a common element in combination chemotherapy regimes for gastric cancer. It has been shown that a combination therapy of paclitaxel with 5-FU has an additive cytotoxic effect in several tumor cell lines [5]. The drugs have different mechanisms for their function and resistance, as well as non-overlapping toxicities [6].

S-1 was recognized as a useful anticancer drug in Japan. And now many trials for gastric cancer are done in Japan combined with S-1 and another anticancer drugs, such as CDDP, CPT11 and TXL/TXT.

In majority of the gastric cancer trials with paclitaxel, a course interval of 3 weeks has been used. Weekly dosing of paclitaxel has been demonstrated to be well tolerated and remarkable for a lack of overall and cumulative myelosuppression [7]. However, experience with metastatic breast cancer patients has raised the question if biweekly administration of paclitaxel could lead to even better response rates.

Biweekly infusion of paclitaxel is an alternative to the triweekly schedule, but only a small number of clinical trials with biweekly infusions have been reported [8, 9].

Based on these studies, a phase I clinical trial was initiated to determine the maximum tolerated dose (MTD) of paclitaxel in combination with S-1. We also designed a specific protocol utilizing multi-fractionated administration biweekly, to minimize toxicity while potentially increasing the dose intensity for the component agents.

We designed a specific protocol combined of two drugs with different mechanisms of action and with almost no overlapping toxicity.

Materials and methods

Patient eligibility

Patients with histologically documented adenocarcinoma of the stomach were enrolled in the study between February 2002 and April 2003. The eligible patients included patients with unresectable advanced disease, metastatic disease, or relapsed disease after resection.

Patients who had been previously treated with chemotherapy were also eligible if they had a treatment-free period of at least 4 weeks prior to initiation of the trial, and had recovered from all reversible toxicities. Patients whose survival duration was expected to be less than 3 months were not eligible. All patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of two or less. Other eligibility criteria included: age between 20 and 74 years, adequate hematological results ($4.0\times10^9 \leq$ total leukocyte count $\leq 12.0\times10^9$/L, neutrophils $\geq 2.0\times10^9$/L, Hemoglobin ≥ 9.5 g/dl, platelets $\geq 100.0\times10^9$/L), adequate hepatic function (total serum bilirubin ≤ 1.5 mg/dl, liver transaminase AST/ALT less than 2.0 times the upper limit of normal values), and adequate renal function (serum creatinine ≤ 1.5 mg/dl).

Patients were excluded when they were pregnant, lactating, or of childbearing age. Patients were not eligible for the study if they had a previous serious medical illness, particularly cardiac disease or prior reactions to drugs containing Cremophor EL. All patients provided informed consent prior to the initiation of the therapy. The study was approved by the ethics committee of our institute and the procedures were in accordance with the Helsinki Declaration (1964, amended in 1975, 1983, 1989, 1996 and 2000) of the World Medical Association. Pretreatment evaluation consisted of a complete history and physical examination, EKG, chest X-ray, complete blood cell count, and serum biochemical analysis that included a liver profile. Computed tomographic (CT) scans or echograms of the abdomen were performed. Complete blood cell counts were repeated every week to record hematological toxicity. Radiographic studies were reassessed as indicated by the clinical situation or following every other treatment cycle.

Treatment regime

S-1 was administered orally at a fixed dose of 80 mg/m^2/day from day 1 to day 14.

S-1 was administered orally at a fixed dose of 80 mg/m^2/day once in the morning and once in the evening twice after meals from day 1 to day 14 and then with 2 weeks rest.

The initial dose of paclitaxel was 100 mg/m^2 and was given biweekly for 60 min on day 1 and 15.

Each cycle was performed every 4 weeks.

Premedication

Dexamethasone 20 mg and ranitidine hydrochloride 50 mg 30 min. d.i.v. or i.v. prior to the 60 min pacritaxel administration, and diphenhydramine hydrochloride 50 mg p.o. prior to the 60 min pacritaxel administration. The dose of paclitaxel in each group of three patients was increased by 10 mg/m^2. Level 1 consisted three patients who received the chemotherapy using the dose of paclitaxel was 100 mg/m^2 in every cycles (2–5 cycles). Level 2 was another three patients who received the chemotherapy using the dose of paclitaxel was 110 mg/m^2 (3–7 cycles). Level 3 was another three patients who received the chemotherapy using the dose of paclitaxel was 120 mg/m^2 (2–6 cycles).

Level 4 was another six patients who received the chemotherapy using the dose of paclitaxel was 130 mg/m^2 (2–9 cycles). Dosage was not increased during successive treatment courses for individual patients. Three patients that could be evaluated were enrolled at each dose level. The dose level was not increased until all three patients completed one cycle without any problems regarding safety and tolerance. If a dose-limiting toxicity (DLT) of any type was detected in one of the three patients within the first cycle of the treatment, three new patients were enrolled. A dose level was defined as the MTD if two or more of the six patients experienced DLT, and the previous level was considered as the dose recommended for the phase II study. For this dose level more detailed data for toxicity and feasibility was obtained. DLT was defined as the dose at which patients displayed the following: (1) an absolute leukocyte count $< 1.0\times10^9$/L (grade 4) for 4 or more days, (2) a body temperature higher than 38°C or the occurrence of an infection with an absolute granulocyte count $< 0.5\times10^9$/L (grade 4), (3) a platelet count $< 20.0\times10^9$/L (4) a grade 3 or greater non-hematological toxicity with the exception of loss of appetite, nausea and vomiting, (5) a treatment delay of 1 week or more because of toxicity. Toxicity was recorded every week according to the National Cancer Institute Common Toxicity Criteria (version 2.0). All patients enrolled in the study could be evaluated for their response according to the Japanese Classification of Gastric Carcinoma.

Results

Fifteen patients were enrolled in the trial between February 2002 and April 2003. Characteristics for patient profiles are listed in Table 1. The median age was 54 years, with a range of 33–70, and the predominant gender was female, at a ratio of six to nine. Eleven out of 15 patients had a distant metastatic disease at the beginning of the treatment. Tumors in the remaining four patients were non-resectable due to locally progressed disease. Three patients had a prior resection and a subsequent relapse. Two patients had prior chemotherapy as adjuvant chemotherapy. However they did not receive S1 and TXL. The ECOG performance status was 0–1 for all patients. The median number of cycles of chemotherapy was 3, ranging between 1 and 5.

Toxicity and maximum tolerated dose

All patients were fully evaluated for toxicity. Table 2 summarizes the incidence of toxic effects occurring at various dosage levels. Dose-limiting hematological toxicity during cycle 1 did not occur in any patient even at 120 mg/m^2 of paclitaxel. However, the dose-limiting hematological toxicity (leukocytopenia (an absolute leukocytes count $< 1.0\times10^9$/L (grade 4) for 4 or more days), fever with an absolute granulocyte count $< 0.5\times10^9$/L (grade 4), and thrombocytopenia [an absolute thombocytes count of 4.1×10 (grade3)] did occur in one patient at 130 mg/m^2 of paclitaxel. This dose level was expanded to an additional three patients. In these three patients, the first patient had a fever (a body temperature higher than 38°C) with an absolute granulocyte count $< 0.5\times10^9$/L (grade 4) and a grade 3 leukocytopenia. Non-hematological toxicity was modest. Three patients (with paclitaxel at 100 mg/m^2, 110 mg/m^2, and 130 mg/m^2, respectively) experienced grade 1 myalgia/arthralgia. Alopecia was observed in 13 patients (87%).

Table 1 Patient's characteristics of 15 patients with advanced gastric carcinoma

Age (years)	
Median	55
Range	33–70
Sex	
M/F	6/9
Performance status (ECOG)	
0	11
I	4
II	0
Prior surgery	
None	12
Curative	2
Palliative	1
Sites of metastasis	
Liver	4
Lung	1
Abdomen/periotoneum	2
Lymph node	12
Bone	1
Krukenberg	3
Local relapse	1
Pleural effusion	1

Fifteen patients with advanced gastric carcinoma enrolled. The median age was 54 years. Eleven out of 15 patients had distance metastasis. Three patients had prior resection with relapse. Two patients had prior chemotherapy

Response

All patients were evaluated for response to the therapy according to the Japanese Classification of Gastric Carcinoma, having received at least two cycles of chemotherapy. Eight patients achieved a partial response. The overall response rate was 53%. Five patients received a gastrectomy after they achieved a partial response (two patients: 100 mg/m^2, two patients 110 mg/m^2, one patient 120 mg/m^2). Median survival time was 428 days and the 1 year survival rate was 53%.

Discussion

Several drugs have currently been shown to exert reproducible, modest to moderate anti-tumor activity in patients with advanced gastric cancer when used as a single agent. Clinical trials for a combination therapy of these cytotoxic agents have been reported with a response rate of 30–40%. Unfortunately, complete responses are not common; the duration of the response was usually short and the toxicity significant [10]. New cytotoxic agents, such as irrinotecan, a topoisomerase inhibitor, or paclitaxel and docetaxel, representative taxoids, appear to be promising and innovative anticancer agents for the treatment of gastric carcinoma [4]. Recently, Ajani et al. [4] and Garcia et al. [11] used paclitaxel in patients with gastric cancer and reported that 17 and 11% of patients achieved a response rate, respectively. Initial phase I trials with paclitaxel have used a wide range of schedules and it was found that short infusion times were safe when premedication was administered. Hence, it became important to evaluate further the optimal dosage and schedule of administration.

Since 5-FU and paclitaxel have an additive effect regarding cytotoxicity in different tumor cell lines [5, 12] and there is no overlap in toxicity, a phase I study was initiated to evaluate the feasibility of such a combination regime.

S-1 was developed to prolong the blood concentration of 5-FU following oral administration and was expected to produce a more potent antitumor effect and reduce gastrointestinal toxicity [13, 14]. S-1 is tegafur (FT), a precursor of 5-FU. Gimeracil (5-chloro-2,4-dihydroxypyridine, CDHP) reversibly inhibits the enzyme dihydropyrimidine dehydrogenase (DPD), which degrades 5-FU to an inactive metabolite, thus prolonging the active 5-FU concentration in blood and tumor. Oteracil (potassium salt) [monopotassium 1,2,3,4-

Table 2 Toxic effects encountered in relation to paclitaxel dose levels and number of patients with toxicity

Toxic effect	Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2
		Leuocopenia				Neutrophilia				Thrombocyto penia				Arthralgia/ myalgia				Peripheral neuropathy				Alope-tia	
100 mg/m^2	$n=3$	1	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	2
110 mg/m^2	$n=3$	2	1	0	0	2	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	1	2
120 mg/m^2	$n=3$	0	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0
130 mg/m^2	$n=6$	2	1	2	1	1	1	1	2	1	0	1	0	1	0	0	0	0	0	0	0	3	2

Dose-limiting hematological toxicity during cycle 1 did not occur in any patient even at 120 mg/m^2 of paclitaxel. Leukocytopenia (an absolute leukocytes count $< 1.0\times10^9$/L (grade 4) for 4 or more days) occurred in one patient, fever (temperature more than 38°C) with an absolute granulocyte count $< 0.5\times10^9$/L (grade 4) occurred in two patients, and thrombocytopenia [an absolute thombocytes count of 4.1×10 (grade3)] occurred in one patient at 130 mg/m^2 of paclitaxel. Non-hematological toxicity was modest

tetrahydro-2,4-dioxo-1,3,5-triazine-6-carboxylate(Oxo)], inhibits orotate phosphoribosyl transferase (OPRT), the enzyme that phosphorylates 5-FU, and this Oxo is highly distributed in the gastrointestinal tract after oral administration. Thus, concomitant use of Oeteracil (Oxo) alleviates the 5-FU-induced gastrointestinal toxicity. When these three drugs are combined at a ratio of FT:CDHP:Oxo = 1:0.4:1, CDHP prolongs the 5-FU concentration in blood and tumors, while Oxo reduces the 5-FU-induced gastrointestinal toxicity. The response rate of S1 was reported as 44 to 54% on phase II study in Japan [15, 16, 17]. S1 was permit to administration for patients with gastric cancer from 1999.

Since the initial studies with paclitaxel it has been required to define the optimal schedule for delivering the drug for chemotherapy. Biweekly schedules for paclitaxel infusion are also dose intense. Although it appeared that the tolerance for a biweekly paclitaxel administration was similar to that of a weekly schedule, biweekly paclitaxel was expected to be more convenient for the patients [9].

Our results showed that biweekly administration of paclitaxel could be safely combined with a 2-weekly administration of S-1 in patients with advanced gastric cancer. Besides alopecia, toxicity was mild. The worst side effect was a grade 4 leukopenia in one patient (130 mg/m^2), and a grade 4 neutrophilia in two patients (130 mg/m^2) (Table 2). The low incidence of myelosupression might be in part due to a shorter duration of paclitaxel infusion (1-h instead of a 24-h infusion), which generally requires hospitalization of patients. Thus, an hour infusion of paclitaxel can be more convenient and allows treatment in an outpatient environment. In a randomized trial on ovarian cancer, a 24-h infusion of paclitaxel caused a significantly higher incidence of myelosuppression than a 3-h infusion, but failed to produce a higher response rate [18]. Shepard et al. have recently reported similar data in patients with non-small cell lung cancer [19].

Neuropathy is an issue with paclitaxel administration. Since previous studies have shown that the prolonged administration of higher doses of paclitaxel is poorly tolerated by patients because of myalgia and neurotoxicity [20, 21].

Arthralgia and myalgia were present for 2 or 3 days after paclitaxel administration in three patients receiving a dose of 100 mg/m^2, 110 mg/m^2, and 130 mg/m^2 (Table 2).

DLT occurred in two patients at a dose of 130 mg/m^2 paclitaxel, so we determined that the recommended dose for the phase II study was 120 mg/m^2 of paclitaxel. This study was designed as a phase I trial to determine the optimal dosage for paclitaxel and S-1. However, it was also possible to assess the efficacy of this combination of drugs for its antitumor activity. Eight patients achieved an objective response: a partial response at paclitaxel doses between 100 mg/m^2 and 130 mg/m^2. Mean survival time was 428 days and the 1 year survival rate was 53%. The relatively low toxicity with a definitive activity of taxanes could be promising for the treatment of gastric cancer patients who often cannot receive aggressive chemotherapy because of age and poor performance status.

Many trial for gastric cancer are on going in Japan combined with S-1 and another anticancer drugs, such as CDDP, CPT11 and TXL/TXT. But there are few reports concerning the duration of response and/or time to progression.

Koizumi W et al. [22] reported phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer in 2003. The RR was 74%, and the median survival day was 383. Iwase H et al. [23] reported A phase II multicentric trial of S-1 combined with 24 h-infusion of cisplatin in patients with advanced gastric cancer in 2005. The median survival time was 342 days. The 2-year survival rate was 22.9%.

In conclusion, biweekly paclitaxel and S-1 administration can be safely combined for the treatment of advanced gastric cancer. This combined therapy can represent a novel and active treatment regime with low toxicity and can be defined as safe and effective.

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