Salvage chemotherapy with irinotecan and cisplatin in patients with metastatic gastric cancer failing both 5-fluorouracil and taxanes

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We conducted a phase II study to assess the efficacy and tolerability of irinotecan and cisplatin as salvage chemotherapy in patients with advanced gastric adenocarcinoma, progressing after both 5-fluorouracil (5-FU)- and taxane-containing regimen. Patients with measurable metastatic gastric cancer, progressive after previous chemotherapy that consisted either of a 5-FU-based regimen followed by second-line chemotherapy containing taxanes or a 5-FU and taxane combination were treated with irinotecan and cisplatin. Irinotecan 70 mg/m^2 was administered on day 1 and day 15; cisplatin 70 mg/m^2 was administered on day 1. Treatment was repeated every 4 weeks. For 28 patients registered, a total of 94 chemotherapy cycles were administered. The patients' median age was 51 years and 27 (96%) had an ECOG performance status of 1 or below. In an intent-to-treat analysis, seven patients (25%) achieved a partial response, which maintained for 6.3 months (95% confidence interval 6.2–6.4 months). The median progression-free and overall survival were 3.5 and 5.6 months, respectively. Major toxic effects included nausea, diarrhea and neurotoxicity. Although there was one possible treatment-related death, toxicity profiles were generally predictable and manageable.

We conclude that irinotecan and cisplatin is an active combination for patients with metastatic gastric cancer in whom previous chemotherapy with 5-FU and taxanes has failed. *Anti-Cancer Drugs* 16:621–625 © 2005 Lippincott Williams & Wilkins.

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Introduction

Gastric cancer remains the most common cause of cancer-related death in South Korea [1]. For patients with unresectable, recurrent or metastatic disease, chemotherapy can provide significant palliation of symptoms [2,3]. A variety of chemotherapeutic agents such as 5-fluorouracil (5-FU), anthracyclines, cisplatin and mitomycin C as well as newer agents including taxanes (paclitaxel or docetaxel), oxaliplatin and irinotecan (CPT-11; Campto) have been proposed to have a place in the treatment of gastric cancer. Most trials using varied combinations of these drugs have provided durations of survival ranging from 6 to 10 months in patients with recurrent or metastatic gastric cancer [4]. Apart from 5-FU, taxanes are currently the most extensively studied chemotherapeutic agents for metastatic gastric cancer. Both docetaxel and paclitaxel demonstrated significant activity against metastatic gastric cancer, and are usually administered in combination with cisplatin [5–7] and/or 5-FU [8–11]. However, none of these regimens has been recognized as a standard or superior to 5-FU alone in the treatment of metastatic gastric cancer [12–14].

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Moreover, the treatment of metastatic gastric cancer patients after failure with 5-FU and taxanes remains controversial. Among other agents, irinotecan is a semisynthetic, water-soluble derivative of the plant alkaloid camptothecin. Following conversion to its active metabolite, SN-38, irinotecan acts by inhibiting DNA topoisomerase I, thereby interfering with DNA replication and cell division [15]. Results of irinotecan-containing regimen in the treatment of metastatic gastric cancer are encouraging. Irinotecan demonstrated activity in both first- and second-line treatment of metastatic gastric cancer as a single agent [16], and has been reported to yield a response rate of 31–48% when combined with cisplatin [17–20]. Based on these data we initiated a phase II study of irinotecan and cisplatin as a salvage regimen in patients with metastatic gastric cancer, previously treated with both 5-FU and taxane-containing chemotherapy.

Methods

Patients

Eligibility criteria included measurable metastatic gastric cancer, progressive after previous chemotherapy for

metastatic disease, that consisted either of a 5-FU-based regimen followed by second-line chemotherapy containing paclitaxel or docetaxel, or a 5-FU and taxane combination; age < 75 years; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; normal bone marrow functions with neutrophil count $> 1.5 \times 10^9$/l and a platelet count $> 150 \times 10^9$/l; normal hepatic and renal functions; and the provision of a signed written informed consent. Patients with active central nervous system metastases, extensive radiotherapy within the previous 4 weeks, uncontrolled systemic illness and/or active infections were excluded.

Treatment

Irinotecan was administered as a 90-min i.v. infusion at a dose of 70 mg/m^2 on day 1 and 15. Cisplatin 70 mg/m^2 was infused over 2 h on day 1 after irinotecan administration [21]. Each cycle of chemotherapy was given every 4 weeks if the patient's blood count had returned to normal and non-hematologic toxic effects had resolved. Treatment was repeated up to 6 cycles, or until disease progression and/or unacceptable toxicity was detected. Dosage of the subsequent cycles was adjusted according to the toxic effects that developed during the preceding cycle. All patients received standard supportive regimen including adequate hydration and anti-emetics. No prophylactic administration of hematopoietic growth factors or diarrhea remedies was allowed. Follow-up history, physical examinations and toxicity assessments were performed before each 4-week cycle of therapy.

Tumor response was evaluated according to WHO criteria [22], and was assessed by abdominopelvic computed tomography (CT) scan and by the same tests used initially to stage the tumor. All tumor measurements were recorded by gastrointestinal radiologists in millimeters with two dimensions in all measurable lesions. Responses were assessed every two courses of chemotherapy and reviewed by an independent investigator later at the time of analyses. Toxicity grading was based on the National Cancer Institute Common Toxicity Criteria [23]. This study protocol was reviewed and approved by the Gil Medical Center Institutional Review Board.

Statistical consideration

Twenty-five patients were required in a single-stage phase II clinical study assuming that the expected overall response rate would be 30% and the minimum acceptable response rate 10% (α 0.05, β 0.2). The starting point of various time intervals was the first day of chemotherapy. Response duration was the time from the first date of chemotherapy to progression in responding patients. The date of disease progression or death from causes other than metastatic gastric cancer was used in calculating progression-free survival (PFS). Time to death, whatever the cause, was used to calculate overall survival (OS). The Kaplan–Meier product-limit method was used to estimate survival rates and $p < 0.05$ was considered significant. All analyses were performed using SPSS for Windows 11.5.

Results

Patient characteristics

Between February 2003 and September 2004, 28 eligible patients entered the study (Table 1). Three patients were not evaluable for responses due to early discontinuation of treatment. However, in an intent-to-treat analysis these patients were included in the denominator for treatment outcomes. All patients but one had an ECOG performance status of 1 or below. Most common sites of metastatic disease were intra-abdominal lymph nodes (89%), peritoneum (57%) and liver (11%). Seventy percent of the patients had received two or more lines of chemotherapy for metastatic disease. All patients were previously treated with taxane and 5-FU-based chemotherapy [24], and 68% were treated with cisplatin in their previous chemotherapy regimen.

Toxicity

In total, 94 treatment cycles were given (median 3; range 1–6) and 32 (34%) of the planned cycles were delayed because of toxic effects. Dose reduction was required in 10 (11%) cycles. As we planned the dose intensities of irinotecan 35 mg/m^2/week and cisplatin 17.5 mg/m^2/week,

Table 1 Patient characteristics

	N	%
Patients		
treated	28	
evaluable for response rates	25	89
Age (years) [median (range)]	51 (42 – 70)	
Male gender	20	71
ECOG performance status		
0	5	18
1	22	79
2	1	4
Site(s) of metastatic disease[a]		
abdominal lymph node	25	89
peritoneum	16	57
liver	3	11
lung and/or malignant pleural effusion	4	14
ovary	1	4
bone	3	11
supraclavicular lymph node	3	11
Interval from the last dose of prior chemotherapy (months) [median (range)]	1.4 (0.8 – 7.9)	
No. of prior chemotherapy regimens		
1	9	32
2	18	64
3	1	4
Characteristics of prior chemotherapy		
paclitaxel + 5-FU	16	57
docetaxel + 5-FU	12	43
epirubicin + cisplatin + 5-FU	12	43
5-FU, infusional	3	11
5-FU + cisplatin	5	18

[a]Because patients could have metastases at multiple sites, the total numbers of metastases are greater than the number of patients.

the relative dose intensity of both drugs was 82% [95% confidence interval (CI) 68–96%].

All eligible patients were evaluable for toxic effects (Table 2). The most frequently encountered toxic effects were gastrointestinal toxicities and neurotoxicity, which were managed with rest, dose reduction or treatment discontinuation. Although difficult to differentiate from the symptoms of the underlying disease, grade 3 or 4 nausea and vomiting were observed in 13 patients. Even if all patients were heavily pretreated with cytotoxic chemotherapy, only one episode of febrile neutropenia occurred. Hematologic toxicities were infrequent and no patient received hematopoietic growth factors. One patient received platelet transfusion during the treatment. Five patients discontinued treatment because of toxic effects. One patient died after the first cycle due to septic shock which occurred as a complication of pneumonia at the time of recovery from myelosuppression. In one patient, a period of dialysis was required for oliguric renal failure. Three patients who were previously treated with cisplatin refused to continue treatment because of severe peripheral neurotoxicity.

Table 2 Worst toxic effects in 28 patients

	Grade 1/2 [*n* (%)]	Grade 3/4 [*n*(%)]
Neutropenia	2 (7)	3 (11)
Thrombocytopenia	2 (7)	3 (11)
Nausea/vomiting	9 (32)	13 (46)
Stomatitis	1 (4)	2 (7)
Diarrhea	8 (29)	7 (25)
Abdominal pain	1 (4)	
Fatigue	6 (21)	3 (11)
Peripheral neurotoxicity	11 (39)	12 (43)
Skin	1 (4)	
Nephrotoxicity		1 (4)

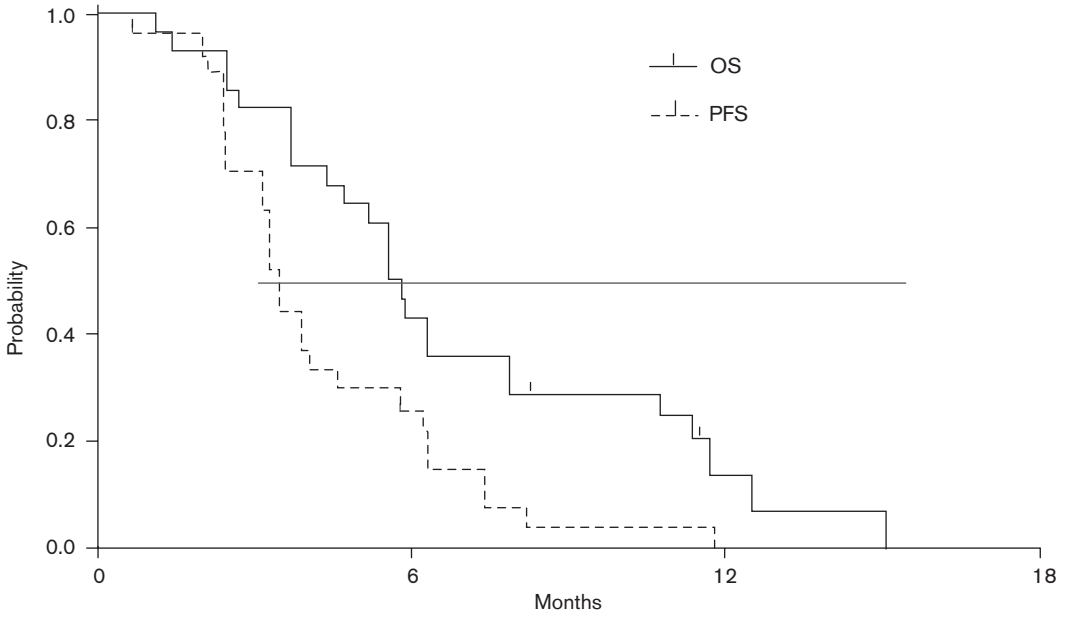
Outcomes

We obtained seven partial responses (25%; 95% CI 9–41%) which maintained for 6.3 months (95% CI 6.2–6.4 months), four stable diseases and 14 progressions. At a median follow-up of 12.6 months, the median PFS was 3.5 months (95% CI 3.2–3.8 months) and the median OS was 5.6 months (95% CI 4.8–6.3 months), as shown in Figure 1. The PFS was significantly higher in patients with objective response (3.1 versus 6.3 months; $p < 0.01$); however, we observed no significant difference in OS between responders and non-responders ($p = 0.11$). At the time of present analyses, 25 patients (89%) had died.

Discussion

Patients with recurrent or metastatic gastric cancer can benefit from palliative chemotherapy. Some controlled trials of chemotherapy have revealed a significant improvement in survival and quality of life compared with best supportive care alone [2,3]. However, there is no generally accepted standard regimen and no substantial progress has been achieved in the chemotherapy of metastatic gastric cancer during the past decade. Over half of patients with metastatic gastric cancer who received chemotherapy failed to achieve any response

Fig. 1



PFS and OS.

and even in these responders the duration of responses was as short as a few months. Patients with metastatic gastric cancer who fail to respond or have relapse after first-line chemotherapy have a grim prognosis and standard salvage treatment is not available.

In studies using a variety of chemotherapeutic agents and their combinations, second-line chemotherapy usually demonstrated activity in this patient population [25–27]. However, because many patients with advanced gastric cancer are treated with a first-line combination chemotherapy that includes 5-FU and/or taxanes, it seems more prudent to avoid 5-FU and taxanes in salvage regimen for reasons of efficacy and toxicity. Shimada *et al.* evaluated the efficacy and safety of irinotecan and low-dose cisplatin as a second-line therapy for advanced gastric cancer unresponsive to 5-FU-based chemotherapy [28]. They achieved a response rate of 52% which maintained for a median of 7.9 months. In another study, Kinoshita *et al.* used FEPMTX combination chemotherapy with 5-FU, methotrexate, leucovorin, cisplatin and epirubicin, resulting in a 52% objective response [29]. However, we did not attempt to include anthracyclines for this study, as we believe that the safety and tolerability of treatment are indispensable in the salvage setting in the treatment of solid tumors.

It is unlikely that third- or even fourth-line chemotherapy in patients with metastatic disease will result in substantial prolongation of survival and there is potential for toxicity from the treatment. Since patients with progressive disease usually have a poor performance status, aggressive chemotherapy may not be feasible. However, it is known that response rates for chemotherapy decline with each subsequent regimen, and patients and physicians have difficulty with accepting only supportive care without the possibility of systemic anticancer effects. Therefore, there is a need for effective drugs as salvage treatment after 5-FU and taxanes failure, especially for selected patient populations with preserved performance status. This phase II study was on a relatively small group of patients, but it is distinctive in the target patient population. We investigated the activity and tolerability of irinotecan and cisplatin combination in patients with metastatic gastric cancer, failing both 5-FU and taxanes. Using this 4-week dose schedule of irinotecan and cisplatin, we obtained an impressive response rate of 25% and a median PFS of 3.5 months. Although there was one possible treatment-related death, toxicity profiles in our study were generally predictable and manageable. Relative dose intensity of both drugs was 82%. This satisfactory dose intensity, together with relatively good performance status of patients, may in part account for the favorable outcomes in this heavily pretreated patient population. Ajani *et al.* reported that the administration of irinotecan 50 mg/m^2 and cisplatin 30 mg/m^2 weekly for 4 consecutive weeks showed a response rate of 31% and a median PFS of 7 weeks in pretreated patients with advanced gastric cancer [19]. However, because of the high incidence of severe toxicities, they suggested that dose and schedule modifications were warranted to improve the tolerability of the regimen. In another phase II study with weekly irinotecan, the objective response rate was 20%, yet 68% of patients experienced grade 3/4 neutropenia and 19% experienced grade 3 diarrhea [30]. In the current study, only 11 and 25% of patients experienced grade 3/4 neutropenia and diarrhea, respectively.

From our study we conclude that the use of irinotecan in combination with cisplatin for metastatic gastric cancer failing after prior 5-FU and taxane treatment is effective and feasible. Therefore, we hope that this study could result in a prospective study to determine whether this activity translates into actual improvement in survival and quality of life in patients with pretreated metastatic gastric cancer. Given our data and pending the results of larger randomized studies, a reasonable practice at this point would be to offer a chance of salvage chemotherapy to metastatic gastric cancer patients with good performance status and who failed both 5-FU and taxanes.

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