SPANDIDOS PUBLICATIONS

Paclitaxel and leucovorin-modulated infusional 5-fluorouracil combination chemotherapy for metastatic gastric cancer

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Abstract. As no standard chemotherapy regimen has been established for advanced gastric cancer, this study sought to evaluate the efficacy and safety of combination chemotherapy that included paclitaxel and leucovorin (LV)-modulated infusional 5-fluorouracil (5-FU) in metastatic gastric cancer. Patients received a three-hour infusion of 175 mg/m^2 of paclitaxel on day 1. A bolus of 20 mg/m^2 of LV was then administered, followed by a 24-h infusion of 1,000 mg/m^2 of 5-FU on days 1 through 3. The treatment cycle was repeated every 3 weeks until disease progression. Response evaluation was performed according to the RECIST criteria, with toxicity determined by NCI-CTC (version 2.0). A total of 66 patients, including 21 (31.8%) with a history of prior chemotherapy, were enrolled. Fifteen (71.4%) of the 21 patients with prior chemotherapy received prolonged infusional 5-FU. In the 56 evaluable patients (37 in the chemotherapy-naïve group and 19 in the prior chemotherapy group), tumor responses according to prior exposure to chemotherapy were as follows: 17 (45.9%) partial response (PR), 6 (16.2%) stable disease (SD) and 14 (37.8%) progressive disease (PD) in the chemotherapy-naïve group; 1 (7.1%) complete response, 3 (15.8%) PRs, 8 (42.1%) SDs and 7 (36.8%) PDs in the prior chemotherapy group. The overall median response duration was 20 weeks (range, 8-61 weeks), with a median progression-free survival of 20 weeks [95% confidence interval (CI), 13.4-26.6 weeks] and 12 weeks (95% CI, 5.7-18.3 weeks) in the chemotherapy-naïve and prior chemotherapy groups, respectively. The median overall survival was 48 weeks (95% CI, 38-58 weeks) in the chemotherapy-naïve group and 28 weeks (95% CI, 22-34 weeks) in the prior chemotherapy group. The most frequent grade III/IV toxicity was neutropenia. Non-hematological toxicity of grade III/IV was rare. Paclitaxel in combination with 5-FU/LV is clinically beneficial for patients with advanced gastric cancer and is a feasible salvage regimen for 5-FU-refractory gastric cancer patients.

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Introduction

Despite its declining incidence in the Western world, gastric cancer is still among the most common malignancies. The control of metastatic gastric cancer has not progressed with medical advances; it remains an incurable disease with a median survival time of only 4-8 months (1). Randomized studies have demonstrated both a survival benefit and a positive impact on quality of life for patients with metastatic gastric cancer when treated with chemotherapy plus supportive care rather than the best supportive care alone (2,3). While it may not cure the disease, chemotherapy has become widely accepted for advanced gastric cancer.

Second-generation regimens for treating advanced gastric cancer are primarily based on 5-fluorouracil (5-FU), high-dose methotrexate, cisplatin, and anthracycline (1,4-6). In phase II trials, response rates of up to 60% have been reported for regimens such as FAMTX (5-FU, doxorubicin, methotrexate), EAP (etoposide, doxorubicin and cisplatin), ELF (etoposide, leukovorin, 5-FU), FUP (infusional 5-FU, cisplatin), and ECF (epirubicin, cisplatin, infusional 5-FU). In subsequent phase III trials, however, this high level of activity has only been confirmed for the ECF regimen, whereas for the FAMTX, ELF or FUP regimen, response rates were between 20 and 25% (6-8). In addition, the FAMTX and EAP regimens were associated with severe toxicity. While ECF appears, to date, to be the most active regimen, a definitive standard regimen for the palliative treatment of metastatic gastric cancer has not yet been defined. The need is clear for a new combination regimen so that response rate and survival can be improved in patients with metastatic gastric cancer.

Paclitaxel is one of the most promising cytotoxic agents, acting as a mitotic spindle poison and thereby inducing a mitotic block (9). Moreover, the drug exhibits anti-tumor activity against various tumors, including gastric cancer cell lines (10). As a single agent, it was reported to have overall response rates of between 17 and 29% (11-13). Results of paclitaxel-containing combinations in the management of gastric cancer are also encouraging (14-19). A three-drug

combination, including paclitaxel, 5-FU, cisplatin and etoposide, yielded response rates as high as 50% with a median survival of 7-14 months (14-17). The two-drug combination of paclitaxel and 5-FU, which would expose the patient to fewer harsh side effects, has not been extensively explored as a treatment for gastric cancer, although there have been a few preliminary studies. Murad *et al* (18) documented a response rate of 65.5% in 29 patients treated with 5-FU 1,500 mg/m^2 and paclitaxel 175 mg/m^2 in a 3-h infusion every 3 weeks. Bokemeyer *et al* (19) treated 22 chemonaïve gastric cancer patients with 5-FU as a weekly 24-h continuous infusion plus folinic acid and paclitaxel at 3-week intervals, resulting in a response rate of 32% and overall survival of 11 months.

The present study sought to evaluate the anti-tumor activity of paclitaxel and LV-modulated infusional 5-FU combination chemotherapy in patients with metastatic gastric cancer. Leucovorin was incorporated into the regimen because most patients with a history of prior chemotherapy had received 5-FU at our institution, and because the addition of LV to 5-FU has been shown to exhibit anti-tumor activity in patients who previously progressed on 5-FU-containing combinations (20).

Materials and methods

Patient eligibility. Eligibility criteria for this study were as follows: i) histologically-proven adenocarcinoma with metastatic disease; ii) Eastern Cooperative Oncology Group (ECOG) performance scale score 0-2; iii) chemotherapeutically-naïve or one prior chemotherapy regimen completed at least 3 weeks before entry into study; iv) adjuvant chemotherapy completed at least 6 months before study entry for patients with recurrent disease; v) age ≤75 years; vi) adequate organ function (neutrophil count ≥4,000/μl, platelet count ≥100,000/μl, serum total bilirubin ≤2 mg/dl, transaminase ≤2.5x normal upper limit, serum creatinine level ≤1.5 mg/dl); vii) no concurrent uncontrolled medical illnesses or active malignancies. Patients who had undergone palliative resection, and therefore had no measurable lesion on CT scan, were also included in this study. Patients were excluded from the study if they had peripheral neuropathy of grade ≥2 according to the National Cancer Institute's common toxicity criteria (NCI-CTC).

Throughout this report, the term 'palliative resection' refers to the surgical resection of a primary tumor (D2 type resection) with residual tumors remaining grossly in neighboring organs, lymph nodes or peritoneum, or remaining microscopically in the resection margin.

Chemotherapy regimen. Chemotherapy was given according to the following schedule: dexamethasone 20 mg, diphenhydramine 25 mg and cimetidine 300 mg administered intravenously (i.v.) 30 min before paclitaxel for hypersensitivity prophylaxis. A three-hour infusion of 175 mg/m^2 of paclitaxel was administered on day 1. A bolus of 20 mg/m^2 of LV, followed by a 24-h infusion of 1,000 mg/m^2 of 5-FU, was administered once a day for three consecutive days (days 1-3). This chemotherapy course was repeated every three weeks, except in cases of disease progression or patient refusal, for a maximum of 9 cycles. Patients were required to have an absolute neutrophil count (ANC) ≥1,500/μl without evidence of active infection, platelet count ≥100,000/μl, and resolution of any non-hematological toxicity to less than grade 2 before receiving subsequent cycles of chemotherapy. Planned dose modifications included 20% dose reduction of paclitaxel in cases of grade 3 peripheral neurotoxicity; complete stoppage of paclitaxel in cases of grade 4 skin toxicity or grade 3 anaphylactic reaction; and 20% dose reduction of paclitaxel and 5-FU in cases of febrile neutropenia, grade IV hematological toxicity, or grade III/IV non-hematological toxicity. Anti-emetic therapy was routinely given prior to chemotherapy. Granulocyte colony stimulating factor (G-CSF) was not planned as a prophylactic aim.

Patient evaluation. For each patient, baseline evaluations included a complete history, physical examination, complete blood count (CBC), serum chemistry and electrolytes, tumor markers (CEA and CA 19-9) and electrocardiogram. Computed tomography (CT) scans of the measurable lesions were performed no more than four weeks prior to treatment. During the course of chemotherapy, CBC was evaluated once a week, with the frequency increasing during the myelosuppressed resting period. Physical examination and performance status, tumor markers and serum chemistry were repeated before each chemotherapy cycle. Tumor evaluation was conducted every two cycles by X-ray, bone scintigraphy and/or CT scan. Toxicity was graded every cycle and calculated as worst toxicity per patient according to NCI-CTC (version 2.0).

The primary efficacy end-point of this study was objective response rate, evaluated according to WHO criteria. Complete response (CR) was defined as the complete disappearance of all measurable disease for a duration of at least four weeks, with partial response (PR) as a >50% reduction of all measurable tumor sites. Stable disease (SD) was defined as a <50% reduction of tumor lesions and ≤25% progression in tumor diameter. Secondary efficacy end-points included the duration of response, progression-free survival (PFS) and overall survival (OS).

Statistical analysis. PFS defined the period from the start of chemotherapy to the progression of cancer, while OS was from the start of chemotherapy to the date of death or last follow-up. Deaths from all causes were considered in the analysis of overall survival. Response duration was measured from the day of response documentation to the day of disease progression (or death if the patient died without disease progression).

Survival curves were estimated using the Kaplan-Meier method and the differences in survival between the groups were assessed by a log-rank test. Univariate and multivariate analyses were performed using the Cox regression analysis model to identify prognostic factors and the risks associated with them.

Results

Patient characteristics. Patient characteristics are shown in Table I. A total of 66 patients with a median age of 50 years (range, 24-70 years) were treated in this study. Fifty-five (83.3%) patients had an ECOG performance status of 1. Histologically, 17 patients (25.7%) had well- to moderately

atients' characteristics (n=66).

Characteristic	No. of patients (%)	
Sex		
Male	42	(63.6)
Female	24	(36.4)
Age (year)		
Median (range)	50	(24-70)
ECOG		
1	55	(83.3)
2	11	(16.7)
Histology		
Well/moderately differentiated	17	(25.7)
Poorly differentiated	36	(54.5)
Signet ring cell	13	(19.8)
Stage at diagnosis		
II	4	(6.1)
III	8	(12.1)
IV	54	(81.8)
Previous operation		
Unresectable	37	(56.1)
Radical	19	(28.8)
Palliative	10	(15.1)
No. of disease sites per patient		
0	9	(13.6)[a]
1	34	(51.5)
2	13	(19.7)
3	8	(12.1)
≥4	2	(3.1)
Disease sites[b]		
Lymph nodes	35	
Peritoneum	31	
Liver	14	
Lung	4	
Bone	3	
Ovary	2	
Adrenal	1	
Previous chemotherapy		
None	45	(68.2)
FAM	7	(10.6)
FP	8	(12.1)
IP	6	(9.1)
Median cycle of previous chemotherapy (range)	6	(2-12)
Median RDI of previous chemotherapy (range)	0.86	(0.75-0.95)

[a]Patients who had undergone palliative resection had no evaluable lesions. [b]Some patients had more than one site of metastases. ECOG, Eastern Cooperative Oncology Group; FAM, 5-FU + doxorubicin + mitomycin-C; FP, 5-FU + cisplatin; IP, irinotecan + cisplatin

differentiated adenocarcinoma, 36 (54.5%) had poorly differentiated adenocarcinoma and 13 (19.8%) had signet ring cell carcinoma. Nineteen patients (28.8%) experienced recurrence after radical gastrectomy. Ten patients had undergone palliative resection immediately prior to the treatment associated with this study. Of these 10 patients, 9 without any measurable lesion on CT scan were excluded from the response assessment but included in the toxicity assessment and survival analysis.

Twenty-three patients (34.9%) had multiple metastatic lesions, with the main metastatic sites being the lymph nodes (n=35), peritoneum (n=31) and liver (n=14). The most common non-measurable lesion was bone metastasis (n=3) documented on bone scan. Twenty-one patients (31.8%) received chemotherapy that was completed three or more weeks prior to entry into this study. Fifteen (71.4%) of the 21 prior chemotherapy patients received prolonged infusional 5-FU, whereas 6 (28.6%) received platinum-based therapy. The median number of cycles of previous chemotherapy was 6 (range, 2-12 cycles), with a median relative dose intensity (RDI) of 0.86.

Treatment and dose intensity. A total of 338 cycles of chemotherapy were administered, with a median of 6 cycles per patient (range, 2-9 cycles). For chemotherapy naïve patients, the median number of chemotherapy cycles was 6 (range, 2-9 cycles) while, for patients with a history of prior chemotherapy, the median was 4 cycles (range, 2-9 cycles). The median duration of chemotherapy for all patients was 15 weeks (range, 6-27 weeks). Twenty-eight patients (42.4%) received ≤4 cycles of chemotherapy, with only two of these patients (7.1%) expressing the desire to terminate the treatment before the end of the specified cycle. The remaining 38 patients (57.6%) received ≥5 cycles, approximately half of whom received >7 cycles.

Median actual dose intensities of 5-FU and paclitaxel were 928.1 mg/m^2/week (range, 584.2-1,000 mg/m^2/week) and 54.9 mg/m^2/week (range, 26.3-58.0 mg/m^2/week), respectively. The median relative dose intensities (RDI) of 5-FU and paclitaxel were 0.93 (range, 0.58-1.0) and 0.94 (0.58-1.0), respectively.

There were 30 cases (45.5%) of chemotherapy delay or dose reduction. The causes of dose reduction or schedule delay were as follows: 13 (43.4%) neutropenia, 9 (30%) requests from patients, 4 (13.3%) febrile neutropenia, 3 (10%) non-hematological toxicity and 1 (3.3%) sepsis due to urinary tract infection.

Efficacy. A total of 56 patients were assessable for response (37 in the chemotherapy-naïve group and 19 in the prior chemotherapy group). The remaining 10 patients were not assessable for response either because they had no measurable lesion (9 patients, 7 in the chemotherapy-naïve group and 2 in the prior chemotherapy group) or they refused (1 patient in the chemotherapy-naïve group). The objective response rates (ORRs) according to prior chemotherapy are listed in Table II.

Among 37 chemotherapy-naïve patients, 17 showed a PR. The ORR was 45.9%. Six patients had SD, so the resulting disease control rate (DCR) reached 62.2%. The median time to response in this group was 8 weeks, while the median response duration was 20 weeks (range, 8-61 weeks).

Table II. Response evaluation (n=56)[a].

Treatment group	Response (n)			ORR (%)	DCR (%)
	CR	PR	SD		
Chemotherapy-naïve (n=37)	0	17	6	45.9	62.2
Prior chemotherapy (n=19)	1	3	8	21.1	63.2

[a]Presented by WHO criteria. CR, complete response; PR, partial response; SD, stable disease; ORR, objective response rate; DCR, disease control rate (CR + PR + SD).

Table III. Response evaluation by metastasis sites.

Metastatic sites	No.of evaluable lesions	CR	PR	SD	PD	RR[a]
Lymph nodes	35	0	15	7	13	42.9
Peritoneum	31	1	9	11	10	32.3
Liver	14	0	4	3	7	28.6
Lung	4	0	1	1	2	25.0
Bone	3	0	1	0	2	33.3
Ovary	2	0	2	0	0	100
Adrenal	1	0	0	0	1	0

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RR, response rate. [a]Presented by WHO criteria.

Among 19 patients with a history of chemotherapy, there was 1 CR and 3 PRs, resulting in an ORR of 21.1%. Eight patients had SD; the resulting DCR was 63.2%. As for the other group, the median time to response was 8 weeks, although the median response duration was significantly less at 8 weeks (range, 8-12 weeks). One patient with a CR presented with a tumor at the primary site and peritoneal nodules. Following palliative gastrectomy and four cycles of chemotherapy, CR was proven by CT scan. The duration of CR in the patient is currently 24+ weeks. When the response rate was analyzed according to metastatic sites, similar results were found (Table III).

Survival. With a median follow-up du ation of 32 weeks (range, 12-76 weeks), 58 patients had progressed, while 8 patients had not. The most common site of progression was carcinomatosis. Of the 58 patients who had progressed, 43 patients (74.1%, 29 in the chemotherapy-naïve group and 14 in the prior chemotherapy group) were switched to a salvage regimen.

The median PFS was 20 weeks (95% CI, 13.4-26.6 weeks) for the chemotherapy-naïve group and 12 weeks (95% CI, 5.7-18.3 weeks) for the prior chemotherapy group (Fig. 1). The median OS for the same groups was 48 weeks (95% CI, 38-58 weeks) and 28 weeks (95% CI, 22-34 weeks),

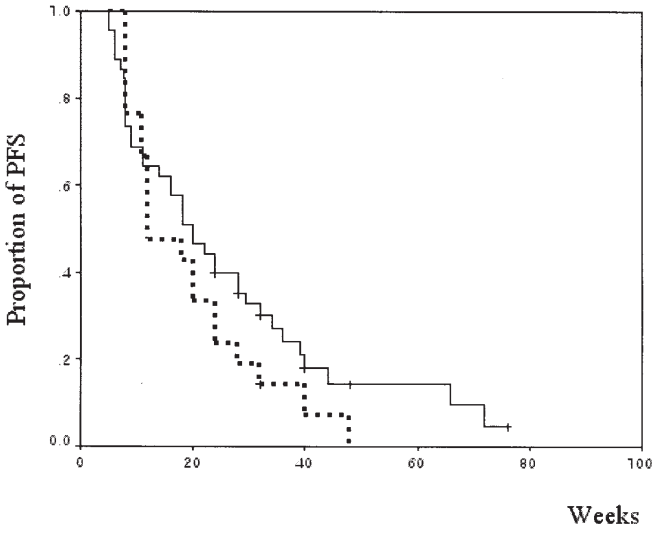

Figure 1. Progression-free survival according to history of prior chemotherapy. The median PFS was 20 weeks for the chemotherapy-naïve group (——) and 12 weeks (------) for the prior chemotherapy group, respectively.

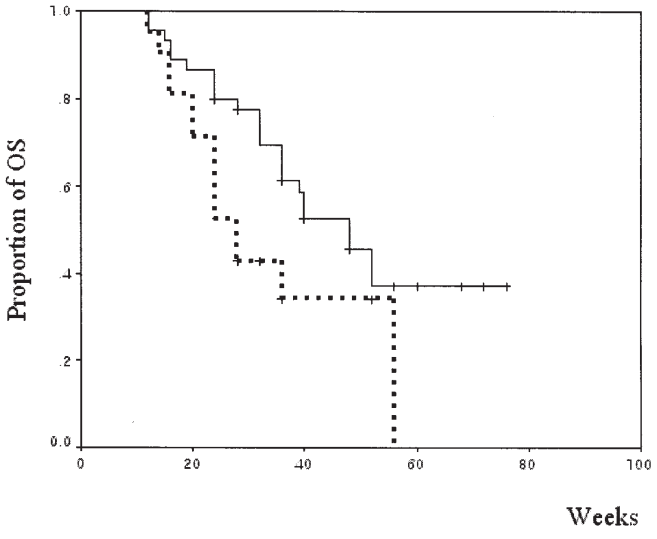

Figure 2. Overall survival according to history of prior chemotherapy. The median OS was 48 weeks for the chemotherapy-naïve group (——) and 28 weeks (------) for the prior chemotherapy group, respectively.

respectively (Fig. 2). The 1-year OS rates were 45.7% for the chemotherapy-naïve group and 34.3% for the prior chemotherapy group. The median PFS of palliatively-resected patients was significantly higher than that of unresected patients (40 vs. 14 weeks, P=0.0007). The median OS was not reached for palliatively-resected patients, and the 1-year OS rate, at 88.9%, was significantly higher than unresected patients (P=0.022).

Prognostic factors for survival. Univariate and multivariate analyses for the prognostic value of PFS and OS were performed (Table IV). In the univariate analysis, the response to chemotherapy and palliative resection were selected to be significant for PFS, whereas the response to chemotherapy, palliative resection, histology and history of previous chemotherapy were the important variables influencing OS. In

Prognostic factors influencing progression-free survival and overall survival.

	Progression-free survival		Overall survival	
	Univariate P-value	Multivariate P-value	Univariate P-value	Multivariate P-value
Sex	0.704	NS	0.156	NS
Age	0.263	NS	0.055	NS
ECOG (1 vs. 2)	0.301	NS	0.099	NS
Histology	0.108	NS	0.023	NS
Previous chemotherapy	0.407	NS	0.017	NS
Response to chemotherapy	0.0048	0.002	0.0026	0.013
Palliative resection	0.003	0.004	0.012	0.014

NS, not significant.

Table V. Adverse reactions.

Adverse reaction	Grade (no. of patients) I	II	III	IV	Grade III and IV (%)
Hematological					
Neutropenia	5	7	18	13	47.0
Anemia	9	29	1	0	1.5
Thrombocytopenia	17	0	1	0	1.5
Febrile neutropenia	0	0	4	0	6.1
Non-hematological					
Nausea/vomiting	13	3	0	0	0
Diarrhea	12	2	1	0	1.5
Infection	0	1	1	0	1.5
Fever	1	0	0	0	0
Hypersensitivity reaction	0	0	0	0	0
Peripheral neuropathy	13	11	1	0	1.5
Myalgia	15	0	0	0	0
Mucositis	26	2	0	0	0
Lethargy	24	12	0	0	0

multivariate analysis, the response to chemotherapy and palliative resection showed an independent prognostic effect on both PFS and OS.

Toxicity. All 66 patients in the study were assessed for toxicity. The frequencies of hematological and non-hematological adverse events are shown in Table V. The most common grade III and IV hematological toxicity was neutropenia, found in 27.3 and 19.7% of patients, respectively. Febrile neutropenia was documented in four patients (6.1%) and completely recovered with supportive care. The incidence of grade III/ IV neutropenia was similar in the chemotherapy-naïve and previous chemotherapy patients (P=0.253). Grade III anemia and thrombocytopenia were documented in 1.5% of patients in both groups.

Common non-hematological toxicity included lethargy (54.5%), mucositis (42.4%), and peripheral neuropathy (37.9%), although grade III toxicities were observed only as peripheral neuropathy (1.5%) and diarrhea (1.5%). Most patients with peripheral neuropathy required low-dose analgesics. There was one case of grade III infection during chemotherapy (urinary tract infection) that was recovered completely by supportive care. There was no treatment-related mortality.

Discussion

The present study is one of few reports on the efficacy and safety of the combination treatment of paclitaxel plus LV-modulated 5-FU in patients with metastatic gastric cancer. The rationale for the combined use of these drugs was: a) documented activity of both drugs in gastric cancer when used individually (1,10-13); b) the combination of 5-FU and LV has shown activity in patients who have previously progressed on 5-FU-containing combinations (20); c) apparent additive cytotoxicity and safety of this combination in patients with breast and esophageal cancer (21,22); and d) encouraging results of recently published reports of treatment with a combination of 5-FU and the semi-synthetic taxoid, docetaxel (23).

With an ORR of 45.9%, median PFS of 20 weeks, and median OS of 48 weeks for the chemotherapy-naïve group, the results of the present study suggest high anti-tumor activity for this combination of agents in metastatic gastric cancer. The observed anti-tumor potential, in agreement with the previously mentioned phase II studies of Murad *et al* (ORR 65.5%, median survival 12 months), and Bokemeyer *et al* (ORR 32%, median survival 11 months), indicates that paclitaxel/5-FU-based combination chemotherapy might be as active as second-generation regimens, including the ECF regimen. Our results further suggest that this combination is at least as efficacious as more intense and toxic three-drug

combinations such as the PFC (paclitaxel, 5-FU and cisplatin) or TPE (paclitaxel, cisplatin, etoposide) regimens (14-17). Consequently, the 5-FU/paclitaxel combination is a possible option for patients with poor performance status or cardiac and renal dysfunction unsuitable for intensive hydration. These promising results must be interpreted with caution, however, until they face confirmation in a randomized trial setting.

Interestingly, the DCRs between the chemotherapy-naïve and prior chemotherapy groups were similar (62.2 and 63.2%, respectively). One possible explanation for the high DCR, even for patients who had previously been treated with 5-FU, is that the addition of LV to 5-FU has activity in patients who have previously progressed on 5-FU-containing combinations (20). The combination of paclitaxel and 5-FU also has an additive cytotoxicity and different mechanism of action (24).

The median OS and TTP achieved in our study are also comparable with those described in other studies. Of particular note are the results of chemotherapy-naïve patients; the overall survival of 48 weeks was at the higher end of the survival achieved by other combination studies.

In our cohorts, several factors may have either positively or negatively influenced survival. First, one would expect a high tumor burden to hinder patient survival. About 35% of our patients had multiple metastatic lesions, and 47% had combined peritoneal seeding. Even with these high tumor burdens, our regimen induced a considerable DCR (63%), reaffirming the activity of paclitaxel and 5-FU/LV in advanced gastric cancer. Second, the fact that 71.4% of the 21 patients with a history of prior chemotherapy received prolonged infusional 5-FU was of great concern. Third, palliative resection, which was an important variable in multivariate analysis, might have exerted a beneficial influence on survival in both chemotherapy-naïve and prior chemotherapy patients (25,26).

When assessing the value of an anticancer treatment, it is important to consider the impact on quality of life, determined principally by the toxicity of the chemotherapy. This is particularly so for patients with advanced gastric cancer, whose life expectancy is short. With this in mind, our combination regimen was generally well-tolerated. In this study and others, 5-FU was administered as a protracted, 24-h infusion, since this mode of action appears to be less toxic (14-16,19). The primary limiting toxicity was neutropenia, although this toxicity can potentially be overcome by prophylactic administration of G-CSF to patients.

Although the hematological toxicity in our study was nearly the same as in other reports, our regimen seems preferable in terms of tolerability of non-hematological toxicity. While peripheral neuropathy, a side effect specific to paclitaxel, occurred in 37.9% patients, grade III neuropathy occurred in just 1.5% of patients and was manageable with low-dose analgesics. The incidence of this reaction tended to increase with repeated administration of the drug, and improvements were noted in most patients after the end of chemotherapy. The high RDI of our regimen suggests that the toxicity, especially the non-hematological toxicity, was quite manageable.

In conclusion, paclitaxel in combination with 5-FU/LV is active in patients with advanced gastric cancer and is a feasible salvage regimen for 5-FU-resistant patients. The results of this study suggest that this regimen is at least as efficacious as second-generation regimens or paclitaxel-containing three-drug combinations.

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