

A multi-center, late phase II clinical trial of Genexol[®] (paclitaxel) and cisplatin for patients with advanced gastric cancer

SOOK RYUN PARK¹, DO-YOUN OH¹, DONG-WAN KIM¹, TAE-YOU KIM¹, DAE SEOG HEO¹,
YUNG-JUE BANG¹, NOE KYEONG KIM¹, WON KI KANG², HEUNG-TAE KIM³,
SEOCK-AH IM⁴, JAE-HONG SUH⁵, HARK-KYUN KIM⁶ and HOON-KYO KIM⁷

¹Department of Internal Medicine, Seoul National University College of Medicine; ²Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine; ³Division of Haematology and Oncology, Department of Internal Medicine, Korea Institute of Radiological and Medical Science; ⁴Department of Internal Medicine, Ewha Womans University College of Medicine; ⁵Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Seoul; ⁶Research Institute and Hospital, National Cancer Center, Goyang; ⁷Department of Internal Medicine, St. Vincent's Hospital, Catholic University College of Medicine, Suwon, Korea

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Abstract. Because of unsatisfactory treatment results with 5-fluorouracil-based palliative combination chemotherapy for advanced gastric cancer, the evaluation of new effective and well-tolerated regimens is needed. We conducted a multi-center, late phase II trial to evaluate the efficacy and safety of Genexol[®] (a paclitaxel formulation) combined chemotherapy with cisplatin in patients with previously untreated metastatic or unresectable measurable gastric adenocarcinoma. All patients were between 18 and 75 years of age, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and had an adequate baseline major organ function. Genexol 175 mg/m² was administered as a 3-h infusion, followed by cisplatin 75 mg/m² as an intravenous infusion day 1, once every 3 weeks. Thirty-six patients were enrolled from 7 hospitals between November 2002 and April 2003. Of these, 33 patients were assessable for efficacy and 35 for toxicity. Based on an intent-to-treat analysis, 16 patients (46%) achieved a partial response, 7 (20%) stable disease, and 10 (29%) progressed, giving an overall response rate of 46% (95% CI, 29% to 63%). The median duration of response was 7.1 months (95% CI, 6.3 to 7.9 months), and the median time to progression and overall survival were 4.9 months (95% CI, 3.2 to 6.6 months) and 13.8 months (95% CI, 10.8 to 16.8 months), respectively. The major toxicity was neutropenia, with grade 3/4 intensity in 10 patients (29%). However, no febrile neutropenia occurred, and non-hematologic toxicity

was usually mild. Grade 3/4 toxicities included nausea (9% of the patients), vomiting (9%), peripheral neuropathy (9%), alopecia (9%), and myalgia (6%). In conclusion, the combination of Genexol and cisplatin was found to be an active and relatively well-tolerated regimen for the treatment of advanced gastric carcinoma.

Introduction

Gastric cancer represents a major cause of cancer death worldwide. According to 2002 statistics, the death rate of gastric cancer in Korea reached 24.5 cases per 100,000 persons, and the incidence rate of gastric cancer reached 20.2%, making it the most prevalent cancer (1). The prognosis of patients with metastatic disease is poor, with a 5-year survival of <5% (2). Although chemotherapy represents the standard treatment for these patients, none of the regimens evaluated until now have demonstrated significant clinical activity. In a recent randomized phase III trial run by the European Organization for Research and Treatment of Cancer, a comparison of 3 frequently used regimens, FAMTX (fluorouracil (5-FU), doxorubicin and methotrexate), ELF (etoposide, leucovorin and bolus 5-FU) and FP (infusional 5-FU and cisplatin), was performed. The median survival times were approximately 7 months for the 3 regimens, and the response rate was 12% with FAMTX, 9% with ELF, and 20% with FP, without significance (3).

New active anticancer agents are therefore needed to improve the prognosis of patients with advanced gastric cancer.

Originally extracted from the bark of Pacific yew (*Taxus brevifolia*) by the National Cancer Institute (US), paclitaxel (Taxol[®]; Bristol-Myers Squibb Company, Princeton, NJ, USA) acts as an antimetabolic agent by binding to microtubules, and has demonstrated substantial clinical and preclinical activity (4-6). Paclitaxel has been demonstrated to be active against previously treated ovarian carcinoma (7-9), breast carcinoma (10), and lung cancer (11), and against head and

Correspondence to: Dr Tae-You Kim, Department of Internal Medicine, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Korea
E-mail: kimty@snu.ac.kr

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neck carcinoma (12). In addition, paclitaxel has demonstrated substantial activity against gastric carcinoma cell lines *in vitro* (13,14). In several phase II studies, paclitaxel, as a single agent, demonstrated promising activity against advanced gastric carcinoma, with a response rate of approximately 20% (15-18).

In vitro, paclitaxel exhibits sequence-dependent synergy with platinum compounds against gastric cancer (19). Cisplatin has been used in many kinds of combined chemotherapies for gastric cancer for neoadjuvant, adjuvant, or palliative use. Combination paclitaxel and cisplatin chemotherapy has already been used widely for ovarian cancer, non-small cell lung cancer, and head and neck cancer. Recently, combined paclitaxel or docetaxel and cisplatin or carboplatin chemotherapy was reported to be effective in gastric cancer (20-23).

Paclitaxol bulk used for the formulation of Genexol injection (a paclitaxel formulation; Samyang Corporation, Korea) was produced from the cell line of *Taxus chinensis* using commercial scale plant cell culture facility. The chemical structure and molecular weight of Genexol are the same as those of reference paclitaxel (Sigma and Indena) (24,25). And, the toxicities and anticancer effects of Genexol and Taxol are similar by *in vitro* and *in vivo* tests. A phase II trial on metastatic breast cancer patients suggested that Genexol is similar to Taxol in terms of response with no considerable toxicity other than that previously reported (26). In a phase II study with non-small cell lung cancer patients, the Genexol and cisplatin combination was found to be effective and well tolerated (27).

We conducted a multi-center, late phase II trial to evaluate the efficacy and safety of combination chemotherapy of Genexol and cisplatin in patients with unresectable locally-advanced or metastatic gastric cancer.

Materials and methods

Eligibility criteria. Patients with metastatic, unresectable locally-advanced, or relapsed gastric adenocarcinoma after resection, and not previously treated palliatively by systemic chemotherapy were enrolled in this study. All patients had at least one clinically or radiographically measurable lesion. Prior radiation therapy and surgery were permitted if they were completed at least 4 and 3 weeks, respectively, before entry into the study. Patients were between 18 and 75 years of age, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and had an adequate baseline hematologic function (absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/l$, platelet count $\geq 100 \times 10^9/l$), hepatic function (serum bilirubin $\leq 1.25 \times$ upper normal limit (UNL), serum AST and ALT $\leq 3.0 \times$ UNL, alkaline phosphatase $\leq 3.0 \times$ UNL), renal function (serum creatinine ≤ 1.5 mg/dl), and had a life expectancy of at least 3 months. The patients gave written informed consent, and the study protocol was approved by the local institutional review boards.

Exclusion criteria. Patients were ineligible if they had a history of a cancer other than gastric cancer (except for cervical carcinoma *in situ* or non-melanoma skin cancer treated by surgery or radiotherapy), brain metastasis,

symptomatic peripheral neuropathy \geq grade 2 on the basis of the National Cancer Institute Common Toxicity Criteria (NCI CTC), atrial or ventricular arrhythmia, congestive heart failure, myocardial infarction within 6 months before enrollment, active infections, or any other underlying medical condition that would interfere with participation in the study.

Treatment schedule. Genexol was supplied by Samyang Corporation as a concentrated sterile solution for intravenous (IV) administration in 5 ml vials containing 30 mg of paclitaxel in polyoxyethylated castor oil and dehydrated alcohol (Cremophor EL/ethanol). Patients were premedicated with hydrocortisone (or corresponding drugs) 100 mg IV, pheniramine melete (or corresponding drugs) 45.5 mg IV, and cimetidine 300 mg or ranitidine 50 mg (or corresponding drugs) IV 30 min before paclitaxel for hypersensitivity prophylaxis. The patients then received paclitaxel 175 mg/m^2 (in cases with a calculated body surface area (BSA) $>2 \text{ m}^2$, the dose administered was adjusted as $\text{BSA}=2 \text{ m}^2$) as a 3-h IV infusion, followed by cisplatin 75 mg/m^2 as an IV infusion with a standard hydration method on day 1. Antiemetic therapy was given routinely before the chemotherapy. This combination chemotherapy was administered on outpatient basis.

The treatment was repeated every 3 weeks for up to 6 cycles if the disease did not progress or substantial toxicity did not develop. After 6 cycles, the test drugs were administered for an additional 2 cycles if the patients wished or if the investigator believed that additional administration would be beneficial.

Dose modification for adverse events. Toxicity was evaluated before each treatment cycle according to NCI CTC version 2.0. If the hematopoietic function had not recovered on the first day of the next cycle (ANC $<1.5 \times 10^9/l$ and a platelet count $<100 \times 10^9/l$), the administration of paclitaxel was delayed for a maximum of 3 weeks. For patients that experienced severe neutropenia (ANC $<0.5 \times 10^9/l$), thrombocytopenia (platelet $<25 \times 10^9/l$), febrile neutropenia, serious hemorrhage, mucositis with ulcer or severe peripheral neurotoxicity of CTC grade 3, the dosage of paclitaxel was reduced by 20%, i.e., to 140 mg/m^2 from the next cycle. If the above toxicities occurred after dose reduction, the dose of paclitaxel was reduced by an additional 20%, i.e., to 112 mg/m^2 . If a patient could not tolerate a dosage of 112 mg/m^2 , the administration of drugs was discontinued. Drug administration was also discontinued if a patient showed symptomatic arrhythmia, atrioventricular block (except 1st grade), other cardiac arrests, other major toxicities (excluding alopecia, nausea, and vomiting) of CTC grade >2 , grade 4 neurotoxicity, or grade 3 neurotoxicity that did not reverse within 2 weeks of dose reduction. Dose adjustment criteria for cisplatin were based on serum creatinine levels or creatinine clearance immediately prior to each cycle. If serum creatinine was ≤ 1.5 mg/dl or creatinine clearance was >50 ml/min, full-dose cisplatin was given; if serum creatinine was between 1.5 mg/dl and 2.0 mg/dl, or creatinine clearance was between 10 ml/min and 50 ml/min, 50% cisplatin was administered; if serum creatinine was >2.0 mg/dl or

Table I. Patient characteristics.

	Number of patients	%
Number of patients enrolled	36	
Assessable for response	33	
Assessable for toxicity	35	
Median age in years (range)	59 (28-72)	
Gender		
Male	28	80
Female	7	20
ECOG performance status		
0	6	17
1	29	83
Disease status		
Metastatic	27	77
Recurrent	7	20
Locally advanced	1	3
Metastatic site		
Liver	19	54
Lymph nodes	16	46
Peritoneum	4	11
Ovary	4	11
Lung	3	9
Abdominal wall	1	3
Number of metastases		
1	20	57
2	10	29
≥3	4	11
Previous therapy		
Curative surgery	7	20
Palliative surgery	3	9
Adjuvant chemotherapy	3	9
Adjuvant chemoradiotherapy	1	3

creatinine clearance was ≤ 10 ml/min, the patient was excluded from the study.

Response and toxicity evaluation. Physical examination, complete blood counts and biochemical tests were carried out before each cycle of therapy. Tumors were measured every 2 cycles by imaging studies.

The definition of response was based on standard World Health Organization criteria. Complete response (CR) was defined as the disappearance of all clinical evidence of a tumor for a minimum of 4 weeks. Partial response (PR) was defined as a $\geq 50\%$ reduction in the sum of the products of the largest bipерpendicular diameters of all measurable lesions, for bidimensionally measurable lesions, and no appearance of a new lesion for at least 4 weeks. For unidimensionally measurable lesions, partial response was defined as a $\geq 50\%$ reduction in the sum of the longest diameters of all lesions for at least 4 weeks. Stable disease (SD) was defined as no

change in tumor size, a $<25\%$ increase, or $<50\%$ reduction for at least 4 weeks. An evaluation of SD was accepted only after at least 6 weeks (2 cycles) from the beginning of treatment. Progressive disease (PD) was defined as the development of any new lesions or a $>25\%$ increase in the sum of the perpendicular diameters of any measured lesion.

The duration of response was calculated from the first day of treatment to the first confirmed date of disease progression in patients with partial or complete responses. The time to progression (TTP) was defined as the duration from the first day of treatment to the date of first confirmation of progressive disease, in all subjects, and the overall survival (OS) from the date of enrollment to the date of death or the last follow-up.

Data of patients who received at least one cycle of chemotherapy was included in the safety analysis. Toxicities observed were evaluated according to NCI CTC in relation to the test drugs. The severity of any adverse reaction not defined in NCI CTC was graded as 1, mild; 2, moderate; or 3, serious.

Statistical analysis. All enrolled patients were included in the intent-to-treat analysis of efficacy. The trial was conducted according to the 3-stage design suggested by Chang *et al* (adjusted to 2-stage) (28) with response rate as the primary endpoint. The sample size of this study was calculated based on a target activity level of 37% and a minimum activity level of 20%, with α error of 0.05 and β error of 0.20. Therefore, the required number of patients was 50. The interim analysis was carried out when the first 30 assessable patients had been recruited. The trial would be terminated if 11 or more responses were observed (with the conclusion that the regimen was sufficiently active to be submitted for further evaluation), or if 4 or fewer responses were observed (with the conclusion that the regimen was not worthy of further study). If 5 to 10 subjects showed a response, 20 additional subjects would be evaluated. If 15 or fewer subjects among total 50 subjects showed a response, the null hypothesis would be selected (judging that the regimen was not effective), and if 16 or more subjects showed a response, the null hypothesis would be rejected (judging that the regimen was effective). Duration of response, TTP, and OS were estimated as secondary endpoints using the Kaplan-Meier method. The SPSS (SPSS, Inc, Chicago, IL) for Windows package was used for statistical computations.

Results

A total of 36 patients were enrolled in this study from 7 hospitals between November 2002 and April 2003 and 35 subjects received Genexol + cisplatin. One patient did not receive the test drugs because he withdrew. There were 2 drop-out subjects; one subject showed SD after 2 cycles, but did not visit after the 4th cycle. The other was evaluated as SD after 2 cycles but refused further treatment. Therefore, the tumor response evaluation could not be confirmed in either.

Patient characteristics. The median age of the patients was 59 years (range, 28-72 years). Baseline characteristics are shown in Table I. Most patients (83%) had an ECOG

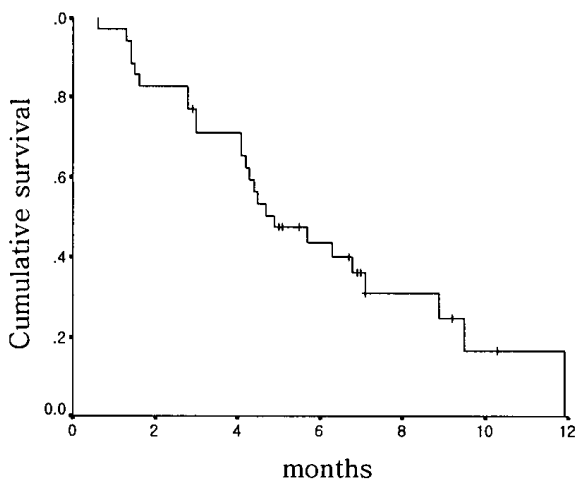


Figure 1. Time to progression of all patients.

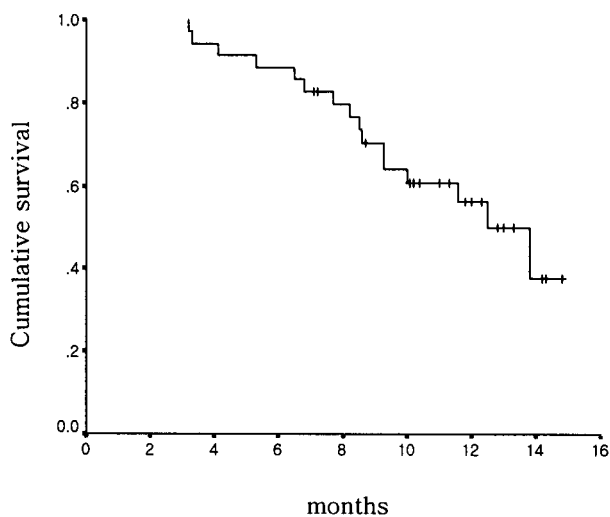


Figure 2. Overall survival of all patients.

performance status of 1. One case was of unresectable locally-advanced gastric cancer, and the remaining 34 cases were of metastatic gastric cancer; 27 patients had primary metastatic disease and 7 had recurrent disease. Metastatic sites were in the liver (n=19, 54%), lymph nodes (n=16, 46%), peritoneum (n=4, 11%), ovary (n=4, 11%), lung (n=3, 9%) and abdominal wall (n=1, 3%). Ten patients (29%) had previously received surgery for gastric cancer with curative (n=7) or palliative (n=3) intent, and 4 of these patients (11%) had received adjuvant therapy after curative surgery with 5-FU/leucovorin (n=1), 5-FU/leucovorin + radiotherapy (n=1), FP (n=1) and FAMTX (n=1).

Treatment administration. Genexol and cisplatin was administered to 35 patients. A total of 165 treatment cycles were delivered, with patients receiving a median of 5 (range, 2 to 8) cycles. Seventeen of the patients received the full 6 cycles of chemotherapy. A dose reduction of Genexol or cisplatin was required in only 2 patients, due to grade 3 neurotoxicity and an elevated serum creatinine level, respectively.

Table II. Response to combination chemotherapy.

Overall best response	Number of patients	%
Complete response	0	0
Partial response	16	46
Stable disease	7	20
Progressive disease	10	29
Not evaluable	2	5

Thirty-five patients in the intent-to-treat analysis, 33 evaluable patients.

Table III. Hematologic toxicity (NCI-CTC).

Toxicity	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)
Anemia	4 (11)	5 (14)	1 (3)	0 (0)
Leukopenia	8 (23)	6 (17)	2 (6)	0 (0)
Neutropenia	11 (31)	6 (17)	6 (17)	4 (11)
Thrombocytopenia	1 (3)	0 (0)	0 (0)	0 (0)

NCI-CTC, National Cancer Institute common toxicity criteria; N, number of patients whose worst degree of toxicity was at this grade.

Table IV. Non-hematologic toxicity (NCI-CTC).

Toxicity	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)
Nausea	12 (34)	10 (29)	3 (9)	-
Vomiting	8 (23)	8 (23)	3 (9)	0 (0)
Diarrhea	4 (11)	6 (17)	0 (0)	0 (0)
Alopecia	1 (3)	30 (85)	3 (9)	0 (0)
Myalgia	8 (23)	8 (23)	2 (6)	0 (0)
Peripheral neuropathy	13 (37)	3 (9)	3 (9)	0 (0)
Elevated liver enzyme	4 (11)	1 (3)	2 (6)	0 (0)

NCI-CTC, National Cancer Institute common toxicity criteria; N, number of patients whose worst degree of toxicity was at this grade.

Efficacy and survival. Among the 35 patients that received the test drugs, 33 were evaluable for response. By intent-to-treat analysis, 16 patients (46%) achieved PR, 7 (20%) SD, and 10 (29%) progressed. Thus, the overall response rate was 46% (95% CI, 29 to 63%) (Table II). Since the response rate met the early stopping rules (i.e., 11 or more responses among the 30 patients in the first stage), this clinical trial closed early with the conclusion that the regimen was sufficiently active to be submitted for further evaluation.

The median follow-up duration was 12.7 months (range, 7.1 to 14.8 months), and the median duration of response was 7.1 months (95% CI, 6.3 to 7.9 months). The median TTP

and OS were 4.9 months (95% CI, 3.2 to 6.6 months) and 13.8 months (95% CI, 10.8 to 16.8 months), respectively, for the intent-to-treat population (Figs. 1 and 2). One-year survival was 50.2%.

Toxicity. All 35 patients that received therapy were assessable for toxicity. The treatment was generally tolerated, and there were no toxic deaths. Hematologic toxicity was mild (Table III), and the most common hematologic toxicity was neutropenia, which occurred at grade 3/4 intensity in 10 patients (29%); however, no patient experienced febrile neutropenia. Grade 3/4 thrombocytopenia was not noted, and grade 3/4 anemia occurred in one patient (3%, grade 3 only). Non-hematologic toxicity was also mild (Table IV). The most common non-hematologic toxicity was alopecia (34/35 patients, 97%), followed by nausea (26/35 patients, 74%), vomiting (21/35 patients, 60%) and neuropathy (19/35 patients, 54%). Three patients (9%) experienced grade 3 nausea, 3 patients (9%) grade 3 vomiting, 3 patients (9%) grade 3 neuropathy, 3 patients (9%) grade 3 alopecia, and 2 patients (6%) grade 3 myalgia. These toxicities were reversible and easily manageable. No patient discontinued therapy due to toxicity and only 2 patients required a dose reduction of the test drugs due to grade 3 neurotoxicity and mild azotemia (serum creatinine 1.7 mg/dl), and recovered thereafter.

Discussion

5-FU-and/or cisplatin-based combination chemotherapy is commonly used in patients with advanced gastric cancer, but the benefits of such therapy are modest. Recently, several new classes of drugs have demonstrated activity against advanced gastric cancer. These include the taxanes (paclitaxel and docetaxel), camptothecins (irinotecan) and oral fluoropyrimidines (UFT, S-1 and capecitabine). Paclitaxel has shown encouraging activity as a single agent in gastric cancer, with a response rate of approximately 20% (15-18). Also, the combined chemotherapies of paclitaxel and cisplatin or carboplatin were reported to be effective on gastric cancer, with a response rate of 33 to 44% (20,23).

We reported here the result of a phase II clinical trial of Genexol (a paclitaxel formulation), and cisplatin in patients with unresectable locally-advanced or metastatic gastric cancer, to evaluate its efficacy and safety. The Genexol + cisplatin regimen demonstrated promising efficacy, with tumor response rates of 46% (95% CI, 29 to 63%), a median TTP of 4.9 months (95% CI, 3.2 to 6.6 months), a median response duration of 7.1 months (95% CI, 6.3 to 7.9 months), and a median OS of 13.8 months (95% CI, 10.8 to 16.8 months), and thus it compared favorably with the reported efficacy of common 2- or 3-drug combinations including FAMTX (3,29), ELF (3,30,31), FAP (5-FU, doxorubicin and cisplatin) (32), or FP (3,33). Also, the outcome of the present study seemed to be similar to the results of the other studies in which paclitaxel and cisplatin/carboplatin were used for the treatment of advanced gastric cancer. Kornek *et al* (23) reported a response rate of 44%, a median TTP of 7 months, and a median survival time of 11.2 months with 2-weekly courses of paclitaxel

and cisplatin. Gadgeel *et al* (20) reported a response rate of 33%, a median response duration of 4.9 months, and a median survival of 7.5 months with paclitaxel and carboplatin.

In addition to chemo-naïve patients, paclitaxel alone or the combination of paclitaxel and carboplatin were reported to be moderately effective in patients that received prior chemotherapy for metastatic gastric cancer (17,18,34,35); Yamada *et al* (17) reported a response rate of 26% for paclitaxel alone in patients that had undergone prior palliative chemotherapy based on 5-FU or cisplatin. In the present study, 4 patients had received previous adjuvant 5-FU-based chemotherapy, one of 3 evaluable patients achieved PR with the Genexol + cisplatin combination. The Genexol + cisplatin regimen could be further evaluated in 5-FU-based 1st line palliative chemotherapy-failed gastric cancer patients.

The current combination of Genexol and cisplatin was well tolerated in this group of patients. No patient discontinued therapy because of toxicity. A dose reduction of Genexol or cisplatin was required in only 2 patients, due to grade 3 neurotoxicity and elevated serum creatinine, respectively. The major toxicity was grade 3/4 neutropenia, which occurred in 10 patients (29%). However, no patient experienced neutropenic fever. Peripheral neuropathy, which is a specific adverse reaction to paclitaxel and cisplatin, was moderate, and only 3 patients (9%) experienced grade 3 neuropathy. No severe hypersensitivity reaction occurred. No considerable toxicity, other than that previously reported for paclitaxel and cisplatin regimens, was observed in this study.

Considering administration in the outpatient setting and a one-day treatment duration, this combination of Genexol and cisplatin is also easier to prescribe than infusional 5-FU-based combination chemotherapy regimens or FAMTX, which requires the administration of the drug on day 15. This convenience and acceptable toxicity makes the current combination regimen an attractive option in the palliative setting.

In conclusion, the combination of a paclitaxel formulation, Genexol, with cisplatin provides an active and relatively well-tolerated regimen in the treatment of advanced gastric carcinoma. In addition, this combination could be further evaluated as a salvage treatment in 5-FU-based 1st line palliative chemotherapy-failed gastric cancer patients.

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