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A Phase II Study of Genexol® (paclitaxel) in Metastatic Breast Cancer

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Purpose: **Paclitaxel is a very effective agent in the treatment of breast cancer. Samyang Corporation has developed its own process to produce paclitaxel in a large volume using plant cell culture technology. To evaluate the efficacy and safety of Genexol® in patients with metastatic breast cancer who have failed to respond to standard therapy, we performed a prospective, multicenter phase II clinical trial.**

Materials and Methods: **Patients with metastatic breast cancer were included in this study. Enrollees were required to have histologically confirmed breast cancer with bidimensionally measurable metastatic disease. Genexol® was administered at 175 mg/m^2 as a 3-hour intravenous infusion every 3 weeks. All patients were premedicated with hydrocortisone, pheniramine maleate, and H2 blocker 30 minutes prior to paclitaxel. We planned to administer at least 4 courses of paclitaxel unless there was disease progression or unacceptable toxicity and to continue treatment up to a total of 6 courses in cases of objective response following 4 courses.**

Results: **The median duration of follow-up was 8.9 (2.07 13.7) months. Forty-five patients were registered and 43 were eligible. The performance status of patients was ECOG 0 1 in 39 patients (90.7%) and 2 in 4 (9.3%). The location of metastases at the start of the study were the lung (15 patients), liver (8 patients), lymph nodes (22 patients), and other (7 patients). Among the 40 evaluable patients, 15 patients obtained partial responses (PRs) (37.5%, 95% CI: 22.5 52.5%). The median duration of response was 11.67 (4.1 11.7) months and the median time to progression was 7.73 (2.8 11.7) months. The median survival time was not reached at 13.7 months, and the overall survival rate at 13.7 months was 70.1%. The hematologic toxicity was primarily neutropenia with grade 3 or 4 in 10 patients (23.3%). The grade 3 or 4 non-hematologic toxicities included alopecia (17, 39.5%), myalgia (2, 4.7%), neuropathy (2, 4.7%), and pruritus (1, 2.3%). Mild hypersensitivity reaction was observed in 2 patients, although it did not cause withdrawal of the test drug.**

Conclusion: **The results suggest that the Genexol® injection is an effective anticancer formulation for the treatment of metastatic breast cancer and toxicity is acceptable.** ***(Cancer Research and Treatment 2001;33:451−457)***

Key Words: **Breast neoplasm, Chemotherapy, Genexol, Phase II study**

INTRODUCTION

Breast cancer is one of the most common cancers in women and is second only to lung cancer as a cause of cancer death (1). In Korean women, breast cancer is the second most common among all cancers and ranks fifth as a cause of death (2). Metastatic breast cancer essentially remains incurable and almost all women so diagnosed will eventually die from their disease. The median survival time from diagnosis of metastases is approximately 3 years (3). Systemic treatment with hormonal therapy or chemotherapy is of significant palliative benefit in patients with metastatic disease (4,5). Anthracyclines, alkylating agents, antimetabolites and vinca alkaloids are considered active agents in the treatment of metastatic breast cancer and the average response rate is between 20% and 50%. With

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monotherapy by the above regimen, complete response is rare and the average duration of response is between 6 and 9 months (6,7). With combination chemotherapy, the response rate has been increased without significant prolongation of survival duration or signs of more severe toxicities (6 9). Furthermore, in the case of no response to the above regimen, in particular with anthracycline, no active regimen had been followed.

Paclitaxel (Taxol®; Bristol-Myers Squibb Company, Princeton, NJ) is a naturally existing substance found in trace amounts in the bark of Pacific Yew tree (*Taxus brevifolia*) and semi-synthetic methods have been used to produce paclitaxel in commercial quantities. The mechanism of paclitaxel at the cellular level is the stabilization of microtubules by promotion of a microtubule assembly from the tubulin dimer and prevention of the multiplication of cancer cells by inhibition of the G2/M phase (mitosis) (10). The anticancer chemotherapeutic effect was confirmed in ovarian cancer (11), breast cancer (12,13) and non-small cell lung cancer (14). In metastatic breast cancer, paclitaxel has been reported to elicit a 20 62% response rate as a first-line therapy and a 4 32% rate in previously treated patients (12 16).

Samyang Corporation has developed its own process using plant cell culture technology to produce paclitaxel in large quantities. This form is physically, chemically and biologically equivalent to commercialized paclitaxel. The injectable formulation of paclitaxel developed by Samyang Corporation is branded as Genexol® (Samyang co, Korea) in Korea. The chemical structure and molecular weights of Genexol® are the same as standard paclitaxel (SIGMA and INDENA) and the purity of Genexol® bulk is equal to or even higher than Taxol® (17,18). The toxicity and anticancer effect of Genexol® and Taxol® are similar in *in vitro* and *in vivo* tests. These results suggest that Genexol® may be safe and possess significant antitumor activity in breast cancer, although the efficacy and safety of Genexol® in patients with breast cancer has not yet been evaluated by clinical trial.

Therefore, we performed a phase II study of Genexol® in patients with metastatic breast cancer in order to evaluate the response rate, duration of response, time to progression, survival and toxicities.

MATERIALS AND METHODS

1) Patients

The trial was conducted from August 1999 to May 2000 and enrolled patients from 6 hospitals. Patients with histologically confirmed metastatic breast cancer were eligible for study. They were required to be between 18 and 70 years of age, have an ECOG performance status of 0 to 2, have a life expectancy of more than 12 weeks, and provide written informed consent in accordance with institutional review board guidelines. Prior chemotherapy was permitted, providing it was only one (adjuvant or metastatic disease) or two regimens (one adjuvant and the other for metastatic) and was completed at least 4 weeks (6 weeks in the case of treatment with mitomycin C or nitrosourea) before entry into the study. Prior taxane therapy and concurrent palliative radiotherapy were not allowed. Prior hormonal therapy, immunotherapy, and localized radiotherapy for disease were permitted.

All patients were required to have clinically or radiographically measurable disease, and to have adequate renal, hepatic and bone marrow functions defined as follows: serum creatinine $\leq 1.5 \times$ upper normal limit (UNL); total bilirubin $\leq 1.25 \times$ UNL; absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L, AST and ALT $\leq 3.0 \times$ UNL, and alkaline phosphatase $\leq 3.0 \times$ UNL. Pretreatment evaluation was performed within 3 weeks of therapy initiation and included full history, physical examination, CBC, biochemical screening profile, chest X-ray, bone scan, site-specific imaging (especially liver) and quality-of-life assessment.

Patients were ineligible if they had a history of neoplasm of other than breast carcinoma (excepting nonmelanomatous skin cancer or curatively treated cervical carcinoma in situ), a history of ventricular arrhythmias or congestive heart failure, pre-existing motor or sensory neuropathy more than grade 1 or any other underlying medical condition that would hinder study participation. Pregnant or lactating females or patients of child-bearing potential who did not implement adequate contraceptive measures were also ineligible.

2) Therapeutic plan

Genexol® was supplied by Samyang Corporation as a concentrated sterile solution for intravenous (IV) administration in a 5 ml vial containing 30 mg of paclitaxel in polyoxyethylated castor oil and dehydrated alcohol (Cremophor EL/ethanol). The drug was diluted with either a 0.9% sodium chloride solution or a 5% dextrose solution to a final concentration of 0.3 1.2 mg/ml. The solutions were prepared and stored in glass, polypropylene or polyolefin containers. In-line filters (0.2 μm, Sartorius, Germany) were used to filter microprecipitation during the infusion of Genexol®.

The drug was administered within 7 days after subject registration. The initial dosage of paclitaxel was 175 mg/m^2 (in case of calculated BSA ≥ 2 m^2, administered dose was adjusted as BSA=2 m^2) administrated for 3 hours, every 3 weeks. All patients were premedicated with the following regimen 30 minutes prior to paclitaxel infusion; hydrocortisone (or corresponding drug) 100 mg IV, pheniramine maleate (or corresponding drug) 45.5 mg IV, and cimetidine 300 mg (or ranitidine 50 mg) IV. In cases of delayed hematopoietic recovery at the first day of the next cycle, that is ANC $< 1.5 \times 10^9$/L and the platelet count $< 100 \times 10^9$/L, paclitaxel administration was postponed for a maximum of 2 weeks. For a patient who experienced severe neutropenia (ANC $< 0.5 \times 10^9$/L), thrombocytopenia (platelet $< 25 \times 10^9$/L), febrile neutropenia, mucositis with ulcer or severe peripheral nerve disease, the dose was reduced to 135 mg/m^2 from the next cycle. In the case of recurrent febrile neutropenia or severe infection or severe drug-related bleeding, the dose was reduced to 110 mg/m^2.

The planned duration of therapy was at least 2 courses unless disease progression was rapid. We stopped treatment when there was disease progression or intolerable (grade 3 or 4) toxicity, and the patients could refuse to continue treatment at any time.

3) Response and toxicity assessment

Tumor measurements were assessed every cycle by physical examination and every other cycle by imaging studies. Patients with measurable disease receiving at least two courses of therapy were assessable for response. All responses were centrally reviewed.

A complete response (CR) was defined as the disappearance of all clinical evidence of active tumor and absence of disease-related symptoms for a minimum of 4 weeks. Partial response (PR) was defined as 50% or greater reduction in the sum of the products of the biperpendicular diameters of all measurable lesions and no appearance of new lesions for at least 4 weeks. When there were multiple sites of metastases, the largest masses (up to five) were considered as the index lesions. Stable disease (SD) was defined as no change in tumor size or a less than 25% increase for at least 4 weeks. The 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 unequivocal appearance of any new lesions or a greater than 25% increase in the sum of the perpendicular diameters of any measured lesion or in the estimated size of a non-measurable lesion.

The clinical period was established at 6 cycles and the follow-up was performed to identify disease progression and death of subjects after the end of clinical period. If patients wanted to continue treatment, the test drug was administered continuously at the discretion of investigator with the same examinations as done during the clinical study period.

The duration of response was defined as the period from the date of response documented to the first confirmed date of disease progression in patients with partial responses. Time to progression was defined as the duration from the administration of Genexol® to the confirmation of disease progression. Survival was defined as the duration from the first administration of Genexol® to the confirmed date of death or to the last follow-up date at the end of the clinical trial for those who survived the clinical trial. The median survival was calculated according to Kaplan-Meier method.

The dose intensity (DI), expressed as $mg/m^2/wk$, was defined as the dose supplied per week and was calculated by summing each cycle dose in mg/m^2 divided by the number of weeks from the first day of the first cycle to the date of the last cycle plus a fixed time of 3 weeks.

Data from all patients who received at least one dose of Genexol® injection was included in the safety analysis. The adverse reactions observed were classified by involved organ and observed toxicity and were evaluated according to National Cancer Institute-Canada's Common toxicity grading (NCIC-CTG) criteria in relation to the test drug. The severity of any adverse reaction not defined in NCIC-CTG was graded as "1=mild, 2=moderate, 3=severe, 4=very severe".

RESULTS

1) General characteristics of eligible patients (Table 1)

A total of forty-five patients were enrolled in the study and forty-three subjects were eligible and received Genexol®. Two subjects were excluded before treatment because one subject had cervix cancer and the other subject had brain metastasis.

The median age of the patients was 47 (range 32 63) years. Eighteen (41.9%) patients were premenopausal, 3 patients were in menopause and others were unknown. Most patients (90.7%) scored from 0 to 1 in ECOG. The median duration of breast cancer before the trial was 34.4 (2.33 190.39) months. Predominant metastatic sites were the liver (8, 13.8%), lung (15, 34.9%), skin (6, 14.3%), lymph node (22, 51.2%) and breast (same side; 1, 2.3%). Pathologic diagnosis was ductal carcinoma in 38 patients (95.0%), lobular carcinoma in 2 patients (5.0%) and unknown in 3 patients. Positive estrogen receptors were observed in 9 patients (29%) and positive progesteron receptors were seen in 10 patients (32.3%). Eighteen patients (41.9%) had previously undergone radiotherapy and 40 patients (93%) had received surgery for breast cancer. Twenty-four patients (55.8%) were exposed to anthracycline. The number of chemotherapeutic regimens was one (30, 69.8%) or two (13, 30.2%). Sixteen patients (39.0%) had previously received hormonal therapy.

2) Treatment administration

Genexol® was administered to forty-three patients who had been registered in the clinical trial. A total of 197 treatment cycles were delivered with 4.58 cycles per patient. Through the courses of this study, only one case required a dosage adjustment to 135 mg/m^2 from the second cycle because of neutropenia. The median cumulative dosage per subject administrated was 1050 (175 1,050) mg/m^2 (1,490 mg in total dose). Two patients were found not to meet inclusion criteria because of a high level of alkaline phosphatase and concomitant medication of tamoxifen, respectively. One patient was dropped because she refused to continue treatment during the first cycle. As a result, a total of 40 patients were evaluable for response.

Table 1. Patient characteristics

Characteristics	
Total number of patients (administered)	43
Age (years) [median (range)]	47 (32 63)
Performance status ECOG [0/1/2]	16/23/4
Predominant metastatic site [No (%)]	
Liver	8 (17.8)
Lung	15 (34.9)
Skin	6 (14.3)
Lymph Node	22 (51.2)
Breast	1 (2.3)
Receptor status [No (%)]	
Estrogen receptor positive [No (%)]	9 (29.0)
Progesteron receptor positive [No (%)]	10 (32.3)
Prior therapy [No (%)]	
Radiotherapy	18 (41.9)
Operation	40 (93.0)
Chemotherapy	43 (100.0)
Anthracycline	24 (55.8)
Hormonal therapy	16 (37.2)

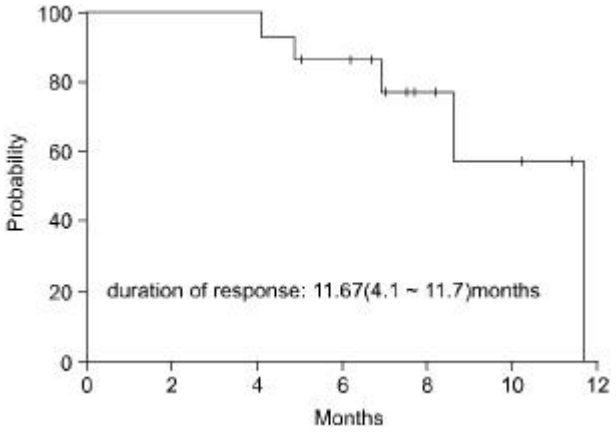

Fig. 1. Kaplan-Meier estimate of duration of response

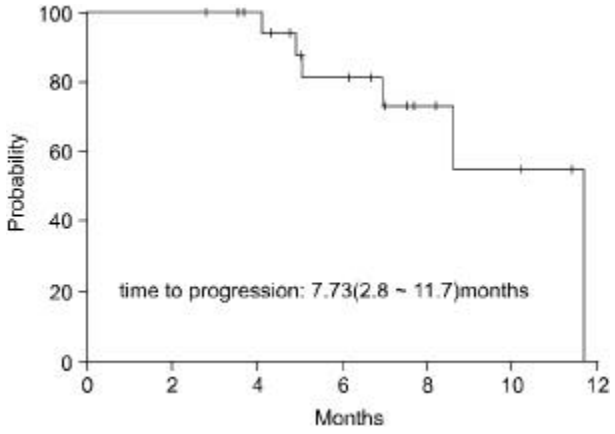

Fig. 2. Kaplan-Meier estimate of time to progression

Table 2. The factors that affect the response to Genexol

	Response rate (%)	p-value
Age		
<50	10/23 (43.5%)	0.283
≥50	5/17 (29.4%)	
Performance status (ECOG)		
0 1	13/36 (36.1%)	0.484
2	2/4 (50.0%)	
Hormonal receptor		
ER (+);(−)	4/8 (50.0%); 6/21 (28.6%)	0.302
PR (+);(−)	5/10 (50.0%); 5/19 (26.3%)	0.251
Total (+);(−)	6/11 (54.5%); 4/18 (22.2%)	0.161
Chemotherapy		
Anthracycline-based	7/22 (31.8%)	0.311
CMF based	8/18 (38.9%)	
Metastases		
Visceral organ	12/27 (44.4%)	0.169
Non-visceral organ	3/13 (23.1%)	
Duration of breast cancer		
<34.7 months	4/21 (19.1%)	0.024
≥34.7 months	10/19 (52.4%)	

3) Efficacy results

Among the 40 evaluable patients, fifteen patients (37.5% (95% CI: 22.5 52.5)) obtained PRs and eight cases of SD and 17 cases of PD were observed.

We evaluated the impact of various factors (study center, prior history of therapies, etc.) on the anticancer response rate (Table 2). Only the duration of breast cancer appeared to influence the anti-cancer response. The duration of breast cancer affected the response rate. The group experiencing a longer period of breast cancer (more than 34.7 months) registered a higher response rate (52.4%) than the shorter period group (19.1%); this difference was statistically significant (p= 0.024). A history of radiotherapy (43.5%) or surgery (35.9%) for breast cancer did not show a significant effect on response rate (p>0.05). A prior history of chemotherapy showed no significant influence on response rate (p=0.155). Patients with a prior exposure to anthracycline also showed lower response (22.7%) than those with no exposure (52.9%) although this was not statistically significant (p>0.05). The number of regimen showed no significant influence on the response rate (p>0.05).

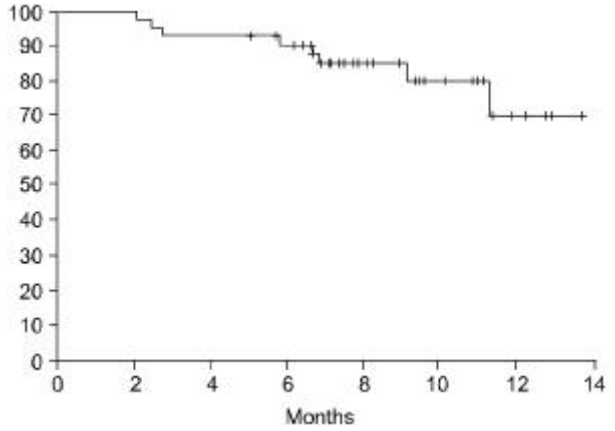

Fig. 3. Kaplan-Meier estimate of overall survival

The median follow-up duration was 8.9 (2.07 13.7) months. The median duration of response was 11.67 (4.1 11.7) months (Fig. 1) and the median time to progression was 7.73 (2.8 11.7) months (Fig. 2).

Eight patients died, the median survival period was longer than 13.7 months and the overall survival rate at 12 months was 70.1% (Fig. 3).

4) Toxicity (Table 3)

All forty-three patients who received therapy were assessable for toxicity. Overall, therapy was well tolerated. Most of the adverse drug reactions (ADRs) were limited to mild to moderate toxicity and no patients discontinued therapy for treatment-related adverse events.

The median dose intensity was 70 (51.4 116.7) mg/m^2/ week, which was more than 90% of the expected administered

Table 3. Toxicities (NCIC-CTG grading criteria)

Hematologic toxicity	Grades [No. of cycles (% of cycles)]			
	I	II	III	IV
Neutropenia	3 (1.5)	14 (7.1)	10 (5.1)	3 (1.5)
Anemia	1 (0.5)	4 (2.0)	1 (0.5)	0
Thrombocytopenia	0	2 (1.0)	0	0
Non-hematologic toxicity	**Grades [No. of patients (% of patients)]**			
	I	II	III	IV
Nausea/vomiting	14 (32.6)	6 (14.0)	0	0
Diarrhea	5 (11.6)	2 (4.7)	0	0
Elevated liver enzymes	1 (2.3)	5 (11.6)	0	0
Myalgia	8 (18.6)	24 (55.8)	2 (4.7)	0
Arthralgia	3 (7.0)	3 (7.0)	0	0
Peripheral neuropathy	4 (9.3)	15 (34.9)	2 (4.7)	0
Alopecia	2 (4.7)	4 (9.3)	17 (39.5)	0
Pruritus	11 (25.6)	8 (18.6)	1 (2.3)	0

dose. A total of thirteen cycles were delayed because of the patients had not fully recovered from hematological toxicity.

Grade 3 and 4 adverse reactions were recorded in 101 treatment cycles (15.2%) and 3 treatment cycles (1.5%), respectively. All grade 4 ADR were neutropenia. Neutropenia was the most frequent hematologic toxicitiy (30 cycles, 15.2%) and grade 3 or 4 neutropenia was observed in 13 cycles (6.6%). Anemia was observed in 6 cycles (3.0%) and grade 3 anemia in 1 cycle (0.5%).

The most frequent non-hematologic toxicity was myalgia (34/43, 79.1%), which was followed by alopecia (22/43, 51.2%) and pruritus (20/43, 26.5%). The grade 3 or 4 non-hematological ADRs were alopecia (17/43, 39.5%), peripheral neuropathy (2/43, 4.7%), myalgia (2/43, 4.7%) and pruritus (1/43, 2.3%). Most of the other non- hematological ADRs were less severe than grade 3. Nausea and vomiting were the most common gastrointestinal ADRs (20/43, 46.6%) related to Genexol® and the severity was less than grade 3.

Two patients experienced hypersensitivity reactions at the first cycle, although following the treatment for hypersensitivity reactions they recovered and received the drug again. The severity of hypersensitivity was mild(nausea, vomiting, dizziness and mild hypotension) and the symptoms were reversed with IV infusion, antiemetics and hydrocortisone. The remaining drug was diluted to 1,000 ml of 5% dextrose solution or normal saline and administered slowly for 24 hours; hypersensitivity reactions did not recur.

DISCUSSION

This phase II clinical trial was performed to evaluate the efficacy and safety of Genexol® injection in metastatic breast cancer patients. Paclitaxel represents the prototype of a novel class of anticancer agents with a completely new mechanism of action. The major activity of paclitaxel in metastatic breast cancer has been confirmed in many previous studies (12 16). Holmes *et al* (12) reported that the use of paclitaxel (250 mg/m2 continuous infusion for 24 hours every 3 weeks) in breast cancer patients with prior chemotherapy (adjuvant or primary chemotherapeutic role) showed a 56% response rate and a median of 8 months survival duration. Reichman *et al* (13) reported that paclitaxel (250 mg/m^2 infusion for 24 hours every 3 weeks) used in metastatic breast cancer patients showed a 62% response rate. Previously, our group also reported a 43.3% response rate and 7.2 months duration of response by paclitaxel (175 mg/m^2 infusion for 3 hours every 3 weeks) in metastatic breast cancer (16).

The response rate in this study is similar with those of other clinical trials in terms of response rate using a paclitaxel formulation in metastatic breast cancer in other countries (12,13,16, 19,20). These results suggest that Genexol is a clinically effective and equally responsive against breast cancer and that the Genexol injection, like another paclitaxel formulation, Taxol, is an effective anticancer chemotherapeutic formulation for metastatic breast cancer.

We evaluated the influence of baseline characteristics on the response rate. The median duration of disease appeared to have an influence on response rate. Patients with a shorter duration of disease ($<$3 months) had a better response rate (51.9%) as compared to those with a longer duration of disease ($p<0.05$).

Our examination of the response rate in patients with a prior history of radiotherapy or surgery for breast cancer showed no statistically significant effect on the response rate ($p>0.05$). A prior history of chemotherapy also showed no statistically significant influence on response rate ($p>0.05$). Prior exposure to anthracycline had no significant effect on response rate ($p>0.05$) and it was similar with the results from other studies

(16,19,20). The response rate of the anthracyclin-resistant group in another study was 20 30% and prior exposure to anthracycline did not affect the response rate by paclitaxel. These results would suggest an incomplete cross-resistance between anthracycline and Genexol®.

The median survival for patients in this clinical trial cannot be calculated because of the small number of reported deaths and short duration of follow-up. The overall survival rate at 1 year was 71.7% and the median survival has not been reached at 13.7 months. A longer follow-up is required in order to evaluate the effect of Genexol® on the duration of survival.

The optimal effective dose for paclitaxel has not yet been determined. Because of the time- and concentration-dependency of paclitaxel, a higher level and longer duration of exposure to the drug may induce a higher response rate. However, the higher the dose of paclitaxel that is used, the more drug-induced ADRs are observed. In previous studies, the dose-limiting toxicity of paclitaxel was reversible neutropenia and life-threatening anaphylaxis (12 14,21,22). Abrams *et al* (21) reported the result of using paclitaxel (175 mg/m^2 civ for 24 hours every 3 weeks) in metastatic breast cancer patients with history of 2 or more prior rounds of chemotherapy. This showed a 23% of response, 45% rate of febrile neutropenia and a 49% rate of admission, results which suggest that the anticancer efficacy of paclitaxel was meaningful, although the resulting ADRs were severe. In a comparison of the efficacy and safety of two doses (135 *vs* 175 mg/m^2) of paclitaxel (22), the higher dose increased progression-free survival, but did not increase the duration of overall survival. Furthermore, more severe neutropenia was observed in the higher dose treatment group and 16% of patients reduced their dose because of prolonged neutropenia. Although grade 3 or 4 ADRs were observed and some were associated with Genexol®, all were transient and reversible. These results suggest the following: 1) The efficacy of Genexol® is maintained with a dose of 175 mg/m^2, and, 2) Genexol® induces tolerable and reversible toxicity based on a comparison with the results of a previous study of Taxol® (21,22).

The hypersensitivity response is thought to be caused by a high concentration of Cremophor EL, which can be reduced by an increase of infusion time and premedication (dexamethasone, H2 receptor blocker). As mentioned above, Genexol® was infused for 3 hours, not for 24 hours as used to mitigate against a hypersensitivity response. In this study, hypersensitivity reactions were mild, reversible and did not interrupt the study. This may suggest that Genexol® induces less severe hypersensitivity and a 3-hour schedule of paclitaxel can be used without severe hypersensitivity reaction.

The high individual activities of anthracyclines and paclitaxel, and their incomplete clinical cross-resistance make them an attractive combination for the treatment of metastatic breast cancer. Encouraging response rates were observed with a combination of paclitaxel and anthracyclin for metastatic breast cancer in many phase II trials and in randomized phase III trials (23 25). Recently, in a phase III study of doxorubicin/paclitaxel versus doxorubicin/cyclophosphamide/fluorouracil, the overall response rate (87%), time to progression (8.3 months) and overall survival (23.3 months) favored patients receiving the paclitaxel-based therapy (25). Therefore, further studies concerning the efficacy of a combination regimen including Genexol® and anthracycline derivatives in the treatment of metastatic breast cancer is warranted.

CONCLUSIONS

According to the results obtained in this clinical trial to determine the safety and efficacy of Genexol® in metastatic breast cancer, Genexol® injection is evaluated to be an effective and safe anticancer drug formulation for the treatment of metastatic breast cancer.

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