Jpn J Clin Oncol 2001;31(10)477–481

Original Articles

Salvage Therapy with Single-agent Paclitaxel by Three-hour Infusion in Metastatic Breast Cancer: an Experience in Taipei Veterans General Hospital

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Received February 13, 2001; accepted June 5, 2001

Background: Paclitaxel is an active agent in the treatment of breast, ovarian, lung and head and neck cancers. In previous phase I and II trials, it exerted novel cytotoxic effect on several malignancies. Various doses and regimens of paclitaxel have been assessed in metastatic breast cancer, with responses between 20 and 62%. However, combination therapy with other anti-cancer drugs leads to a high incidence of side effects. Our aim was to evaluate the efficacy of paclitaxel given by 3 h infusion as salvage chemotherapy for patients with metastatic breast cancer.

Methods: Between May 1999 and April 2000, 14 women with metastatic breast cancer were enrolled in this study and all the patients had to have measurable lesions. The median age of the patients was 48.7 years (range 39–56 years). All of them were definitely evidenced as having metastatic breast cancer and received complete courses of anthracycline-containing agents before applying paclitaxel. The protocol was single-agent paclitaxel (Anzatax, Faulding, Australia) at a moderate dosage of 175 mg/m^2 by 3 h intravenous infusion every 3 weeks.

Results: A total of 75 cycles were administered to these 14 patients with a median of four delivered cycles (range 3–14) and the response rate was 28.6% (95% CI: 21–40%), including four partial remission, three stable disease and seven progressive disease. The median time to progression was 3 (range 3–7) months. Hematological toxicities were minimal with no evidence of severe (grade 3 or 4) leukopenia and thrombocytopenia. Hepatic toxicities were observed in 12 cycles with five in grade 3.

Conclusions: Our study indicates that utilizing single-agent paclitaxel exerts moderate activity on anthracycline-refractory metastatic breast cancer patients without excessive toxicities.

Key words: metastatic breast cancer – chemotherapy – paclitaxel – Anzatax

INTRODUCTION

Chemotherapy plays an important role in the treatment of breast cancer (1). In stage IV breast cancer, chemotherapy offers a significant opportunity for palliation and longer survival (2). Anthracycline is among the most active agents for this disease; it has been reported that the response rate of single-agent doxorubicin can be up to 43% in untreated or not heavily metastatic breast cancer and 29% in pretreated metastatic breast cancer (3).

Recent advances in treatment have led to increasingly higher response rates, although many of these advances provide more palliative than curative effects (4). Paclitaxel is one of the most exciting new anticancer drugs and has shown significant clinical activity in breast, ovarian, lung and head and neck cancers (5). Utilizing paclitaxel as salvage chemotherapy on patients with metastatic breast cancer has been documented with satisfactory tolerability and definite activity (6).

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Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CT, computed tomography

Paclitaxel, first extracted from the bark of *Taxus brevifolia* (Pacific yew) during the 1960s, is a potent inhibitor of cell proliferation by acting on microtubule formation (7) and shows cytotoxic activity against several murine tumors, including breast, ovarian, lung and head and neck cancers (8). Although this medication was characterized in 1971 by Wani et al. (7), the clinical potential became apparent only when Schiff and colleagues described the unique mechanism of paclitaxel in 1979 (9).

Several toxicities have been reported, including hematological, neuromuscular, cardiac, gastrointestinal and hypersensitivity reactions (10). Leukopenia, anemia and neuromuscular side effects, including paresthesias and arthralgia are most frequently encountered (10). Hypersensitivity reactions now can be controlled by giving standard premedication including steroids before the chemotherapy (11). Neutropenia is a dose-limiting toxicity in most studies and is dose and schedule dependent, but with less neutropenia seen with 3 h infusion. Thrombocytopenia and anemia are also not common in the 3 h infusion regimen (8). Based on the above, we utilized a 3 h infusion protocol to prevent unnecessary adverse reactions.

Prolonged infusion of paclitaxel increases the possibility of cytotoxicity; hypersensitivity reactions and the response rate may also increase (12). In our study, however, considering the safety of infusion in moderate doses (175 mg/m^2), paclitaxel was given over a 3 h duration, leading to less side effects and toxicities.

Table 1. Patients' characteristics

Characteristic		No.
No. of patients		14
Course of treatment	Total	75
	Average	5.35
	Range	3–14
Age (years)	Average	48.7
	Range	39–56
Performance status	0	0
	1	12
	2	2
Site of metastases	Liver	2
	Lung	6
	Liver and lung	1
	Lymph nodes	2
	Contralateral breast	1
Prior adjuvant chemotherapy	Yes	14
	No	0
Estrogen receptor	Yes	8
Progesterone receptor	Yes	4

PATIENTS AND METHODS

PATIENTS

Between May 1999 and April 2000, 14 women with metastatic breast cancers were eligible to be enrolled in this study (Table 1). The median age of the remaining 14 patients was 48.7 years (range 39–56 years). All of them were definitely evidenced as having metastatic breast cancers and received complete courses of anthracycline-containing agents (FAC; fluorouracil 500 mg/m^2, adriamycin 50 mg/m^2, cyclophosphamide 500 mg/m^2) before applying paclitaxel.

All patients eligible for this study had to fulfil all of the following criteria: histological proof of metastatic breast cancer; measurable disease, unless a subsequent progression was documented; age older than 18 years; and a life expectancy of more than 3 months. Prior adjuvant chemotherapy was allowable if it had been completed at least 3 months before this study. All patients were required to have an ECOG performance status of <2 and to have adequate hematopoietic function as evidenced by leukocyte count >4000/μl and platelet count >100 000/μl.

TREATMENT

The chemotherapy regimen utilized single-agent paclitaxel (Anzatax, Faulding, Australia) at a dose of 175 mg/m^2 over a 3 h infusion and the treatment was repeated every 3 weeks. All patients were pretreated with hydrocortisone 20 mg intravenously 1 h, allermin 20 mg intravenously 30 min and cimetidine 150 mg intravenously 20 min before each treatment. For prevention of vomiting, all patients received ondansetron as antiemetic treatment.

RESPONSE CRITERIA

Response was evaluated using Eastern Cooperative Oncology Group (ECOG) criteria. Complete response (CR) was defined as the complete disappearance of all known lesions documented by two separate observations at least 4 weeks apart and without the appearance of any new lesions. Partial response (PR) required at least a 50% reduction in the cross-sectional area of the indicator lesion (or sum of areas if there was more than one indicator lesion), again documented by two separated observations at least 4 weeks apart, with no individual lesion growing and no new lesion appearing. Stable disease (SD) was defined as a <50% reduction or <25% increase in the sum of cross-sectional areas of all measurable lesions, with no appearance of new lesions for at least 4 weeks. Patients were considered to have progressive disease (PD) when any lesion grew >25% in cross-sectional area or when any new lesion appeared.

EVALUATION AND FOLLOW-UP

Pretreatment evaluation included a detailed medical history, physical examination, complete blood and biochemical surveys, ECG, chest X-ray, bone scan, liver ultrasound and/or abdominal computed tomography (CT) scan. Complete blood

Table 2. Response to chemotherapy

Response	Overall	Metastatic site		
		Liver	Lung	Lymph nodes
CR	0% (0)	–	–	–
PR	29% (4)	–	2/7	2/2
SD	21% (3)	1/2	2/7	–
PD	50% (4)	1/2	3/7	–

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3. Comparison between several studies on utilizing paclitaxel as salvage therapy

Trial	Dose (mg/m^2)	Schedule	Assessable patients	Overall response rate (%)
Nabholtz et al. (23)	175	q 3 wk	38	26
Michael et al. (24)	175	q 3 wk	24	25
Seidman et al. (25)	175	q 3 wk	21	21
Fountzilas et al. (26)	175	q 3 wk	33	42
Gianni et al. (27)	175	q 3 wk	50	38
This study	175	q 3 wk	14	29

count (CBC), blood biochemistry and carcinoembryonic antigen were repeated prior to each course of chemotherapy. However, patients underwent CBC between courses only in case of fever or severe mucositis. Antitumor response was assessed every three cycles by giving a required abdominal sonography or CT scan to document measurable or evaluable disease or after every cycle if the clinical examination results were adequate for response evaluation. All material pertaining to assessing tumor response and tumor progression was evaluated by one of the authors and one independent radiologist. Adverse effects were evaluated according to the ECOG criteria. Patients with CR, PR or SD remained in the protocol until progressive disease or unacceptable toxicity was documented. This study was divided into a two-stage design as presented by the Early Clinical Trials Group (ECTG) of the EORTC. Such trials usually had a two-stage design. In the first stage, 14 evaluable patients were entered and if no response was observed or the response was not satisfactory, then the trial was closed. This approach ensured that if the aim was to identify a drug with at least a 20% response rate, the chance of rejecting it wrongly was 0.044. So, finally, there were 14 patients enrolled in this phase II paclitaxel trial.

RESULTS

Response to Therapy

All of the patients had received adjuvant chemotherapy with a prior anthracycline-based regimen and were considered evaluable for response. A total of 75 cycles were administered with paclitaxel (Anzatax) and all of them were at full dose. The average of treatment courses was 5.35 courses with a median of four delivered cycles (range 3–14). The overall response rate was 28.6% (95% CI: 21–40%). None of these patients achieved complete remission, with four partial remission, three stable disease and seven progressive disease. The response data with the respective response to each target organ are summarized in Table 2.

Toxicity

Toxicities were evaluated and graded according to the ECOG criteria (Table 4). These toxicities were generally tolerable. Hematological toxicities were the major adverse effects, including leukopenia and thrombocytopenia. Hepatic dysfunction of grade 2 and 3 was found in 12 courses of treatment, total 16%. No treatment-related death was observed.

Survival

The median time to progression was 3 months. With a maximum follow-up of 13 months at the time of data collection, the median survival was 5 months.

DISCUSSION

Breast cancer is one of the most common malignancies and currently is the fifth leading cause of cancer deaths in Taiwan (13). It is still distressingly common to encounter metastatic breast cancer despite improvements in screening, locoregional control and adjuvant therapy (14). In this situation, systemic chemotherapy is widely adopted for hormone-refractory patients as adjuvant therapy for preventing cancer recurrence or as salvage therapy for metastatic breast cancers (14,15). There is increasing use of anthracycline in the adjuvant setting, and it shows a response rate of 40–70% with a duration of about 12 months (15,16). However, considering the level of relapsed disease after giving anthracycline, more patients are receiving palliative therapy with non-anthracycline-containing

Table 4. Treatment-related toxicity, graded according to ECOG criteria ($n = 14$)

Toxicity	Grade				
	1	2	3	4	Total (%)
Leukopenia	3	15	0	0	18 (24)
Thrombocytopenia	0	0	0	0	0 (0)
Nausea	0	0	0	0	0 (0)
Vomiting	0	0	0	0	0 (0)
Hepatic	0	7	5	0	12 (16)
Renal	0	0	0	0	0 (0)
Cardiac	0	0	0	0	0 (0)
Neurological	0	0	0	0	0 (0)
Infection	0	0	0	0	0 (0)

regimens, such as paclitaxel, vinorelbine or gemcitabine (17). Single-agent paclitaxel has been reported to give an overall response rate of 26–38% (Table 3) (15).

The therapeutic activity of paclitaxel comes through a disruption in the tubulin-microtubular system (18). It binds reversibly and specifically to the β-subunit of tubulin, promoting its assembly and stabilizing the microtubules after spindle formation has occurred. These compounds induce the formation of stable microtubule bundles, impairing reorganization of the microtubular skeleton and blocking the cells in the G_2-M phase of the cell cycle (1). In 1989, the first study of the administration of paclitaxel to patients with ovarian cancer was reported and soon several reports followed with encouraging results, which led to the approval of paclitaxel in many countries for treating recurrent or metastatic ovarian and breast cancer (8). In 1991, Holmes et al. reported a response rate of 56% (12% complete response, 44% partial response) with a 9 month duration of response in patients with metastatic breast cancer, which attracted attention to the use of paclitaxel in this disease (19).

Paclitaxel causes several treatment-related adverse reactions. Hypersensitivity, neutropenia and thrombocytopenia were common, but could be minimized by moderate dosage with 3 h infusion (8,11). Furthermore, utilizing a moderate dosage also prevented possible cumulative adverse reactions, such as neuromuscular toxicities and the appearance of hand–foot syndrome (20). Fixed doses of paclitaxel of 175 mg/m^2 were given as our standard treatment and resulted in only 24% grade I–II bone marrow suppression and 16% grade II–III hepatotoxicity (Table 4).

Attention had always been paid to the issue of bone metastases, which appeared in >80% of patients with metastatic breast cancers, and this disease entity usually caused pain and local bone destruction (21). Hortobagyi et al. indicated that cytotoxic chemotherapy played a major role in treatment of metastatic breast cancer patients with bone metastases (22).

Concerning the responses for visceral organs and soft tissues, based on our experience on utilizing paclitaxel with metastatic breast cancer patients, we found that patients with lymph node involvement (2/2) were much more sensitive to paclitaxel than patients with lung or liver metastases.

CONCLUSION

We have reported data on interim analysis for a two-stage design, although it was not a standard presentation for a clinical study because it was only a small-scale phase II trial with poor reliability of the response rate. However, the present study could be useful in demonstrating that single-agent paclitaxel at 175 mg/m^2 delivered by 3 h infusion has moderate activity in metastatic breast cancer and can be easily administered in the clinic with manageable toxicity.

Acknowledgements

We especially thank Centapharm, Taiwan, for providing assistance. The paclitaxel that we utilized (Anzatax) was obtained from Faulding (Australia). This work was financially supported by the Taiwan Cancer Clinic Foundation.

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