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Clinical report

Single-agent docetaxel in metastatic breast cancer patients pre-treated with anthracyclines and paclitaxel: partial cross-resistance between paclitaxel and docetaxel

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The purpose of this study was a retrospective analysis of docetaxel in a cohort of anthracyclines and paclitaxel pre-treated patients with metastatic breast cancer. From July 1998 to June 1999, 24 consecutive patients were included for this study. The regimen consisted of docetaxel 75 mg/m^2 in combination with a 3-day schedule of dexamethasone every 3 weeks until disease progression or unacceptable toxicity. The median age of patients was 53 (ranged 32–67) years with a median performance status of 2. Twenty of the 24 patients (84%) had measurable disease. The median number of organs involved was 2 (range 1–4). A total of 146 cycles chemotherapy were given with a mean of 6. There was a 25% (six of 24) overall response rate including one complete response, 37.5% stable disease and 37.5% progressive disease. The major toxicity included grade 3–4 leukopenia (41.7%) and eight episodes of infection. No treatment-related death was observed. The responders included patients refractory to or resistant to prior paclitaxel treatment. The median survival and median time to disease progression was 12 and 9 months, respectively. We conclude that docetaxel has a modest activity in breast cancer patients pre-treated with anthracyclines and paclitaxel, indicating a partial cross-resistance between paclitaxel and docetaxel. [© 2000 Lippincott Williams & Wilkins.]

Key words: Breast cancer, chemotherapy, docetaxel.

Introduction

Treatment of metastatic breast cancer is usually disappointing despite the recent advance in systemic chemotherapy. Often, there is little impact on overall survival. With any single or combination agents, the purpose of chemotherapy for metastatic breast cancer should be that of controlling symptoms, improving quality of life and prolonging survival. Furthermore, tumors resistant to first-line chemotherapy generally are less responsive to second- and third-line drug regimen.[1,2] Anthracyclines play a central role in the treatment of breast cancer for patients with endocrine therapy-resistant metastatic disease. Anthracycline-based regimens produced a 50–75% response rate with a less than 15% complete response rate and the median survival ranged from 12 to 24 months.[3] In the early 1990s the development of a novel class of chemotherapeutic agent, taxanes, led to a new era of chemotherapy for breast cancer. In a review by Pivot *et al.* only studies using taxanes (paclitaxel or docetaxel) reported an activity in anthracycline-resistant populations, allowing a response rate of 6–50 and 32–57% for both agents, respectively.[4] Taxanes have moved from initial marketing approval of second-line therapy to the current time point of front-line therapy in both adjuvant and metastatic settings.[5] However, after taxanes, there is no universal consensus for salvage treatments. In clinical practice, treatment should be justified individually for palliation and prolonging disease-free survival with the least toxicity. The approval of capcitabine after failure of paclitaxel therapy in metastatic breast cancer represents one of these opinions.[6]

Both of the taxanes share a similar mechanism of action: they promote microtubule assembly and inhibit the depolymerization of tubulins.[7,8] There are differences in the formation of the stable, non-

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functional microtubule bundles and in the affinity of the two compounds for binding sites.[9] In addition, taxanes have been linked with induction apoptosis and antiangiogenesis.[10,11] *In vitro* analyses demonstrate docetaxel to be 100-fold more potent than paclitaxel in bcl-2 phosphorylation and apoptotic cell death.[10] *In vivo* evidence has postulated that both drugs have partial cross-resistance despite the fact they share similar anti-tumor mechanisms.[12] Clinically, anti-tumor activity of docetaxel in several phase II studies as monotherapy has reached approximately 60%.[13] Randomized studies have shown the superiority of docetaxel over doxorubicin in alkylating agent and mitomycin C, vinblastine pre-treated anthracycline-resistant breast cancer.[14,15] As a single-agent, docetaxel appears to be one of the most active drugs against metastatic breast cancer, either as frontline or salvage chemotherapy.

In Taiwan, both taxanes were approved as second-line chemotherapy after anthracyclines for metastatic breast cancer. In 1998, 3 years after the approval of paclitaxel in Taiwan, docetaxel was approved for metastatic breast cancer. Our practice routinely used anthracycline-based regimens, most commonly in combination with 5-fluorouracil and cyclophosphamide as first-line chemotherapy for metastatic breast cancer. A paclitaxel-based regimen, using 3-h infusion of 175 mg/m^2 paclitaxel and cisplatin, was used for second-line chemotherapy. Therefore, the delay in drug approval of docetaxel allowed us an opportunity to try it as salvage therapy for patients who were pre-treated with anthracycline and paclitaxel. The current study analyzed the result of a dose of docetaxel at 75 mg/m^2 in this patient population.

Materials and methods

From July 1998 to June 1999, 24 consecutive female patients with recurrent or metastatic breast cancer who received docetaxel were included for analysis. All patients were required to have histology-proven breast cancer. All patients received at least one regimen of anthracycline-based chemotherapy as their adjuvant chemotherapy or as first-line chemotherapy for metastatic disease and one regimen of paclitaxel-based chemotherapy by a 3-h infusion schedule after failure of anthracyclines. All patients have failed this paclitaxel-based chemotherapy by histology or clinical criteria. The definition of chemo-resistance to a regimen was: (i) in patients who receive adjuvant chemotherapy, the recurrence occurred after 12 months of the last dose of chemotherapy or (ii) in patients receiving chemotherapy for metastatic disease, the patient had initial response but subsequently developed recurrent disease. The definition of chemo-refractory to a regimen was: (i) in patients who received adjuvant chemotherapy, the recurrence occurred within 12 months of the last dose of chemotherapy or (ii) progressive disease during induction chemotherapy for a metastatic disease. All patients were required to have adequate hematological studies, renal and liver function, and a performance status on Zubrod's scale equal or less than 2. Chemotherapy consisted of single-agent docetaxel at a dose of 75 mg/m^2 infusion over 1 h every 3 weeks. All patients received a 3-day schedule of dexamethasone orally to prevent complications from docetaxel. Patients continued chemotherapy until disease progression or unacceptable toxicity.

The evaluation of response included physical examination, serum tumor markers, chest roentgenography, bone scan and abdominal computerized tomography scan. Patients were re-assessed after three or four cycles of chemotherapy for response. Concurrent radiotherapy for symptom relief was allowed but the radiation sites were excluded for analysis. Complete response (CR) was defined as disappearance of all measurable disease based on the image studies. Partial response (PR) was defined as 50% or greater decrease in the sum of the products of the largest perpendicular diameters of all measurable lesions or decrease of at least 50% of one dimension of the evaluable lesions for at least 4 weeks without progression of any lesion or appearance of new lesions. Stable disease (SD) was defined as a decrease of the lesion for at least 4 weeks, which did not reach the criteria of PR, or a less than 25% increase of lesions. PD was defined as a 25% or greater increase in the size of one or more evaluable lesions, or the appearance of new lesions. In patients with bone disease only, the image-based criteria could not be applied to evaluate responses. However, if their clinical symptoms improved, no new lesion appeared on the bone scan and serum tumor markers decreased, this patient was classified as having SD. The time to disease progression was measured from the start of therapy to the date of progression for patients who achieved CR, PR and SD. The survival time was calculated from the start of the therapy to the time of death. The survival curves were established by the Kaplan–Meier method. The differences in survival among several prognostic factors were determined by the log-rank test ($p < 0.05$ was considered to be significant).

Results

Patient characteristics

From July 1998 to June 1999, 24 consecutive patients were registered in this study. The patient characteristics are summarized in Table 1. The median age was 53 years. The median performance status was 2 and median number of organs involved was 2. The pre-treatment level of mean serum markers, carcinoembryonic antigen (CEA) and CA 15.3, were 64.4 ± 125.4 ng/ml and 501 ± 1127.8 U/ml, respectively. There were four patients who had bone disease only; the other 20 patients had radiographic bi-dimensional lesions.

Course of treatment

A total of 146 cycles of chemotherapy were given (range 1–13) with a median of 6. One patient received only one dose of chemotherapy and progressed rapidly, she was classified as having PD. All patients received full-dose chemotherapy without dose reduction. The majority of the chemotherapy was given at outpatient clinics.

Table 1. Patient characteristics

Age [years (median)]	32–67 (53)
Performance status (Zubord scale)	
0	1
1	10
2	13
Sites of metastasis	
skin	10
lung	10
liver	10
lymph node	13
bone	11
Number of organs involved	
1	5
2	11
3	6
4	2
Median time to progression [months (range)]	14 (5–55)
Prior chemotherapy	
anthracycline resistant	17
anthracycline refractory	7
paclitaxel resistant	9
paclitaxel refractory	15
Mean CEA (ng/ml)	64.4 ± 125.4
Mean CA 153 (U/ml)	501 ± 1127.8

Response

One patient achieved a CR. This patient had multiple chest wall recurrence as well as contralateral breast metastases. After chemotherapy, all of the lesions disappeared as documented by ultrasound. There were an additional five partial responses totally accounting for a 25% overall response rate. Three of the four patients who had bone disease only had improved pain symptoms and performance status as well as a more than 50% reduction of pre-treatment serum markers. However, according to our criteria, these patients were classified as having SD. There were nine patients with SD and nine patients had PD. The relationship between the response to docetaxel and to prior chemotherapy is summarized in Table 2. It appeared that there was partial cross-resistance between docetaxel and paclitaxel or anthracyclines. In addition, the response to docetaxel shows no correlation between the response to prior paclitaxel or anthracyclines.

Survival

The median survival was 12 months in a median follow-up period of 14 months. The time to disease progression among the 15 patients with response or SD was 9 months. The survival analysis has not shown any difference among various prognostic factors, including tumor steroid receptors status, response to prior chemotherapy, performance status, sites of disease (visceral versus soft tissue disease) and times from metastatic disease to docetaxel treatment (12 months or less versus more than 12 months).

Toxicity

The most severe toxicity according to NCI toxicity criteria observed in each individual patient is summar-

Table 2. Response stratified by prior chemotherapy

	Anthracycline		Paclitaxel	
	Refractory	Resistance	Refractory	Resistance
Response	1	5	3	3
Non-response[a]	6	12	12	6
Total	7	17	15	9

[a]Includes PD and SD.

Table 3. Toxicity

	Grade				
	0	1	2	3	4
Leukopenia	11	1	2	2	8
Asthenia	13	7	4	0	0
Vomiting	19	2	2	0	1
Neurotoxicity	8	11	4	1	–
Allergy	23	1	0	0	0
Skin	19	5	0	0	0
Fluid retention	18	4	1	1	0

ized in Table 3. Grade 3 and 4 leukopenia was the most common side effect with eight episodes of infectious complications. There were no thrombocytopenia. No treatment-related death was observed. Many patients experienced mild and transient myalgia or other neurological problems. It usually disappeared within 3–5 days. Vomiting was not a common problem but one patient developed grade 4 toxicity. This was controlled with ondansetrone in the subsequent cycles. Fluid retention is a notorious complication of docetaxel, especially after multiple doses. It occurred in seven (29%) patients, but only one patient had to stop the chemotherapy due to grade 3 fluid retention. In general, the dose of 75 mg/m^2 docetaxel was tolerable and the related toxicity was manageable even in such a heavily pre-treated patient population.

Discussions

The retrospective analysis demonstrated a 25% response rate with docetaxel in patients pre-treated with paclitaxel and anthracyclines. The response occurred in patients who had prior resistance or were refractory to paclitaxel or anthracyclines. In addition, three patients who had bone disease only had a clinical significant improvement, i.e. reduced bone pain and improved performance status. The median survival was 12 months. This was not frequently observed for a cohort of third-line chemotherapy. The toxicity was manageable, even in such a heavily pre-treated patient population. Our analysis suggests that docetaxel exhibited partial cross-resistance with paclitaxel and is a feasible regimen for patients with metastatic breast cancer after failure from frontline therapy.

The present 25% response rate was understandably low in comparison with those of other phase II trials of single-agent docetaxel used as first- or second-line chemotherapy.[12,16–20] However, this result was comparable with a prospective phase II study conducted by Valero *et al.* who used single-agent docetaxel at a dose of 100 mg/m^2 in patients with paclitaxel-resistant metastatic breast cancer.[21] Although the overall response rate was only 18%, for those patients who received 1- or 3-h infusion of paclitaxel, the response rate reached 25%. Archer *et al.* reported a series of single-agent docetaxel in patients who had received at least two prior chemotherapy regimens for metastatic breast cancer. In their retrospective analysis of 22 patients who received an initially planned 100 mg/m^2 of docetaxel, a 24% response rate with one CR was reported.[21] It seemed, even as third-line chemotherapy, docetaxel could reach a response rate of about 25%. Valero *et al.* suggested a partial cross-resistance between paclitaxel and docetaxel. However, the present observation as well as their observation was based on patients who received 1- or 3-h infusion of paclitaxel. It is unclear if this phenomenon also occurs with 24-h infusion of paclitaxel.

Our study differed from those of the prior two studies on the planned dose of docetaxel. It was recommended and tried in many series to start docetaxel at the dose of 100 mg/m^2, dose reduction is allowed to 75 mg/m^2 and even 55 mg/m^2.[16–20] A number of studies have postulated that the response rates of single docetaxel were higher at the dosage of 100 mg/m^2.[18,19,22] We chose 75 mg/m^2 as our starting dose for two reasons. All patients were heavily pre-treated with anthracyclines and paclitaxel, and the tolerance of further chemotherapy with a regimen of moderate myelo-toxicity was poor. In the series of Archer *et al.* 50% of the patients had to reduce dosage—three of them reduced to 55 mg/m^2.[22] In addition, a first-line phase II study conducted by Dieras *et al.* used 75 mg/m^2 as a starting dose. The response was even up to 52% and the incidence of febrile neutropenia reduced to 7.7%.[17] Second, although there were no documented phase I studies in the Chinese population, docetaxel was approved in Japan at the dose of 60 mg/m^2 because of the concerns about toxicity following earlier phase trials in Japan. At this relatively lower dosage, a 44% response rate was observed as first- or second-line therapy.[23] Compared with a similar study from Valero *et al.*, who used 100 mg/m^2 of docetaxel, our frequency of febrile neutropenia was comparable even though the dosage of our series was smaller.[20] In addition, there was no dose reduction in our series and no patient discontinued treatment due to neutropenia or treatment-related death. It is suggested that 75 mg/m^2 perhaps is the optimal dosage for heavily pre-treated patients and for the Asian patient population.

Serious side effects observed in our patients were leukopenia and febrile neutropenia. A grade 3 or 4 leukopenia (42%) was the most serious side effect. In

addition, asthenia and transient myalgia or neuralgia were commonly observed. The overall toxicity was acceptable; only one patient discontinued chemotherapy due to fluid retention after eight cycles of treatment. It was reversible after discontinuation and administration of diuretics. No treatment-related death occurred. The acceptable toxicity of this dosage regimen reached the goal of palliation and relieving symptoms at the minimal toxicity.

In conclusion, our study further demonstrated partial cross-resistance between paclitaxel and docetaxel. Single-agent docetaxel at a dose of 75 mg/m^2 is an active regimen after anthracycline and paclitaxel for metastatic breast cancer with manageable toxicity.

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