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Original Paper

Phase II Study of Semisynthetic Paclitaxel in Metastatic Breast Cancer

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The aim of this phase II study was to characterise the efficacy and toxicity of semisynthetic paclitaxel in patients with metastatic breast cancer. Eligible patients had measurable disease and had been treated with one prior chemotherapy regimen either as adjuvant or for metastatic disease. Semisynthetic paclitaxel was given at a dose of 175 mg/m^2 over 3 h every 21 days with dexamethasone, cimetidine and diphenhydramine premedications. 31 patients were entered. All were evaluable for toxicity. 30 patients were evaluable for response because 1 patient was lost to follow-up after receiving one cycle. One patient achieved a complete response and 10 patients achieved partial responses for an overall response rate (CR+PR) of 37% (95% confidence interval 20–56%). 17 patients (55%) experienced at least one episode of grade 3 or 4 neutropenia. There were two episodes of febrile neutropenia complicating 155 cycles of therapy. One of these resulted in a treatment-related death in a patient with pulmonary metastasis. 3 patients required dose reductions for grade 3 sensory neuropathy. Our study shows that the antitumour activity and toxic effects of semisynthetic paclitaxel appear to be identical to the naturally occurring product. © **1997 Elsevier Science Ltd.**

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INTRODUCTION

PACLITAXEL IS an antimicrotubule agent derived from the bark of the Pacific yew, *Taxus brevifolia*, a slow growth tree native to the old-growth forests of the Pacific Northwest. This agent was originally isolated in 1971 and was subsequently developed as an antineoplastic agent because of its unique mechanism of action: promotion of microtubule polymerisation and inhibition of microtubule depolymerisation preventing reorganisation of the cytoskeleton, thus interfering with vital cellular functions [1, 2].

Phase II clinical trials showed significant antitumour activity for paclitaxel using a variety of doses administered over 24 h in patients with ovarian and breast cancers [3–5]. Subsequently, trials of the 3 h infusion schedule also showed significant antitumour efficacy in both minimally and extensively pretreated patients with ovarian and breast cancers [6–9]. A multicentre phase III randomised trial comparing 3 h infusions of paclitaxel at doses of 135 or 175 mg/m^2 showed 22% and 29% response rates, respectively [10]. Based on these data, the U.S. Food and Drug Administration approved paclitaxel for use in metastatic breast cancer at a dose of 175 mg/m^2 via 3 h infusion in 1994 following its earlier approval for refractory ovarian cancer [11].

When the significant antineoplastic activity of paclitaxel was recognised, concerns arose because of its limited availability from the source, the Pacific yew tree. Paclitaxel is present in the yew's bark in such small amounts that the sacrifice of a 100-year old tree will yield approximately 3 kg of bark containing 300 mg of paclitaxel, which is often enough

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for only one dose [12]. Thus, a search for alternative sources was undertaken. Potential options for increasing the supply of paclitaxel while not depleting the natural supply include semisynthesis, total synthesis and cellular culture production. Plant tissue culture methods are still being explored at this time and have not yet yielded supplies of paclitaxel. Total synthesis has been accomplished by two groups led by K.C. Nicolaou of the Scripps Research Institute and Robert Holton of Florida State University, U.S.A. [13, 14]. However, these total synthetic processes require over 30 steps to make paclitaxel and thus are not yet commercially viable options to mass produce paclitaxel. Thus, the only reasonable option presently available is the semisynthesis of paclitaxel from a precursor molecule 10-deacyl baccatin III. This can be isolated from the needles of various *Taxus* species including *Taxus baccata* and is used in the preparation of semisynthetic paclitaxel [15–17]. 10-deacyl baccatin III is modified by adding β-lactam side chains and after a series of chemical manoeuvres yields paclitaxel. This semisynthesis overcomes the supply problem as the needles which yield the precursor regenerate and can be derived from younger *Taxus* bushes and thus may provide continuous available sources of precursor molecule. The same precursor molecule is used to produce docetaxel semisynthetically, using different side chain surrogates, namely oxazolidines. Despite the fact that the molecular structure of paclitaxel is the same whether it is produced semisynthetically or from natural sources, evidence of its safety and efficacy was necessary before it could be widely substituted for the naturally derived product. Hence, we conducted this phase II study to identify the efficacy and toxicities of semisynthetic paclitaxel in patients with metastatic breast cancer.

PATIENTS AND METHODS

Patient selection

Eligibility criteria included histologically confirmed breast cancer with clinical evidence of metastatic disease and at least one bidimensionally measurable lesion. Patients were required to have received one prior non-taxane containing chemotherapy regimen either as adjuvant therapy or as treatment for metastatic disease. They could not have received chemotherapy within 3 weeks of study entry and no radiation therapy within 4 weeks of entry. Hormonal treatment used in either the adjuvant or metastatic setting must have been discontinued at least 3 weeks before study entry.

All patients were required to have a Karnofsky performance status $\geq$ 60%, estimated life expectancy $\geq$ 12 weeks, adequate haematological function (absolute neutrophil count (ANC) $\geq$ 1500 cells/μl, haemoglobin $\geq$ 8.0 g/dl, and platelet count > 100 000/μl), adequate hepatic and renal function (total serum bilirubin < 1.5 mg/dl and serum creatinine < 1.4 mg/dl) and normal serum calcium (serum calcium 8–10.5 mg/dl).

The protocol was approved by the institutional review boards of the Memorial Sloan-Kettering Cancer Center and the M.D. Anderson Cancer Center and all patients provided informed consent. All data were managed in a central data registry at each site with the main registry located at Memorial Sloan-Kettering Cancer Center.

Methods

Pretreatment evaluation consisted of a complete medical history, physical examination, and blood tests including complete blood count (CBC), liver and kidney functions, and pregnancy test by beta-human chorionic gonadotropin (β-HCG) if appropriate. All patients had an electrocardiogram and a baseline echocardiogram or MUGA scan. A baseline chest X-ray and nuclear bone scan as well as other appropriate imaging studies to document the extent of disease were also obtained before treatment began. CBCs were obtained weekly between treatments. Liver and kidney function tests as well as a repeat history and physical examination with documentation of toxicity and tumour measurements (if obtainable by physical examination) were performed before each cycle. Appropriate imaging studies to assess objective response were performed after every two cycles of treatment.

Treatment consisted of semisynthetic paclitaxel at a dose of 175 mg/m^2 administered as a 3 h intravenous infusion every 3 weeks. To prevent hypersensitivity reactions, all patients were premedicated as follows: dexamethasone 20 mg orally self-administered 12 and 6 h before semisynthetic paclitaxel, diphenhydramine 50 mg and cimetidine 300 mg intravenously 30 min before treatment.

The National Cancer Institute (NCI) common toxicity criteria grading system was used [18]. For toxicities not included in the NCI grading system, a similar four-level scale was employed. Dose modifications were specified based on the observed toxicities. Semisynthetic paclitaxel doses were reduced one level (to 140 mg/m^2) for grade 4 neutropenia lasting $\geq$ 7 days, for grade 3 or 4 thrombocytopenia, or for grade 3 non-haematological toxicities. Doses were reduced two levels (to 110 mg/m^2) for febrile neutropenia (defined as oral, tympanic or rectal temperature $\geq$ 38°C with ANC < 1000 cells/μl), for bleeding requiring transfusions, or for grade 4 non-haematological toxicities. Dose escalations to 200 mg/m^2 and subsequently to 250 mg/m^2 were permitted if the ANC nadir was > 1000 cells/μl and the platelet nadir was > 75 000/μl in the absence of grade 2 or greater non-haematological toxicity.

Complete response (CR) was defined as the disappearance of all clinical evidence of tumour by physical examination and imaging studies for a minimum of 4 weeks. Partial response (PR) was defined as a $\geq$ 50% reduction in the sum of the products of the biperpendicular diameters of all measurable lesions without the appearance of any new lesion, for at least 4 weeks. Stable disease (SD) included regression not meeting the criteria of complete or partial responses. Disease progression (PD) was defined as the appearance of any new lesions, an increase by $\geq$ 25% of an indicator lesion or sum of the product of the biperpendicular diameters of the measured lesions or any increase in the estimated size of a non-measurable lesion [19].

RESULTS

Patient characteristics

31 patients were enrolled from July 1994 to September 1995 at the Memorial Sloan-Kettering Cancer Center and the M.D. Anderson Cancer Center. All patients were off-study as of April 1996. 2 patients were found to be ineligible because they had received two prior chemotherapy regimens, but are included as fully evaluable for toxicity and response. Hence, 31 patients are evaluable for toxicity and 30 patients are evaluable for response because one other patient received only one dose of semisynthetic paclitaxel and was lost to follow-up.

Patient characteristics are listed in Table 1. The median number of sites of disease was two and visceral disease was present in 77% of patients. 29 patients had received one prior

Table 1. *Patient characteristics*

Characteristic	Number (%)
Total number of patients treated	31
No. evaluable for response	30
No. evaluable for toxicity	31
Median age (years)	54
Range	28–77
Median Karnofsky performance status (%)	90%
Range	70–100%
Median no. of sites of disease	2
Range	1–5
Involved organ systems*	
Breast	1 (3%)
Skin/soft tissue	5 (16%)
Lymph node	8 (26%)
Bone	6 (19%)
Visceral	24 (77%)
Lung	15 (48%)
Pleura	6 (19%)
Liver	12 (39%)
Other viscera	2 (6%)
Prior anthracycline	21 (68%)

*Total % of involved organ sites is greater than 100% because the median number of disease sites was 2, i.e., most patients had multiple sites of disease.

chemotherapy regimen: 20 in the adjuvant setting and 9 for metastatic disease. The two ineligible patients had received adjuvant chemotherapy more than 10 years before protocol entry, in addition to more recent chemotherapy for metastatic disease. Anthracycline therapy had been previously received by 68% of patients. Of the 20 patients who had received prior adjuvant treatment, the median interval from adjuvant treatment to therapy for metastatic disease was 21 months (range 1–99 months); 13 of these patients had been treated with prior hormone therapy; and one patient's disease progressed within 6 months of anthracycline-based adjuvant therapy. Of the 11 patients who received semisynthetic paclitaxel as second-line therapy for metastatic disease, 2 patients were anthracycline-refractory (i.e. progression of disease while on or within 2 months of discontinuing anthracycline therapy). The median interval between the cessation of anthracycline therapy and study entry in these patients was 5 months (range 1–67 months).

Response

Among 30 patients evaluable for response, one patient (3%) achieved a CR and 10 patients (33%) achieved PR yielding a response rate of 37% (95% confidence interval 20–56%). 8 patients (27%) had SD while 11 patients (37%) had PD (Table 2).

Table 2. *Response to therapy* (n = 30 *patients)*

Response	Number (%)
CR	1 (3%)
PR	10 (33%)
CR+PR*	11 (37%)
SD	8 (27%)
PD	11 (37%)

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

*Median duration of response was 5 months with a range of 3–7.5 months.

Of the 7 patients who received semisynthetic paclitaxel as second-line therapy for metastatic disease, 4 patients had SD and 3 had PD as their best response with the study treatment. Of the 3 patients who progressed within 6 months of anthracycline therapy (1 in the adjuvant setting and 2 in the metastatic setting), 2 had SD while one experienced PD after paclitaxel treatment.

Responses were seen at all sites of disease. There were no responses in the 3 patients with greater than three sites of disease involvement.

The median duration of response for the 10 patients with CR or PR was 5 months (range 3–7.5). One of the 11 responding patients was not evaluable for duration of response because she withdrew from study after reaching a PR to undergo high-dose stem-cell supported chemotherapy. For the 18 patients with SD, PR or CR (S.D. = 8, PR + CR = 10), the median time to progression was 5 months (range 1–7.5). For the entire cohort ($n = 30$), the median time to progression was 4 months (range 1–7.5).

Toxicity

17 patients (55%) had grade 3 or 4 neutropenia (Table 3). The frequency of neutropenia was similar across multiple cycles. During a total of 155 cycles of therapy, there were two episodes of febrile neutropenia. One patient was admitted to the hospital with fever, pulmonary metastasis and hypoxia and died while neutropenic after the first cycle of semisynthetic paclitaxel. Her chest X-ray showed previously recognised pulmonary nodules without an associated infiltrate and sputum cultures only revealed normal pharyngeal flora. Another patient was hospitalised for a catheter-related bacteraemia and was treated with intravenous antibiotics 10 days after semisynthetic paclitaxel. There were nine episodes of minor infections that did not require hospitalisation. These occurred with $\leq$ grade 2 neutropenia and were treated with oral antibiotics.

4 patients (13%) had $\geq$ grade 1 thrombocytopenia. No grade 4 thrombocytopenia was seen and no platelet transfusions were required. 10 patients (32%) became anaemic (defined as haemoglobin < 10 g/dl). 2 more patients (6%) were anaemic (haemoglobin of 8–9 g/dl prior to starting treatment) and required packed red blood cell transfusions during therapy.

The non-haematological side-effects observed in this study are listed in Table 4. Nausea and vomiting, although common, were mild. One-third of patients experienced stomatitis but this was always $\leq$ grade 2. The most commonly reported cutaneous effect was pruritis which was usually mild, but 2 patients (6%) required additional antihistamine medications. Alopecia was reported in 26 of 31 patients (84%) and was grade 2 in 68% of patients in this study.

Neurosensory toxicity was common. The most frequent manifestation of neurotoxicity was mild numbness and tingling in the fingers and toes, seen in 44% of patients.

Table 3. *Haematological toxicity* (n = 31 *patients)*

	NCI grade				
	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)
Neutropenia	0	8 (26)	6 (19%)	8 (26)	9 (29)
Thrombocytopenia	27 (87)	2 (6)	1 (3)	1 (3)	0
Anaemia	19 (61)	9 (29)	1 (3)	2 (6)	0

Table 4. Non-haematological toxicities (grade ≥ 2) (n = 31 patients)

	NCI grade		
	2 (%)	3 (%)	4 (%)
Nausea	6 (19)	0	0
Vomiting	2 (6)	0	0
Diarrhoea	1 (3)	0	0
Stomatitis	3 (10)	0	0
Cutaneous	2 (6)	2 (6)	0
Alopecia	21 (68)		
Neurosensory	7 (22)	3 (10)	0
Neuromotor	1 (3)	0	0
Infection	5 (16)	0	2 (6)
Amylase	0	0	1 (3)
	Non-NCI grade		
	Mild (%)	Moderate (%)	Severe (%)
Myalgias/arthralgias	7 (22)	15 (48)	6 (19)
Fatigue	9 (29)	5 (16)	5 (16)

3 patients (10%) experienced grade 3 neurotoxicity requiring dose reduction. These were the only dose reductions in this study. One patient (3%) experienced grade 2 neuromotor toxicity after eight cycles of semisynthetic paclitaxel.

Moderate or severe myalgias and arthralgias were noted in 68% of patients. 14 patients (45%) experienced some fatigue and 5 patients (16%) experienced severe fatigue.

One patient experienced an episode of supraventricular tachycardia 10 days after semisynthetic paclitaxel and was successfully treated with adenosine. This did not recur with subsequent cycles of treatment.

One patient developed pancreatitis. This was manifested by abdominal pain in the setting of an elevated amylase and lipase after the first cycle of paclitaxel. The patient was hospitalised for 3 days and was treated conservatively with intravenous fluids with resolution of the pancreatitis. An additional cycle of paclitaxel was then administered without a recurrence of pancreatitis, but the patient had disease progression and was removed from study. No patients refused continued treatment or were removed from study due to toxicity.

There were 5 patients who received dose escalations to 200 mg/m^2 during the study and were maintained at that dose level until removal from study for PD.

DISCUSSION

In our study, semisynthetic paclitaxel appears to be indistinguishable from the naturally derived product in both its antitumour efficacy and its toxic effects. Previous studies in similar patients with metastatic breast cancer using the naturally occurring product given at a dose of 175 mg/m^2 over 3 h showed objective response rates of 30–40% [6, 7, 10]. Our objective response rate of 37% is consistent with those results.

The toxicity profile we observed for semisynthetic paclitaxel also appears to be identical to the naturally derived product [4–7, 10, 20–22]. In the multicentre randomised trial by Nabholtz and associates using 175 versus 135 mg/m^2 paclitaxel over 3 h, the toxicities reported were similar to those in this study [10]. Grade 3 and 4 neutropenia occurred in 67% in the 175 mg/m^2 dose arm in the multicentre trial and was 55% in our trial. Grade 3 and 4 thrombocytopenia was 3% in both studies; grade 3 and 4 anaemia was seen in 4% compared with our 6%; febrile neutropenia was seen in 4% compared with our 6%. Grade 3 and 4 neuropathy occurred in 10% of our patients and in 7% of the patients in the multicentre study. We did, however, observe pancreatitis which was previously an unpublished toxicity. However, as part of the compound's safety monitoring performed by Bristol-Myers Squibb, isolated cases of pancreatitis occurring in patients given naturally sourced paclitaxel have been identified and reported to regulatory authorities (Dr Renzo Canetta, Bristol-Myers Squibb, 8/21/96) [23]. Hence, this toxicity is not unique to the semisynthetic product. Furthermore, there is no evidence that semisynthetic paclitaxel is associated with any other unique risks such as the poorly understood syndrome of fluid retention associated with the other semisynthetic taxane, docetaxel [24–26].

Semisynthetic paclitaxel provides a good solution to the problems of the limited availability of the naturally occurring product and the known deleterious environmental impact of harvesting the natural source. Moreover, it represents a step forward toward reaching complete independence from the risks associated with reliance on agricultural sources. The fact that the end product is indistinguishable from the naturally derived one is reassuring and provides additional motivation for the ongoing efforts aimed at commercially viable complete synthesis.

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