Anti-Cancer Drugs 1996, **7** (suppl 2):17–19

Treatment of patients resistant to paclitaxel therapy

V Valero

University of Texas MD Anderson Cancer Center, Department of Breast and Gynecologic Medical Oncology, 1515 Holcombe Blvd, Box 56, Houston, Texas, USA.

Although the taxoid drugs, paclitaxel (Taxol®) and docetaxel (Taxotere®) have a broadly similar mechanism of action, there are notable differences in their activities and they are distinct agents. Docetaxel is more potent than paclitaxel with regard to the promotion of the polymerization of tubulin and the inhibition of depolymerization, and has greater antitumour activity in many *in vitro* and *in vivo* tumour model systems. The development of drug resistance is a major problem in the treatment of metastatic breast cancer and observations indicating only partial cross-resistance between docetaxel and paclitaxel *in vitro*, combined with supporting clinical evidence of activity in patients with previously-treated tumours, including anthracycline-resistant breast cancer, led to the implementation of a prospective study of docetaxel treatment in patients with paclitaxel-resistant disease. Preliminary results in 27 patients recruited to this ongoing study indicate that docetaxel has activity in paclitaxel-resistant metastatic breast cancer.

Keywords: Metastatic breast cancer, docetaxel (Taxotere®), paclitaxel (Taxol®), drug resistance.

Introduction

The taxoid drugs, paclitaxel (Taxol®) and docetaxel (Taxotere®), have a similar mechanism of action but are distinct drugs, with notable differences in their preclinical and clinical profiles of activity. In this review, the preclinical differences between the drugs will be summarized before the clinical differences are considered, and the preliminary results of the trial of docetaxel therapy in paclitaxel-resistant patients will be discussed.

Review of preclinical data

Both the taxoid drugs act by promoting the polymerization of tubulin and inhibiting the depolymerization of microtubules. Docetaxel is about twice as potent as paclitaxel in lowering the critical tubulin concentration at which polymerization takes place [1] and as an inhibitor of microtubule depolymerization [2]. Docetaxel is also taken up into cells more rapidly than paclitaxel and has a greater affinity for the tubulin binding site which is common between the two drugs [3,4]. The efflux of docetaxel from cells is also about three times slower than the efflux of paclitaxel [4]. These differences mean that a greater proportion of the docetaxel administered is taken up into cells and it is retained for longer than paclitaxel, which suggests that the effective dose of docetaxel should be lower than that for paclitaxel. This has been confirmed *in vitro* in many, though not all, murine and human tumour cell lines when docetaxel and paclitaxel are used at equitoxic doses [5,6]. Docetaxel has also been shown to be more active than paclitaxel in tumour models *in vivo* [7–9]. Docetaxel is also less schedule-dependent than paclitaxel [5] and shows a stronger correlation between dose and plasma concentration and the area under the plasma concentration–time curve (AUC) [4,10,11].

Clinical differences between docetaxel and paclitaxel are more difficult to define as there have been no direct comparative studies. Both drugs are active in first- and second-line treatment of breast cancer, and in patients with anthracycline-resistant disease, although there is some evidence for greater efficacy with docetaxel (see reports by Trudeau and Ravdin, in this volume). There are some differences between the sensitivities of cancers such as melanoma, gastric cancer and pancreatic cancer, with these two agents [12].

These studies indicate that docetaxel and paclitaxel may have different profiles of activity. Although complete cross-resistance might be expected between two such similar drugs, some preclinical studies indicated only partial cross-resistance between paclitaxel and docetaxel in cell lines in which resistance to paclitaxel had been induced [2,13], and in cells expressing the multidrug-resistance gene [14].

These preclinical and clinical results led to the implementation of a prospective study at four centres in the United States. This study is still ongoing, and interim results are reported here.

Correspondence to V Valero

Methods

Patient selection criteria were standard phase II criteria and included histologically confirmed metastatic breast cancer with at least one bidimensionally measurable lesion and Karnofsky performance status of at least 60%. Patients must have had no more than two prior regimens of therapy for metastatic disease and must have experienced disease progression after at least two cycles of paclitaxel therapy. The recommended dose and schedule of docetaxel, 100 mg/m^2, intravenously over 1-h every 3 weeks was given until progressive disease was apparent, or toxicity became unacceptable. The two arms of this study involve patients who have been given a) paclitaxel 135–175 mg/m^2, or b) 176–250 mg/m^2. All patients were treated with prophylactic corticosteroids from the day prior to docetaxel infusion for a total of 5 days, in each treatment cycle. The objectives of this study are to determine the response rate, duration of response, and toxicity of docetaxel in this patient population, and to assess changes in the quality of life of patients receiving docetaxel. Quality of life scores will be correlated with response rates and toxicity frequencies at the end of the study. The characteristics of the patients recruited onto this study to date are summarized in Table 1.

Results

The objective responses obtained to date are summarized in Table 2. The objective response rate for the 24 evaluable patients treated to date is 12.5%, with one complete response and two partial responses, and 22% of patients have stable disease. The response durations cannot be assessed at this early stage. The toxicities experienced have been those seen in other studies. Febrile neutropenia has occurred in 22% of patients. Severe fluid retention has occurred in only two patients (7.4%) and severe asthenia has been reported in seven patients (26%). Other severe toxicities have been uncommon, with two patients (7.4%) suffering grade 3 sensory neuropathy, three patients (11%) grade 3 diarrhoea, and three patients (11%) grade 3 infection.

Table 1. Patient characteristics: prior treatment with paclitaxel

Characteristic	Prior paclitaxel dose 130–175 mg/m^2	Prior paclitaxel dose > 175 mg/m^2
Evaluable patients	19	8
Age range (years)	26–65	29–61
Median Karnofsky status (range)	90 (60–100)	90 (70–100)
Median number of sites (range)	2 (1–3)	2 (1–4)
Disease sites (%)		
Liver	58	50
Bone	26	50
Skin/soft tissue/nodes	74	75
Lung	32	50
Other	0	13
Prior anthracycline treatment	95	88

Table 2. Efficacy results for treatment with docetaxel following disease progression with paclitaxel

Type of response	Patients (n = 27)
Complete	1 (3.7%)
Partial	2 (7.4%)
Stable	6 (22.2%)
Progression	15 (55.6%)
Non-evaluable	3 (11.1%)

Conclusions

These preliminary results show that docetaxel has activity in patients with paclitaxel-resistant metastatic breast cancer and that there were no unexpected toxicities in this patient population. These results add to the pool of evidence that paclitaxel and docetaxel have some clinically relevant differences.

References

1. Diaz JF, Andreu JM. Assembly of purified GDP–tubulin into microtubules induced by Taxol and Taxotere: reversibility, ligand stoichiometry, and competition. *Biochemistry* 1993; **32**: 2747–2755.
2. Ringel I, Horwitz SB. Studies with RPR 56976 (Taxotere): a semisynthetic analogue of Taxol. *J Natl Cancer Inst* 1991; **83**: 288–291.
3. Riou JF, Petitgenet O, Combeau C, *et al.* Cellular uptake and efflux of docetaxel and paclitaxel in P388 cell line [abstract]. *Proc Am Assoc Cancer Res* 1994; **35**: 2292.
4. Lavelle F, Bissery MC, Combeau C, *et al.* Preclinical evaluation of docetaxel (Taxotere). *Semin Oncol* 1995; **22** (suppl 4): 3–16.
5. Kelland LR, Abel G. Comparative *in vitro* cytotoxicity of Taxol and Taxotere against cisplatin-sensitive and -resistant human ovarian carcinoma cell lines. *Cancer Chemother Pharmacol* 1992; **30**: 444–450.
6. Braakhuis BJM, Hill BT, Dietel M, *et al. In vitro* antiproliferative activity of docetaxel (Taxotere), paclitaxel (Taxol) and cisplatin against human tumors and normal bone marrow cells. *Anticancer Res* 1994; **14**: 205–208.
7. Bissery MC, Guénard D, Guéritte-Voegelein F, *et al.* Experi-

mental antitumor activity of Taxotere (RP 56976, NSC 628503), a Taxol analogue. *Cancer Res* 1991; **51**: 4845–4852.

8. Boven E, Venema–Gaberscek E, Erkelens CAM, *et al.* Antitumor activity of Taxotere (RP 56976, NSC 628503), a new Taxol analogue, in experimental ovarian cancer. *Ann Oncol* 1993; **4**: 321–324.
9. Dykes DJ, Waud WR, Bissery MC, *et al.* Response of human tumor xenografts in athymic nude mice to Taxotere. *Invest New Drugs* 1995; **13**: 1–11.
10. Gianni L, Munzone E, Capri G, *et al.* Paclitaxel in metastatic breast cancer: a trial of two doses by 3-hour infusion in patients with recurrence after prior therapy with anthracyclines. *J Natl Cancer Inst* 1995; **87**: 1169–1175.
11. Extra JM, Rousseau F, Bruno R, *et al.* Phase I and pharmacokinetic study of Taxotere (RP 56976; NSC 628503) given as a short intravenous infusion. *Cancer Res* 1993; **53**: 1037–1042.
12. Verweij J, Clavel M, Chevallier B. Paclitaxel (Taxol®) and docetaxel (Taxotere®): not simply two of a kind. *Ann Oncol* 1994; **5**: 495–505.
13. Hanauske AR, Degen D, Hilsenbeck SG, *et al.* Effects of Taxotere and Taxol *in vitro* colony formation of freshly explanted human tumor cells. *Anti-Cancer Drugs* 1992; **3**: 121–124.
14. Riou JF, Naudin A, Lavelle F. Effects of Taxotere on murine and human tumor cell lines. *Biochem Biophys Res Commun* 1992; **187**: 164–170.