Pergamon

European Journal of Cancer Vol. 31A, Suppl. 4, pp. S7–S10, 1995

0959-8049/95 $9.50 + 0.00

0959-8049(95)00360-6

Early Clinical Studies with Docetaxel

M. Aapro and R. Bruno
on behalf of the Docetaxel Investigators Group*

Docetaxel has been evaluated in six phase I studies involving a total of 234 patients with a wide variety of tumour types (50% had breast or ovarian cancer). The aims of these studies were to determine the optimal dosage schedule of docetaxel for use in subsequent phase II studies, and to characterise the pharmacokinetic and tolerability profiles of docetaxel. Intravenous (i.v.) doses of docetaxel (5–115 mg/m^2) were administered in various treatment schedules for a total of 790 courses. Cycles were repeated every 2–3 weeks. Dose-dependent neutropenia was the major dose-limiting adverse effect of docetaxel. Other adverse events reported included hypersensitivity, fluid retention, skin reactions, asthenia and alopecia. Anaphylactoid reactions occurred rarely. No abnormal cardiac activity was detected, and neurological adverse events were mild. Docetaxel 100 mg/m^2 administered as a 1 h i.v. infusion every 3 weeks combined acceptable tolerability with complete neutropenic recovery. This dosage schedule was thus considered to be optimal for further investigation in phase II studies.

Key words: docetaxel, phase I clinical studies, pharmacokinetics, adverse events, neutropenia
Eur J Cancer, Vol. 31A, Suppl. 4, pp. S7–S10, 1995

INTRODUCTION

WITH THE exception of interleukin-2, no major new chemotherapeutic agents have been marketed in the past decade. However, research efforts have intensified more recently, and it is expected that several important antineoplastic drugs will be launched worldwide before the end of the century.

Among these new drugs are the taxoids, docetaxel and paclitaxel, both of which have demonstrated interesting activity in a variety of tumours in animals and humans. Paclitaxel, which is obtained from the bark of the Pacific yew tree, was first isolated in 1967, and was subsequently shown to have anticancer properties *in vitro* [1]. Research was later abandoned because of supply and formulation problems; however, interest in the taxoids was rekindled in 1979, when Schiff and colleagues demonstrated that paclitaxel had a novel mechanism of action, causing metaphase arrest through stabilisation of the microtubule infrastructure [2]. Difficulties in procuring sufficient quantities of paclitaxel for clinical investigation led to the investigation of alternative sources of taxoids. Docetaxel (Taxotere®) was a result of this research.

Docetaxel is synthesised from 10-deacetylbaccatin III, a non-cytotoxic constituent of European yew needles. It has been shown to be highly active against a variety of human and rodent tumours *in vitro* and *in vivo* [3–7]. These findings led to the selection of docetaxel for further development in clinical trials. This review summarises the results of early (phase I) clinical studies with docetaxel.

Correspondence to M. Aapro at the European Institute of Oncology, 435 via Ripamonti, 20141 Milan, Italy.
M. Aapro was at University Hospital, Geneva and Clinique de Genolier, Genolier, Switzerland at the time of the study; and R. Bruno is at Rhône-Poulenc Rorer, Paris, France.
*M. Clavel and colleagues, Lyon, France; S. Kaye and colleagues, Glasgow, U.K.; M. Marty and colleagues, Paris, France; R. Pazdur and colleagues, Houston, U.S.A.; M. Piccart and colleagues, Brussels, Belgium; D.D. von Hoff and colleagues, San Antonio, U.S.A.

FORMULATION AND PREPARATION

For use in phase I studies, docetaxel was initially formulated at a concentration of 15 mg/ml, in a diluent consisting of 50% polysorbate 80 and 50% ethanol. However, as the dose of docetaxel was increased during phase I studies, possible adverse effects due to the ethanol component of the vehicle necessitated reformulation. Docetaxel was subsequently reformulated as a 40 mg/ml solution in polysorbate 80.

TREATMENT PROTOCOLS AND PATIENTS

The aims of the phase I studies with docetaxel were:

(i) to determine the dosage schedule to be used in phase II clinical trials
(ii) to determine the tolerability profile of docetaxel in humans
(iii) to characterise the pharmacokinetic properties of docetaxel.

Six phase I studies were performed with docetaxel, and are summarised in Table 1 [8–13]. In total, 234 patients received the drug, and 790 courses of the drug were administered. Patients received total doses of 5–115 mg/m^2, and the maximum tolerated single dose of docetaxel in any study was 115 mg/m^2. Infusion times ranged from 1 to 24 h; however, in one study the dose was divided into five 1 h infusions administered on consecutive days [12] and, in another study, docetaxel was given as two 1 h infusions on days 1 and 8 of each treatment cycle [13]. To allow time for full neutropenic recovery, schedules of docetaxel were administered at intervals of 3 weeks in all studies except one [11], in which some patients received docetaxel treatment every 2 weeks.

Table 1. Dose schedules of docetaxel used in phase I studies

Schedule (reference)	No. of patients	No. of courses	Range of total doses studied (mg/m^2)	Dose-limiting adverse events
1 h [8]	10	32	70–100	Neutropenia
24 h [9]	30	70	10–90	Neutropenia, fever, mucositis
6 h [10]	40	166	5–100	Neutropenia, fever
2 h [10]	18	40	100–115	Neutropenia
1–2 h [11]	65	248	5–115	Neutropenia
1 h × 5 days [12]	39	106	5–80	Neutropenia, fever, mucositis
1 h, days 1 + 8 [13]	32	128	20–110	Neutropenia
Total	234	790	5–115	

Patients

Because other taxoids had demonstrated good activity against breast and ovarian cancer, patients with these tumour types were recruited specifically for phase I clinical evaluation of docetaxel. In addition, patients with tumours of the gastrointestinal tract, lung, kidneys, testes, skin, soft tissue, thyroid and other organs were entered into these phase I studies (Figure 1).

TOLERABILITY

Phase I studies demonstrated that neutropenia is the major dose-limiting side-effect of docetaxel, irrespective of the schedule used. The maximum tolerated dose (MTD) of docetaxel was 115 mg/m^2 (Table 2); of the 9 patients who received this dosage over 1–2 h, 8 developed grade IV neutropenia, 1 of whom became febrile, but was not hospitalised [11]. According to the classic definition of MTD (50% incidence of non-cumulative and dose-dependent neutropenia), the MTD of docetaxel as a single 1–2 h infusion every 3 weeks should be 70–85 mg/m^2; however, because neutropenia at higher doses was of short duration and rarely complicated by fever, patients could tolerate a dose of 115 mg/m^2 [11]. Compared with this higher dose, however, the previous dose level of 100 mg/m^2 produced neutropenia without other severe adverse effects and was recommended for further investigation in phase II studies.

Table 2. Relationship between maximum tolerated total doses of docetaxel and administration schedule

Schedule (reference)	Maximum tolerated total dose (mg/m^2)
1–2 h [11]	115
2 h [10]	115
1 h, days 1 + 8 [13]	110
1 h [8]	100
6 h [10]	100
24 h [9]	90
1 h × 5 days [12]	80

All schedules were repeated every 3 weeks except [11], in which the scheduled was repeated every 2–3 weeks.

The severity of neutropenia was found to be proportional to the dose of docetaxel. Between the MTD range of 85 to 115 mg/m^2 there was a trend for worsening neutropenia at the higher doses. Grade IV neutropenia was uncommon at doses <70 mg/m^2, but at higher doses, 70–100% of patients exhibited myelosuppression (Figure 2). The neutropenia associated with docetaxel therapy was characterised by a median onset of 8 (range 5–15) days, a median duration of 8 days and full recovery within 21 days. The occurrence of concomitant fever and

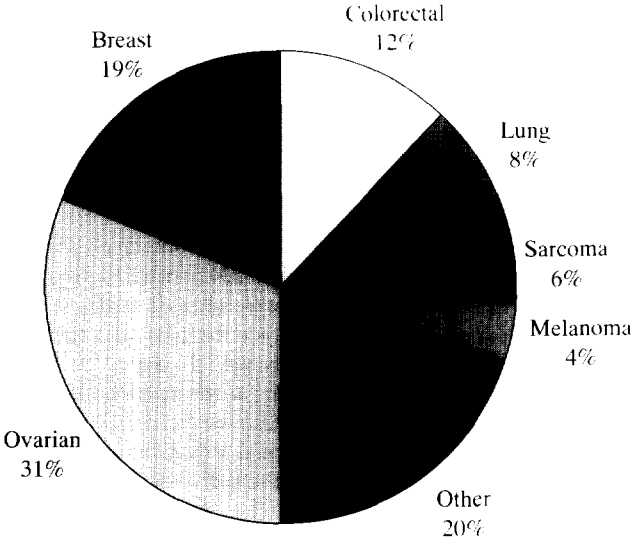

Figure 1. Percentage of various tumour types investigated during phase I studies of docetaxel. A total of 234 patients were treated.

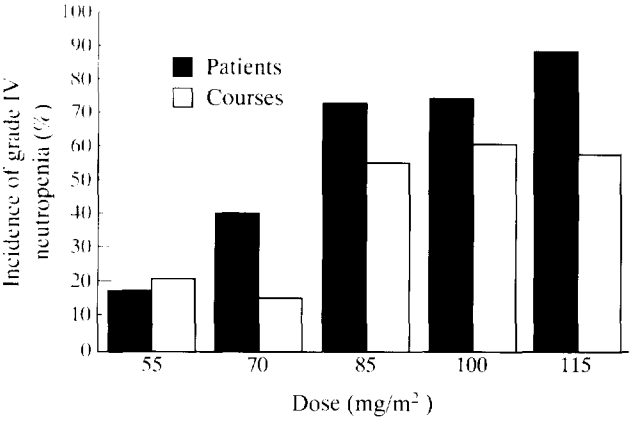

Figure 2. Incidence of grade IV neutropenia in patients receiving 1–2 h intravenous infusions of docetaxel 55–115 mg/m^2 every 2–3 weeks [11].

severe mucositis was associated with more protracted infusion schedules of docetaxel (e.g. 6 or 24 h infusions every 3 weeks or a 1 h infusion on days 1–5 every 3 weeks) [9, 10, 12]. It appears that concurrent oral mucosal ulceration provides a portal of entry for infections. Moreover, longer infusion times were associated with lower MTDs of docetaxel (Table 2). Thus, the infusion time of 1 h was selected as optimum for use in phase II studies.

Docetaxel is known to cause hypersensitivity reactions (HSRs). Overall, definite type I HSRs occurred in 4% of treated patients, and were characterised by flushing, hypotension or hypertension, dyspnoea and bronchospasm (data not shown). In one study, investigators observed anaphylactoid reactions, characterised by flushing, rash and pruritus, in 7/65 patients [11].

In addition to the immediate HSRs, patients treated in these phase I studies also exhibited skin reactions, most commonly pruritis, localised maculopapular eruptions and nail changes [8, 10, 11, 13]. Typically, skin reactions occurred after the first or second course of docetaxel and were dose-related, although some changes (e.g. nail changes) were related to the cumulative dose.

Docetaxel-induced peripheral fluid retention was reported in one study in patients who had received a sufficiently large cumulative dose of the drug. Of 32 patients who received docetaxel as a 1 h infusion on days 1 and 8 of the treatment cycle, 10 experienced peripheral fluid retention, mainly affecting the face and hands, but sometimes generalised, and associated with weight gain, pleural effusions or pleural thickening. Fluid retention appeared after a median of six courses (range 1–9) and with the exception of one patient, occurred in patients treated with $\geq$100 mg/m^2 [13].

Mild neurological adverse events (grade I or II) were experienced by 7/17 (41%) patients receiving docetaxel 100 or 115 mg/m^2 over 1–2 h [11]. These side-effects occurred dose-dependently, with only 4/46 (9%) patients affected at doses $\leq$85 mg/m^2. It is unclear, however, whether docetaxel exerts a direct neurological effect, or whether the paraesthesias and dysaesthesias experienced by some patients receiving higher doses were a secondary consequence of skin reactions.

Monitoring of patients with cardiac telemetry during and after the first one or two infusions of docetaxel revealed no clinically relevant bradycardia or cardiac rhythm disturbances [8, 9, 11–13]. One patient developed atrial flutter with 2:1 block which was resistant to therapy 24 h after completion of the first course of docetaxel 90 mg/m^2, but was subsequently found to have pericardial metastatic involvement [9].

Accidental drug extravasation was reported in 5 patients [12]. Localised pain and erythema occurred, but no specific treatment was given. Skin peeling continued for a further 6 weeks, but there was no necrosis or ulceration of the skin or underlying tissues.

Other adverse events reported during docetaxel therapy included asthenia, conjunctivitis, gastrointestinal effects (anorexia, diarrhoea, nausea, vomiting), and headache [11, 13]. Alopecia was almost universal at doses of 100 mg/m^2.

PHARMACOKINETICS

The pharmacokinetic profile of docetaxel was determined through repeat plasma concentration measurements, using high performance liquid chromatography (sensitive to 10 μg/l). The mean plasma concentration–time profile of docetaxel obtained from measurements in 11 patients who received a 1 h intravenous (i.v.) infusion of 100 mg/m^2 is shown in Figure 3. Pharmacokinetic data derived from the studies of Extra and colleagues [11] and Aapro and co-workers [8] are provided in Table 3.

For individual patients, plasma drug concentrations at the end of an infusion correlated well with the area under the concentration–time curve (AUC), but there was considerable intersubject variation [9, 11]. Although peak plasma concentrations were poorly related to the dose, AUC was linearly related to dose up to a dosage of 70 mg/m^2 [9] or up to 115 mg/m^2 [10, 11]. At lower dosages of docetaxel ($\leq$70–80 mg/m^2), plasma concentrations decreased in mono-exponential or bi-exponential fashion whereas at higher doses, plasma disappearance was triphasic [10, 11].

The relationship between AUC and the percentage decrease in neutrophil count was observed using a sigmoid E_{max} model. Using this model, the AUC_{50} (the dose which results in 50% of the maximum decrease in neutrophil count) of docetaxel was estimated to be from 1.0 to 3.5 μg/ml h [9, 11, 12].

CONCLUSION

During phase I studies, 234 patients received docetaxel for a total of 790 courses. The MTD of docetaxel by short-term infusion in these studies was 115 mg/m^2. However, because the dose of 100 mg/m^2 appeared to offer optimal antitumour activity and tolerability, it was recommended for use in phase II studies.

The major dose-limiting adverse effect of docetaxel was neutropenia, and other adverse effects reported included HSRs, fluid retention, skin reactions, asthenia and alopecia. Protracted administration schedules (e.g. 6 or 24 h infusions) were associated with a higher incidence of fever and mucositis and hence a shorter infusion time of 1 h was chosen for subsequent studies. HSRs occurred in some patients, but anaphylactoid reactions were extremely rare. The occurrence of an anaphylactoid reaction was not an absolute contraindication to the administration of further doses of docetaxel, and routine premedication for HSRs was not recommended for future studies. Cardiological adverse events were not observed during phase I studies with docetaxel, and neurological adverse effects were mild.

In conclusion, the results of phase I studies suggest that a docetaxel dose of 100 mg/m^2 administered as a 1 h i.v. infusion is appropriate for use in subsequent studies. A 3 week dosage interval appears to be sufficient to permit full marrow recovery. Importantly, docetaxel showed promising antitumour activity in these studies and confirmation of this activity in disease-specific phase II studies is awaited with interest.

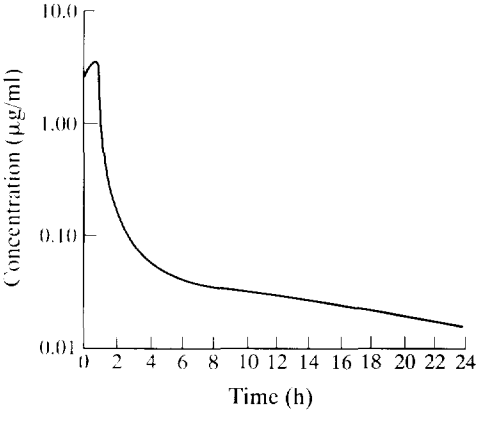

Figure 3. Mean concentration–time curve of docetaxel measured in 11 patients following 1 h intravenous administration of docetaxel 100 mg/m^2.

Table 3. Pharmacokinetics of docetaxel, as determined in phase I studies

Parameter	Reference	
	[11]	[8]
No. of patients	16	10
Dose (mg/m^2)	70–115	70–100
Infusion duration (h)	1.4–1.8	1.1
C_{max} ($\mu g/ml$)	1.91 ± 0.32 to 2.68 ± 0.93	2.57 ± 0.64 to 3.67 ± 0.76
AUC ($\mu g/ml$ h)	2.79 ± 0.85 to 5.19 ± 0.16	3.13 ± 1.18 to 4.83 ± 0.78
Elimination half-life (h)	11.3 ± 8.1	13.6 ± 7.6
Clearance ($l/h/m^2$)	22.2 ± 6.1	21.3 ± 4.6
V_{ss} (l/m^2)	60.3 ± 42.3	102 ± 88.9
Percentage of dose renally excreted in 24 h	2.5 ± 1.6	3.8 ± 1.4

Unless otherwise indicated, all values represent mean ± S.D.
AUC, area under the plasma concentration–time curve; C_{max}, peak plasma concentration; h, hours; V_{ss}, volume of distribution at steady-state.

1. Wani MC, Taylor HL, Wall ME, *et al.* Plant antitumour agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. *J Am Chem Soc* 1971, **93**, 2325–2327.
2. Schiff PB, Fant J, Horwitz SB. Promotion of microtubule assembly *in vitro* by taxol. *Nature* 1979, **277**, 665–667.
3. Bissery MC, Bayssas M, Lavelle F. Preclinical evaluation of intravenous Taxotere (RP 56976, NSC 628503), a taxol analog. *Proc Am Assoc Cancer Res* 1990, **31**, 417.
4. Bissery MC, Guénard D, Guéritte-Voegelein F, Lavelle F. Experimental antitumor activity of Taxotere (RP 56976, NSC 628503), a taxol analogue. *Cancer Res* 1991, **51**, 4845–4852.
5. Vogel M, Hilsenbeck SG, Depenbrock H, *et al.* Preclinical activity of Taxotere (RP 56976, NSC 628503) against freshly explanted clonogenic human tumour cells: comparison with taxol and conventional antineoplastic agents. *Eur J Cancer* 1993, **29A**, 2009–2014.
6. Ringel I, Horwitz SB. Studies with RP 56976 (Taxotere): a semisynthetic analogue of taxol. *J Natl Cancer Inst* 1991, **83**, 288–291.
7. Riou J-F, Naudin A, Lavellé F. Effects of Taxotere on murine and human tumor cell lines. *Biochem Biophys Res Commun* 1992, **187**, 164–170.
8. Aapro MS, Zulian G, Alberto P, Bruno R, Oulid-Aissa D, Le Bail N. Phase I and pharmacokinetic study of RP 56976 in a new ethanol-free formulation of Taxotere. *Ann Oncol* 1992, **3** (suppl. 5), 5.
9. Bissett D, Setanoians A, Cassidy J, *et al.* Phase I and pharmacokinetic study of Taxotere (RP 56976) administered as a 24 hour infusion. *Cancer Res* 1993, **53**, 523–527.
10. Burris H, Irvin R, Kuhn J, *et al.* Phase I clinical trial of Taxotere administered as either a 2-hour or 6-hour intravenous infusion. *J Clin Oncol* 1993, **11**, 950–958.
11. Extra J-M, Rousseau F, Bruno R, Clavel M, Le Bail N, Marty M. Phase I and pharmacokinetic study of Taxotere (RP 65976; NSC 628503) given as a short intravenous infusion. *Cancer Res* 1993, **53**, 1037–1042.
12. Pazdur R, Newman RA, Newman BM, *et al.* Phase I trial of Taxotere: five-day schedule. *J Natl Cancer Inst* 1992, **84**, 1781–1788.
13. Tomiak E, Piccart MJ, Kerger J, *et al.* Phase I study of docetaxel administered as a 1-hour intravenous infusion on a weekly basis. *J Clin Oncol* 1994, **12**, 1458–1467.