Pergamon

European Journal of Cancer Vol. 30A, No. 8, pp. 1061–1064, 1994

0959-8049/94 $7.00+0.00

0959-8049(94)00199-5

Docetaxel (Taxotere) in Advanced Malignant Melanoma: a Phase II Study of the EORTC Early Clinical Trials Group

S. Aamdal, I. Wolff, S. Kaplan, R. Paridaens, J. Kerger, J. Schachter, J. Wanders, H.R. Franklin and J. Verweij

The antitumour activity of docetaxel was investigated in patients with advanced malignant melanoma. Docetaxel, 100 mg/m², intravenous, over 60 min, was administered every 3 weeks. Response evaluation was performed after two cycles. No prophylactic treatment with steroids or antihistamines was given. 38 patients were included, 36 were eligible and evaluable for toxicity and 30 patients were evaluable for response. The main haematological toxicity was neutropenia [17 patients with common toxicity criteria (CTC) grade 4 and 11 CTC grade 3] with nadir after 5–8 days and rapid recovery. The most frequent non-haematological toxicity was generalised alopecia (83% of the patients). Asthenia, malaise and fatigue were also seen in 58%. Skin toxicity was also frequent. Hypersensitivity reactions (erythematous rash, urticaria, blood pressure changes and tachycardia), seen in 42% of the patients, were mild to moderate. Oedema was registered in one fifth of the patients and developed after four or more treatment cycles. The overall response rate in the evaluable patients was 17% (five partial responders). We conclude that docetaxel has activity in advanced malignant melanoma.
Eur J Cancer, Vol. 30A, No. 8, pp. 1061–1064, 1994

INTRODUCTION

DOCETAXEL IS a semisynthetic taxoid synthesised from 10 deacetyl-baccatin III, a compound isolated from the needles of *Taxus Baccata L*, the European yew. Docetaxel binds to microtubules, induces tubulin polymerisation and forms extremely stable and non-functional microtubules in the cell [1].

In preclinical test systems, docetaxel has demonstrated a broad spectrum of antitumour activity against both murine and human tumours [1–4]. Compared to paclitaxel, another recently developed taxoid, docetaxel was more active in subcutaneously growing murine B16 malignant melanoma. Docetaxel gave 2.7-times higher log cell kill than paclitaxel with equitoxic doses [1]. Against a paclitaxel-resistant cell line, docetaxel was found to be a five times more potent inhibitor than paclitaxel [5] and, in two ovarian tumour cell lines, docetaxel was more active than conventional cytostatic agents like cisplatin, cyclophosphamide and doxorubicin [3]. In addition, in freshly explanted clonogenic human tumour cells, docetaxel was more active than paclitaxel and clearly more active than a variety of conventional potent antitumour agents tested in the same tumour cells [3].

In clinical phase I trials, the dose-limiting toxicity has been neutropenia [5–9]. When the infusion time was shortened from 6 and 24 h to 1 h, oral mucositis, which had been the dose-limiting toxicity in several phase I trials, was significantly reduced [8]. Other toxicities observed were moderate anaemia, skin toxicity, infrequent thrombocytopenia and dose-dependent alopecia. Hypersensitivity reactions were usually mild. Partial responses were observed in heavily pretreated patients with ovarian carcinoma [4, 7], mammary carcinoma [5, 7], small cell [7] and non-small cell lung carcinoma [6].

The present phase II trial was initiated in order to investigate the antitumour activity of docetaxel in advanced malignant melanoma.

PATIENTS AND METHODS

Eligibility criteria included informed consent, histological or cytological documentation of malignant melanoma, locally advanced, non-resectable or metastatic disease with measurable progressing lesions. Patients with brain or leptomeningeal metastasis, second malignancies, other serious illnesses, symptomatic peripheral neuropathy common toxicity criteria (CTC) grade ≥ 2, prior or concurrent treatment with colony-stimulating factors or concomitant treatment with prednisone (more than 10 mg/day), were not eligible for inclusion. Other eligibility criteria were age between 18 and 75 years, life expectancy of more than 3 months, performance status (WHO) ≤ 2, neutrophils $\geq 2000/\mu l$, platelet count $\geq 100\,000/\mu l$ and serum creatinine ≤ 140 μmol/1. If serum creatinine was 100–140 μmol/1, creatinine clearance was measured and the required value for study inclusion was ≥ 60 ml/min. The hepatic enzyme, SGOT (serum glutamic oxaloacetic transferase), had to be within twice the upper limit of normal (within three times if proven liver metastases) and bilirubin within 1.25 times the upper normal value.

Correspondence to S. Aamdal at the Dept. of Oncology, Norwegian Radium Hospital, 0310 Oslo, Norway.
I. Wolff is at the Medizinische Klinik, Nuremberg, Germany; S. Kaplan is at the Kantonsspittal, Division of Oncology, Basel, Switzerland; R. Paridaens is at the Dienst Gezwelziekten UZ St Raphael, Leuven; J. Kerger is at the Institut Jules Bordet, Brussels, Belgium; J. Schachter is at the Beilinson Medical Center, Petach Tikva, Israel; J. Wanders and H.R. Franklin are at 6 EORTC New Drug Development Office, Amsterdam, The Netherlands; and J. Verweij is at the Rotterdam Cancer Institute, Rotterdam, The Netherlands.
Revised 11 Apr. 1994; accepted 20 Apr. 1994.

Prior chemotherapy, except for adjuvant regional chemotherapy with extracorporal circulation with a treatment-free interval of more than 4 weeks, was not allowed. Prior immunotherapy with interferon and or interleukin-2 was accepted provided there was a minimum 4-week treatment-free interval. A minimum of 4 weeks should have elapsed since radiotherapy (8 weeks in case of extensive radiation) before entry into the protocol. The indicator lesions must not have been irradiated, but new lesions within a previously irradiated field were acceptable.

Medical history, physical examination and blood chemistries were repeated before every cycle. Complete blood cell counts were repeated once a week. The tumour parameters were assessed by physical examination every 3 weeks and by X-ray, computed tomography scan or ultrasound every 4–6 weeks. The sample size was determined according to the Gehan method.

The patients were accrued between May 1992 and September 1992.

Drug administration

Docetaxel was administered intravenously (i.v.) over 60 min, every 3 weeks at a dose of 100 mg/m^2. The drug was supplied by Rhone-Poulenc Rorer as a sterile solution containing 40 mg/ml in 2-ml vials in polysorbate 80 (Tween 80). Each vial was reconstituted with 6 ml of dextrose solution (or 0.9% saline), yielding a concentration of 10 mg/ml. The solution was immediately shaken for 20 s using a mixer in order to obtain a clear solution. The solution was further diluted in 5% dextrose (or 0.9% saline). The maximum docetaxel concentration did not exceed 1 mg/ml.

No routine premedication for emesis or for hypersensitivity reactions was allowed and no prophylactic antibiotics were given.

Dose modifications

In patients with neutropenia <500/μl lasting more than 7 days, or complicated with fever (≥38.5°C) requiring antibiotic treatment, or with thrombocytopenia <25 000/μl at nadir, the docetaxel dose was reduced by 25% in the subsequent treatment cycle. In the event of neutropenia <1500/μl and or thrombocytopenia <100 000/μl at the planned start of the next cycle, the treatment was postponed for 1 week. If no recovery occurred after 1 week, the patient was taken off the protocol.

In case of cutaneous reactions and peripheral neuropathy CTC grade ≥2, the dose was reduced or the treatment postponed. When hypersensitivity reactions occurred and the reaction was mild, the rate of docetaxel infusion was reduced. In case of moderate reaction with generalised pruritus, flushing, rash, dyspnoea or hypotension with blood pressure >80 mmHg, the infusion was stopped and i.v. treatment with antihistamines and steroids was given. The docetaxel infusion was resumed when the symptoms had abated. In the case of a severe hypersensivity reaction with bronchospasm, generalised urticaria, hypotension with blood pressure ≤80 mmHg, the infusion was stopped and i.v. treatment administered as above. Before rechallenge after a severe reaction, premedication with diphenhydramine and dexamethasone was administered and, if the severe reaction recurred, the patient was taken off the study.

Response and toxicity evaluation

Patients must have received a minimum of two cycles of treatment (i.e. 6 weeks on the study) to be considered evaluable for response unless early progression occurred, in which case they were considered evaluable. Early progression is defined as progressive disease before 6 weeks after entry into the study.

Patients with progressive disease at the end of the second cycle went off the study. The treatment was continued in patients with partial or complete responses until disease progression or excessive toxicity. In patients with stable disease, the treatment could be discontinued after three cycles. Duration of partial response was calculated from the start of therapy until documentation of progression, while the duration of complete response was calculated from the date the complete response was established.

The CTC were used for assessment of toxicity and WHO criteria for response evaluation.

RESULTS

A total of 38 patients entered the study. 2 patients were not eligible due to lack of histological confirmation and due to previous systemic chemotherapy with vindesine. Table 1 summarises the characteristics of the 36 eligible patients included in the study. The main tumour target lesions were visceral in 28 (liver in 8 patients; lung in 11 patients; 9 patients with both) and soft tissue in 15, nodes in 16 patients and 9 with skin metastases. 2 of the patients had received previous chemotherapy as isolated limb perfusions, 4 had received immunotherapy, 6 local radiotherapy and 1 patient had received hormonal therapy.

Dose reductions and treatment delays

In 25/145 cycles, the drug dose was reduced and 11 cycles delayed. In 7 patients, the dose was reduced to 75 mg/m^2 and 2 required a further reduction to 55 mg/m^2. The reasons for dose reduction were non-haematological in 10 cycles, haematological in seven and both non-haematological and haematological in seven cycles. In one cycle, the reduction was non-drug-related. The median dose intensity delivered (mg/m^2/week) was 32.8 (range 20–34.8). The median cumulative dose (mg/m^2) given was 293 (range 99–1375).

Antitumour activity

6 of the patients were not evaluable for response. 4 of them died within 2 weeks after the first cycle had been given. The causes of death were rapidly progressing disease, cerebrovascular accident, pulmonary embolism and in 1 case, an unknown cause.

Table 1. Patients' characteristics

	No. of patients
No. of eligible patients	36
Sex (male/female)	24/12
Age (years)	
Median	52
Range	26–74
Performance status (WHO)	
0	15
1	17
2	4
Prior treatment	
Surgery	33
Radiotherapy	6
Chemotherapy*	2
Immunotherapy	4
Hormone therapy	1

*Adjuvant regional isolated limb perfusion.

*Table 2. Docetaxel toxicity in 36 patients**

	Common toxicity criteria grades			
	I	2	3	4
Haematological toxicity (nadir values)				
Leucopenia	0	10	15	5
Neutropenia	0	2	11	17
Thrombocytopenia	1	0	0	0
Anaemia	17	12	1	0
Non-haematological toxicity				
Alopecia	10	20	0	0
Asthenia/malaise/fatigue	13	7	1	0
Skin	5	12	1	0
Diarrhoea	11	5	0	0
Sensory neuropathy	14	2	0	0
Nausea	13	2	0	0
Hypersensitivity reaction	9	3	0	1
Stomatitis	9	3	0	0
Fever	5	7	0	0
Infection	4	3	0	0
Pain	3	3	1	0
Oedema	1	4	1	1
Myalgia	4	1	0	0
Pleural effusion	3	1	0	0
Hypotension	0	1	0	0

*Maximum toxicity per patient.

One patient refused further treatment after the first cycle and 1 did not complete the second cycle due to acute hypersensitivity reaction.

In the remaining 30 patients strictly evaluable for response, there were five partial responses (95% confidence intervals 6–35%). The median duration of response was 9.0 months (range 3.7–14.4). The median survival was 6.5 months (range 0.2–21+). All five responses were confirmed by an independent external review. The sites of response were soft tissue in 4 patients, lung in 3, nodes in 2, skin in 2 and liver in 1. In 2 other patients, tumour size was significantly reduced by 80 and 68% respectively but, as the required reconfirmation of these findings within the 4–6 weeks time limit was not performed, they were not counted as responders.

In the other patients, there were 10 with no change, 9 with progression and 4 with early progression.

Haematological toxicity

All 36 eligible patients, who received a total of 145 courses of treatment, were evaluable for haematological toxicity. Table 2 reports the overall incidence of leucopenia, neutropenia, anaemia and thrombocytopenia observed. Neutropenia was the main haematological side-effect of the treatment, with 11 patients experiencing CTC grade 3 and 17 patients CTC grade 4. The onset was quite rapid with nadir at 5–8 days following the docetaxel infusion. Recovery was also quick. Seventeen courses (12%) were complicated by febrile neutropenia. Anaemia was less frequent and usually mild, and thrombocytopenia was a rare event with only 1 patient experiencing CTC grade 1 toxicity.

Non-haematological toxicity

The most frequent non-haematological side-effect of docetaxel was alopecia, registered in 30 patients (83%), which was generalised and occurred usually 2–4 weeks after start of treatment. Asthenia, malaise and fatigue were seen in 21 patients (58%). Nausea occurred in 15 patients, and vomiting in 6 patients but both were mild to moderate. Almost half of the patients experienced diarrhoea. Skin toxicity with symptoms such as pruritus, dry skin, erythema and desquamation was usually mild to moderate. Some of the patients developed nail changes consisting of calcification and onycholysis. Moderate sensory neurological toxicity with paresthesis and numbness was also found in 16 patients (44%).

Fluid retention was usually in the form of peripheral oedema (7 patients), but some patients developed facial oedema and 1 patient experienced a generalised oedema. Two-thirds of the patients developing oedema had received four or more cycles of treatment. Acute hypersensitivity reactions, which consisted of erythematous rash, urticaria, blood pressure changes and tachycardia, occurred in 15 patients (42%) and appeared within the first 5 min of the first or second docetaxel infusion. The reaction was mild in the majority of the cases and in only 1 patient was it necessary to stop the treatment. 3 patients went off study for reasons of toxicity.

DISCUSSION

Advanced malignant melanoma is a difficult disease to treat, and the tumour is often unresponsive to conventional cytotoxic agents. Dacarbazine, DTIC is still the most commonly used drug for this disease and 15–20% of the tumours will respond to the treatment [10].

Docetaxel is a new antitumour drug which in preclinical models has shown promising results in solid tumours. In the present study, the antitumour activity of docetaxel in patients with metastatic malignant melanoma was studied. The overall response rate in the 36 eligible patients was 14% (5/36) while 17% of the 30 patients strictly evaluable for response achieved a partial response. Compared to other drugs, the antitumour activity of docetaxel in malignant melanoma is similar to single-agent activity of other mitotic inhibitors (vindesine, vincristine and vinblastine) and also similar to the activity of paclitaxel (Table 3).

Hypersensitivity reactions are well known side-effects of taxoid treatment. Initially it was assumed that the drug solvent (Cremophor EL) used in the paclitaxel preparation could have caused the reaction. It is now realised that the drug itself contributes and mast cell activation may be the mechanism. Prophylactic treatment with dexamethasone, diphenhydramine or promethazine and cimetidine, now routinely used before paclitaxel, has reduced the incidence of hypersensivity reactions which now only occurs in 6–9% of the patients [11].

Table 3. Single agent activity in the treatment of metastatic malignant melanomas

Chemotherapy agent	No. of patients evaluable	Overall response rate (%)
DTIC	1868	20
BCNU	122	18
Fotemustine	153	24
Vincristine	52	12
Vinblastine	62	13
Vindesine	273	14
CDDP	114	15
Taxol	71	17

DTIC, dacarbazine; BCNU, carmustine; CDDP, cisplatin [13].

In the present study with docetaxel, no prophylactic treatment was given and hypersensitivity reactions were seen in one third of the patients. It has previously been reported [12] that oral pretreatment with the combination of methylprednisone, citrizine and ketotifen significantly reduces the development of hypersensitivity reaction after docetaxel administration.

Peripheral oedema, which seems cumulative, is another side effect registered during docetaxel treatment. Oedema has thus far not been reported in connection with paclitaxel treatment. However, nearly all patients treated with paclitaxel for prolonged periods have received prophylactic regimens, and there are indications that the pretreatment may limit the development of oedema [12].

In summary, docetaxel has antitumour activity in advanced malignant melanoma comparable to that of DTIC and other conventional potent cytotoxic drugs. Docetaxel toxicities are significant but it is likely that the hypersensitivity reactions and oedema will be alleviated with the routine use of prophylactic drug regimens.

1. Bissery MC, Guenard D, Gueritte-Voegelein F, *et al.* Experimental antitumor activity of taxotere (RP56976, NSC628503), a taxol analogue. *Cancer Res* 1991, **51**, 4845–4852.
2. Vogel M, Hilsenbeck H, Depenbrock, *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.
3. Boven E, Venema-Garberseck E, Erkelsen CAM, Bissery MC, Pinedo M. Antitumor activity of taxotere (RP 56976, NSC 628503), a new taxol analog in experimental ovarian carcinoma. *Ann Oncol* 1993, **4**, 321–324.
4. Ringel I, Horwitz SB. Studies with RP 56976 (taxotere): a semisynthetic analog of taxol. *J Natl Cancer Inst* 1991, **83**, 288–291.
5. Pazdur R, Newman RA, Newman BM, Bready B, Bayssas M, Raber MN. Phase I trial of Taxotere (RP56976). *Proc Am Soc Clin Oncol*, 1992, **11**, A266.
6. Tomiak E, Piccart M, Kerger J, *et al.* A phase I study of Taxotere (RP 56976, NSC 628503) administered as a one hour intravenous infusion on a weekly basis. *Eur J Cancer* 1991, **27** (suppl. 2), 1184.
7. Burris H III, 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.
8. Extra JM, Rousseau F, Bruno R, Clavel M, Le Bail N, Marty M. Phase I and pharmacokinetic study of Taxotere (RP 56976; NSC 628503) given as short intravenous infusion. *Cancer Res* 1993, **53**, 1037–1042.
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. Houghton AL, Legha S, Bajorin DF. Chemotherapy in metastatic melanoma. In Balch CM, Houghton AL, Wilton GW, Sober AJ, Soogs S-J, eds. *Cutaneous Melanoma*. Philadelphia, JB Lippincott, 1992.
11. Rowinsky EK, McGuire WP, Taxol: present status and future prospects. *Contemp Oncol*. 1991, 29–36.
12. Schrijvers D, Wanders J, Dirix L, Prove A, Vonck I, van Oosterom A, Kaye S. Coping with toxicities of docetaxel (Taxotere™). *Ann Oncol* 1993, **4**, 610–612.
13. Buzaid AC, Murren J. Chemotherapy in advanced malignant melanoma. *Int J Lab Res* 1992, **21**, 205–209.

Pergamon

European Journal of Cancer Vol. 30A, No. 8, pp. 1064–1067, 1994

0959–8049/94 $7.00+0.00

0959-8049(94)00201-O

Docetaxel (Taxotere) in Advanced Renal Cell Cancer. A Phase II Trial of the EORTC Early Clinical Trials Group

U. Bruntsch, B. Heinrich, S.B. Kaye, P.H.M. de Mulder, A. van Oosterom, R. Paridaens, J.B. Vermorken, J. Wanders, H. Franklin, M. Bayssas and J. Verweij

Docetaxel (Taxotere), an analogue of paclitaxel, was tested in a phase II study in advanced renal cell carcinoma. Consenting patients with measurable lesions, adequate organ functions and no prior chemotherapy received 100 mg/m² of docetaxel as a 1-h infusion every 3 weeks. No premedication to avoid hypersensitivity reactions or nausea and emesis was given. 32 eligible patients received 100 treatment cycles. Short-lasting neutropenia was the dose-limiting toxicity. Acute hypersensitivity reactions (HSR), oedema and skin changes were other important side-effects. HSRs regressed spontaneously or were treated with antihistamines with or without corticosteroids. One partial remission was documented. At the dose and schedule used, docetaxel has only low activity against renal cell carcinoma.
Eur J Cancer, Vol. 30A, No. 8, pp. 1064–1067, 1994

INTRODUCTION

RENAL CELL cancer (RCC) is only curable by surgical means. It is insensitive to all tested cytotoxic drugs and hormones with response rates below 15% [1]. Biological response modifiers like the interferons or interleukin-2, used alone or in combination with LAK (lymphokine-activated killer) cells, have led to objective responses in up to 30% of cases in small series of highly selected patients [1, 2]. New cytotoxic drugs are clearly needed