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

in this disease. We, therefore, conducted a phase II study with docetaxel (Taxotere), a closely related analogue of paclitaxel (Taxol).

Although the antitumour activity of paclitaxel was first noted in the 1960s, its broad spectrum of activity was only discovered comparatively recently. The major reason for the slow development of the agent was the limited supply, as it had to be isolated from the bark of the Pacific yew. In contrast, docetaxel is a semisynthetic compound prepared from a non-cytotoxic precursor which is extracted from the needles of the European yew, *Taxus baccata*, an easily renewable source. It was developed by researchers from Rhône-Poulenc Rorer in cooperation with the French Centre National de la Recherche Scientifique.

The mechanism of action of both taxoids is very similar [3]. They promote microtubule assembly and inhibit the depolymerisation of tubulin. Docetaxel has a higher potency compared to paclitaxel on a mole-for-mole basis [4]. It is also slightly more soluble than paclitaxel.

Five phase I studies have been conducted evaluating different schedules. A single dose every 3 weeks allowed the highest dose intensity. With this schedule, the maximum tolerated dose (MTD) was determined at 115 mg/m^2. Dose-limiting toxicity was neutropenia without cumulative myelotoxicity, but stomatitis and dermatitis were also frequently observed [5–9]. Hypersensitivity reactions were rare, and routine prophylaxis was not given in the phase I trials.

In this present phase II study, docetaxel was tested for antitumour activity in advanced renal cell carcinoma.

PATIENTS AND METHODS

Patients

To be eligible, patients had to have histologically or cytologically verified renal adenocarcinoma with bidimensionally measurable lesions outside previously irradiated areas. No previous chemotherapy was allowed, but prior therapy with hormones or biological substances like interferons or interleukins were permitted, and for these latter substances, no treatment clearance period was mandatory. Other requirements included adequate bone marrow reserve (neutrophils > 2000/μl, platelets ≥ 100000/μl) and adequate renal function defined as a serum creatinine below 1.6 mg/dl or a creatinine clearance above 60 ml/min. Total bilirubin had to be ≤ 1.25-fold the upper normal limit, SGOT not above twice this value, unless the rise was due to liver metastasis when a 3-fold increase was accepted. WHO performance status of 2 or better with a life expectancy of at least 12 weeks and the patient's informed consent according to local rules were required.

Treatment

Docetaxel, dissolved in polysorbate 80, was provided by Rhône-Poulenc Rorer (France). Immediately prior to use, it was diluted in 250 ml of 5% dextrose or 0.9% saline and infused over 1 h, using an infusion pump. The patients were observed by a physician at least during the first 10 min of the infusion. The planned dose was 100 mg/m^2 every 3 weeks. Doses were adjusted according to greatest toxicity. No dose escalation was planned. A dose reduction by 25% was to be implemented for neutropenic fever requiring antibiotics, for neutrophil counts below 500/μl lasting more than 7 days, for platelet counts below 25000/μl and for grade 2 skin or neurotoxicity. For prolonged myelosuppression or skin toxicity, treatment was to be postponed. No routine premedication was given either to prevent hypersensitivity reactions or against nausea and vomiting. Patients were treated until disease progression or unacceptable toxicity. For evaluation of response, patients had to be on study for at least 6 weeks with two courses of treatment. Patients with documented progression after only one drug administration were classified as early progression. Standard WHO criteria were used for response evaluation. All patients treated were evaluated for toxicity; the common NCI toxicity criteria (CTC) were used.

RESULTS

Patients

Between May and September 1992, 33 patients with locally recurrent or metastatic adenocarcinoma of the kidney were entered into the study. Patients' characteristics are given in Table 1. One patient was ineligible because of an increased serum creatinine level prior to therapy. This patient was excluded from all further analyses. In 1 patient, by error, a dose of only 65 mg/m^2 was given for two courses, for the third cycle the error was corrected. This patient was included in all evaluations. None of the patients receiving prior immunotherapy or hormone therapy responded to that treatment. One hundred treatment cycles were applied, 94 at full dose (Table 2). In four courses, doses had to be reduced due to haematological toxicity. The infusion was temporarily interrupted in 14 and slowed down in another four administrations due to acute hypersensitivity reactions.

Table 1. Patients' characteristics

	No. of patients
No. of eligible patients	32
Male/female	26/6
Age (years)	
Median (range)	63 (30–72)
Performance status (WHO)	
0	9
1	19
2	4
Prior therapy	
Nephrectomy	19
Immunotherapy	9
Hormone therapy	3
Radiotherapy	4
No therapy	7
Site of lesions	
Primary or local recurrence	17
Lymph nodes	14
Lung	25
Liver	10
Soft tissue	9
Bone	10
Skin	2

Correspondence to U. Bruntsch at 5. Med. Klinik, Nuremberg, Germany.
B. Heinrick is at the Klinikum rechts der Isar, Munich, Germany; S.B. Kaye is at the University of Glasgow, Glasgow, U.K.; P.H.M. de Mulder is at the Sint Radboud Ziekenhuis, Nijmegen, The Netherlands; A. van Oosterom is at the University Hosp. Antwerp, Antwerp; R. Paridaens is at the Katholic University Leuven, Leuven, Belgium; J.B. Vermorken is at the Free University Hospital, Amsterdam; J. Wanders and H. Franklin are at the NDDO Free University, Amsterdam, The Netherlands; M. Bayssas is at the Rhône-Poulenc Rorer, Antony, France; and J. Verweij is at the Rotterdam Cancer Institute, Rotterdam, The Netherlands.
Revised 11 Apr. 1994; accepted 20 Apr. 1994.

Table 2. Number of treatment cycles per patient

							Total
No. of courses	1	2	3	4	5	6	100
No. of patients	2	12	9	3	1	5	32

Table 3. Haematological toxicity during 100 treatment cycles

	WHO grade				
	1	2	3	4	Total
Leucopenia	17	30	37	3	87
Neutropenia	2	22	25	33	82
Anaemia	28	15	3		46
Thrombocytopenia	3				3

Values expressed are number of courses with toxicity.

Toxicity

As expected, neutropenia was the most important toxicity, being grade 4 in one third of all courses (Table 3). The myelosuppression usually was of short duration, two episodes of fever during neutropenia were observed. Other important toxicities were acute hypersensitivity reactions (HSR), oedema and skin changes (Table 4). Most of the HSR occurred during the first 5 min of infusion. Reactions were observed in 9 patients during 18 cycles. In 2 patients, HSR was seen during the first infusion, in the others it first occurred with the second treatment. Symptoms included facial flushing, generalised rash, bronchospasm with dyspnoea, tachycardia, chills and drug fever. Most reactions were moderate or mild and treatment could be resumed after short interruption of the infusion. Twelve episodes were treated with an antihistamine with or without corticosteroids, on the other six occasions no treatment was given and regression of symptoms occurred spontaneously. In only 1 patient was the treatment discontinued permanently after a severe HSR, including bronchospasm. Oedema usually began insidiously and was progressive with prolonged therapy; 1 patient with oedema also developed pleural effusion. Skin toxicity developed especially on hands and feet; the skin became dry, pruritic, and erythematous. Nail changes were seen in 5 patients and progressed to onycholysis in 2 of them. Regular use of ointments ameliorated the symptoms. Alopecia was almost universal and progressive with continued treatment, although in 3 patients it remained mild through five or six courses. Nausea and vomiting were frequent but in most instances easily controlled by low doses of a dopamine antagonist.

Table 4. Non-haematological toxicity in 100 treatment cycles

	% of courses	Grade 3/4
Alopecia (% of patients)	84	na
Asthenia, fatigue	44	7/1
Nausea	32	6/0
Vomiting	23	4/1
Skin	29	0
Stomatitis	13	0
Diarrhoea	18	2/1
Hypersensitivity	18	6/-
Oedema	17	0
Neuropathy	19	2/-
Hypotension	6*	1/1

na, not applicable. *Five episodes in 1 patient.

Response

Of the 32 eligible patients, 5 were not evaluable for response: 1 patient had inadequate re-evaluation after two courses, 1 refused further therapy and 3 patients were taken off study due to toxicity—severe HSR [1] and excessive skin toxicity [2]. One patient had a partial remission confirmed by external panel review, lasting 3.5 months from start of treatment. The response was seen in the lung and soft tissue. Another patient showed a decrease of more than 50% in the indicator lesions but the PR was not re-evaluated after 4 weeks. 16 patients (50%) had progressive disease, 2 of them already after the first course and 9 patients (28%) had no significant change.

DISCUSSION

At present, the predictive value of preclinical testing for new cytotoxic drugs is unclear; hence, well conducted phase II trials remain as the key determinants of activity. Renal cell carcinoma once it has become inoperable and/or metastatic is a difficult disease to treat. Response rates for all tested chemotherapeutic agents are below 10%. The observed response rate of 3% in this study (95% confidence interval, 0–16%), 1 partial response among 32 eligible patients, is in accordance with this experience. Thus, in the dose and schedule used, docetaxel possesses minimal activity against renal cell cancer.

The observed haematological toxicity of docetaxel was acceptable, neutropenia being pronounced but short lasting. Non-haematological toxicity included a broad range of disturbances, most prominent being the acute hypersensitivity reactions, the skin changes varying from a dry scaling to a generalised erythematous rash, and the oedema which may become a problem in responding patients since it is clearly cumulative.

Comparing the toxicity profiles of the two taxoids is difficult. In this study, as well as in the other phase II studies from our group, patients were not pretreated with corticosteroids or antihistamines to prevent HSR as is the rule for all paclitaxel studies. In addition, no prophylactic anti-emetics were given in this study. Our group is now exploring premedications, including corticosteroids, to prevent both HSR and also the development of oedema [10, 11]. The pathophysiological mechanism of the latter phenomenon is not understood, but it seems to be due to an increased vascular permeability and, therefore, may also be ameliorated or prevented by corticosteroids.

1. Linehan MW, Shipley WU, Parkinson DR. Cancer of the kidney and ureter. In DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*, 4th edition. Philadelphia, Lippincott, 1993, 1033–1042.
2. Giantonio B, Ozols RF, Hudes GR. Genitourinary malignancy. In Pinedo HM, Longo DL, Chabner BA, eds. *Cancer Chemotherapy and Biological Response Modifiers*, annual 14. Amsterdam, Elsevier Science Publishers B.V. Annual 14, 1993, 504–508.
3. Ringel I, Horwitz SB. Studies with RP 56976 (Taxotere): a semisynthetic analog of taxol. *J Natl Cancer Inst* 1991, **83**, 2289–2291.
4. Bissery MC, Guenard D, Gueritte-Voegelein F, Lavelle F. Experimental antitumor activity of taxotere (RP 56976, NSC 628503) a taxol analogue. *Cancer Res* 1991, **51**, 4845–4852.
5. Extra JM, Rousseau F, Bourthis J, Dieras V, Marty M. Phase I trial of Taxotere (RP 56976, NSC 628503). *Proc Am Assoc Cancer Res* 1991, **32**, 1225.

6. Rousseau F, Extra JM, Culine S, *et al.* Phase I and pharmacologic study of Taxotere, a new taxol analog. *Eur J Cancer* 1991, 27(suppl. 2), 1238.
7. Tomiak E, Piccart MJ, 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.
8. Pazdur R, Newman RA, Newman BM, *et al.* Phase I trial of Taxotere: five-day schedule. *J Natl Cancer Inst* 1992, **84**, 1781–1788.
9. 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.
10. Wanders J, Van Oosterom A, Gore M, *et al.* Taxotere toxicity: protective effects of premedication. *Eur J Cancer* 1993, **29**(suppl. 6), 1148.
11. Schrijvers D, Wanders J, Dirix L, Prove A, Vronk I, Van Oosterom A, Kaye S. Coping with toxicities of docetaxel (Taxotere™). *Ann Oncol* 1993, **4**, 610–611.

Pergamon

European Journal of Cancer Vol. 30A, No. 8, pp. 1067–1074, 1994
Elsevier Science Ltd
Printed in Great Britain.
0959-8049/94 $7.00+0.00

0959-8049(94)E0173-2

Neurological and Cognitive Impairment in Long-term Survivors of Small Cell Lung Cancer

A. Cull, A. Gregor, P. Hopwood, F. Macbeth, H. Karnicka-Mlodkowska, N. Thatcher, P. Burt, R. Stout, K. Stepniewska and M. Stewart

Despite its effectiveness in reducing the rate of brain metastases, the role of prophylactic cranial irradiation (PCI) in the management of small cell lung cancer (SCLC) remains controversial because of concern about radiation-induced neurological morbidity. In order to evaluate morbidity and its impact on quality of life 64 patients surviving ≥2 years in remission were recalled for assessment. 52 had received PCI. Most of the patients were well: 95% had performance status ≤1 and nine out of 37 neurological examinations were abnormal. On neuropsychometric testing, only 19% of patients performed at the level expected for their age and intellectual ability on all four tests used. Fifty-four per cent of patients were impaired on two or more of the tests, suggesting a significant degree of measurable cognitive dysfunction. The number of patients who had not received PCI was insufficient for comparative analysis with the number who had, but among those treated with PCI, patients receiving 8 Gy in 1 fraction appeared less impaired than those receiving higher radiation doses in multiple fractions. The study showed that neuropsychometric testing is acceptable to patients, can be administered by non-psychologists in the clinic and is sensitive to otherwise undetected deficits of cognitive function in this patient population. Prospective evaluation of PCI should include neuropsychometric testing.
Eur J Cancer, Vol. 30A, No. 8, pp. 1067–1074, 1994

INTRODUCTION

THE ROLE of prophylactic cranial irradiation (PCI) in the management of small cell lung cancer (SCLC) remains controversial [1]. Cerebral metastases are a common problem in SCLC with estimates of cumulative risk around 50% at 2 years [2]. When they occur, cerebral metastases cause greater deterioration in performance status and require more time in hospital than is the case for relapse at other sites [3], although it is not clear what influence the presence of actively-treated brain metastases exert on length of survival [4, 5]. Data on the effect of therapeutic irradiation of brain metastases have recently been reviewed [1] with the tentative conclusion that more than two thirds of irradiated patients had some improvement in their symptoms, while 40% achieve clinically complete remission. However, Lucas *et al.* [6] reported complete neurological recovery in only 20% of their series while 53% failed to achieve any significant benefit from their palliative irradiation.

PCI significantly lowers the incidence of cerebral metastases [7], thereby reducing the risk of the associated morbidity and social consequences. Howver, PCI has no demonstrable survival effect and is potentially curative only in the few patients whose non-central nervous system (CNS) disease has been eradicated by systemic treatment [8–10]. Radiation dose–response data for the eradication of subclinical CNS involvement do not exist.

Correspondence to A. Cull.
A. Cull and M. Stewart are at the ICRF Medical Oncology Unit, Western General Hospital, Edinburgh; A. Gregor is at the Department of Clinical Oncology, University of Edinburgh; P. Hopwood is at the CRC Psychological Medicine Group; N. Thatcher is at the Department of Medical Oncology; P. Burt and R. Stout are at the Department of Radiotherapy, Christie Hospital, Manchester; F. Macbeth is at the Beatson Oncology Centre, Glasgow; H. Karnicka-Mlodkowska is at the Radiotherapy Department, Medical Academy, Gdansk for EORTC Lung Cancer Co-operative Group; and K. Stepniewska is at the ICRF Medical Statistics Laboratory, London, U.K.
Revised 17 Mar. 1994; accepted 8 Apr. 1994.