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Activity of Docetaxel (Taxotere) in Small Cell Lung Cancer

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Docetaxel (Taxotere) is a new cytotoxic compound with a broad spectrum of activity in preclinical studies. This paper reports a phase II trial in patients with previously-treated small cell carcinoma of the lung. 34 patients received 100 mg/m² of docetaxel in an intravenous infusion given over 1 h every 21 days. Seven partial responses were reported (25% of 28 evaluable patients). Duration of response was 3.5–12.6 months. Toxicities were predominantly neutropenia, alopecia and asthenia. Docetaxel is a new compound with activity in previously-treated patients with small cell lung cancer, and is suitable for evaluation in combination with other cytotoxic drugs active in this disease.

Key words: phase II trial, small cell lung cancer, docetaxel
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INTRODUCTION

DESPITE THE proven sensitivity of small cell carcinoma of the bronchus to a wide range of cytotoxic drugs and to radiation, progress in long-term control remains elusive, and there is an obvious requirement for new systemic treatments. Docetaxel is a new hemi-synthetic taxoid prepared from the needles of *Taxus baccata*, the European yew tree [1]. Docetaxel's mechanism of cytotoxic activity is thought to be due to enhanced tubulin assembly into microtubules and inhibition of the depolymerisation of microtubules [1, 2]. This leads to cell cycle arrest in

the M phase resulting in an inability of the cells to divide. In comparison with paclitaxel, the concentration required to provide 50% inhibition of microtubule disassembly is 0.2 mmol for docetaxel versus 0.4 mmol for paclitaxel [1]. Docetaxel has shown a wide spectrum of activity in preclinical anti-tumour models both *in vitro* [3–5] and *in vivo* [6–8] and in phase I testing there have been hints of anti-tumour activity in patients with small cell lung cancer (SCLC) [9]. The dose-limiting toxicity of docetaxel in phase I studies was neutropenia, but other significant toxicities included skin, asthenia and oral mucositis when given as a 24-h infusion. Pharmacokinetic studies performed during 1–2-h infusions of docetaxel have demonstrated that the drug is cleared from plasma with a three-phase elimination, the terminal half-life being approximately 15 h. Less than 9% of the drug is excreted in urine.

The present phase II study was designed to test the efficacy of docetaxel in patients with metastatic or locally advanced SCLC who may have had prior systemic chemotherapy.

PATIENTS AND METHODS

To be included in this study, patients had to have histologically or cytologically verified SCLC with evidence of progressive disease. Patients had locally advanced unresectable or metastatic extensive disease with at least one target lesion measurable bi-dimensionally, a performance status of ≤2 (WHO) and age between 18 and 75 years. Prior to treatment patients were required to have an absolute neutrophil count >2000/μl and platelets >100 000/μl. A creatinine level of <140 mmol/l and an ASAT (SGOT) level of ≤2 times the upper limit of normal, ≤3 if proven to be due to metastases were required. Regarding prior therapy, no more than one prior chemotherapy regimen was permitted and, if patients had received prior radiotherapy, they were only eligible for the study if this was to a site other than that used to assess response. All patients gave informed consent. During the course of the study, patients did not receive any other anti-cancer therapy nor other experimental drugs. Docetaxel was administered in an intravenous infusion over 1 h in 5% dextrose or 0.9% saline at a dose of 100 mg/m^2 in a final concentration of no more than 1 mg/ml. Treatment cycles were repeated every 21 days. Docetaxel was supplied by Rhone Poulenc Rorer, France. For evaluation of therapeutic efficacy, patients were required to complete two cycles of treatment. Second and subsequent cycles of therapy were modified either on the basis of nadia neutrophil and platelet counts or counts on the day of subsequent treatment, together with assessment of other toxicities graded using the NCI common toxicity criteria (CTC). Docetaxel was given without routine premedication to avoid hypersensitivity or emesis. Assessment of response used conventionally accepted WHO criteria. The duration of response was assessed as follows. Complete remission would have dated from the moment that complete response was documented. The duration of partial response or no change dated from the commencement of treatment until the documentation of progression. Survival was assessed from the date of the commencement of treatment. To evaluate toxicity, full blood counts were monitored weekly, and biochemistry together with electrocardiogram examination every 3 weeks.

Table 1. Patients' characteristics

	No. of patients
Sex	
Male	28
Female	6
Age (years)	
Median	61
Minimum	36
Maximum	72
Performance status (WHO)	
0	8
1	22
2	4
Prior surgery	8
Prior radiotherapy	8
Prior chemotherapy	27

RESULTS

Table 1 illustrates the demographics of the 34 patients entered into this study, the majority of whom had received one prior regimen of chemotherapy. Table 2 gives an overview of the 105 courses administered to these patients, where it is seen that 28 of the 34 patients completed the minimum of two cycles of therapy. All 34 patients were evaluable for toxicity, but 6 patients were inevaluable for response, as defined by the protocol, having received less than two cycles of treatment—3 of those died of sepsis, 1 patient was withdrawn because of severe hypersensitivity reactions during the first cycle of treatment and there were two early deaths. Of the 105 courses of therapy given, 89 were at the protocol dose of 100 mg/m^2, 14 at 75 mg/m^2 and one each at 55 or 25 mg/m^2. The response assessment is shown in Table 3. Excluding the 6 patients who did not receive a minimum of two cycles of therapy, 12 patients showed progression, and there was a total of 9 patients showing a partial response, but in 2 of these

Table 2. Docetaxel administration

	No. of patients
Total number of patients	34
Courses	
1	34
2	28
3	17
4	14
5	7
6	4
7	1
Total number of courses	105

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Table 3. Response

Evaluation	No. of patients
PR	7
PR - (< 4 weeks)	2
NC	7
Progression	12
Not evaluable	6
Total	34

PR, partial response; NC, no change.

Table 4. Haematological toxicity (worst grade per patient)

	Common toxicity criteria grade						
	1	2	3	4	nk	Total	% patients
Leucopenia	1	9	13	9		32	94
Neutropenia		2	7	22		31	91
Anaemia	12	8	1		1	22	65
Thrombocytopenia	2	2			1	5	15

nk, not known.

this was not sustained for the minimum acceptable time and, therefore, 7 partial responses have been recorded. The median duration of response was 4.7 months, ranging from 3.5 to 12.6 months. 4 of the responding patients had received previous chemotherapy (etoposide, cisplatin, carboplatin, doxorubicin or cyclophosphamide) and 2 had also received radiotherapy.

The predominant toxicity observed in this study was haematological, and this is summarised in Table 4. Leucopenia was seen in virtually all patients with a significant number of grade 3 and 4 toxicities. Anaemia and thrombocytopenia were less severe. The non-haematological toxicity is illustrated in Table 5, where it is seen that alopecia occurred in the majority of patients, and 76% experienced skin problems, ranging from erythema to frank desquamation. The other major toxicity was asthenia, recorded in 65% of this patient population. Emesis was mild and, despite the significant neutropenia, infection was only severe or life-threatening in two instances.

DISCUSSION

In this study of 28 evaluable patients with extensive SCLC, 22 of whom had received previous chemotherapy, a 25% response rate was shown with a range of duration up to 12 months. Toxicity, predominantly neutropenia, alopecia and asthenia, was significant but tolerable. The novel mechanism of action of this drug together with this modest but clear demonstration of activity in SCLC justifies the evaluation of docetaxel in combination with other non-myelosuppressive drugs known to have activity against this disease, both for relapsing patients and for selected patients who have not received prior systemic therapy.

Table 5. Non-haematological toxicity per patient (n = 34)

	Common toxicity criteria grade						
	1	2	3	4	nk	Total	% patients
Alopecia	9	18				27	79
Skin	4	19	2		1	26	76
Asthenia/malaise/fatigue	10	5	6	1		22	65
Stomatitis	12	4	2			18	53
Nausea	9	5	2			16	47
Diarrhoea	6	7	1			14	41
Sensory neuropathy	11	1	1		1	14	41
Infection	4	5	2	2		13	38
Vomiting	6	5				11	32

nk, not known.

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