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Phase II Studies of Docetaxel in the Treatment of Various Solid Tumours

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Docetaxel has been evaluated in six tumour types in a total of 189 patients entered into phase II studies. Treatment consisted of a 1 h intravenous infusion of docetaxel 100 mg/m² repeated every 3 weeks. No premedication was administered for possible hypersensitivity reactions. Docetaxel was found to be effective as first-line chemotherapy for head and neck cancer (response rate 44%) gastric cancer (23%) and melanoma (14%) and as second-line chemotherapy for soft tissue sarcomas (21%; 95% confidence interval: 7.5%–43.7%). The results in colorectal and renal cancer were disappointing, with response rates of less than 10%. The most frequent adverse effects were alopecia (81%), grade III–IV leucocytopenia of short duration (66%) and skin reactions (52%). Hypersensitivity reactions were mild and occurred in 26% of patients. Docetaxel is an important new drug in the treatment of solid tumours.

Key words: docetaxel, head and neck neoplasms, iatrogenic disease, kidney neoplasms, melanoma, soft tissue neoplasms, stomach neoplasms

Eur J Cancer, Vol. 31A, Suppl. 4, pp. S21–S24, 1995

INTRODUCTION

THE NUMBER of cytotoxic drugs which are effective in the treatment of solid tumours is still fairly limited. Drug development in the last decade has focused on new classes of compounds, including the taxoid derivatives, which have unique mechanisms of action. Docetaxel (Taxotere®) is a semisynthetic taxoid derived from the needles of the European yew, *Taxus baccata* L. During pharmacological screening it exhibited very promising activity in solid tumours, both *in vitro* and *in vivo*. The main adverse effects reported from phase I studies were granulocytopenia of short duration, general alopecia and mucositis. Hypersensitivity reactions (HSRs) were mild and infrequent.

Based on the findings from phase I clinical trials, the most appropriate regimen for phase II assessment appeared to be a 1 h intravenous (i.v.) infusion of docetaxel 100 mg/m² repeated every 3 weeks. This dosage regimen resulted in the best balance between clinical efficacy and overall tolerability, and was associated with the lowest incidence of mucositis, which was important in view of the concomitant granulocytopenia. A large scale phase II study programme in solid tumours was initiated in 1991.

Phase II studies with docetaxel have been performed or are ongoing in the following tumour types: as first-line chemotherapy for squamous cell head-and-neck cancer [1], gastric cancer [2], pancreatic and colorectal cancer [3], renal cancer [4], bladder cancer and malignant melanoma [5] and as first and second-line chemotherapy for soft tissue sarcomas [6]. The results in breast, ovarian and lung cancers are discussed elsewhere [7–12].

PATIENTS AND METHODS

Patients included in the phase II studies discussed in this report had bidimensionally measurable locally advanced or metastatic cancers [1–6]. Where demographic data were provided, the median age of the patients ranged from 54 to 63 years and the median WHO performance status was 1 (0–2) [1, 3, 4, 6]. Docetaxel 100 mg/m² was administered as a 1 h i.v. infusion every 3 weeks. Docetaxel was supplied in 2 ml vials as a 40 mg/ml sterile solution in polysorbate 80. Immediately prior to use, the solution was diluted according to specific instructions. The correct individual dosage was withdrawn and further diluted in either dextrose 5% or saline 0.9%, and administered by i.v. infusion over 1 h. Patients received a median of two cycles.

In view of the results of phase I studies, neither anti-emetic agents nor prophylactic measures to prevent HSRs were routinely prescribed. However, if HSRs occurred during drug infusion, the infusion was interrupted and 5–10 mg of dexamethasone and an antihistamine were administered, after which the infusion was restarted [1–6]. In the event of delayed HSRs, symptomatic treatment was left to the discretion of the treating physician. Prophylactic measures in subsequent courses of ther-

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apy were optional for patients who experienced mild to moderate HSRs to docetaxel; for patients who experienced severe HSRs, subsequent courses of docetaxel were preceded by a combination of dexamethasone and an antihistamine.

All studies used a common schedule for dose reduction when other types of adverse effects occurred. In general, the dose was reduced by 25% if grade IV granulocytopenia lasted >7 days or if it coincided with fever of $\geq 38.5^{\circ}\text{C}$. Provisions were also made for dosage reduction in the event of skin reactions, mucositis and other side-effects. After any dose reduction, re-escalation for subsequent cycles was not permitted.

RESULTS

Antitumour activity

The broad spectrum antitumour activity of docetaxel observed *in vitro* and *in vivo* appears to be translated into clinical efficacy, as shown by preliminary data from phase II trials (Table 1) [1–6]. The only tumour types with a reported response rate of <10% were colorectal and renal cancer [3, 4], reconfirming the insensitivity of these tumour types to currently available cytotoxic drugs. Docetaxel has demonstrated activity in all other tumour types studied to date. Studies in pancreatic cancer and bladder cancer are still ongoing, but responses have been observed in both tumour types. The reported response rates in head and neck cancer, gastric cancer, melanoma and soft tissue sarcoma must be interpreted cautiously because the studies have only been published in abstract form, and not all the patients have been evaluated. Nevertheless, it is clear that encouraging data are emerging.

Head and neck cancer

The response rate to docetaxel in squamous cell head and neck cancer is unprecedented compared with results obtained with other antineoplastic agents [1, 13]. More than 50% of the patients in the study conducted by the EORTC Early Clinical Trials Group had received prior radiotherapy and 8 patients had received prior neoadjuvant chemotherapy. More than half of the patients had either regional or distant metastases, or both. In this scenario, the 11 responses in 25 evaluated patients reflect impressive antitumour activity. This tumour type may be particularly susceptible to treatment with docetaxel, and the data justify a confirmatory study and an evaluation of combination chemotherapeutic regimens incorporating docetaxel.

Gastric cancer

In 26 patients with metastatic gastric cancer who had not received previous chemotherapy, 6 partial remissions (23%) have been reported [2]. The response rates to individual agents used to treat gastric cancer vary from 20 to 30%; therefore, docetaxel can be considered to be active in this disease [14]. In addition, the value of currently used combinations of active agents in gastric cancer is being questioned, since survival after single agent 5-fluorouracil treatment was similar to survival after combination chemotherapy in a recently reported, randomised study [15]. These encouraging results with docetaxel suggest that its use in combination regimens with other chemotherapeutic agents may improve current response rates.

Melanomas

Metastatic malignant melanoma is a very difficult disease to treat. There is still no widely accepted standard chemotherapy treatment, and reported response rates are usually low. Dacarbazine is considered by many specialists to be the standard treatment, with an overall response rate of approximately 15%. However, this is the cumulative result from a wide variety of studies with response rates ranging from 0 to 30%. In comparison, the 14% response rate presently reported for docetaxel in this disease is favourable [5]. In view of the heterogeneous response to dacarbazine, as well as the unpredictability of response duration, there is an incentive for extending the experience with single agent docetaxel and for assessing its efficacy in combination with other drugs active against malignant melanomas.

Soft tissue sarcoma

Soft tissue sarcomas are rare and, like melanomas, difficult to treat once metastasised. Only three cytotoxic drugs presently available, doxorubicin, dacarbazine, and ifosfamide, yield a response rate of >15% [16]. Therefore, the results obtained with docetaxel by the EORTC Soft Tissue and Bone Sarcoma Group are of particular interest [6]. In 23 evaluated patients who had inadequate response to prior chemotherapy, the response rate was 22%. Of particular note, one additional patient showed a mixed response, a status never before observed in soft tissue sarcomas. The National Cancer Institute of Canada recently started a study in patients with this disease who have not received previous chemotherapy. In view of the limited drug treatment

Table 1. Antitumour activity of docetaxel in phase II trials

Tumour type (reference)	Previous treatment (No. of enrolled patients)	No. of patients evaluated	Response rate (%) (95% CI)
Head and neck cancer [1]	Radiotherapy (22) Neoadjuvant chemotherapy (8)	25	44 (24–65%)
Gastric cancer [2]	None	26	23 (9–44%)
Colorectal cancer [3]	Radiotherapy (8) Chemotherapy (4)	29	3 (0–18%)
Renal cancer [4]	No prior chemotherapy	51	4 (0–10%)
Melanoma [5]	No prior chemotherapy	35	14 (5–30%)
Soft tissue sarcoma [6]	1 prior combination chemotherapy or two single agents	23	22 (7–47%)

options for this disease, investigating the role of docetaxel in combination chemotherapy is warranted.

Adverse events

Many hundreds of patients with different tumour types have now been treated with docetaxel 100 mg/m² as a 1 h i.v. infusion every 3 weeks. Adverse effects reported most frequently in studies published to date are listed in Table 2 [1–12].

Alopecia is a common adverse effect and is usually universal. It occurs 2–4 weeks after the initiation of docetaxel and is fully reversible after treatment discontinuation.

Leucopenia and granulocytopenia may also occur with docetaxel at this dosage and schedule; the incidence of grade IV leucopenia/granulocytopenia is over 60%. The onset is quite early, with the nadir occurring between days 5 and 8, followed by a very rapid recovery. Dosage delays for persisting myelosuppression are very rarely required. The short duration of leucopenia and granulocytopenia is also reflected in the number of concomitant infections, which is low in relation to the severity of myelosuppression. Thrombocytopenia is infrequent and rarely severe.

HSRs with docetaxel appear to be less frequent than with other taxoids and are generally mild. The vast majority of HSRs occur during the first two cycles of docetaxel and always within minutes of starting the infusion [17]. The overall incidence is approximately 25% [17–19]. In patients receiving further cycles without prophylactic measures, the incidence of subsequent HSRs is approximately 30% [17]. Premedication with corticosteroids reduces the incidence of HSRs to a level where they can no longer be considered a major clinical problem.

Docetaxel is occasionally associated with skin reactions, including erythema, desquamation and, infrequently, exfoliation. Nail changes consisting of calcification and onycholysis, which may at times be quite painful, have also been observed. The dermatitic lesions are always reversible, usually after 21 days, and there is some evidence suggesting that premedication with corticosteroids is preventative. Nail changes appear to be related to cumulative dose rather than dose per course, since they do not occur after the first or second courses. Premedication with corticosteroids does not seem to prevent this effect, but it is reversible after treatment is stopped [18].

Nausea and/or vomiting are still the most distressing adverse

Table 2. Adverse effects of docetaxel in phase II studies in patients with solid tumours

Adverse effect	Incidence (% of patients)
Alopecia	81
Grade IV leucocytopenia	66
Cutaneous effects	52
Nausea/vomiting	46
Diarrhoea	40
Mucositis	34
Arthralgia/myalgia	27
Hypersensitivity	26
Infections	21
Fluid retention	18
Fever	17
Constipation	12
Headache	11
Cardiotoxicity	0

effects of other forms of chemotherapy [20], but they are relatively infrequent with docetaxel and easily counteracted with prophylactic use of conventional anti-emetics during subsequent courses. The routine use of 5HT₃ antagonists is not necessary when administering single agent docetaxel.

Fluid retention, which appears to be related to the cumulative dose of docetaxel, is an unusual adverse effect which is generally observed peripherally, but may occur at other sites; pleural effusions and ascites have also been reported. At cumulative doses of <400 mg/m², this side effect is infrequent, but the incidence rapidly increases at doses of ≥400 mg/m² [18]. Corticosteroid premedication may also reduce the incidence of this adverse event [18, 19], but prospective studies are needed before definitive conclusions can be made.

Arthralgia and myalgia, which have been reported during treatment with docetaxel, usually occurred after a few days and disappeared rapidly. In general, the effects are mild and respond to simple analgesics although they may occasionally be troublesome for the patient.

Peripheral neuropathy has rarely been reported and was always mild. Cardiac rhythm disturbances or cardiac function abnormalities have not been reported.

CONCLUSION

Docetaxel is a cytotoxic drug with antitumour activity in a wide range of cancers. These studies have provided evidence of the activity of docetaxel as first-line therapy in head and neck cancer, gastric cancer and melanoma and as second-line therapy in soft tissue sarcoma. It must be noted, however, that because these studies have been published in abstract form only, the results must be considered preliminary until verified by peer review.

Future phase II studies should examine the efficacy of docetaxel in tumour types that have not yet been studied and in combination chemotherapy regimens. Finally, as in the past with drugs like cisplatin, doxorubicin, and bleomycin, methods of circumventing the adverse effects associated with docetaxel must be found.

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