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An Overview of Phase II Studies of Docetaxel in Patients with Metastatic Breast Cancer

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Docetaxel is a new taxoid drug with good activity against human breast cancer cells *in vitro*; a number of partial and minor responses have been obtained during phase I studies in patients with advanced breast cancer. In phase II trials, first-line use of docetaxel has produced an overall response rate (OR) of up to 73%. In addition, docetaxel has shown good activity when given as second-line therapy (OR 38%), particularly in patients with disease refractory to anthracyclines (OR 55%). Indeed, the high response rate in this latter group of patients clearly warrants further investigation of docetaxel in this setting. Neutropenia is the major dose-limiting toxicity of docetaxel, but other haematological effects are rare. Hypersensitivity and cutaneous reactions are ameliorated by premedication with corticosteroids and histamine antagonists; fluid retention may improve with longer use of prophylactic premedication. Docetaxel is mildly emetogenic, but no other premedication is necessary. In summary, docetaxel is an active new drug in the treatment of advanced breast cancer. Its role in the management of early stage disease awaits the results of prospective randomised trials.

Key words: docetaxel, phase II clinical trials, breast cancer
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INTRODUCTION

IN MOST INDUSTRIALISED nations, and increasingly in developing countries, breast cancer is a major health problem. In the U.S.A. alone, approximately 180 000 women are diagnosed with breast cancer, and 46 000 women die from the disease, annually [1]. It has been estimated that the lifetime risk of breast cancer in American women is 12% [2]. However, while the incidence of breast cancer continues to rise each year, mortality in the U.S.A. has remained stable for some time. Possible explanations for this include earlier diagnosis through screening programmes, as well as advances in disease management [1].

Unfortunately, metastatic breast cancer remains incurable. The main objectives of treatment are to palliate symptoms, enhance survival and improve the patient's quality of life. At present, endocrine therapy is the main first-line treatment for patients with metastatic breast cancer in Europe. Chemotherapy is generally reserved for patients with visceral disease and those with disease no longer responsive to endocrine therapy.

Until now, the most active single chemotherapeutic agents in advanced breast cancer have been the anthracyclines, doxorubicin and epirubicin; these produce complete or partial responses in the first-line setting in 20–40% of patients [3]. Combination chemotherapy is generally more effective, inducing complete or partial remissions when used as first-line therapy in up to 60% of patients. To date, no drug combination has been conclusively shown to be superior to CAF (cyclophosphamide, doxorubicin and 5-fluorouracil), although various regimens, incorporating different combinations of epirubicin, methotrexate, mitoxantrone, vincristine and prednisolone, have been investigated.

A retrospective analysis of Danish cancer patients suggested that, since its introduction in the 1960s, chemotherapy has improved the survival of patients with recurrent breast cancer by 9.5 months [4]. However, there has been little improvement in this figure during the past decade [1]. At present, means of minimising drug adverse effects to enable the administration of higher doses are being investigated [5, 6].

In the past few years, several new agents have shown activity in breast cancer. Taxoid derivatives, such as docetaxel (Taxotere®) and paclitaxel, form one of the most interesting new classes of chemotherapeutic agents under investigation. Antitumour activity has been observed in clinical studies in patients with a variety of solid tumours, including breast cancer. Paclitaxel has been reported to have ≥50% response rate in previously untreated breast cancer patients [7]. Docetaxel, a new taxoid compound, is derived from a non-cytotoxic constituent (10-deacetylbaccatin III) from the needles of the European yew tree, *Taxus baccata* L. Like paclitaxel, it is an antimicrotubule agent; however, its mechanism of action is fundamentally different from that of colchicine, epipodophyllotoxins and vinca alkaloids. In brief, taxoids arrest the cell cycle in the M phase by enhancing microtubule assembly and inhibiting tubulin depolymerisation [8]. *In vitro*, docetaxel has been shown to have good activity against breast cancer cell lines, inhibiting colony formation over a range of concentrations between 0.1 and 10 μg/ml [9]. In addition, certain murine transplantable tumours were highly responsive to docetaxel in preclinical studies [10]. Since the discovery of its encouraging activity, phase I and II clinical studies have shown that docetaxel is active in a variety of tumour types, particularly breast cancer.

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ACTIVITY OF DOCETAXEL IN ADVANCED BREAST CANCER

Phase I studies

Interest in the activity of docetaxel in breast cancer arose during the course of the phase I trials of this agent [11–16]. Five intravenous (i.v.) schedules were studied including: 1–2 h infusion; 6 h infusion; 24 h infusion; 1 h infusion daily on days 1–5; and 1 h infusion on days 1 and 8. Each of these treatments were repeated every 3 weeks. Of the 230 patients enrolled in these trials, 8 of 41 (19.5%) patients with breast carcinoma had documented partial responses. Responses were noted at doses ranging from 60 to 115 mg/m^2 per course, and several responses were observed in heavily pretreated patients.

Phase II studies

The observation that docetaxel could produce responses in patients with breast cancer during phase I trials at doses lower than the recommended phase II dose (100 mg/m^2) prompted further investigation in the phase II setting. Docetaxel has now been studied as first, second and third-line treatment in metastatic breast cancer in six phase II studies [17–22], the preliminary results of which are summarised in Table 1. In all studies, patients were required to have had measurable advanced disease, and were treated with a 1 h i.v. infusion of docetaxel 100 mg/m^2 every 3 weeks. Three trials studied docetaxel as first-line treatment [17, 18, 20]. In a total of 68 patients evaluated to date, eight complete (12%) and 36 partial (53%) responses have been reported, giving an overall response rate of 65%. In the individual trials, response rates ranged from 57% (95% confidence interval (CI): 31–83% [18] and 34–78% [20]) to 73% (95% CI: 54–87%) [17]. A trial of docetaxel as second-line therapy yielded complete, partial and overall response rates of 8%, 29% and 37%, respectively [19].

The two remaining trials enrolled patients with disease "refractory" to anthracyclines [21, 22]. Since the results of these studies have only been published in abstract form, a detailed definition of the patient population is not available, although eligible patients in one of these studies had to have progressive disease on either doxorubicin or mitoxantrone [22]. A response rate of 55% was reported by Valero and associates in 33 evaluable patients [21], while Ravdin and colleagues reported a 54% response rate (12% complete) in 26 evaluable patients [22]. Although preliminary, these results indicate a high objective response rate for docetaxel in those patients with a poor prognosis. Confirmation of these findings in further studies is awaited with interest.

In all trials, responses were reported to have occurred in both visceral and non-visceral disease sites, although detailed information on response duration is not yet available.

TOLERABILITY

Phase I and II studies have documented the adverse event profile of docetaxel [11–22]. The most commonly reported severe adverse event was neutropenia, which was dose-limiting in phase I studies. The nadir neutrophil count generally occurred 5–14 days after drug administration, with complete recovery after a further 7 days. Details of infectious complications are not available from all studies as yet, but in one phase II trial the incidence of febrile neutropenia and infection was reported to be 25% and 11%, respectively [20]. In contrast, thrombocytopenia and/or anaemia were rarely reported.

Skin reactions, including erythema, rash and nail changes, were common and occasionally severe. However, these reactions appeared to be reversible following discontinuation of therapy. Alopecia was nearly universal.

Up to 50% of patients experienced hypersensitivity reactions (HSRs), usually during the administration of the first or second dose of docetaxel. A variety of symptoms were described, but flushing and chest tightness were among the most common. Premedication with corticosteroids and H_1- and H_2-histamine antagonists was instigated during the course of the phase II studies, and has been effective in preventing the occurrence of significant HSRs (i.e. those requiring infusion interruption). The incidence of skin rash has also decreased as a result of premedication.

A unique phenomenon of peripheral fluid retention, characterised as peripheral oedema sometimes in association with effusions, has also been observed in breast cancer patients enrolled in phase II studies [17–22]. The onset of fluid retention appears to be related to the cumulative dose of docetaxel administered, with approximately 50% and 80% of patients receiving a total dose of 400 mg/m^2 and 500 mg/m^2, respectively, showing overt fluid retention. Information on the time to resolution of oedema is lacking, although it seems to be slowly reversible in most patients after drug discontinuation. While the mechanism of docetaxel induced fluid retention remains speculative, two groups have suggested that corticosteroids before and (in one trial) after docetaxel seemed to prevent its

Table 1. Phase II studies of docetaxel in breast cancer: response rates

Investigators	Prior chemotherapy for metastases	Number of patients			Response rate	95% CI
		Evaluated	Complete response	Partial response		
Fumoleau *et al.* [17]	None	33	6	18	73%	54–87
Seidman *et al.* [18]	None	14	2	6	57%	31–83
Trudeau *et al.* [20]	None	21	–	12	57%	34–78
Ten Bokkel Huinink *et al.* [19]	One regimen	24	2	7	38%	NA
Valero *et al.* [21]	Anthracycline	33	–	18	55%	NA
Ravdin *et al.* [22]	Anthracycline	26	3	11	54%	NA

NA, not available.

occurrence [22, 23]. This has not been a universal observation since others have found no effect of a single day of steroid premedication on the development of oedema [24]. All of these studies were non-randomised, however, so the data from an ongoing randomised study examining steroid effect will be helpful in assessing the true magnitude of benefit from this approach.

Adverse gastrointestinal effects (nausea, vomiting, diarrhoea, mucositis) reported in trials in breast cancer patients have generally been mild or moderate in severity. Mucositis was more problematic in the phase I studies employing prolonged (24 h) or repeated (daily ×5) docetaxel administration.

CONCLUSION

Docetaxel has shown a very high level of single agent activity in metastatic breast cancer, producing an overall response rate of 65% (12% complete responses) in the first-line setting. In addition, response rates in excess of 50% have been reported for patients previously treated with anthracyclines. No other single agent or combination has shown this level of activity in this poor prognostic group. In all trials, tumour responses were seen in both visceral and non-visceral metastatic disease with apparently the same frequency. Data on the durability of docetaxel-induced responses, overall time to progression and survival are not yet available, but should be part of the final published reports of the studies cited in this review.

This level of single agent activity in the first-line setting is higher than that described for single agent anthracyclines, and is certainly in the range of what has come to be expected from anthracycline- and non-anthracycline-containing combination chemotherapy regimens. Such an observation has increased interest in the potential activity of docetaxel in combination regimens, trials of which are underway.

Some of the adverse effects of docetaxel, notably skin rashes and HSRs, have been ameliorated by the use of routine premedication with corticosteroids and H_1- and H_2-histamine antagonists, although fluid retention has been more difficult to manage. It will be important to develop effective means of preventing or treating fluid retention, since it can lead to the discontinuation of treatment in patients who are in complete or partial response. The suggestion that pre- and postdocetaxel corticosteroid therapy may be helpful in this regard [22] is being further explored in ongoing studies.

In summary, phase II trials have shown docetaxel to be a highly active single agent in patients with advanced breast cancer. Nevertheless, its role in the treatment of these patients will only be established when randomised studies have been published. Additional studies are also required to develop means of decreasing some of the adverse effects related to docetaxel, to assess its activity in combination chemotherapy regimens in advanced disease, and ultimately, to determine its impact in the adjuvant setting. Such studies should also include means of assessing quality of life, clearly an important factor for these patients.

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