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Docetaxel in Combination with Doxorubicin or Vinorelbine

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The rationale for the development of a new drug combination is to combine optimal doses of drugs with single-agent activity that are not cross-resistant or have similar toxicities. Docetaxel, with its unique mechanism of action and its high response rates in metastatic breast cancer, provides both opportunities and challenges for the development of combination chemotherapy. Anthracyclines are widely accepted as the agents of choice for first-line treatment of metastatic breast cancer and they have been studied in combination with taxoids. Preliminary results with a combination of docetaxel and doxorubicin indicate an overall response rate of 74%, with the dose-limiting toxicities being neutropenia and infection. Vinorelbine also has single-agent activity against metastatic breast cancer and preclinical studies have demonstrated synergism when vinorelbine and docetaxel are combined. The dose-limiting toxicities of the vinorelbine–docetaxel combination are febrile neutropenia and mucositis. The overall response rate to treatment with this combination is 67%. We therefore conclude that docetaxel can be combined with doxorubicin or vinorelbine to provide high response rates and acceptable toxicity. Phase II studies are planned to confirm these preliminary results. © 1997 Published by Elsevier Science Ltd.

Key words: metastatic breast cancer, drug combination, docetaxel, anthracyclines, doxorubicin, vinorelbine

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INTRODUCTION

THE BEST therapeutic results in metastatic breast cancer are usually achieved with drug combinations. The goals of combination chemotherapy are to increase the overall dose intensity without increasing toxicity and to decrease the likelihood of drug resistance to improve complete response rates, duration of response and length of survival of patients with metastatic breast cancer.

Docetaxel (Taxotere®) is a semisynthetic compound, prepared from a non-cytotoxic precursor, 10-deacyl baccatin III, which is extracted from needles of the yew tree, *Taxus baccata*. Docetaxel promotes tubulin polymerisation and stabilises the formed microtubules. Given as a single agent for first-line chemotherapy of metastatic breast cancer at a dose of 100 mg/m^2 over 1 hour every 3 weeks, docetaxel is highly active with an overall response rate of 61% [1]. Docetaxel is active in both visceral and non-visceral sites, regardless of whether the patient has received prior adjuvant chemotherapy. This activity appears to be superior to that of other single agents and at least equivalent to some combination chemotherapies. Moreover, the activity of docetaxel persists in second- and third-line chemotherapy, even in cases of anthracycline resistance [2, 3].

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DOCETAXEL IN COMBINATION WITH DOXORUBICIN

Rationale

With a response rate of 29–43%, doxorubicin is widely considered the agent of choice for first-line chemotherapy of metastatic breast cancer [4]. The fraction of complete responses after doxorubicin therapy is less than 20%, the duration of response is 1 year and median survival time is approximately 2 years. A lack of complete clinical cross-resistance between docetaxel and doxorubicin justifies the development of combination regimens with the two drugs [2].

Preclinical studies

Docetaxel has been evaluated *in vivo* in combination with doxorubicin in a preclinical study [5, 6]. No therapeutic synergism was observed when docetaxel was administered simultaneously with doxorubicin, or when docetaxel was given after doxorubicin. This study also revealed an overlap in dose-limiting toxicities, resulting in only 60% of the full dose of each agent being used without additional toxicity.

Clinical studies

A phase I–II trial with doxorubicin given as an intravenous bolus, followed by docetaxel given as a 1-hour infusion, every 3 weeks, without granulocyte colony-stimulating factor

Table 1. Patients' characteristics: phase I–II study of docetaxel–doxorubicin combination

Number of patients who entered study	42
Number who received prior adjuvant chemotherapy (%)	22 (63)
anthracycline-based	20 (57)
Median cumulative dose of anthracycline in mg/m^2 (range)	167 (67–247)
Median number of metastatic sites (range)	3 (1–7)
Sites of metastatic disease (% of patients)	
visceral	72
non-visceral	28

(G-CSF) support, was performed in previously untreated patients with metastatic breast cancer [7]. Patients could have received adjuvant chemotherapy with anthracyclines if there had been a therapy-free interval of at least 1 year. Forty-two patients were included in the study (Table 1), 63% of whom had received adjuvant chemotherapy (57% with anthracyclines). All patients had a normal baseline left ventricular fraction and this was monitored at least every two cycles. Seventy-two per cent of patients presented with visceral metastases.

Six dose levels of docetaxel and doxorubicin were analysed (Table 2). The most common toxicity was febrile neutropenia, which lasted less than 3 days. The maximum tolerated doses of doxorubicin and docetaxel were 50 mg/m^2 and 85 mg/m^2, respectively, with sepsis being the dose-limiting toxicity in 2 patients. With the exception of short-duration grade IV neutropenia, no grade III–IV non-haematological toxicities were reported. Mucositis was not a dose-limiting toxicity and no cases of heart failure or severe fluid retention were observed. The median cumulative dose of doxorubicin was 351 mg/m^2 (range 240–550) although 16 patients received >400 mg/m^2. A reversible decrease in left ventricular ejection fraction (which did not require discontinuation of treatment) was observed in 4 patients.

All patients were evaluable for response and were independently reviewed. Responses were recorded at all dose levels. The overall response rate was 74%, although treatment with doxorubicin 50 mg/m^2 and docetaxel 60–75 mg/m^2 produced a response rate of 88%. An extremely high response rate of 82% was observed in patients with visceral and liver disease (of 17 patients with liver metastases, 14 responded to therapy). These high response rates are similar to those seen with paclitaxel–doxorubicin combinations [8, 9]. However, in these studies patients had not received prior adjuvant chemotherapy with anthracyclines and heart failure was observed.

The recommended doses for further phase II study are docetaxel 75 mg/m^2 and doxorubicin 50 mg/m^2, if used without G-CSF support. A confirmatory phase II study is ongoing. The only dose-limiting toxicity was neutropenia and its complications, thus further dose-escalation studies with G-CSF support are planned.

Table 3. Patients' characteristics: phase I–II study of docetaxel–vinorelbine combination

Number of patients who entered the study	29
Number who received prior adjuvant chemotherapy (%)	24 (83)
anthracycline-based	23
Median number of metastatic sites (range)	2 (1–5)
Sites of metastatic disease (% of patients)	
visceral	76
non-visceral	24

DOCETAXEL IN COMBINATION WITH VINORELBINE (NAVELBINE®)

Rationale

Anthracyclines are increasingly being used in the adjuvant treatment setting and there is now a need to combine a therapy that is non-cross-resistant with an anthracycline-based regimen. Doxorubicin may not be a viable option in patients previously exposed to anthracyclines because of the likelihood of drug resistance or the risk of cardiotoxicity. A different approach would be the combination of two new microtubule-active agents, which have the same target, but which have different mechanisms of action and resistance.

Vinorelbine is a new vinca-alkaloid substituted on the catharantine moiety, which results in a higher and more selective affinity for tubulin, compared with the other vinca-alkaloids [10]. Data from European and American studies suggest that vinorelbine, as a single agent, is highly active against metastatic breast cancer (41% in first-line chemotherapy) and is associated with minimal toxicity [10, 11].

The mechanism of action of vinca-alkaloids is tubulin depolymerisation. The binding sites on tubulin for vinorelbine and the taxoid differ [12, 13]. Preclinical evaluation of the combination of docetaxel and vinorelbine has indicated that it is a highly active combination with no, or minimal, overlapping toxicities [6]. Moreover, cells with altered tubulins, which may contribute to resistance to taxoids, are increasingly sensitive (so-called collateral sensitivity) to drugs such as vinblastine, which act by destabilising microtubules. Given the single-agent activities of docetaxel and vinorelbine, it is of interest to evaluate these two drugs in combination.

Phase I studies

A phase I study was performed to define the maximum tolerated dose, the dose-limiting toxicities and, therefore, the

Table 2. Overall results: phase I–II study of docetaxel–doxorubicin combination

Dose level	Doxorubicin (mg/m^2)	Docetaxel (mg/m^2)	*n*	DLT*	Main toxicities	Responses
I	40	50	3	0	None	1/3
II	40	60	8	2	Febrile neutropenia	4/8
III	50	60	10	3	Febrile neutropenia	9/10
IV	50	75	10	2	Febrile neutropenia	9/10
V	**50**	**85**	5	**2**	**Sepsis**	**4/5**
VI	60	60	6	1	Febrile neutropenia	4/6

*DLT, dose-limiting toxicity.

Table 4. Overall results: phase I–II study of docetaxel–vinorelbine combination therapy

Dose level	Vinorelbine (mg/m²)	Docetaxel (mg/m²)	*n*	DLT*	Main toxicities	Responses
I	20	60	3	0	None	3/3
II	20	75	6†	0	None	3/5
III	**22.5**	**75**	**4**	**3**	**Febrile neutropenia Stomatitis**	**2/4**
IV	20	85	10	1	Febrile neutropenia	7/10
V	**20**	**100**	**4**	**4**	**Febrile neutropenia Infection Stomatitis**	**3/5**

*DLT, dose-limiting toxicity. †Data from only 5 patients was available at time of presentation.

recommended dose for phase II studies [14]. Vinorelbine was administered on days 1 and 5, and docetaxel, on day 1 as a 1-hour infusion, every 3 weeks without the G-CSF support. Twenty-nine patients (median age 50 years, range 30–67 years) with metastatic breast cancer who had not received any chemotherapy for advanced disease were included in the study (Table 3). Patients may have received adjuvant chemotherapy with anthracyclines if there had been a therapy-free interval of at least 1 year. Eighty-three per cent of patients had received prior adjuvant chemotherapy and all but one with anthracyclines. There was a high incidence (76%) of visceral disease.

Five dose levels of docetaxel and vinorelbine were assessed (Table 4) and two maximum tolerated doses were reached. The first maximum tolerated dose was for docetaxel 75 mg/m² on day 1 and for vinorelbine 22.5 mg/m² on days 1 and 5. The dose-limiting toxicities were febrile neutropenia and stomatitis. When the dose of vinorelbine was reduced to 20 mg/m² on days 1 and 5, the dose of docetaxel could be increased to 85 mg/m² and 100 mg/m². The second maximum tolerated dose was reached with docetaxel at 100 mg/m² on day 1 and with vinorelbine at 20 mg/m² on days 1 and 5. Dose-limiting toxicities were febrile neutropenia, infection and grade IV stomatitis. Neurological examinations, including nerve conduction studies, were performed at baseline and every two cycles up to the end of the study. Symptomatic peripheral neuropathy was not observed, although grade I neurosensory toxicity was evident. No patient interrupted treatment because of fluid retention.

Responses were observed at all dose levels and in all disease sites, with an overall response rate of 67%. The recommended dose for the phase II studies is docetaxel 85 mg/m² on day 1 and vinorelbine 20 mg/m² on days 1 and 5, every 3 weeks. A study combining G-CSF support is ongoing.

DISCUSSION

The unique mechanism of action of docetaxel, along with the response rates achieved with the drug in metastatic breast cancer, provide opportunities for development of combination therapies. To date, a combination of docetaxel and doxorubicin appears to be safe and very active. A docetaxel–vinorelbine combination, which also demonstrates excellent activity and safety, may be an alternative to anthracycline-based combinations. In the treatment of metastatic breast cancer, this combination could be used as a first-line therapy in patients who cannot receive further anthracycline treatment, or as a second-line therapy if anthacycline treatment has failed.

The restricted follow-up of combination studies undertaken to date, leaves endpoints such as long-term follow-up of toxicity and activity, as yet, unknown. However, this should not reduce the value of the remarkable responses reported so far and randomised clinical studies using these combination therapies are highly recommended.

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