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Taxoids in combination chemotherapy for metastatic breast cancer

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The rationale for the development of new drug combinations is to combine optimal doses of drugs with single agent activity which are not cross-resistant and have non-overlapping toxicities. Anthracyclines are widely accepted as the agents of choice for first-line treatment of metastatic breast cancer and have been tested in combination with the taxoids, docetaxel (Taxotere®) and paclitaxel (Taxol®). Toxicity problems have emerged using anthracyclines and paclitaxel, with sequence- and schedule-dependent toxic effects including dose-limiting typhlitis and mucositis, as well as febrile neutropenia and, in one study, cardiomyopathy. The dose-limiting toxicities of the combination of docetaxel and doxorubicin are neutropenia and infection, and preliminary results indicate a response rate of 89%. There is a need to develop a combination treatment regimen which is non-cross-resistant with anthracyclines. Vinorelbine (Navelbine®) has single agent activity against metastatic breast cancer and has been used in combination with taxoids. The dose-limiting toxicities of the vinorelbine–paclitaxel combination are febrile neutropenia, pelvic pain, fatigue and paraesthesias. The dose-limiting toxicities of the combination of docetaxel and vinorelbine are febrile neutropenia and mucositis. The overall response rate for this combination was 67% and studies are ongoing.

Keywords: Metastatic breast cancer, drug combinations, docetaxel (Taxotere®), paclitaxel (Taxol®), anthracyclines, vinorelbine (Navelbine®).

Introduction

The best therapeutic results in cancer chemotherapy 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 the occurrence of drug resistance in order to improve the complete response rate, the response duration and survival of patients with metastatic breast cancer. Thus, the rationale for the development of new combinations is to combine full doses of non-cross-resistant drugs with single agent activity, different mechanisms of action and non-overlapping toxicity.

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Paclitaxel (Taxol®) is a highly active single agent against previously untreated metastatic breast cancer when given at 250 mg/m² as a 24-h infusion, with response rates of 56–62% (Table 1) [1,2]. However its activity may vary according to the dose, schedule and prior treatment, with response rates ranging from 16–48% [3,7]. The optimal dose and schedule for administration of paclitaxel have not been established to date [8].

Docetaxel (Taxotere®), given at 100 mg/m² over 1 h every 3 weeks, shows a high level of activity against metastatic breast cancer, even in second- and third-line regimens and in anthracyline-resistant and refractory disease (Table 1) [4,6].

The unique mechanism of action of the taxoids and their response rates in breast cancer provide opportunities and challenges for the development of combination chemotherapy. This review will focus on combinations with anthracyclines and vinorelbine.

Combination trials with anthracyclines

Rationale

With response rates of 29–43%, doxorubicin is widely considered the agent of choice for first-line therapy of metastatic breast cancer [9]. The fraction of com-

Table 1. Activity of taxoids (paclitaxel and docetaxel) in metastatic breast cancer

	Objective response rate	Reference
Paclitaxel		
First-line		
250 mg/m² per 24 h	56–62%	[2]
135–175 mg/m²	25–35%	[1]
Second- and third-line	17–30%	[1,3]
Docetaxel (100 mg/m²)		
First-line	59%	[4]
Second- and third-line	43%	[4]
Anthracycline-resistant	41%	[5,6]
Anthracycline-refractory	37%	[5,6]

plete responses is less than 20%, the duration of response is 1 year, and median survival time in these patients is about 2 years. The lack of complete clinical cross-resistance between taxoids and doxorubicin justifies the development of combination regimens of the two drugs [8,5].

Preclinical studies

Initial *in vitro* preclinical studies did not indicate synergism between taxoids and doxorubicin [10–12].

In vitro studies in human MCF-7 breast cancer cells exposed to paclitaxel for 24 h, followed by a 1-h incubation with varying concentrations of doxorubicin, showed less than additive cytotoxicity for the combination [10]. However, using cell viability assays, another study has shown the combination of paclitaxel and doxorubicin to be partly synergistic [11]. There are few preclinical examples in which paclitaxel in combination with another drug was better than either drug alone. The sequence of administration appeared to be an important determinant of the efficacy and toxicity of paclitaxel combination therapy. For example, in murine 16/C and human MCF7 mammary carcinoma xenograft models, synergistic activity was demonstrated with doxorubicin pretreatment and less than additive activity was seen with concomitant administration, or paclitaxel pretreatment.

Docetaxel has been evaluated *in vivo* in combination with doxorubicin in a preclinical study. No therapeutic synergism was observed either when docetaxel was administered simultaneously with doxorubicin or when it was given after doxorubicin [12]. This study also revealed an overlap in dose-limiting toxicities, which meant that only 60% of the full dose of each agent could be used in combination without additional toxicity [13].

Trials with paclitaxel and doxorubicin

Preliminary clinical results with the combination of paclitaxel and doxorubicin showed interesting activity as first-line chemotherapy for metastatic breast cancer. The preclinical data were not available when clinical studies were initiated. Therefore, clinical studies empirically explored several schedules, dosages and sequences. Several phase I studies evaluated the feasibility of clinically relevant doses of the combination of paclitaxel and doxorubicin in minimally pretreated patients with metastatic breast cancer (Table 2) [14,15]. The first three studies used paclitaxel as a prolonged infusion (72- or 24-h) with different schedules of doxorubicin, with or without granulocyte colony-stimulating factor (G-CSF) support.

At the National Cancer Institute, paclitaxel and doxorubicin were infused simultaneously over 72 h, and both drugs were escalated [16]. Severe gastrointestinal toxicity was observed, including diarrhoea and abdominal pain. Typhlitis (inflammation of the caecum) was documented in three patients. Grade 4 neutropenia was observed in all patients. The maximally tolerated doses were paclitaxel at 160 mg/m^2 with doxorubicin at 75 mg/m^2, and paclitaxel at 180 mg/m^2 with doxorubicin at 60 mg/m^2.

At the MD Anderson Cancer Center (MDACC) paclitaxel (125 mg/m^2) was given as a 24-h infusion on day 1, followed by doxorubicin (60 mg/m^2) as a 48-h infusion on days 2 and 3 [14]. This schedule resulted in unexpectedly severe and dose-limiting mucositis with febrile neutropenia or infection. Thus, the maximally tolerated dose was defined as paclitaxel at 125 mg/m^2 with doxorubicin at 48 mg/m^2. Reversal of the schedule allowed higher doses of doxorubicin (60 mg/m^2) and paclitaxel (150 mg/m^2) to be used. In

Table 2. Paclitaxel (P)–doxorubicin (D) combinations

Reference	Trial design	G-CSF	Dose-limiting toxicity	Maximum tolerated dose (mg/m^2)	*n*	Response rate (%)
Fisherman *et al.* [16]	P + D simultaneously 72-h infusion	+	Neutropenia Thrombocytopenia Typhlitis	P 160/D 75 or P 180/D 60	18	62
Holmes [14]	Sequences	+	Mucositis	P→D, P 125/D 48	10	80
	P 24-h/D 48-h		Neutropenia	D→P, P 150/D 60	21	50
Sledge *et al.* [17]	Sequences	–	Mucositis	D→P	12	42
	P 24-h/D bolus		Neutropenia	D 50/P 150		
Gianni *et al.* [18]	Sequences	–	Mucositis	Either sequence	32	94
	P 3-h/D bolus		Neutropenia	P 200/D 60 Cardiomyopathy		
Gehl *et al.* [19]	D bolus/P 3-h	–	Neutropenia Cardiomyopathy	Too early	32	94

G-CSF, granulocyte colony-stimulating factor.

this schedule, the dose-limiting toxicity was febrile neutropenia. Pharmacokinetic studies demonstrated that paclitaxel reduced the clearance of doxorubicin [20].

A University of Indiana study investigated the sequence-dependency of paclitaxel and doxorubicin [17]. Paclitaxel was administered as a 24-h infusion, and doxorubicin as a rapid intravenous injection. A 4-h interval was allowed between the administration of the drugs, and the drug sequence was alternated for comparison both between and within patients. When paclitaxel (175 mg/m^2) preceded doxorubicin (60 mg/m^2), severe mucositis (grade 3–4) was observed. The occurrence of mucositis appeared to depend on the order of administration and the authors defined the maximum tolerated dose as doxorubicin at 50 mg/m^2 followed by paclitaxel at 150 mg/m^2.

These studies used paclitaxel by prolonged infusion (24 or 72 h) with different schedules of doxorubicin (bolus, 48 h, 72 h) and indicated [21]: schedule-dependent toxicity with the occurrence of typhlitis when paclitaxel and doxorubicin were administered by concomitant 72-h infusion; a sequence-dependent toxicity with an increasing incidence of mucositis and neutropenia when paclitaxel, administered by 24-h infusion, preceded doxorubicin; and high response rates (42–62%) but a low number of complete responses (<10%).

Other paclitaxel–doxorubicin combination studies were performed in Europe using a shorter infusion schedule for both drugs (bolus doxorubicin and 3-h paclitaxel) [18,19]. This schedule resulted in higher dose-intensity for both drugs and high response rates: 94% in both studies, with a 41% complete response rate in one study [18]. However, the combination caused cardiac toxicity, with a 21% rate of cardiac failure in one study [18]. The mechanism responsible for the increased antitumour activity and cardiac toxicity of the combination may in part be the increased exposure to high concentrations of doxorubicin and doxorubicinol caused by paclitaxel [18,20].

Other investigators are testing epirubicin and paclitaxel combinations with similar schedules [22,23].

The paclitaxel–doxorubicin combination needs further preclinical and clinical investigation to understand the drug interaction and to optimize the dose and schedule.

Trials with docetaxel and doxorubicin

A phase I trial with doxorubicin as an intravenous bolus, followed by docetaxel as a 1-h infusion, every 3 weeks, was performed in previously untreated patients with metastatic breast cancer [24]. The patients may have received adjuvant chemotherapy with anthracyclines if there was a therapy-free interval of at least 1 year: 67% of patients had received adjuvant chemotherapy; 57% of patients had received adjuvant chemotherapy with anthracyclines. The main toxicity was febrile neutropenia, but the duration of toxicity was less than 3 days (Table 3). The maximum tolerated dose was reached with doxorubicin at 50 mg/m^2 and docetaxel at 85 mg/m^2, with documented infection as the dose-limiting toxicity. With the exception of short-lasting grade 4 neutropenia, no grade 3–4 non-haematological toxicities were observed, and there was no grade 3 mucositis. There were no treatment interruptions due to fluid retention. To date, this combination has not been found to have significant adverse effects on cardiac function. Although this was a phase I study, all patients were evaluable for response and were independently reviewed. Responses were observed at all dose levels (overall response rate 68%), and more frequently at the higher dose levels (dose levels III and IV; response rate 89%). The trial is still ongoing. The response rate of 60% in visceral and liver disease at all levels was very high. Further dose escalation is ongoing with G-CSF support since the only dose-limiting toxicity was neutropenia and its complications. Studies with epirubicin are also planned.

Table 3. Docetaxel–doxorubicin combination: overall results

Dose level	Doxorubicin (mg/m^2)	Docetaxel (mg/m^2)	No. of evaluable patients	Dose-limiting toxicity	Main toxicities	Responses
I	40	50	3	0	No	1/3
II	40	60	8	2	Febrile neutropenia	4/8
III	50	60	9	3	Febrile neutropenia	8/9
IV	50	75	10	2	Febrile neutropenia	9/10
V	50	85	5	2	Infection	2/5

Combination trials with vinorelbine

Rationale

There is a need to define a treatment which is non-cross-resistant with an anthracycline-based regimen because anthracyclines are increasingly used in the adjuvant setting. Doxorubicin may not be a viable treatment option in patients with prior exposure to anthracyclines because of the occurrence of drug resistance and the risk of cardiotoxicity.

Vinorelbine is a new vinca alkaloid substituted on the catharantine moiety which results in higher and more selective affinity for tubulin, compared with the other vinca alkaloids [25]. Data from European and American studies suggest that vinorelbine, as a single agent, is highly active against metastatic breast cancer, with response rates from 35–60% in previously untreated patients, and 30% when used as a second- or third-line therapy [26,27]. The mechanism of action of vinca alkaloids is tubulin depolymerization. The binding sites on tubulin for vinorelbine and the taxoid, paclitaxel, are different [28,29]. Preclinical studies have demonstrated some synergism when vinorelbine and docetaxel are combined [13]. Moreover, cells with altered tubulins, which may contribute to resistance to taxoids, can exhibit increased sensitivity (so-called collateral sensitivity) to drugs such as vinblastine which act by destabilizing microtubules. Given the single-agent activities of taxoids and vinorelbine, it is of interest to explore these drugs in combination.

Trials with paclitaxel and vinorelbine

In an MDACC study, paclitaxel and vinorelbine were given simultaneously by 3-h infusion on day 1, repeated every 3 weeks [30]. The maximum tolerated dose was 150 mg/m^2 for paclitaxel and 25 mg/m^2 for vinorelbine. The dose-limiting toxicities were febrile neutropenia, grade 3 pelvic pain and grade 3 paraesthesia. In a second study, using the same schedule, with G-CSF given on days 2–12 [31], the maximum tolerated doses were 150 mg/m^2 for paclitaxel and 36 mg/m^2 for vinorelbine. The main toxicities were neutropenic fever, grade 3–4 fatigue and pain. An overall response rate of 54% was observed in the 13 patients treated. A pilot study with paclitaxel and vinorelbine with G-CSF was undertaken in patients with refractory metastatic breast cancer [32]. Vinorelbine was administered on days 1 and 8, and then on day 2 only, because of neutropenic fever on day 8. Paclitaxel (175 mg/m^2) was given as 3-h infusion. Preliminary results from nine patients showed that all patients experienced grade 4 neutropenia, one patient had febrile neutropenia with sepsis and two patients had grade 2, and one patient had grade 1, neuropathy.

Trials with docetaxel and vinorelbine

A phase I study was performed with vinorelbine administered on days 1 and 5, and docetaxel, on day 1 as a 1-h infusion, every 3 weeks, without the support of G-CSF [33]. Two maximum tolerated doses were reached. The first maximum tolerated dose was for docetaxel, 75 mg/m^2 on day 1, and for vinorelbine, 22.5 mg/m^2 on days 1 and 5 (Table 4). The dose-limiting toxicities were febrile neutropenia and mucositis. When vinorelbine was reduced to 20 mg/m^2 on days 1 and 5, this allowed docetaxel to be increased to 85 mg/m^2 and 100 mg/m^2. Subsequently, the second maximum tolerated dose was reached with docetaxel at 100 mg/m^2 on day 1, and vinorelbine at 20 mg/m^2 on days 1 and 5. Dose-limiting toxicities were febrile neutropenia, infection and grade 4 mucositis. Neurological examinations, including nerve conduction studies, were performed at baseline and every two cycles up to the end of the study: symptomatic peripheral

Table 4. Docetaxel in combination with vinorelbine: overall results

Dose level	Vinorelbine, days 1 and 5 (mg/m^2)	Docetaxel, day 1 (mg/m^2)	No. of evaluable patients entered	Dose-limiting toxicities	Main toxicities	Objective responses/ evaluable responses
I	20	60	3/3	0	0	2/3
II	20	75	5/6	0	0	5/5
III	22.5	75	4/4	3	Febrile neutropenia Stomatitis	2/4
IV	20	85	7/8	1	Febrile neutropenia	2/4
V	20	100	6/6	3	Febrile neutropenia Infection Stomatitis	3/5

neuropathy was not observed. 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 at 85 mg/m^2 on day 1 and vinorelbine at 20 mg/m^2 on days 1 and 5, every 3 weeks. A study with G-CSF support is also ongoing.

Conclusion

The unique mechanism of action of the taxoids, paclitaxel and docetaxel, and their response rates in breast cancer, provide opportunities and challenges for development of combination therapies. To date, docetaxel with doxorubicin appears a safe and very active combination. Docetaxel–vinorelbine, with good activity and safety, may represent an alternative to anthracycline-based combinations.

The short median follow-up of combination studies to date means that some important endpoints such as response duration and overall survival are missing. However, these considerations should not lessen the value of the remarkable reported responses, especially in visceral disease. These favourable therapeutic results represent an opportunity to improve treatment in patients with breast cancer. To exploit this possibility fully, studies with G-CSF support are ongoing to reduce the impact of neutropenia. Randomized trials are warranted and optimal integration of these combination therapies in an adjuvant setting is planned.

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