A phase II study of an oxaliplatin/vinorelbine/5-fluorouracil combination in patients with anthracycline-pretreated and taxane-pretreated metastatic breast cancer

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The aim of this phase II study was to evaluate safety and efficacy of an oxaliplatin/vinorelbine/5-fluorouracil (FON) combination in anthracycline and taxane-pretreated metastatic breast cancer patients. The following treatment was given: on day 1 of a 21-day cycle, oxaliplatin 130 mg/m^2 (2-h intravenous infusion); on days 1 and 5, vinorelbine [dose level (DL) 1: 17.5 mg/m^2; DL2: 22 mg/m^2]; on days 1–5, continuous infusion 5-fluorouracil (DL1: 600 mg/m^2/day; DL2: 750 mg/m^2/day). Forty-seven patients were treated (DL1: 43; DL2: 4). Median age was 54 years; 68% had liver metastases, 53% were taxane refractory/resistant and 38% were anthracycline refractory/resistant. Patients received a median of six treatment cycles. Of 46 eligible patients, 16 had partial response; the overall response rate was 34.8% (95% confidence interval 21.3–50.3%), 11 had stable disease lasting more than 4 months. Median follow-up was 13.0 months, median time to progression 5.7 months and estimated overall survival 18.8 months. DL2 was too toxic with three patients having grade 3–4 toxicity, including one death. At DL1, 26 patients (60%) experienced grade 3–4 neutropenia (six febrile neutropenia) and eight had grade 3 oxaliplatin-specific peripheral neuropathy after a median of 646.4 mg/m^2 oxaliplatin (range 124–1619 mg/m^2). Oxaliplatin (130 mg/m^2, day 1)/vinorelbine (17.5 mg/m^2, days 1,5)/5-fluorouracil (600 mg/m^2/day, days 1–5) demonstrate encouraging activity and a manageable safety profile in anthracycline- and taxane-pretreated metastatic breast cancer patients. *Anti-Cancer Drugs* 17:1067–1073

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Introduction

Breast cancer remains the most commonly diagnosed cancer in women of the Western world and is second only to lung cancer in terms of female mortality [1]. Despite improvements in controlling localized disease, recurrent metastatic breast cancer (MBC) remains common and survival from first relapse is approximately 2 years, depending on various prognostic factors [2].

Anthracyclines and taxanes are the most frequently used agents for MBC, and their use in combination both in adjuvant and in first-line metastatic settings is rapidly increasing [3,4]. New treatment strategies are increasingly needed for patients failing these therapies or who are at risk of cumulative toxicities.

The success of further chemotherapies after failure of anthracyclines and taxanes has been generally modest. Active single agents yield response rates of 15–30% in this setting [5–7] and their sequential use is generally preferred for the management of patients with limited asymptomatic disease. For patients with more extensive or symptomatic disease, many oncologists prefer combination therapies because, even if the advantage in terms of survival has not been demonstrated to date, they seem to offer better results in terms of response rate and progression-free survival that could be translated to better control of symptoms. The most promising combinations are those including 5-fluorouracil (5-FU) or capecitabine with platinum compounds, vinorelbine (VNB) or gemcitabine [8–11]. The best choice of

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treatment in this difficult clinical setting, however, is still a matter of controversy and requires further investigation.

5-FU, a thymidylate synthase inhibitor, elicits response rates of 10–44% [12,13] depending on prior exposure to chemotherapy. Continuous intravenous infusion of 5-FU and its oral pro-drug capecitabine are well-established options for treating patients who have received previous bolus 5-FU in the adjuvant setting [6,14]. VNB, a vinca alkaloid derivative that interferes with tubulin assembly during mitosis, is active both as a single agent [5,15], and in combination with taxanes [16], 5-FU [17] and platinum compounds [11] in MBC patients. The main dose-limiting toxicities are neutropenia, sensory neuropathy and neuroconstipation.

Oxaliplatin is a DACH platinum compound that binds DNA, blocking replication and transcription, leading to apoptosis [18]. Cells with mismatch repair deficiency, resistant to a variety of anticancer drugs including doxorubicin and other platinum compounds, remain sensitive to oxaliplatin [19,20]. Human breast cancer cells have shown increased mismatch repair, owing to epigenetic mechanisms, after doxorubicin-based treatment [21], which may in part explain the preclinical activity of oxaliplatin in paclitaxel-resistant and anthracycline-resistant cell lines. Oxaliplatin has shown additive or synergistic cytotoxicity with most agents tested to date [20]. It has also shown activity in MBC patients previously treated with anthracyclines and/or taxanes both as a single agent [22] and in combination with 5-FU [8]. It has a favourable safety profile, limited to mild haematotoxicity and characteristic cumulative neurosensory toxicity that is largely reversible after treatment discontinuation [20,23].

Preclinical and clinical synergy has been observed between VNB, 5-FU and platinum compounds in other indications [20,24]. Thus, this triple combination was a logical avenue to explore for the treatment of taxane-pretreated and anthracycline-pretreated MBC patients, given that each agent has a different mechanism of action that may assist in circumventing resistance.

In this study, the recommended dose of oxaliplatin (130 mg/m^2) every 3 weeks was combined with infusional 5-FU over 5 days (600 or 750 mg/m^2/day). A sub-maximal dose of VNB (17.5 or 22 mg/m^2/day, days 1 and 5) was administered to provide a wider safety profile, given the prevalence of hepatic metastases in MBC, a factor that alters the pharmacodynamics of VNB [25].

Patients and methods

To be eligible for this study, patients had to have confirmed MBC; be women between 18 and 75 years of age; have a performance status [World Health Organization (WHO)] of 2 or better; have received at least one prior taxane-based regimen and prior adjuvant or metastatic anthracycline-based therapy; have not received more than three lines of chemotherapy; have disease progression documented within 12 months of the most recent taxane-containing regimen; have at least one uni-dimensionally measurable target lesion measured by appropriate imaging techniques within 4 weeks of inclusion; have adequate renal, bone marrow and hepatic functions. Patients were excluded if they had received prior chemotherapy within 4 weeks of enrolment (6 weeks for nitrosoureas and mitomycin C and for completed hormonotherapy); prior radiation treatment of any target lesions; brain metastasis; bone metastases, lung carcinomatous lymphangitis, ascites or pleural effusion as the only proof of the only proof of metastatic disease; >2 grade peripheral neuropathy [National Cancer Institute Common Toxicity Criteria (for adverse events) (NCI-CTC, version 2)]; prior treatment with oxaliplatin or VNB, or by 5-FU given as a continuous intravenous infusion. This protocol was approved by the investigating sites ethics committee and signed informed consent was obtained from all patients.

Treatment was started at dose level (DL) 1. On day 1 of a 21-day cycle, patients received an intravenous bolus administration of 17.5 mg/m^2/day VNB followed 15 min later by 130 mg/m^2 oxaliplatin as a 2-h intravenous infusion; 600 mg/m^2/day 5-FU was administered as a 5-day continuous intravenous infusion from day 1 to 5 administered on an out-patient basis. On day 5 of the cycle, patients received a second intravenous dose of 17.5 mg/m^2/day VNB. In the absence of grade 2 or higher toxicity at the end of the first cycle, the VNB dose was increased to 20 mg/m^2/day in the second cycle. Patients treated at DL2 received 22 mg/m^2/day VNB, 130 mg/m^2 oxaliplatin and 750 mg/m^2/day 5-FU.

In the event of grade 3 or 4 toxicity (NCI-CTC), further treatment was delayed until recovery to grade 1 (maximum of 2 weeks); oxaliplatin was reduced to 100 mg/m^2 and for patients receiving 20 or 22 mg/m^2/day VNB the dose was reduced to 17.5 mg/m^2/day. Patients went off study treatment if these toxicities recurred. In the event of grade 3–4 neutropenia and thrombocytopenia and/or grade 2 or higher other non-haematological toxicities after day 1 administration, day 5 administration of VNB was not given. In the event of grade 3 or 4 anaemia, a transfusion of red cell concentrate was to be given before day 5 VNB administration. In the event of severe haematotoxicity, doses were delayed to allow the patient to recover to at least 1500 neutrophils/mm^3 or 100 000 platelets/mm^3, with a maximum delay of 2 weeks before the patient was taken off study. Use of granulocyte-colony stimulating factor was not permitted. In the event of neurotoxicity, a specific oxaliplatin-induced

cumulative neurosensory grading scale as described by Levi *et al.* [26] was used: for paresthesia, dysesthesia, pain or functional impairment persisting between two cycles, oxaliplatin was reduced to 100 mg/m^2 and VNB was reduced by 20%. Treatment was to be discontinued if persistent functional impairment or continuation of symptoms occurred even after dose reduction.

Safety was assessed using NCI-CTC version 2 with the exception of neurotoxicity (see above). Tumour response was assessed according to the RECIST (Response Evaluation Criteria in Solid Tumours) criteria [27] every 8 weeks until study discontinuation. Time to progression (TTP) and overall survival (OS) were analysed using the Kaplan–Meier method. Data acquisition cut-off date was 7 December 2002.

Patients' disease resistance status to taxanes and anthracyclines was prospectively defined and analysed. Several definitions of clinical resistance have been proposed [28–30], but none is universally accepted or prospectively validated, and all are arbitrary and exploratory. For this study, patients were considered to be refractory/resistant when disease progression could reliably be established within 6 months of the last drug administration in the adjuvant setting and/or within 3 months of last administration for metastatic disease. All other patients were assessed as potentially sensitive (modified from the study by Piccart *et al.* [30]).

Using a Simon two-stage minimax design (lowest response rate of 15%, optimal response rate of 30%, α error of 5% and β error of 20%), 48 patients were required [31]. Twenty-three patients were planned for an efficacy assessment in first stage. If four or more responses were observed, a further cohort of at least 25 patients was to be included.

Results

Forty-seven patients, all previously treated with both taxanes and anthracyclines, were enrolled in the study between July 2000 and July 2002 in a total of seven centres in France. Four patients started treatment at DL2, but due to the high level of toxicity, the subsequent 43 patients were treated at DL1. The median age was 54 years (range: 30–68 years) and the majority of patients (94%) had a WHO performance status of 0–1 (Table 1). All patients had metastatic disease and a median of 2 involved organs (range 1–7), including 68% with liver metastases and 28% with four or more affected organs. A large number of patients had evidence of high tumour burden including 35 (77%) with more than 50 IU/ml of CA 15–3 at baseline and 45% with elevated LDH levels.

Table 1 Patient characteristics at study entry by dose level

Number of patients	47
Age (years)	
median	54
range	30–68
Performance status (WHO)	
0/1/2	20/24/3
Number of involved organs	
median (range)	2 (1–7)
Site of involved organs (%)	
liver	32 (68)
bone	25 (53)
lymph	20 (43)
lung	17 (36)
pleural	13 (28)
skin	9 (19)
breast ipsilateral	5 (11)
CA 15-3 (%)	
50–300 IU/ml	20 (44)
>300 IU/ml	15 (33)
LDH: abnormal	21 (45)
Prior surgery (%)	39 (83)
Prior radiotherapy (%)	39 (83)
Number of prior lines chemotherapy[a] (%)	
1	10 (21)
2	29 (62)
3	7 (15)
4	1 (2)
Time since last chemotherapy (%)	
<2 months	17 (36)
2–8 months	15 (32)
≥ 8 months	15 (32)
Median time between last chemotherapy and study treatment (months)	3.44
Clinical resistance status (%)	
taxane refractory/resistant	25 (53)
taxane potentially sensitive	22 (47)
anthracycline refractory/resistant[b]	18 (38)
anthracycline potentially sensitive[b]	28 (60)

[a]Adjuvant/neo and palliative.
[b]One patient not evaluable (no prior anthracyclines).

Efficacy

One patient was considered ineligible for efficacy assessment, as she had not previously been treated with anthracyclines. Sixteen partial responses were reported in the 46 eligible patients, yielding an overall response rate of 34.8% [95% confidence interval (CI): 21.3–50.3%]. No responses were found in patients treated at DL2. Disease stabilization lasting more than 4 months was observed in 11 patients (Table 2). In six patients, it was impossible to assess response; one patient died after cycle 1, possibly because of a treatment-related cause (DL2), and five others (DL1) discontinued treatment after cycle 1 because of adverse events (four of which were considered treatment-related). Fourteen of the 16 responders (88%) received six or more cycles of the study treatment. The ineligible patient achieved a stable disease.

Time-related parameters were calculated in the 46 eligible patients, giving a median TTP of 5.7 months (95% CI: 4.4–7.0; Fig. 1). With a median follow-up of 13.0 months (range: 5.0–28.3 months), 31 patients were still alive at the data cut-off point (66%). Median OS was estimated at 18.8 months (95% CI: 11.7–25.8). The median duration of response was 4.4 months (range: 1.8–16.4 months). The response lasted 6 months or longer in seven of the 16 patients (44%). Twenty-nine patients (62%) were assessed as refractory/resistant to taxanes,

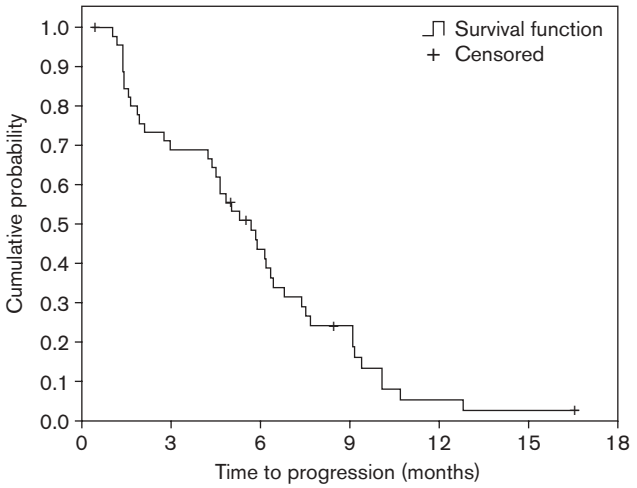
anthracyclines or both. Of the 25 patients who were refractory/resistant to taxanes, nine (36%; 95% CI: 17.2–54.8) responded to treatment, and of the 14 patients who were refractory/resistant to both taxanes and anthracyclines, five responded (36%; 95% CI: 12.8–64.9). This was the same as the global response; prior resistance does not seem to influence the possibility of responding to this treatment. A correlation between clinical response and CA 15-3 response was observed with 17 patients, with partial responses or stable disease for 4 months or more, having a concomitant decrease or normalization of CA 15-3. Of note, most patients (75%) qualifying for a partial response presented concomitant marker decrease.

Table 2 Tumour response according to dose level, eligible patients

	DL1 ($n=42$)	DL2 ($n=4$)	Total ($n=46$)
PR	16	–	16
SD $\geq$ 4 months	10	1	11
SD <4 months	1	–	1
PD	10	2	12
Not evaluable	5	1	6
ORR (95% CI)	37% (23.0–53.3)	0%	34.8% (21.3–50.3)

DL, dose level; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; CI, confidence interval.

Fig. 1



Time to progression in eligible patients censored at the beginning of the next therapy.

Exposure and safety

The first four patients enrolled in this study were treated at DL2, but three experienced major toxicities including one treatment-related death. This patient experienced severe nausea, vomiting, diarrhoea and severe anxiety with left basal thoracic pain 6 days after completing her first cycle of treatment. She died 1 week later at home. Information available was insufficient to determine the cause of death; however, it was conservatively assumed to be treatment-related. Another patient experienced severe stomatitis and asthenia at day 8 of cycle 1. She was also diagnosed with a pulmonary embolism and possible lung carcinomatous lymphangitis related to disease progression and treatment was discontinued. A third patient experienced grade 3 diarrhoea and vomiting and febrile neutropenia after the first cycle of treatment, but after treatment for these conditions she went on to receive eight cycles at a reduced dose of all three agents.

All subsequent patients were treated at DL1; 226 cycles were administered at this DL, with a median of 6 (range: 1–17 cycles) per patient. Twenty-four patients (56%) received at least six cycles, and 10 (23%) received eight cycles or more. Dose intensity decreased in patients receiving more cycles of treatment owing to delays and dose reductions. While for DL1, the median relative dose intensity for the 14 patients receiving fewer than three or equal to three cycles was 0.99 for oxaliplatin, 0.95 for VNB and 0.99 for 5-FU, for the 11 patients receiving more than six cycles, these figures fell to 0.84, 0.80 and 0.87, respectively. The principal cause of cycle delay was neutropenia, accounting for 51% of the 65 delays at DL1. Nevertheless, 75% of these delays lasted less than a week. Fourteen patients at DL1 (33%) had their dose reduced because of neurotoxicity, haematotoxicity and gastrointestinal toxicity.

Table 3 Grade 3–4 toxicity per patient according to dose level (DL), all treated patients (NCI-CTC) [*n*(%)]

	Grade 3			Grade 4		
Patients	DL1 ($n=43$)	DL2 ($n=4$)	Total ($n=47$)	DL1 ($n=43$)	DL2 ($n=4$)	Total ($n=47$)
Neutropenia	9 (21)	–	9 (19)	14 (33)	3	17 (36)
Febrile neutropenia				6 (14)	2	8 (17)
Leukopenia	10 (23)	2	12 (26)	3 (7)	1	4 (9)
Thrombocytopenia	4 (9)	–	4 (9)	–	–	–
Fatigue	6 (14)	1	7 (15)	–	1	1 (2)
Mucositis	5 (12)	–	5 (11)	–	2	2 (4)
Vomiting	3 (7)	1	4 (9)	–	1	1 (2)
Nausea	2 (5)	2	4 (9)	–	–	–
Anorexia	1 (2)	3	4 (9)	–	–	–
Diarrhoea	2 (5)	2	4 (9)	–	–	–
Dyspnea	1 (2)	–	1 (2)	1 (2)	–	1 (2)
Neurotoxicity[a]	10 (23)	1	11 (23)			

[a]According to an oxaliplatin-specific scale.

Table 4 Neurological clinical toxicity according to oxaliplatin cumulative dose, all treated patients[a]

	Grade 0	Grade 1	Grade 2	Grade 3	Total
Cumulative oxaliplatin dose (mg/m^2)					
median	257.9	260.0	729.5	646.4	675.6
range	255–260	126–813	125–2013	124–1619	124–2013
Cumulative vinorelbine dose (mg/m^2)					
median	69.8	70.9	207.2	163.2	172.9
range	69.6–70	32–331	36–557	32–499	32–557

[a]According to an oxaliplatin-specific scale.

Grade 3 and 4 toxicities are presented in Table 3 by dose level. Oxaliplatin-specific neurotoxicity was prevalent, but mild to moderate, and was linked to cumulative doses of oxaliplatin, with all patients who received more than 600 mg/m^2 experiencing some grade of toxicity and all patients who received more than 1000 mg/m^2 showing at least grade 2 neurotoxicity (Table 4).

Discussion

Finding an appropriate treatment for MBC in patients who have exhausted the now standard option of taxanes and anthracyclines given either separately or in combination remains a pressing but difficult clinical problem. In this context, the problem of cumulative toxicity is compounded with the problem of cross-resistance. As the long-term survival prospects are relatively poor, it is important to provide palliative treatment that reduces the tumour burden without excessive toxicity. The single agent versus combination question in this setting is still a matter of controversy. In the absence of randomized trials, combination therapy could be proposed to symptomatic patients with high volume visceral or symptomatic disease in whom rapid tumour shrinkage is crucial. The oxaliplatin/VNB/5-FU combination used in this study aimed to determine the tolerability of the treatment and its efficacy in terms of tumour reduction, progression-free survival and OS. Further, it was intended to establish a safe recommended dose.

The response rate (35%), the TTP (5.7 months) and the OS (18.8 months) observed in this study are at the upper limit of the range of activity elicited by a number of other combination and single-agent regimens that have been tested [5–11,32–37].

The cisplatin and VNB combination [11] yielded the highest response rate ever reported in this setting (47.2% including 5.6% of complete response). With the combination of oxaliplatin and 5-FU [8,34], a response rate of 23–27% was reported. The response rate observed with the combination of 5-FU and VNB was 27.5% with a TTP of 5.3 months and an OS of 16.4 months [34]. One recent study combining oral VNB with capecitabine had a response rate of 40.9% [38], but no information on time-related parameters is provided for comparison.

The ON combination (oxaliplatin 130 mg/m^2, day 1, and VNB 24 mg/m^2 days 1 and 8, every 3 weeks) [36] was initiated at the same time as this study and the response rate observed was 27% with a TTP of 3.4 months and an OS of 12.7 months, lower than that observed in our study, which may be related to the addition of 5-FU.

Single-agent capecitabine has been demonstrated to be effective in this setting with an overall response rate of 9–28%, a median TTP between 3.5 and 4.9 months and OS between 9.4 and 15.2 months in several phase II–III trials [6,7,37,39]. The main drawback observed with capecitabine monotherapy is the 10–20% rate of discontinuation and up to 40% reduction of the recommended dose, mostly because of gastrointestinal toxicity and hand–foot syndrome. Single-agent VNB was demonstrated to have an overall response rate of 27% (CI: 12.1–42.5); however, grade 3–4 neutropenia was seen in up to 51% of patients, requiring frequent use of granulocyte-colony stimulating factor (35%) and/or dose reductions (25%) due to the high prevalence of haematological toxicity [40]. Another study using VNB as a single agent found a response rate of 4% in MBC patients older than 65 years with grade 3 or higher neutropenia (12.5%), bilirubin (4.2%) and neuromotor difficulties (4.2%) [41].

In general, the patients in this study, although in relatively good physical condition, had multiple sites of disease including a prevalence of liver and other visceral metastases, which has been shown to be correlated with poor prognosis and low activity of chemotherapy [42]. Furthermore, a large number of the patients had evidence of high tumour burden according to the high prevalence of increased levels of LDH and CA 15-3. Concerning the characteristics of responders, it should be noted that 75% had liver involvement, 56% were refractory/resistant to taxanes, and 31% were refractory/resistant to both taxanes and anthracyclines, suggesting that the combination is not cross-resistant with these two commonly used agents.

Taking into account the prior exposure of the cohort, the treatment was reasonably well tolerated, particularly at DL1. Fifty-six percent of patients treated at DL1 received at least six cycles of the combination, although the relative dose intensity of both agents decreased in patients receiving more than three cycles because of

treatment delay, principally because of haematotoxicity and neurotoxicity. Neutropenia was widespread and often severe, complicated by fever in 17% of patients, which is higher than the rate observed with other combinations such as 5-FU–oxaliplatin (0–2%) or cisplatin–VNB (0%) and single agents, but is lower than with the 5-FU and VNB combination (up to 33%) in this setting [8,11,34,35,43]. It should be noted, however, that no haematological growth factors were administered during this trial, which are required in almost 50% of patients treated with cisplatin–VNB [11] and 35% with VNB alone [40].

Neurotoxicity, as expected, was linked to the cumulative dose of oxaliplatin. All patients who received more than 600 mg/m^2 oxaliplatin experienced at least grade 1 toxicity. The level of grade 3 oxaliplatin-specific scale neuropathy observed (23%) is higher than that observed with the 5-FU–oxaliplatin [8,34] combination (6–8%) and with the cisplatin–VNB combination (3%) [11]. In the cisplatin–VNB combination trial [11], however, the number of cycles was limited to six and the evaluation of neuropathy was done using a different scale (WHO scale) making observations difficult to compare. The level of peripheral sensory neuropathy was similar to that observed with the ON combination [36]. It is noteworthy that the association with VNB does not appear to increase the frequency or the severity of the oxaliplatin-related neuropathy, when compared with historical series of oxaliplatin monotherapy [23]. Most other toxicities including those particular to the use of oxaliplatin were mild to moderate.

As three of the four patients treated at DL2 experienced significant toxicity, including one death, DL1 should be retained as the recommended dose for this combination in this particularly pretreated and multi-metastatic population: 130 mg/m^2 of oxaliplatin (day 1), VNB at 17.5 mg/m^2 increasing to 20 mg/m^2 (days 1 and 5) with 600 mg/m^2/day 5-FU continuous intravenous infusion on days 1–5. This combination is active and can be safely administered to MBC patients previously treated with taxanes and anthracyclines, and who have had a relapse within 12 months of taxane chemotherapy. Other combinations including both study compounds are being investigated for use in this difficult clinical context.

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