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CLINICAL TRIAL REPORT

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Vinorelbine and docetaxel as first-line chemotherapy in metastatic breast cancer

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Abstract *Purpose*: To evaluate the efficacy and tolerability of a combination of vinorelbine (VNR) and docetaxel (DOC) as first-line chemotherapy in patients with metastatic breast cancer. *Patients and methods*: The study group comprised 40 women with untreated metastatic breast cancer with visceral (85%) and bone (70%) metastases. Of the 40 patients, 24 (60%) had previously received adjuvant chemotherapy, which had included anthracyclines in 12 patients (30%). Treatment consisted of VNR 25 mg/m^2 on days 1 and 5, and DOC 75 mg/m^2 on day 1 every 3 weeks. Depending on the neutrophil nadir (grade 3 or 4 neutropenia by WHO criteria) recombinant human granulocyte colony-stimulating factor (G-CSF) 5 μg/kg on days 2–4 and 6–13 was given for all subsequent treatment cycles. *Results*: The overall response rate (ORR) was 40% (95% confidence interval, CI 15–65). Six patients (15%) achieved a complete response (CR) and ten patients (25%) achieved a partial response (PR). Stable disease (SD) was observed in six patients (15%), and 18 patients (45%) had progressive disease (PD). The median duration of response was 8 months and the median predictive time to progression (TTP) was 6 months. The main toxicity was neutropenia grade 3 and 4 in 28 patients (70%). Febrile neutropenia requiring hospitalization occurred in 12 patients (30%). Grade 3 or 4 anemia was seen in two patients (5%) and grade 3 or 4 thrombocytopenia was seen in one patient (2.5%). Severe non-hematologic toxicity, except alopecia, was uncommon and included stomatitis in two patients (5%), vomiting in two (5%) and diarrhea in one (2.5%). There were no treatment-related deaths. *Conclusions*: The combination of VNR and DOC at the doses used in this study showed moderate activity as first-line chemotherapy in metastatic breast cancer. Neutropenia was considerable despite G-CSF administration.

Keywords Vinorelbine · Docetaxel · First-line chemotherapy · Metastatic breast cancer

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Introduction

Despite adequate locoregional treatment and systemic adjuvant polychemotherapy at the time of diagnosis, metastatic relapses occur in 40% of patients with breast cancer [1]. The increasing use of anthracyclines in adjuvant treatment has led to a limitation of their use in relapsing patients. The need has therefore emerged for active non-anthracyclines-containing regimens in these cases. Among the novel chemotherapeutic drugs introduced in the last decade, docetaxel (DOC) and vinorelbine (VNR) have emerged as promising compounds with remarkable activity when given alone as first-line treatment.

Both drugs act on the mitotic spindle and arrest dividing cells in metaphase by different mechanisms. VNR is a classic antitubulin agent and induces disruption of microtubules by reversible binding to tubulin, leading to the inhibition of tubulin polymerization and microtubule formation [2]. Conversely, DOC exerts its anticancer activity by promoting tubulin assembly into microtubules and inhibits their disassembly to free tubulin [3]. The different mechanisms of action of DOC and VNR on the microtubules suggests a potential clinical synergy and provides the rationale for their combined use in the clinical setting [4, 5]. Synergism has been observed in vitro when both drugs were combined in preclinical evaluation studies [6, 7] and were given simultaneously or with VNR preceding DOC.

First-line chemotherapy with DOC 75–100 mg/m^2 administered every 3 weeks and VNR 30 mg/m^2 weekly yield response rates of 40–68% [8, 9, 10, 11] and 41–50% [12, 13, 14, 15], respectively, which appear to be similar to the responses to anthracyclines. In addition various combinations of DOC or VNR with other drugs are very active regimens in anthracycline-pretreated patients. This observation prompted us to investigate the DOC/VNR regimen as first-line therapy in metastatic breast cancer.

In a phase I study, VNR was administered on days 1 and 5 followed on day 1 by DOC every 3 weeks. Two maximum tolerated doses (MTD) were reached, the first at 75 mg/m^2 of DOC and 22.5 mg/m^2 of VNR, and the second at 100 mg/m^2 of DOC and 20 mg/m^2 of VNR. Dose-limiting toxicities were febrile neutropenia and mucositis [16].

Based on these data, we combined VNR 25 mg/m^2 on days 1 and 5 followed on day 1 by DOC 75 mg/m^2, as initial treatment in metastatic breast cancer patients in order to evaluate the antitumor activity and tolerability in previously untreated patients. Because of prophylaxis with recombinant human granulocyte colony-stimulating factor (G-CSF), VNR was given at a higher dose than the MTD (25 mg/m^2 instead of 22.5 mg/m^2). It was planned that patients who were not exposed to anthracyclines would receive doxorubicin at progression or relapse after DOC/VNR treatment and cross-resistance would be assessed. Apart from one study in which VNR 30 mg/m^2 was given on days 1 and 8 and DOC 30 mg/m^2 on days 1, 8 and 15 every 4 weeks as first-line or second-line therapy, there are no reports of studies in which the efficacy of the VNR/DOC combination in metastatic breast cancer has been investigated.

Patients and methods

Patients

Patients aged between 18 and 72 years with histologically confirmed breast cancer who had relapsed after prior adjuvant therapy were eligible. Patients with metastatic disease at presentation were also included. Previous hormonal and radiation therapy for advanced disease were allowed but must have been discontinued at least 4 weeks before study entry. Patients who had received previous palliative chemotherapy were ineligible.

All patients were required to have bidimensionally measurable disease with defined index lesions >1 cm in size on physical or radiographic examination, or ≥ 2 cm on ultrasound or CT scan and to have a World Health Organization (WHO) performance status of less than 3 and an expected survival time of more than 3 months. Patients with CNS disease and osteoblastic bone lesions as the only metastatic site were excluded.

Other eligibility criteria for entry into the study were: adequate pretreatment hematologic parameters (white blood cell count $\geq 3500/\mu l$, platelet count $\geq 100{,}000/dl$ and hemoglobin ≥ 11 g/dl), serum creatinine ≤ 1.5 mg/dl, serum bilirubin ≤ 1.5 mg/dl and serum transaminase levels not more than twice the upper limit of normal. Pretreatment evaluation included a complete medical history and physical examination, a complete blood count (CBC), an 18-function biochemical profile and an ECG. Tumor size was measured prior to treatment initiation and every two cycles by physical examination, radiography, or ultrasound or CT scan. Effusions and osteoblastic lesions were not regarded as objectively measurable. Informed consent was obtained from all patients, and the study was approved by the ethics committee of St. Savas Hospital.

Treatment protocol

Treatment consisted of VNR 25 mg/m^2 on days 1 and 5, followed by DOC 75 mg/m^2 on day 1. VNR was diluted in 50 ml normal saline (NS) and infused over 10 min. Thereafter, 200 ml NS was given as a bolus for the prevention of VNR-induced chemical phlebitis. DOC was diluted in 250 ml NS and infused over 1 h. Antiemetic therapy with 5-HT$_3$ antagonists was administered in all cases. To avoid fluid retention and anaphylactic reactions, patients were premedicated with dexamethasone 8 mg orally twice daily 24 h before treatment for six doses. The regimen was repeated every 3 weeks in the day clinic until evidence of disease progression or for a maximum of nine courses.

Toxicity

All eligible patients were evaluated for toxicity according to WHO criteria [17]. Local venous tolerability was assessed according to the scale of Rittenberg et al. for venous irritation [18]. Toxicity monitoring included CBC with differential and platelets on days 1, 8, 15 and 21 of every cycle. When a grade 3 or 4 hematologic toxicity was reported, CBC was performed biweekly until recovery. The VNR dose on day 5 was given only in the presence of an absolute neutrophil count (ANC) $>1500/\mu l$ and platelet count $>100{,}000/\mu l$. When grade 3 or 4 neutropenia occurred G-CSF 5 μg/kg was given subcutaneously on days 2–4 and 6–13 for all subsequent treatment cycles. Drug doses were reduced by 25% in cases of febrile neutropenia or persistent grade 4 neutropenia despite G-CSF secondary prophylaxis, grade 4 thrombocytopenia or any severe (grade 3-4) nonhematologic toxicity.

Response

Patients who had received at least one course were considered assessable for response and were evaluated for antitumor activity and time-related parameters. Duration of response was measured from the onset of best response to the date of disease progression.

Complete response (CR) was defined as the disappearance of all sites of disease. For bone lesions, a CR required recalcification of all lytic lesions and return of blastic lesions to normal density. In measurable disease, a partial response (PR) consisted of a $>50\%$ decrease in the sum of the products of the two greatest diameters of all measurable lesions without the appearance of new lesions or progression of any lesion. Patients with unidimensionally measurable lesions were considered to have evaluable disease. In evaluable disease, PR was defined as an estimated decrease in tumor size of at least 50%. Bone lesions that demonstrated healing radiographically were considered a true PR. Progression was defined as an increase of $>25\%$ of at least one measurable or evaluable lesion, or the appearance of new lesions. All other circumstances were classified as stable disease (SD). A confirmed response, verified by two independent radiologists, was defined as PR or CR observed in at least two consecutive evaluations at least 1 month apart.

The intensity of chemotherapy was evaluated by calculation of relative dose intensity which was defined, for each drug, as the ratio of the received dose divided by the scheduled dose to the actual duration of treatment divided by the scheduled duration. It was expressed as a percentage of the projected intensity.

Statistical analysis was performed using the Pearson chi-squared (χ^2) test. Time to progression (TTP) was considered from the date of entry into the study until disease progression and was assessed by means of the Kaplan-Meier product-limit method.

Results

Patient characteristics

Between October 1999 and January 2001 a total of 40 patients entered this trial. All patients were assessable for response and toxicity. Patient characteristics are given in Table 1. The median age of the patients was 55 years (range 38–72 years). Of the 40 patients, 15 were premenopausal and 25 postmenopausal. The median time elapsed from primary diagnosis to progression was 20 months (range 0–144 months). Bone was the most frequently affected site (70%), followed by liver (47.5%), lung (37.5%), lymph nodes (35%), chest wall/skin (22.5%) and pleural effusion (12.5%). Of the 40 patients, 11 (27.5%) had one metastatic site, 12 (30%) had two and 17 (42.5%) had three or more. Hormonal therapy had previously been given to 25 patients (62.5%). Adjuvant endocrine therapy was given in 14 patients (35%) and both adjuvant and palliative therapy in 11 patients (27.5%). Adjuvant chemotherapy, received by 24 patients (60%), had included anthracyclines in 12 (30%), cyclophosphamide/methotrexate/fluorouracil (CMF) in 10 (25%) and high-dose chemotherapy in 2.

Response to therapy

The overall response rate (ORR) was 40% (95% CI 15–65%) including six CRs (15%) and ten PRs (25%). Detailed data on the responses to VNR/DOC are shown in Table 2. SD was observed in six patients (15%). The median duration of response was 8 months (range 4–12 months). After a median follow-up of 13 months at the time of this report, 31 patients (77%) were still alive and 11 patients (27.5%) showed no evidence of disease progression. The majority of objective responses were observed in lung (47%) and in lymph nodes (43%).

Five out of six complete responders had one metastatic site (three lymph node and two lung) and one patient had two metastatic sites (lymph node and lung). The response rates according to the number of involved target sites were: one site 45%, two sites 42%, three or more sites 35%. There were no statistically significant differences between the response rates of various tumor sites ($P = 0{,}885$) or the number of metastatic sites ($P = 0{,}858$), respectively. The median predictive TTP was 6 months (95% CI 3.25–8.75%) and the median survival had not been reached at the time of this report.

Table 1 Patient characteristics (*CMF* cyclophosphamide/methotrexate/fluorouracil)

	Median (range)	*n* (%)
Number of patients entered		40
Age (years)	55 (38–72)	
Menopausal status		
Premenopausal		15 (37.5)
Postmenopausal		25 (62.5)
Estrogen receptors		
Positive		20 (50)
Negative		11 (27.5)
Unknown		9 (22.5)
Time from diagnosis to progression (months)	20 (0–144)	
Prior hormonal therapy		25 (62.5)
Adjuvant		14 (35)
Adjuvant plus palliative		11 (27.5)
Prior adjuvant chemotherapy		24 (60)
Anthracyclines		12 (30)
CMF		10 (25)
High-dose[a]		2 (5)
Number of metastatic sites		
1		11 (27.5)
2		12 (30)
≥3		17 (42.5)

[a]Carboplatin/etoposide/melphalan

Table 2 Responses to DOC/VNR

	Median (range)	*n* (%)
Overall response		16 (40)
Complete response		6 (15)
Partial response		10 (25)
Stable disease		6 (15)
Disease progression		18 (45)
Duration of response (months)	8 (4–12)	
Time to progression (months)	6 (3–6)	
Responses according to tumor site		
Bone		8/28 (29)
Liver		7/19 (37)
Lung		7/15 (47)
Lymph nodes		6/14 (43)
Chest wall/skin		3/9 (33)
Pleural effusion		2/5 (40)
Responses according to number of metastatic sites		
1		5/11 (45)
2		5/12 (42)
≥ 3		6/17 (35)

Treatment and tolerability

A total of 182 courses were administered. The mean number of treatment cycles was 4.5 per patient (range 1–9). Doses of VNR and DOC were reduced in 107 cycles (60%) and 93 cycles (52%), respectively. The mean dose intensity for DOC was 0.90 (range 0.8–1.0) and for VNR was 0.84 (range 0.6–1.0). For VNR the mean dose per injection was 21 mg/m^2. Only four day-5 doses of VNR were missed, as neutropenia was usually observed later.

Toxicity was largely hematologic (Table 3). Grade 3 or 4 neutropenia was observed in 28 patients (70%). Febrile neutropenia was observed in 16 patients (40%) and 12 of these (30%) were hospitalized for intravenous antibiotics. No toxic deaths occurred. G-CSF was administered in 28 patients (70%) because of grade 3 or 4 neutropenia. Anemia was rare (two patients with grade 3; 5%) and grade 3 thrombocytopenia occurred in

Table 3 Worst toxicity observed in 40 evaluable patients

	WHO grade					
	1	2	3	4	3+4	%
Neutropenia	4	5	8	20	28	70
Anemia	15	3	2	0	2	5
Thrombocytopenia	2	2	1	0	1	2.5
Stomatitis	2	4	2	0	2	5
Diarrhea	2	1	1	0	1	2.5
Nausea/vomiting	10	3	2	0	2	5
Alopecia	6	4	13	0	13	32
Peripheral neurotoxicity	2	1	0	0	0	0
Phlebitis	1	1	0	0	0	0
Fluid retention	2	0	0	0	0	0
Anaphylactic reaction	1	0	0	0	0	0

only one patient (2.5%). Grade 3 stomatitis was uncommon (5%) and diarrhea was rare (2.5%). Chemical phlebitis at the infusion site (grade 1 or 2 on the scale of Rittenberg et al. [18]) was seen in two patients (5%). Nausea and vomiting were generally mild. Alopecia was the most common nonhematologic toxicity and was severe in 13 patients (32%). Severe peripheral neuropathy was not observed.

Discussion

A significant number of patients with breast cancer will relapse despite adequate locoregional treatment and systemic adjuvant therapy [1]. Nowadays an increasing number of patients receive adjuvant anthracycline-containing regimens which essentially limits their use in relapse. Therefore, not uncommonly, administration of nonanthracycline containing regimens becomes necessary as first-line treatment in metastatic breast cancer. Among the new agents investigated in recent years, DOC and VNR have been found to be the most active. Thus, investigation of the above drugs in combination as first-line treatment in metastatic disease remains a challenge. The combination has shown acceptable toxicity in non-small-cell lung cancer [19, 20].

The response rate we observed was lower than that observed in the study by Kornek et al. [21] (64%) and was similar to that in a study in which the combination of DOC and VNR was administered as first-line treatment in a similar regimen to ours [22]. However, comparison of different phase II studies is not valid in general.

In our study, six patients (15%) achieved a CR and ten patients (25%) achieved a PR with an ORR of 40%; SD was observed in six patients (15%). A CR occurred in patients with a low tumor burden with soft tissue and/or lung disease. Patients with liver and bone metastases were not among the complete responders. The median duration of response was 8 months and the median TTP was >12 months. After a median follow up of 12 months, 31 patients (77%) were alive and 11 patients (27.5%) were free of disease progression. The combination was shown to have similar activity at all sites of disease. The response rate was not affected by the number of metastatic sites, as patients with three or more sites responded in a manner similar to patients with fewer than three involved sites.

The main toxicity of the combination was neutropenia, while severe anemia and thrombocytopenia were rare. Grade 3 or 4 neutropenia was seen in 70% of patients, and these were supported with G-CSF. Febrile neutropenia was seen in 16 patients (40%) and 12 (30%) of these had to be hospitalized for a few days in order to receive treatment with intravenous antibiotics. Despite the high rate of neutropenia, toxicity was manageable and no toxic deaths occurred. Regarding nonhematologic toxicity, grade 3 alopecia occurred in 32% of patients and stomatitis occurred in ten patients with only two (5%) showing grade 3 toxicity. Despite the potential neurotoxicity of both drugs, peripheral neuropathy was rare and invariably mild (grade 1 and 2). In general, the toxicity seen in our study was similar to that recorded in the study by Kornek et al. [21], in which grade 3 and 4 neutropenia was encountered in 64% of patients.

In a phase II trial by Romero et al. [23], VNR in combination with paclitaxel was administered to 49 previously untreated patients with advanced breast cancer. A response rate of 60%, a median time to treatment failure of 7 months and a median survival of 17 months were observed. Grade 3 and 4 neutropenia occurred in 92% of patients with two treatment-related deaths.

As the combination of DOC and VNR in the present phase II study yielded a 40% response rate, it can be argued that similar results might have been obtained with single-agent DOC. However, the almost 55% response rates obtained with single-agent DOC in the early phase II studies [24, 25] should be regarded as preliminary, since these were based on small numbers of patients and subsequent randomized studies of single-agent DOC versus mitomycin C plus vinblastine or versus methotrexate plus 5-fluorouracil in anthracycline-refractory or heavily pretreated patients yielded response rates of 30% and 42%, respectively, for DOC [26, 27]. Therefore, randomized phase III studies of single-agent DOC versus combined DOC plus VNR might establish the value of adding VNR to DOC.

DOC and VNR when administered as single agents in first-line metastatic breast cancer patients achieve over 40% [8, 9, 10, 11, 12, 13, 14, 15] response rates. The results of our study, in terms of response rates, do not provide evidence for clinical synergy, in contrast to the findings of in vitro studies [6, 7], in which a synergistic interaction between the two drugs has been observed. Due to the fact that both VNR and DOC act on microtubules but with a completely different mechanism, we assume that in order to achieve synergy, the method and timing of their administration may play a significant role. When paclitaxel (a taxane with a similar mechanism of action to DOC) was administered following VNR, rather than simultaneously, clear antagonism was

observed [28]. On the other hand, in another in vitro study [29] the highest synergy for both drugs was found when cells lines were exposed for an extended period (48 h) to VNR before paclitaxel. The response rate of 40% with the DOC/VNR combination despite the high CR rate (15%) is inferior to that observed with the DOC/capecitabine [30] and VNR/cisplatin [31] combinations (even in anthracycline-pretreated patients).

In conclusion, the combination of DOC (day 1) and VNR (days 1 and 5) does not appear to improve response rate or TTP when compared to either drug alone but does result in increased toxicity. We consider that this combination should not be investigated further.

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