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Short Communication

Vinorelbine and Epirubicin in Metastatic Breast Cancer. A Dose Finding Study

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The aim of the study was to define the maximum tolerated dose (MTD) of vinorelbine given as one or two weekly doses in combination with epirubicin 60 mg/m² every third week. The MTD was defined as the dose resulting in a WHO grade III or IV leucopenia exceeding 50% of patients. Patients were treated in groups of 10 at escalating doses of vinorelbine. The number of patients at the final dose level was expanded to 20. The dose of epirubicin was kept constant at 60 mg/m² every third week. At dose level 1, 15 mg/m² vinorelbine was given on day 1 at level 2, 20 mg/m² was given on day 1 and at level 3, 20 mg/m² was given on days 1 and 8. The MTD was reached at dose level 3. WHO haematological toxicity grade IV occurred in 0, 10 and 45% and grade III at 60, 30 and 30% of patients at dose levels 1, 2 and 3, respectively. Despite the common occurrence of grade IV haematological toxicity, only two serious infections were noted. Non-haematological toxicity of vinorelbine included neurotoxicity, manifesting as muscle weakness, constipation and paresthesias in the majority of patients. Neurotoxicity was usually mild and did not require treatment discontinuation. Phlebitis at the injection site was troublesome in many patients. Alopecia and nausea, probably due to epirubicin, occurred in most patients. The response rates were 22% (95% CI (confidence interval) 3–60%), 40% (12–74%) and 60% (36–81%) at levels 1, 2 and 3, respectively (non-significant).

Key words: breast neoplasm, chemotherapy, metastases
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INTRODUCTION

ANTHRACYCLINE combinations have for two decades been the most active cytotoxic regimens in advanced breast cancer, yielding objective response rates in approximately 50% of patients [1]. During recent years, several new drugs, including paclitaxel, docetaxel and vinorelbine have been introduced with single drug efficacy rivalling that of doxorubicin or its daughter compound, epirubicin. Previous studies on vinorelbine monotherapy have documented responses in 24–60% [2–6].

A few small studies have documented the feasibility of combining vinorelbine with doxo- or epirubicin [7, 8]. The purpose of the present study was to determine the appropriate dose level of vinorelbine when combined with epirubicin at a dose of 60 mg/m², the dose used in our previous trial with cyclophosphamide and fluorouracil (the FEC-regimen) as well as in other large studies [9, 10].

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PATIENTS AND METHODS

Those eligible for treatment were ambulant patients not more than 70 years old with measurable or evaluable progressing metastases from histologically proven breast cancer. Response to treatment was assessed according to UICC criteria [11]. The study was approved by the local ethics committee.

The dose escalation scheme is shown in Table 1. 10 patients were treated at each dose level, and the doses were escalated until 50% or more of the patients at that dose level developed WHO grade 3 or 4 leucopenia. The number of patients at the final dose level was expanded to 20. Haematological nadir values were investigated on days 9–14 (day 11 recommended) after treatment and pretreatment values on days −3 to 1.

The statistical significance of differences in haematological nadir values and treatment response between dose levels was tested, paired (group 1 versus 2 and group 2 versus 3), with the Mann–Whitney test. The statistical significance of differences in time to progression and survival between the three dose levels was tested in a Cox proportional hazards model with dose level as the only covariate. Dose intensity was calculated as the cumulative amount of given drug divided by total treatment

Table 1. Dose escalation schedule

Drug	Dose	Day
Level 1		
Epirubicin	60 mg/m² i.v.	1
Vinorelbine	15 mg/m² i.v.	1
Level 2		
Epirubicin	60 mg/m² i.v.	1
Vinorelbine	20 mg/m² i.v.	1
Level 3		
Epirubicin	60 mg/m² i.v.	1
Vinorelbine	20 mg/m² i.v.	1
Vinorelbine	20 mg/m² i.v.	8

i.v., intravenous.

time (day 1 of first treatment to day 1 of last +21 days) and expressed as a percentage of planned dose.

RESULTS

According to the trial's protocol, dose escalation was discontinued at level 3. Thus the total number of patients in the study was 40 (10 each at levels 1 and 2 and 20 at level 3). One patient died suddenly shortly after the first treatment course and is excluded from response evaluation and analyses of toxicity, except with respect to haematological toxicity and infections. There were no significant differences between the patients at the three dose levels. 12 patients had received previous adjuvant chemotherapy (CMF, cyclophosphamide–methotrexate–fluorouracil) and 13 previous endocrine treatments.

The total number of delivered courses was 245, with a median number of five courses (range 1–13) and a mean of 6.1 per patient. Nadir haematological values were available from 205 courses (values unavailable after the last course in all but one patient given only one course, and one missing value in one paient at dose level 3 after the first course).

Haematological toxicity is shown in Tables 2 and 3. The haematological toxicity was predominantly due to neutropenia. The proportion of grade 3 or 4 neutropenia (neutrophil counts $< 1.0 \times 10^9$/l) at the three dose levels was 50, 40 and 75%, respectively, and grade 3 to 4 leucopenia was 44, 20 and 60%, respectively. Significant anaemia and thrombocytopenia occurred in only a few patients.

There were no statistically significant differences in non-haematological toxicity between the three dose levels in paired comparisons. 2 patients had severe infections. One patient at dose level 1 died suddenly at home after only one course of treatment at a neutrophil level of 0.7×10^9/l. One patient at dose level 3 was hospitalised and successfully treated with intravenous antibiotics for granulocytopenic fever. Alopecia (WHO grade 3) was almost universal at all dose levels. Grade III nausea occurred in 6 patients (15%), grade III stomatitis in one patient (3%) and grade III diarrhoea in one patient (3%). Otherwise, no grade III–IV non-haematological toxicity occurred. Mild (grade I–II) constipation was reported by 27 patients (69%), phlebitis at the injection site by 30 patients (77%), mild muscle weakness and paresthesias by 34 (87%) and 19 patients (49%), respectively. 9 patients (23%) reported transient post-treatment cardiac arrhythmia, none of which required treatment.

Treatment delays due to neutro- or leucopenia on at least one occasion were necessary in 20% of patients at dose level 1 (17% of courses), 30% at level 2 (17% of courses) and in 75% at level 3 (21% of courses). Dose reductions due to neutropenia were performed in 10 patients at level 3 (50%). Median dose intensity was 99% (range 78–113%), 96% (range 72–113%), and 79% (range 61–115%) for dose levels 1, 2, and 3, respectively.

The response rates were 22% (11% CR (complete remission)), 40% (20% CR) and 60% (20% CR) at levels 1, 2, and 3, respectively (non-significant),with an overall response rate for all three levels of 46% (18% CR). Median time to progression was 3.1, 5.4 and 5.1 months for dose levels 1, 2 and 3, respectively ($P = 0.92$). Median overall survival for all patients was 15.6 months ($P = 0.7$).

DISCUSSION

According to the criteria in this study (grade III–IV leucopenia in ≥ 50% of patients), the maximum tolerated dose of vinorelbine given on days 1 and 8 combined with an epirubicin dose of 60 mg/m² was 20 mg/m². No differences in toxicity were noted between dose levels 1 and 2. The leucocyte nadirs, however, were significantly lower at level 3, and similar trends were seen also in platelet and neutrophil nadirs. Since the only difference between dose levels 2 and 3 was the addition of a second vinorelbine dose, it can be concluded that this second dose contributes significantly to haematological toxicity.

Neutropenia seemed to be rapidly reversible, in accordance with previous studies [12], since by day 20 the mean neutrophil count had returned to within the normal range (data not shown). The frequency of severe neutropenia at the final dose level might have been higher if the nadir values had been investigated later than day 11, as recommended.

Three previous small studies of the combination of vinorelbine

Table 2. Haematological toxicity

	WHO Grade				
	0	I	II	III	IV
Number of patients, all courses					
Level 1 ($n = 10$)	1 (10%)	0	3 (30%)	6 (60%)	0
Level 2 ($n = 10$)	0	2 (20%)	4 (40%)	3 (30%)	1 (10%)
Level 3 ($n = 20$)	1 (5%)	0	4 (20%)	6 (30%)	9 (45%)
Number of courses					
Level 1 ($n = 42$)	5 (12%)	6 (14%)	23 (55%)	8 (19%)	0
Level 2 ($n = 62$)	4 (6%)	20 (32%)	20 (32%)	17 (27%)	1 (2%)
Level 3 ($n = 101$)	7 (7%)	16 (16%)	43 (43%)	23 (23%)	12 (12%)

Table 3. Haematological nadir means

	At day 11 (9–14)			
	Leucocytes ($\times 10^9$/l)	Neutrophils ($\times 10^9$/l)	Platelets ($\times 10^9$/l)	Haemoglobin (g/l)
Level 1	2.4	0.99	148	121
Level 2	2.45	1.15	184	117
Level 3	1.6	0.89	130	106
P, 1 versus 2	0.46	0.50	0.37	0.93
P, 2 versus 3	0.02	0.06	0.06	0.03

and doxo- or epirubicin with vinorelbine doses varying from 25 to 30 mg/m^2, similar to dose level 3 in the present study, also indicate that leucopenia may be a prominent problem with this combination. Grade III–IV leucopenia was reported in 41% of patients, 67% of patients and 66% of courses, respectively in these three studies [7, 13, 14]. The relatively common severe leucopenia in the present study was not reflected in a high infection rate. Only two serious infections occurred (5%), one which may have contributed to the patient's death at dose level 1. The relatively low infection rate, despite severe granulocytopenia, is in accordance with two previous studies, both reporting a frequency of neutropenic fever of 16% [7, 14]. Thus, the maximal tolerated dose of vinorelbine on days 1 and 8 when combined with doxorubicin 50 mg/m^2 or epirubicin at 60 mg/m^2 day 1 seems to be approximately 40–50 mg/m^2 per cycle if serious neutro- or leucopenia is to be avoided.

The non-haematological toxicity of vinorelbine was dominated by various aspects of neurotoxicity (constipation, muscle weakness, paresthesia) and phlebitis at the infusion site. Neurotoxicity occurred relatively frequently but was mild in all patients, and did not lead to treatment discontinuation. Phlebitis at the infusion site seemed to be a prominent problem with vinorelbine when infused through a peripheral vein as in this study, and was painful and severe in many cases.

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