Pergamon

European Journal of Cancer Vol. 33, No. 2, pp. 301–303, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(96)00426-1

Short Communication

Pharmacokinetics and Tolerance of Vinorelbine in Elderly Patients with Metastatic Breast Cancer

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25 patients older than 65 years with metastatic breast cancer were treated with vinorelbine 30 mg/m^2 i.v. days 1 and 8 every 3 weeks; the pharmacokinetics were studied in 10 of them. Vinorelbine showed a large apparent volume of distribution (mean 23.4 l/kg), a long terminal half-life (mean 26.2 h) and a large systemic clearance rate (mean 1.2 l/kg). These results are similar to those reported in younger patients. No correlation has been found between toxicity, age and drug exposure. We observed 6 partial responses out of 20 evaluable patients despite a relatively low mean dose intensity (67%). Severe neutropenia occurred in 37% of the patients; other side-effects were acceptable. This study does not provide a pharmacokinetic rationale for reducing the dosage of vinorelbine in selected elderly patients. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: vinorelbine, metastatic breast cancer, elderly patients, pharmacokinetics

Eur J Cancer, Vol. 33, No. 2, pp. 301–303, 1997

INTRODUCTION

AGE IS one of the main risk factors for breast cancer: 30% of newly diagnosed cases are older than 70 years of age, and metastatic breast cancer (MBC) is a major cause of death in women aged over 65 years [1].

Vinorelbine (VRB) (5'nor-anhydrovinblastine; Navelbine®, Pierre Fabre Medicament, Boulogne, France) is a semi-synthetic vinca-alkaloid with intense hepatic uptake: 70–80% of the drug is eliminated via biliary excretion [2]; it is active in MBC [3, 4] and has favourable toxic profile, which makes it potentially useful in elderly patients. Since the hepatic metabolism of antineoplastic drugs might be altered in this patient population [5], we performed a pharmacokinetic (PK) study of VRB in patients in whom age was, in theory, the only factor influencing PK parameters. In order to achieve this objective, we selected 10 untreated women with MBC and normal renal and hepatic function tests, out of a group of 25 who were treated with VRB.

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Received 11 Mar. 1996; revised 28 Aug. 1996; accepted 18 Sep. 1996.

PATIENTS AND METHODS

Eligibility

The criteria for the PK study were as follows: MBC in progression after tamoxifen in patients aged 65 years or older; evaluable or measurable parameters; PS ≤ 2 (WHO); absence of concomitant disease; normal renal and hepatic function tests.

The protocol was approved by the institute's Ethics Committee, and informed consent was obtained.

Patients who had diffuse liver metastases and/or altered liver function tests (LFT), had received pretreatment with chemotherapy, or had a PS (performance status) of 3, were treated but not included in the PK study.

Study design

VRB was administered at a dose of 30 mg/m^2 i.v. (intravenously) on days 1 and 8 every 3 weeks; blood counts were made weekly, and other tests every 3 weeks. The infusion was delayed for a week if neutrophils $\leq 2000/\mu l$, platelets $\leq 100000/\mu l$, or other grade 2–3 non-haematological toxicity occurred. In case of severe toxicity, the dose was reduced by 50%.

Table 1. Pharmacokinetic parameters

	Close up	Mean	SD
C_{max}	(ng/ml)	1222	1100
$T_{1/2}$ (gamma)	(h)	26.2	4
V_{ss}	(l/k)	23.4	14
MRT	(h)	18	8.6
$AUC_{0-\infty}$	(mg/l.h)	0.75	0.30
CI	(l/h.k)	1.20	0.57

C_{max}, peak concentration; $T_{1/2}$, half-life; V_{ss}, apparent volume of distribution at steady state; MRT, mean residence time; AUC, area under the concentration–time cure; CI, total body clearance.

After two courses (four injections), response was evaluated according to WHO criteria and toxicity according to NCI-CTC criteria.

Pharmacokinetic procedures

Following the first dose of VRB, 13 blood samples were drawn in heparin tubes during a 5-day hospitalisation period (0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96 h after the beginning of VRB infusion). Plasma concentrations were measured using an ion-pair reverse phase HPLC method with fluorescence detection [6]. The pharmacokinetic analysis was performed using a non-compartmental method [7].

RESULTS

Pharmacokinetic results

Data of 10 patients—all untreated and with normal LFTs—were available for the PK analysis. The concentration versus time curve displayed a three-exponential decay. VRB was undetectable (i.e. < 2 ng/ml) in the plasma of any patient after 48 h. PK parameters are listed in Table 1, and PK-PD relationships are shown in Table 2. VRB had a very large apparent distribution volume (mean 23.4 l/k), a long-terminal half-life (26.2 h) and a rapid systemic clearance rate (1.2 l/h/k). Interpatient variability was important for all parameters. We found no correlation between the clearance of VRB and patients' age, and no relationship between systemic exposure to VRB and haematological toxicity.

The mean AUC was similar in patients with severe haematological toxicity and in those with lower grade toxicity.

Clinical results

We treated 25 patients (median age 70 years; range 65–81; median PS = 2). Of these, 13 had been pretreated with one ($n = 6$) or two ($n = 7$) chemotherapeutic regimens. In total, 149 injections were administered (median 7, range 1–19); the mean dose intensity (DI) was 67% (equivalent to a dose of 13.5 mg/m^2/week).

24 patients were evaluable for toxicity (1 patient received only one injection). Neutropenia was observed in 18 patients (grade 4 in three, grade 3 in six, and grade 2 in nine—2 of these were persistent); three cases of thrombocytopenia and three cases of grade 2 anaemia were also noted.

Fever complicated 2/3 cases with grade 4 and 2/6 cases with grade 3 neutropenia. Neuroconstipation was observed in 7 patients (four grade 2, and three grade 3), and only one case of local toxicity (phlebitis) was seen.

Other toxicities were asthenia grade 2 (2), vomiting grade 2 (1), stomatitis grade 2 (2), epigastralgia grade 2 (3), local pain (1), mild angina without ECG alterations (1), alopecia grade 1 (2). There was no evidence of cumulative toxicity, and three patients had no side-effects at all.

5 patients did not receive at least two cycles (4 patients missed the scheduled controls, one for persistent leucopenia) and were not considered evaluable for response.

Six partial responses (30% OR, 95% CI = 12–54) were documented: two in untreated patients, three in patients pretreated with one regimen (2 epirubicin based), and one in one patient pretreated with two regimens (one containing cyclophosphamide, methotrexate and 5-fluorouracil and one epirubicin-based). The sites of response were skin (three cases), lymph node (two), liver (one), lung (one); the duration of response was 2 months for 3 patients, 5 months for 1 and 6 months for 2. The median survival time was 13 months (range 2–21).

DISCUSSION

The ageing process may be the cause of the reduction in the hepatic clearance of some antineoplastic drugs [8].

We studied the VRB in a selected group of elderly patients with normal LFTs, in whom age was, in theory, the only factor influencing PK parameters.

The pharmacokinetics are similar to those reported in a number of published studies on younger subjects [9, 10]. Systemic clearance is approximately 20% of cardiac index, that is, in the range of hepatic blood flow. This confirms

Table 2. Pharmacokinetic/pharmacodynamic relationship

Patient no.	Age (years)	PS (WHO)	Disease site	Haematological toxicity grade	Response	Systemic clearance (l/h/k)	AUC (mg/l/h)	$T_{1/2\ \gamma}$ (h)
1	69	0	skin	2	PR	0.68	0.941	23.4
2	66	2	skin, bone	NE	NE	1.30	0.621	31.6
3	73	2	bone	2	NE	0.50	0.624	25.0
4	73	2	skin, bone	2	PD	1.90	0.400	25.2
5	81	1	lung	0	PR	0.76	0.971	27.7
6	77	2	liver, bone	3	PD	0.74	1.020	24.3
7	66	0	liver	0	NC	1.30	0.579	26.6
8	71	2	node, bone	3	PD	1.95	0.363	33.1
9	70	2	bone	2	NE	1.36	0.631	26.0
10	76	2	liver, bone	4	PD	1.20	0.730	20.3

PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable.

the very high extraction of VRB by the liver. V_{ss} and MRT are similar in younger patients (19 l/k; 21 h) and ours (23.4 l/k; 18 h) [11].

We are aware of the limits of the comparison with historical controls; however, in our group of elderly patients, we observed no reduction in VRB clearance and no prolonged half-life, in disagreement with some studies reporting a possible PK alteration in elderly patients [12].

No correlation between PK and PD parameters was found, probably due to the small number of patients: a limited sampling strategy could be employed to address this issue on a larger number of patients.

The alleged reduction in hepatic function in older subjects is probably not sufficient to alter VRB PK. Similar observations have been made in patients with liver metastases: VRB PK is altered only where there is a major hepatic involvement [13].

VRB was reasonably tolerated in these elderly patients, with evidence of activity, even in pretreated patients.

Data regarding elderly patients should be evaluated with caution, since they usually pertain to selected groups eligible for clinical trails; no age-related differences have been, thus far, documented in terms of PD [14] or PK [15] behaviour of antineoplastic drugs. However, this may not be applicable to very old patients.

In conclusion, our data do not provide a PK rationale for reducing VRB dosage in elderly patients.

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Acknowledgements—The authors wish to thank Ms P. Benjamin for editorial assistance. Partially supported by a grant of the Italian Association for Cancer Research (AIRC). I.R. is supported by the European School of Oncology (Milan) and Ministero della Sanità (RF91).