Cancer Chemother Pharmacol (1996) 39: 150–156

CLINICAL TRIAL REPORT

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Vinorelbine-induced neurotoxicity in patients with advanced breast cancer pretreated with paclitaxel – a phase II study

Received: 5 November 1995/Accepted: 11 April 1996

Abstract Vinorelbine (VNB) shows high antitumoral activity in advanced breast cancer due to its high affinity for mitotic tubulin and differs from the other vinca alkaloids with regard to its low degree of neurotoxicity because of its low affinity for axonal tubulin. Preclinical data show the existence of different binding sites on tubulin for vinca alkaloids and paclitaxel (P), suggesting a lack of cross-resistance. Thus, VNB was chosen eligible for a phase II study to evaluate both the therapeutic efficacy and the toxicity of VNB in patients (pts) with advanced breast cancer failing first- or second-line chemotherapy with P. A total of 14 pts with advanced breast cancer pretreated with P were entered into the study. Therapy consisted of VNB at 30 mg/m^2 diluted in 500 ml of normal saline given over 30 min after a minimal interval of 4 weeks since the last application of P. For the first four cycles, injections were repeated at 2-week intervals; thereafter they were repeated at 3-week intervals until evidence of progressive disease or severe toxicity developed. All but one pt was considered assessable for response and all pts were evaluable for toxicity. No objective response was observed; two pts showed no change in their disease. In four pts therapy had to be stopped because peripheral neurotoxicity increased from a pretherapeutic level after therapy with P from National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 1 ($n = 3$) and 2 ($n = 1$) to neurotoxicity grade 3 after 1, 2 ($n = 2$), and 3 cycles of therapy with VNB, respectively. In addition, constipation of grade 2 occurred in 10 pts. Hematologic toxicity was negligible. No other evaluable toxicity exceeded NCI-CTC grade 1. Both observations of this study, the complete resistance to VNB and the increase in peripheral neuropathy, let us assume the existence of a preclinically not anticipated but clinically relevant cross-resistance between these two spindle poisons and the presence of common functional targets. Therefore, P-pretreated pts should be excluded from consecutive VNB-containing therapies.

Key words Neurotoxicity · Vinorelbine · Paclitaxel · Breast cancer

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Introduction

In Europe and in the United States, breast cancer is the most common malignancy among women and accounts for 25% of their cancers. Despite adequate primary treatment, 25–30% of patients (pts) with histologically negative axillary nodes and 75–80% of those with axillary node involvement at the time of mastectomy will have recurrent and/or metastatic breast cancer within the decade following surgery and will subsequently die of this disease [12, 27]. Current medical treatment of advanced breast cancer has not produced a substantial improvement in survival in recent years, remaining palliative in nature and intent. Therefore, the identification of new active agents with a better therapeutic index remains a principal goal of continuous investigations in oncology. Anthracyclines continue to represent the standard agents used to treat advanced breast cancer, but the cytotoxic drugs of

actual main interest are the taxoid paclitaxel (P) and the vinca alkaloid vinorelbine (VNB).

VNB is a new semisynthetic vinca alkaloid, which chemically differs from vinblastine-type compounds by a substitution affecting the catharantine moiety [14, 21]. VNB shows very low acute and subacute toxicity, on the one hand, sparing both the bone marrow and the nervous system, and exerts high antitumoral activity in advanced breast cancer, on the other hand, with objective response rates varying between 41% in first-line treatment and 24% in second-line therapy [1, 13, 23]. VNB is known to dispose on the unique ability of relative selectivity for mitotic microtubules by sparing axonal microtubules, a particularity that can explain its potent antitumor effect in the face of its minor neurotoxic potential [4, 11]. Furthermore, there is preclinical evidence for the existence of separate binding sites on tubulin for vinca alkaloids and P; whereas P binds preferentially to microtubules and therefore inhibits depolymerization, the vinca alkaloids bind basically to alpha-beta-dimers and therefore inhibit the polymerization of tubulin to microtubules [11, 20]. On this basis, we started this phase II study with the aim of assessing the efficacy and toxicity of VNB in P-pretreated pts with advanced breast cancer.

Patients and methods

Patients' selection

Women who entered the study were required to have a histologically confirmed diagnosis of breast cancer and evidence of metastatic disease along with clear progression of disease under first- or second-line P pretreatment after a minimal interval of 4 weeks before the start of VNB therapy. P was given as single-agent therapy at doses ranging between 135 and 225 mg/m^2 on a 3- or 24-h schedule. Eligibility criteria included a life expectancy of more than 3 months; all pts should have measurable disease with defined tumor lesions on either physical examination. X-ray, ultrasound examination, or computed tomography. Bone marrow infiltration was accepted as the only tumor manifestation in a single pt. Other eligibility criteria were as follows: a Karnofsky index of $\geq 60\%$; adequate bone marrow reserve and liver functions (unless due to tumor involvement) as defined by a peripheral blood leukocyte count of $\geq 3{,}500/\mu l$, an absolute neutrophil count of $\geq 1{,}500/\mu l$, a platelet count of $\geq 100{,}000/\mu l$, and ALAT, ASAT, bilirubin, and alkaline phosphatase levels not exceeding 1.25 times the upper limit of normal; as well as adequate renal function with a seruem creatinine value not exceeding 1.25 times the upper limit of normal. All pts who entered the study gave written informed consent and the study was started after approval had been obtained from the ethics committee. Ineligibility criteria were as follows: the presence of CNS and leptomeningeal metastases, pleural effusion, or malignant ascites as the only evidence of metastatic disease; pretreatment with any vinca alkaloid; the presence of other concomitant cancer; and an age of > 75 years.

Treatment plan

Therapy consisted of VNB at 30 mg/m^2 diluted in 500 ml of normal saline given over 30 min. Infusions were repeated every 2 weeks for the first four cycles and at 3-week intervals thereafter until evidence of disease progression or severe toxicity developed.

Pretreatment and follow-up evaluation

Before the start of VNB treatment, a complete history and physical examination as well as staging investigations with tumor measurement/evaluation were performed for all pts. The first evaluation of tumor response was executed after the fourth cycle or after any stop of therapy and, in case of bone marrow infiltration, by means of iliac crest biopsy after the eighth cycle. The degree of tumor cell involvement was given as the percentage of tumor cells in relation to the total number of bone marrow cells. Further response evaluation was repeated after cycles 8 and 12, respectively. Complete blood cell counts with differential and platelet counts as well as biochemistry profiles were repeated before each cycle of therapy.

Neurological assessment

After the occurrence of severe neurotoxic side effects after cycle 2 in pt 5, neurological assessment before the start as well as after the termination of VNB therapy became mandatory. Because of missing neurotoxic side effects in pts 1–4 and since pts 6 and 7 were treated in parallel with pt 5, neurological assessment beyond a rough clinical assessment without electrophysiological measurements either was not executed at all (in the previous pts 1–4) or was first done after cycle 2 (in pts 5–7). Consecutively a detailed clinical pretreatment evaluation and at least one sequential posttreatment evaluation within 2 weeks of the end of therapy were performed in 7 pts (pts 8–14).

The electrophysiological investigation included examination of the median nerve [motor and sensory antidromic nerve-conduction velocity (NCV)], the peroneal nerve (motor NVC), and the sural nerve (sensory orthodromic NCV) before and after VNB treatment except in the above-mentioned pts. Results were compared with the reference values listed by Schaumburg et al. [25]. The skin temperature was recorded with a surface thermistor and ranged between 33.5° and 35.3 °C after heating with an infrared lamp (Astralux, Austria). All peripheral–nerve conduction data were recorded, analyzed, and printed using a Medelec Mystro MS 20 apparatus.

Response and toxicity assessment criteria

Response evaluation was foreseen as detailed, above under Pretreatment and follow-up evaluation. The clinical response was assessed in accordance with WHO guidelines [17]. For assessment of toxicity the National Cancer Institute Common Toxicity Criteria (NCI-CTC) were used [18].

Results

Response

A total of 14 women with advanced breast cancer, including 2 (pts 10 and 11) with inflammatory breast cancer, were entered into the study. The characteristics of the pts are listed in Table 1. Pts received VNB as second- or third-line therapy. All pts were pretreated with P at total doses ranging between 890 and

Table 1 Patients' characteristics: *a* adjuvant, *p* palliative, *K.I.* Karnofsky index, *PD* progressive disease, *NC* no change, NE not evaluable, *R* radiation, *H* hormones, *C* chemotherapy

Patient number	Age (years)	Tumor sites	Pretreatment prior to *P*				P			VNE		
			R	H	C	Anthracycline-containing[a]	Cycles *n*	Total dose		K.I. before start in %	Cycles *n*	Response
								mg	mg/m^2			
1	67	Pleural effusion Ascites Lymph nodes	–	a/p	p	–	6	1,722	1,050	70	4	PD
2	53	Pleural effusion Local relapse	a	a/p	a	–	10	2,190	1,350	70	4	PD
3	63	Lymph nodes	–	p	a	–	10	2,430	1,350	80	4	PD
4	44	Liver Bones Local relapse	a	a	a/p	+	6	1,332	890	90	2	PD
5	61	Liver Suprarenal gland	a	–	a/p	+	14	3,549	2,450	70	2	PD
6	64	Liver Pleural effusion	–	a	a	+	10	2,090	1,350	90	3	PD
7	69	Lymph nodes	–	p	p	–	8	2,312	1,400	80	12	NC
8	70	Liver Local relapse	–	a	a	+	12	3,780	2,100	100	4	PD
9	57	Liver, lung Pericardial effusion Lymph nodes	a	p	a/p	+	12	3,959	2,325	90	4	PD
10	50	Bone marrow	a	a	a	+	8	3,120	1,600	90	8	NC
11	42	Lung	a	a	a	+	12	5,016	2,600	100	4	PD
12	54	Liver, Lung Lymph nodes Bones	–	a/p	p	+	12	3,039	1,720	90	4	PD
13	52	Liver	–	a	a/p	+	16	6,479	3,485	90	2	PD
14	61	Lung	a	a	a/p	+	16	6,079	3,525	90	1	NE

[a] + containing anthracyclines, – not containing anthracyclines

3,525 mg/m^2, resulting in ten partial responses (PRs), three cases of no change (NC), and one case of progressive disease (PD). Pts with PRs had received a median cumulative dose of 3,664 mg (range 2,090–6,479 mg) of P, pts with NC had received 2,430 mg (range 1,332–3,120 mg), and the only pt with PD had received 1,722 mg. None of the pts had previously been given any vinca alkaloid, and 10 pts (71%) had received anthracycline-containing regimens in the adjuvant- or first-line-therapy setting. The median age of the pts at their inclusion in the study was 58 years (range 42–70 years); the median Karnofsky index was 90% (range 70–100%). All pts were assessable for response except for one who received only a single cycle of therapy because of a dramatic increase in peripheral neurotoxicity after the first VNB infusion. Pts received between 1 and 12 cycles of VNB. No objective response was obtained; 11 pts progressed after 2–4 cycles of therapy. Only 2 pts showed NC; 1 of the latter showed no alteration in bone marrow infiltration after 8 cycles but then refused any further therapy, and the other displayed no alteration in lymph-node metastases after 4 and 8 cycles but exhibited progression after 12 cycles of therapy.

Toxicity

Whereas objective responses to this salvage therapy were completely missing, relevant peripheral neurotoxic side effects occurred. After treatment with P, 8 of the 14 pts presented with clinically mild sensory neuropathy, i.e., NCI-CTC grade 1 (pts 5–9, 12, and 13) or grade 2 (pt 14) (Table 2) mostly affecting the acral portions of the lower extremities and sparing the upper extremities. Signs of sensory toxicity consisted of

Table 2 Clinical evidence of neuropathy before VNB treatment. ND not done, + symptoms present, − symptoms absent, "*plus*" *symptoms* hyperesthesia and/or burning feet and/or tingling, "*minus*" *symptoms* hypesthesia and/or impaired vibration sense, *KR* knee reflex, *AR* ankle reflex

Patient number	NCI-CTC Grade	Sensory neuropathy		Sensory ataxia	Motoric neuropathy	Tendon reflexes	
		"plus" symptoms	"minus" symptoms			Upper extremities	Lower extremities
1	0	ND		ND	ND	ND	
2	0	ND		ND	ND	ND	
3	0	ND		ND	ND	ND	
4	0	ND		ND	ND	ND	
5	1	+	ND	−	−	ND	
6	1	+	ND	−	−	ND	
7	1	+	ND	−	−	ND	
8	1	−	+	−	−	Normal	KR normal AR missing
9	1	+	+	−	−	Missing	KR missing AR missing
10	0	−	−	−	−	Normal	KR decreased AR missing
11	0	−	−	−	−	Normal	KR normal AR normal
12	1	−	+	−	−	Normal	KR normal AR missing
13	1	+	+	−	−	Missing	KR missing AR missing
14	2	+	+	−	−	Missing	KR missing AR missing

numbness in the acral portions of the feet and paresthesias.

Treatment with VNB exerted an additional neurotoxic side effect and changed symptoms of the peripheral nervous system in seven pts as documented by an overall increase in NCI-CTC grades (Table 3). The type of neuropathy induced was a distal-axonal-ataxic sensorimotor neuropathy and resulted in termination of therapy in 4 cases (pts 5, 6, 13, and 14). In these 4 pts NCI-CTC grade increased from 1 ($n = 3$) or 2 ($n = 1$) after therapy with P to grade 3 after therapy with VNB. Sensory ataxia developed after 1 (pt 14) and 2 (pts 5 and 13) cycles of therapy and made pts unable to walk unaided. Impairment of motor function was noted in 3 cases (pts 5, 13, and 14) and resulted in bilateral foot drop occurring simultaneously with the sensory ataxia. Clinical sensory testing revealed predominant large-fiber-type damage after exposure to VNB as characterized by absent vibration on distal lower extremities in 3 pts and reduced vibration in 5 pts, with preservation of small-fiber qualities (pain, temperature) being noted in all pts. In 6 pts, acral dysesthetic painful sensations were noted. The distribution of neuropathy appeared in a typical stocking-glove fashion. The reflex pattern in the lower extremities remained unchanged except for the knee reflex in pt 8. NCV values showed signs of axonal neuropathy. The lower extremities were more affected both clinically and in electrophysiological testing than were the upper extremities; in pt 13 the median sensory action potential was absent after VNB treatment, and in pt 14 it was not recordable before or after VNB therapy. Only one pt (pt 7) showed a marked delay in the NCV of the sural nerve, suggesting demyelination; however, no preexisting value was evaluable. Sensory sural-nerve action potentials were absent in pt 14 before VNB treatment and, in addition, were not elicitable after termination in pts 5, 8, or 13. In 3 cases (pts 5, 13, and 14), motor NCV values were no longer elicitable in the lower extremities after VNB treatment

Constipation was a quite common side effect; 10 pts showed constipation of NCI-CTC grade 2. Hematological toxicity was negligible, with no pt requiring dose modification or delay of therapy application. Nausea/vomiting (but no other evaluable toxicity) exceeded NCI-CTC grade 1. Alopecia was not evaluable because of pertreatment of the pts with P.

Discussion

With regard to our data on the first 8 pts of this study, previously presented in part at the American Society for Clinical Oncology meeting in 1994 [10] and in a letter to *Annals of Oncology* [8], the therein reported preliminary trend of missing objective responses as well as dramatic increases in neurotoxicity in 2 (pts 5 and 6)

Table 3 Clinical evidence of neuropathy after VNB treatment[a]

Patient number	NCI-CTC Grade	Sensory neuropathy		Sensory ataxia	Motoric neuropathy	Tendon reflexes	
		"plus" symptoms	"minus" symptoms			Upper extremities	Lower extremities
1	0	ND		ND	ND	ND	
2	0	ND		ND	ND	ND	
3	0	ND		ND	ND	ND	
4	0	ND		ND	ND	ND	
5	3	+	−	+	+	Normal	KR normal AR missing
6	3	+	+	−	−	Normal	KR normal AR missing
7	1	+	+	−	−	Normal	KR missing AR missing
8	1	−	+	−	−	Normal	KR missing AR missing
9	1	+	+	−	−	Missing	KR missing AR missing
10	1	−	+	−	−	Normal	KR decreased AR missing
11	1	−	−	−	−	Normal	KR normal AR normal
12	2	−	+	−	−	Normal	KR normal AR missing
13	3	+	+	+	+	Missing	KR missing AR missing
14	3	+	+	+	+	Missing	KR missing AR missing

[a] For definitions see Table 2

of the first 8 pts (pts 1–8) was confirmed by data involving further 6 pts (pts 9–14). Therefore, this study was closed and this, report represents the final evaluation.

Recently, the introduction of completely new anticancer agents, such as the taxanes and the semisynthetic vinca alkaloid VNB, has raised expectations of a more significant impact on the treatment outcome in pts with advanced breast cancer either following their inclusion in combination regimens when aggressive therapy is needed or on their use as single agents when the aim is palliative. A different mode of action and/or different targets for consecutively used drugs seem to be important requirements. Thus far there has been a lack of the side effects and response rates that would be expected if P and VNB were used in a consecutive therapy setting. Nevertheless, the availability of salvage treatments of low toxicity is of particular importance since pts with advanced breast cancer often suffer from symptoms of disease progression or present with side effects from prior therapies. VNB seemed to meet the following criteria for this specific therapeutic situation: i.e., a mechanism of action on microtubules that is the inverse of that of previously applied P (with VNB inhibiting the formation of microtubles and P inhibiting the depolymerization of microtubules), the preclinical evidence for the existence of separate binding sites on tubulin for vinca alkaloids and P [11, 20], a high level of antitumoral activity in the first-line [13, 23] and the second-line [19, 22] therapy setting, and minor neurotoxicity [3, 16].

Nevertheless, our study provides clear evidence of a striking difference between this theoretical basis and the clinical outcome achieved with VNB. Our patient population compares with those included in other studies using VNB as second- or third-line therapy in terms of prognostic factors, such as tumor involvement and numbers of tumor sites, median age, and numbers of previous treatments. However, in none of these studies were pts pretreated with P. Response rates ranging between 16% and 24% have been reported [7, 9, 22]. For the missing objective responses after treatment with VNB in our study and the primarily unexpected neurotoxicity, the following possible reasons should be considered. First, the dose intensity of the schedule used in our study is lower than the weekly schedule recommended for phase II trials [3, 13]. This was confirmed by the lack of VNB's usual dose-limiting granulocytopenia. Although this could account, at least in part, for the low response rate reached in our study consequently, a much lower extent of neurotoxicity should have been expected. In accordance with our setting, Degardin et al. [7] recently recommonded a dose of 20 mg/m^2 for the salvage treatment of advanced breast cancer because the usual dose of 30 mg/m^2 was not tolerated due to severe hematotoxicity in their study. Second, the existence of differencing

sensitivity of VNB to mitotic and axonal tubulin seems to be more likely. It is known that an incomplete cross-resistance exists between VNB and anthracyclines, mitomycin-C, and mitoxantrone [1], the classic drugs used in the treatment of breast cancer. Although cross-resistance between VNB and P was preclinically not anticipated [11, 20], it should be considered whether P-induced, VNB-resistent mitotic tubulin mutants may occur, resulting in missing therapeutic efficacy, whereas the axonal microtubules would remain sensitive to consecutive treatment with VNB, thereby creating relevant neurotoxicity. Interestingly, it has been reported that vinca-alkaloid-induced tubulin mutants leading to decreased inhibition of microtubule formation may become sensitive to P, an event from which it could be concluded that the inverse therapy sequence for the two antimitotic agents – VNB first, followed by P – would result in better response rates and, presumably, in minor neurotoxicity [2, 5].

Contrary to the proposed absence of neurotoxic side effects of VNB, our study revealed neurotoxicity in P-pretreated pts that resembled the neurotoxic pattern of vinca alkaloids [15]. The main feature was a distal-axonal-ataxic sensorimotor neuropathy with preponderance in the lower extremities and predominant large-fiber-type damage in clinical sensory testing. However, in 3 pts (pts 5, 13, and 14), sensory ataxic neuropathy associated with bilateral foot drop occurred unexpectedly after low total VNB doses of 30 and 60 mg/m^2 after the first and second VNB infusions, respectively. In all, 10 of the 14 pts suffered from severe constipation for up to 6 days. This may be interpreted as a sign of autonomic neuropathy such as that well-known in vinca-alkaloid-induced neuropathy [15]. This clinical impression was not substantiated by electrophysiological testing. The type of P-induced nerve damage observed before VNB therapy in 8 of our pts was a clinically mild distal sensory neuropathy. In 5 of these pts, pre-VNB nerve-conduction studies were performed and revealed mild axonal neuropathy as documented by a reduction in distal latency and a reduction in compound action potential. In only one pt was the sural-nerve sensory action absent. The severity of P-induced neurotoxicity is known to correlate with both the cumulative dose [6] and the absolute single dose beyond 250 mg/m^2 of P [24, 28, 29]. Nevertheless, the preceding total dose of P could not be identified as the factor predicting the extent of neurotoxicity to be expected under subsequent VNB therapy in our study. Only two pts who developed neurotoxicity of NCI-CTC grade 3 had received high doses of P, whereas the other two pts were comparable with those only slightly affected by VNB. It remains unknown whether VNB neurotoxicity as observed in our investigation depends specifically on pretreatment with P or can be triggered by any preexisting neuropathy, such as diabetes mellitus, a known risk factor for the development of neuropathies [26], as found in pt 6.

In conclusion, although experimental systems demonstrate different target structures for P and VNB, this holds at least not completely true for the clinical situation. This phase II study let us assume cross-resistance to VNB after progression on P. Moreover, not only pts who have received high cumulative doses of P are at danger of experiencing a dramatic increase in peripheral neuropathy. According to our experience, all pts who have been pretreated with P should be excluded from VNB-containing therapies due to the missing objective response as well as the appearance of partly intolerable neurotoxicity under this drug sequence. To elucidate the mechanism of this neurotoxicity, electrophysiology and ultrastructure investigations of VNB monotherapy in animals and humans should be performed in the future.

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