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A phase I study of vinblastine tryptophan ester

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Summary. Vinblastine tryptophan ester (VTrpE) is a new vinca alkaloid derivative that achieves antitumor activity in a large variety of animal models. In this phase I study the drug was given as an i. v. injection over 5 min, once a week or once every 2 weeks. Twenty patients with advanced cancer were entered in this trial. The doses ranged from 2.5 mg/m^2 to 35 mg/m^2. Myelosuppression is the dose-limiting toxicity, with the risk of leukopenia being more serious than that of thrombocytopenia, but the myelosuppression is always reversible. Neurotoxicity, well documented when other vinca alkaloid derivatives are used, is insignificant. Two cases of disease stabilization have been observed in patients with non-small cell lung cancer. For VTrpE, a dose schedule of 30 mg/m^2 per week may be recommended for phase II studies in non-small cell lung cancer.

Introduction

The *Catharanthus* alkaloids [12], vinblastine (VBL) and vincristine (VCR), differ from each other structurally only in the functional group on the dihydroindole nitrogen. This minor structural distinction is responsible for differences in the oncolytic spectrum potency and toxicity of the two compounds [9, 11]. The deacetyl vinblastine amide (VDS) is a semisynthetic derivative of VBL, and it differs from VBL by having an amide group in place of the ester group at position C23. In its activity spectrum against rodent tumor systems it is more like VCR than the parent compound, VBL. Moreover, its neurotoxicity is reported to be less than that of VCR [1].

Twenty- one vinblastine-23-oyl amino acid derivatives were synthesized by linking the amino acid carboxylic ester to the vinblastine-23-oyl moiety through an amide linkage [2–5]. The physicochemical data support their chemical structures [3]. The chemotherapeutic activities of these derivatives were evaluated extensively in P388 and L1210 murine leukemias [2, 3]. Among the derivatives tested a few compounds emerged as promising for further evaluation. Of these the *N*-(*L*-tryptophan ethyl ester)-4-*O*-deacetyl vinblastine-3-carboximide (VTrpE) derivative, especially, was very interesting. Comparison with the parent alkaloids VBL, VCR, and VDS suggested that this derivative was more active and less toxic [3].

The LD_{50} values following i. v. administration of this derivative are, respectively: 101, 94, and 110 mg/kg for NMRI, Swiss, and CD1 mice, as opposed to 27.4, 26, and 28 mg/kg for VBL.

As a result of these preliminary studies a clinical phase I study was initiated.

Materials and methods

All patients had histologically confirmed malignant solid tumors or acute leukemia. Characteristics of the patient population are shown in Table 1. Expected survival was longer than 2 months.

The starting dose for the study was 2.5 mg/m^2 VTrpE, one-fourth of the usual VBL dose. The drug was administered once a week, as is usual for the vinca alkaloids. The dose for individual patients was increased provided no toxicity was encountered in preceding treatment courses. For the first ten patients (Table 2), the doses were increased weekly by 2.5–5 mg/m^2 per week. For the next six patients (patients 11–16), VTrpE was given as a single administration of 30 mg/m^2 every week. Four patients (patients 17–20) received lower starting doses (15 or 20 mg/m^2) because their leukocyte or platelet counts were lower than 4000/mm^2 or 100000/mm^3 or their Karnofsky per-

Table 1. Patient characteristics

Total number	20	
Male/female	12/8	
Adults/children	16/4	
Primary tumors		
Fibrosarcoma	2	
Head and neck	1	
Breast	3	
Gastrointestinal	7	
Lung	2	
Ewing's sarcoma	1	(child)
Acute lymphoblastic leukemia	3	(2 children)
Acute myeloblastic leukemia	1	(child)
Previous treatment		
Surgery	11	
Chemotherapy only	4	
Radiotherapy + chemotherapy	12	

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Table 2. Patient treatment details and hematotoxicity

Patient no.	Tumor	Number of injections	Duration of treatment (weeks)	Doses per week (mg/m^2) min./max.	Cumulative dose before leukopenia (mg/m^2)[a]
3	Fibrosarcoma	5	7	10/25	45
5	Head and neck carcinoma	3	3	20/25	n.o.[b]
6	Colorectal carcinoma	3	3	20/25	67.5
7	Stomach carcinoma	6	6	25/35	179
8	Colorectal carcinoma	4	4	22.5/30	60
9	Fibrosarcoma	3	4	25/30	62.5
10	Breast carcinoma	2	2	25/25	n.o.
11	Colorectal carcinoma	2	4	30/30	n.o.
13	Colorectal carcinoma	6	9	30/30	60
14	Colorectal carcinoma	21	21	30/30	n.o.
15	Lung carcinoma	8	13	30/30	90
16	Lung carcinoma	15	29	30/30	60
17	Breast carcinoma	2	3	25/30	55
18	Colorectal carcinoma	4	4	20/25	70
19	Breast carcinoma	3	4	15/20	35
20	Ewing's tumor	6	6	20/30	45
1	Acute lymphoblastic leukemia	8	8	2.5/27.5	
2	Acute lymphoblastic leukemia	7	7	15/35	
4	Acute lymphoblastic leukemia	3	3	20/27.5	
12	Acute myeloblastic leukemia	5	5	30/30	

[a] leukopenia: <4000 WBC/mm^3
[b] n.o., never observed

formance status was low (<60). Whenever medullary toxicity occurred, treatment was resumed when the leukocyte level regained the normal value. The treatment was stopped when the Karnofsky performance status decreased to less than 40. Seven patients were hospitalized for convenience, while the others were treated in the 'outpatients' unit. Complete blood cell counts were performed each week. VTrpE, supplied by OMNICHEM as a lyophilized powder (20 mg/vial), was diluted in 5 ml solvent (5% glucose and 0.2% propylene glycol) and infused over 5 min. The vein was then flushed with 150 ml 5% glucose. Renal and hepatic functions were measured before each treatment.

Results

A total of 20 patients entered the trial. Their characteristics are shown in Table 1. The starting dose was 2.5 mg/m^2, and this was increased to 35 mg/m^2. Moderate leukopenia (2000–3800 WBC/mm^3) was observed in five of the first ten patients (Table 2) after they had received cumulative doses ranging from 45 mg/m^2 to 179 mg/m^2. Taking this result into account, we decided to inject VTrpE at 30 mg/m^2 each week, to assess the cumulative myelotoxicity, while closely monitoring neurotoxicity. Two patients received cumulative doses of 450 mg/m^2 and 630 mg/m^2 of VTrpE, respectively, without the occurrence of clinical neurotoxicity. For these two patients, electromyographies performed at the cumulative dose of 450 mg/m^2 were normal. Two patients with non-small cell carcinoma of the lung developed leukopenia (2000/mm^3) after two and three weekly courses of 30 mg/m^2 of VTrpE. In these two patients, bi-weekly infusion of 30 mg/m^2 of VTrpE kept the WBC count at greater than 4000/mm^3. The drug does not seem to affect the platelet count to any significant extent (Table 3). We did not observe any renal or hepatic biological modification. The only nonhematological side effect was a temporary dryness of the mouth, which occurred in 50% of the patients immediately after the first injection and disappeared after 2 or 3 weeks.

Patients were closely monitored for possible disease regression; two patients with non-small cell lung carcinoma previously treated with a combined therapy of cisplatinum and VP16-213 had stabilization of their disease for 13 and 29 weeks.

Table 3. Hematological toxicity

Patient	Leukocytes		Platelets	
	Starting count	Minimum	Starting count	Minimum
3	4300	3600	308700	210000
5	9400	7900	289000	176000
6	4900	2100	258000	125000
7	6400	3800	265000	210000
8	6800	2600	195000	96400
9	5700	2000	201000	201000
10	9400	6100	170000	130000
11	7400	4000	222000	200000
13	10200	3200	224000	175000
14	11000	5580	318000	292000
15	4300	1800	281000	171000
16	6600	1900	363000	222000
17	6400	2000	325000	316000
18	9200	2400	355000	275000
19	4600	2500	85000	85000
20	3600	3400	69000	69000

Discussion

VTrpE is a vinblastine derivative, which was subjectively very well tolerated. The only dose-limiting toxicity observed was leukopenia at a dose of 30 mg/m^2 per week. Leukopenia was rapidly reversible in all patients. No platelet toxicity was observed.

No other side effect was observed except for a temporary mouth dryness in half the patients. At a dose of 35 mg/m^2 weekly, VTrpE is not neurotoxic compared with other vinca alkaloids. VBL-induced neurotoxicity is observed in 90% of subjects receiving VBL at 10 mg/m^2 weekly [6, 10, 14, 15]. One hundred percent of patients receiving VCR manifested neurotoxicity at doses of 12.5–75 μg/kg per week or 2 mg/m^2 every 10–14 days [8, 10, 13]. With VDS, after five or six weekly doses of 3–4 mg/m^2, 65% of patients suffered from paresthesias, decreased deep-tendon reflexes, constipation, and joint pain [7]. In contrast, with VTrpE, we administered 21 doses to one patient and 15 doses at 30 mg/m^2 to another without either clinical or electrophysiological neurotoxicity.

Two patients with non-small cell lung carcinoma showed disease stabilization when they had relapsed after a first treatment with cisplatinum and VP16-213.

We conclude that the vinca alkaloid derivative, VTrpE, can be used at a weekly dose of 30 mg/m^2 for at least 21 weeks. The limiting toxicity at this dosage is granulocytopenia. We did not observe neurotoxicity, which is a well-known side effect of the other vinca alkaloids.

A phase II trial is warranted in non-small cell lung carcinoma.

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