Cancer Chemother. Pharmacol. 2, 233–237 (1979)

Cancer Chemotherapy and Pharmacology

Original Articles

Vindesine
A Clinical Trial with Special Reference to Neurological Side Effects

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Summary. *A good tumoricidal activity of vindesine (VDS) has been reported in a variety of animal tumors and in human leukemias and lymphomas. We treated 22 patients who had received no prior chemotherapy and were suffering from a variety of malignant neoplasms with 0.5 mg/m² to 3.0 mg/m² VDS i. v. once or three times at weekly intervals and recorded the clinical, hematologic, and especially, neurological side effects.*

Clinically we observed fatigue in nine patients, paresthesias in seven, myalgias in three, vertigo and diarrhea in two, and skin pains, tinnitus, gastric pains, alopecia, and tremor in one patient each. There was no obvious dose-action relationship. Paravenous injection caused cellulitis similar to that seen with vincristine. No side effects were apparent in liver (SGPT) and renal (creatinine) function tests. Hematologically there was a clear trend toward leukopenia with higher doses of DVA and a mean increase in the thrombocyte count by $51 \times 10^3/mm^3$ was found (sign test: $P<0.05$). The hemoglobin level did not change.

Clinical neurological examination and monitoring by electroneurography revealed no changes in tensiometer performance, motor and sensory nerve conduction velocity, motor or sensory nerve action potential amplitudes, or H-reflex responses. There was dose-related diminution of the proprioceptive reflexes, especially in the lower extremities. Even with as little as 2.0 mg/m² VDS i. v. at weekly intervals for 3 weeks Achilles and patellar tendon reflexes were diminished or absent in all patients.

Introduction

Vindesine (desacetyl vinblastine amide sulfate, VDS) is obtained by minor molecular alterations of the original vinblastine (VBL) molecule. The tumoricidal activity of VDS seems to be between that of vincristine (VCR) and that of VBL, resembling the VCR spectrum rather more closely than the VBL spectrum. Nevertheless, in large animal studies the drug has been shown to be less neurotoxic than VCR [13]. The results of several clinical trials indicate that VDS has dose-limiting myelotoxic and gastrointestinal side effects [6, 17, 23]. In addition, neurotoxic side effects have been found in humans, but probably to a lesser degree than with VCR [14, 17, 18]. They seem to depend on the administration rate, being more severe with twice-weekly than with once-weekly administration [14]. Although electrophysiological studies are mentioned by Blum and Dawson in an abstract of a recent clinical trial [5], detailed results have not been published. The neurological side effects produced by VCR have been the subject of numerous clinical [10, 21], pathologic [16], and electrophysiological studies [7, 9, 15]. Therefore we decided to conduct a similar clinical and electrophysiological study with VDS, trying to establish a safe dose range, to ascertain the clinical, hematologic, and especially, neurological side effects, and to look for similar electroneurological side effects to those seen in patients treated with VCR.

Patients and Methods

To be eligible for inclusion in the trial, patients had to have microscopically confirmed malignant disease and a life expectancy of more than 2 months, as it is known that terminal tumor patients have an elevated incidence of paraneoplastic neurological syndromes [11]. The hematologic parameters and renal and liver function tests had to be normal. No patient had received previous treatment with another vinca alkaloid.

There were 12 male and 10 female patients, all of whom gave their informed consent to the investigation. The age range was 19–74 years, the median 55.5 years. Five patients had breast carcinoma, four had lung tumors, three had non-Hodgkin lymphomas, two had melanoma, two had malignant teratoma, two had multiple

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0344-5704/79/0002/0233/$ 01.00

Table 1. Patient characteristics

No.	Sex	Age	Body surface area (m^2)	Diagnosis	Total dose (mg)
1	M	75	1.6	CLL	0.8
2	F	65	1.7	Breast carcinoma	0.85
3	M	39	1.8	Malignant teratoma	1.8
4	F	19	1.5	Osteosarcoma	1.5
5	M	61	1.8	Myeloma	5.4
6	F	52	1.9	Breast carcinoma (adj.)	5.7
7	M	60	1.65	Non-Hodgkin lymphoma	2.0
8	F	47	1.7	Non-Hodgkin lymphoma	2.5
9	M	53	1.9	Lung tumor	4.5[a]
10	M	50	2.2	Non-Hodgkin lymphoma	4.5[a]
11	F	74	1.6	Breast carcinoma	2.0[a]
12	M	53	1.9	Lung tumor	2.0[a]
13	F	51	2.0	Melanoma	12.0
14	F	59	1.75	Myeloma	10.5
15	M	52	1.9	Melanoma	2.0[a]
16	M	58	2.0	Lung tumor	5.0
17	M	62	1.6	Lung tumor	12.0
18	F	59	1.6	Breast carcinoma	12.0
19	F	68	1.7	Breast carcinoma	5.0
20	M	33	2.0	Hodgkin's disease	6.0
21	M	20	1.7	Malignant teratoma	12.5
22	F	65	1.5	Colon carcinoma	13.5

[a] Protocol deviation

myeloma, and colon carcinoma, chronic lymphocytic leukemia, Hodgkin's disease, and osteosarcoma were each found in one patient (Table 1).

Two patients received a single dose of 0.5 mg/m^2 as an i. v. pulse. With doses of 1.0 mg/m^2 up to 3.0 mg/m^2 four patients were treated at each dose level, the first pair receiving only one injection and the second pair, three injections at weekly intervals. The dose increment was 0.5 mg/m^2. The parameters studied included hemogram, renal and liver function tests, uric acid and serum calcium (all checked weekly). The neurological examinations were performed every 2 weeks. Clinical parameters were the deep tendon reflexes of the upper and lower extremities, the muscular strength, measured with a grip tensiometer, and vibration sensitivity, measured with a 124-Hz tuning fork on the hands and feet of each patient. The mean time lapse (of three measurements) to complete disappearance of the vibration was calculated. The electroneurographical measurements were conducted according to standard procedures. Motor and sensory conduction velocity and action potential amplitudes were determined. The motor action potential amplitudes were recorded in the abdominal-tendon setting by means of surface electrodes. Sensory nerve action potential amplitudes were measured with antidromic stimulation. The H-reflex was recorded while patients were recumbent, the knees bent at 120° and the legs supported. We only evaluated the temporal order of the H- and M-responses in relation to the stimulation threshold.

Results

All 22 patients were evaluable. Five minor protocol deviations concerning drug dosage did not interfere with the evaluation of the results.

Table 2. Clinical side effects of DVA among 22 patients (range of total dose 0.8 – 13.5 mg)

Sign or symptom	No. of patients affected
Depressed ankle jerks	17
Fatigue	9
Paresthesia	7
Myalgia	2
Dizziness	2
Diarrhea	2
Skin pains	1
Tinnitus	1
Gastric pains	1
Alopecia	1
Tremor	1
Cellulitis	1[a]

[a] This patient had to be withdrawn from the study

Clinical Side Effects

The clinical side effects observed are summarized in Table 2. For the patients they were minimal, and only one patient had to be withdrawn from the study, due to cellulitis after paravenous injection: this female patient refused any further treatment with VDS. The most frequent clinical side effect was depressed ankle jerks. This will be discussed in detail below. Nine patients felt some nonspecific fatigue, seven had paresthesias in their hands and feet (one of them only for 10 min following the injection); three patients complained of myalgias (like 'flu'), two of slight dizziness, two of diarrhea, and one of gastric pains. One patient who received a total dose of 6 mg had alopecia. One patient had polyuria in one night, serum sodium levels being normal before and after this event. One woman had a short episode of postmenopausal bleeding during the second week after VDS and 9 months after her last menstruation. No patient had impaired renal or liver function. We could not find any dose-action relationship in any of these patients.

Hematologic Side Effects

The hemoglobin level and the leukocyte count did not change significantly, the mean hemoglobin being 0.6 mg %, and the mean leukocyte count $1.5 \times 10^3/mm^3$ lower than before treatment. In one patient receiving 3.0 mg/m^2 we had to reduce the third dose by 50% due to leukopenia. Compared with their own pretreatment levels, 15 patients had lower hemoglobin and leukocyte levels, four patients had no change in their hemoglobin level, and three had increased hemoglobin and seven increased leukocyte levels. Interestingly, 16 patients

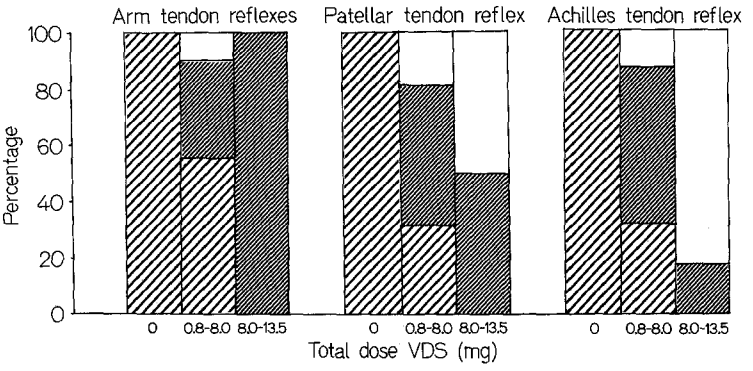

Fig. 1. Percentages of deep tendon reflexes present, diminished, and absent before and after VDS. ▨, reflex present; ▨ reflex diminished; □, reflex absent

Table 3. Motor and sensory conduction velocities before and after VDS and VCR in various trials

	Conduction velocity (m/s)		No. of pts.	Reference
	Before	After		
Motor[a]				
VDS	48.7±4.3	49.2±4.5	22	Present study
VCR	46.1±7.8	43.3±3.5	8	[19]
VCR	48.5	46.3	12	[21]
VCR	55.5±3.0	48.3±5.6	14?	[9]
Sensory[b]				
VDS	53.7±4.0	53.8±3.8	22	Present study
VCR	58.3±3.16	62.4±0.32	14?	[9]

[a] Lateral popliteal nerve
[b] Median nerve

Table 4. Motor and sensory action potential amplitudes before and after VDS and VCR in various trials

	Action potential amplitudes (mV, uV)		No. of patients	Reference
	Before	After		
Motor[a]				
VDS	3.0±1.3	3.6±1.3	22	Present study
VCR	4.3±3.9	0.9±1.0[c]	8	[19]
VCR	4.4±0.65	2.5±0.55	14?	[9]
Sensory[b]				
VDS	24.5±8.5	26.9±13.3	22	Present study
VCR	14.3±4.7	9.9±2.5	8	[19]
VCR	33.5±7.0	7.8±1.3	14?	[9]

[a] Lateral popliteal nerve
[b] Median nerve
[c] Significant decrease ($P < 0.001$)

had a rise in their thrombocyte count, the mean increase being $+51 \times 10^3/mm^3$. This is statistically significant at the 5% level [12]. There seems to be a rough relationship to the dose, with a correlation of 0.53 to the linear regression line.

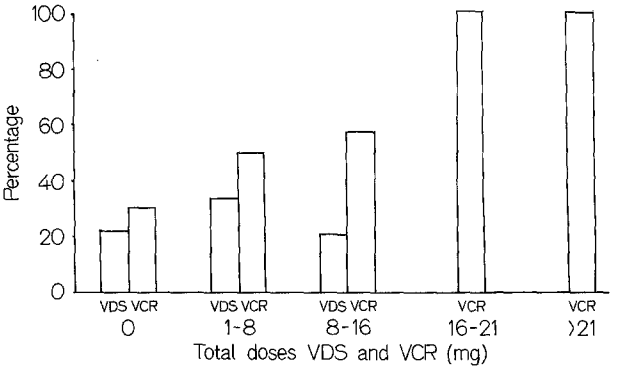

Fig.2. Percentages of abnormal H-reflexes after VDS and VCR [15]

Neurological Side Effects

There was no change in the muscle strength or vibration sensitivity after VDS. The deep tendon reflexes showed a clear and significant reduction to 33% of the pre-treatment controls. This is shown in more detail in Fig. 1. No patient who had received a total dose of more than 8 mg had normal reflexes, and less than half the patients with lower doses. It seems that the Achilles reflex was the most sensitive, even patients who had received total doses of only 0.85 mg showing a diminution of this reflex.

Electroneurological Parameters

The electroneurological findings are summarized in Tables 3 and 4. The motor conduction velocity did not show any changes after VDS. The sensory nerve conduction velocity showed a slight tendency to lower values with higher doses, but not to a significant degree (not shown). The motor potential amplitudes increased rather than decreased.

This is consistent with the clinical findings: there was no motor impairment among our patients. The sensory nerve action potential amplitude was always

normal, regardless of the drug dosage and the symptoms reported by the patients.

Figure 2 shows the results of the H-reflex testing. Freund et al. [15] found an increasing percentage of earlier M-responses with increasing doses of VCR, but this was not found with VDS.

Discussion

Our clinical findings support those of other authors [6, 13, 14, 17, 18, 23]. There are comparatively mild side effects with the dose range we used. Certainly higher doses have to be evaluated-especially with regard to the myelotoxic and gastrointestinal side effects. The observed bone marrow depression was minimal and only once was a dose reduction necessary due to leukopenia. The interesting phenomenon of mild thrombocytosis has also been found by others [14]. In the light of the recent results obtained by Ahn et al. [2, 3] in the treatment of idiopathic and secondary thrombocytosis with VCR and VBL, the possibility of a selective toxicity of VDS on spleen macrophages cannot be ignored. This leads to speculation concerning the possible mode of the tumoricidal action of VDN, as tumor-cell-stimulating factors produced by macrophages have been postulated [20].

The neurological side effects are also minimal. The only consistent finding is early depression of the deep tendon reflexes, with no concomitant electroneurological changes. The exact localization of the neurotoxic action of VCR has been the subject of considerable dispute. Evidence has been reported for the lesion being at the sensory ganglion [8, 25], the anterior horn cell [15, 22], the nerve axon [7, 9, 16, 19], the myelin sheath [1], the motor end plate [4], the muscle spindle [21, 24], and the muscle itself [4]. As far as the electrophysiological data are concerned, the lesion could be located at the nerve axon, because the nerve action potential amplitude decreases after VCR [19]. It could be at the anterior horn cell because of the above-mentioned changes in the H-reflex [15], or it could be at the muscle spindle, because of unaltered H-reflexes together with depressed Achilles reflexes [24]. This last interpretation is the only one that could also fit in with our data. We do think, however, that higher doses of VDS have to be evaluated before any conclusions are drawn.

In conclusion, we feel that up to 3.0 mg/m^2 VDS is probably safe and has no intolerable side effects. Depressed ankle jerks are the first sign of VDS-induced neurotoxicity. Neutropenia is only rarely so servere as to make dose adaptations necessary. Thrombocytosis occurs regularly in patients with intact bone marrow function. Finally, there are no electrophysiological alterations.

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Received September 25, 1978/Accepted January 29, 1979