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Neurological Toxicity of Vindesine Used in Combination Chemotherapy of 51 Human Solid Tumors

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Summary. *The authors treated 51 patients with solid tumours with vindesine 4 mg/m², generally every third week, in combination chemotherapy protocols scheduled according to diurnal variability of kinetics.*

No dose-related sensory disorders were observed: On the contrary, motor toxicity appeared cumulative:

1) Early depression of osteotendinous reflexes from the first course onward, with progressive deterioration. No more normal reflexes could be evoked after 55 mg;

2) Early appearance of neurogenic pattern in the electromyograph after 5–10 mg. Progressive alteration with no normal detection recordings after 45 mg;

3) Late slowing down of conduction speeds (normal in 50% of cases up to 55–60 mg).

Improvement or even complete recovery of neuropathy was documented following reduction of the unit dose, increased time interval between doses, or discontinuation of the treatment. The drug had to be withheld in only three patients: in two cases a low dosage related to individual sensitivity was being used.

Introduction

The neurotoxicity of the vinca alkaloid derivatives is well documented in the literature [5–7, 21, 22, 24, 25, 28–30, 35, 36, 42, 46–50, 54, 56, 58, 59]. The administration of vincristine (VCR) or high doses of vinblastine (VLB) induces a progressive peripheral neuropathy expressed predominantly at the motor level, or particular manifestations such as paresias of cranial nerves, mono- or polypareses or -plegias, convulsions, or inappropriate ADH secretion [5–7, 21, 22, 24, 25, 28–30, 35, 36, 42, 46–50, 54, 56, 58, 59].

The recent introduction into chemotherapeutic practice of a semi-synthetic derivative of vinblastine (vindesine, VDS, desacetylvinblastine amide sulphate [9, 10, 19, 20, 23, 26, 32, 33, 37, 45, 51] led to questions about the neurotoxicity of this drug. The first pharmacokinetic evaluations of VDS in human subjects justified prediction of a lower neurotoxic potential than for vincristine, on the basis of biological distributions comparable to those observed with vinblastine. In the same way, appropriate animal models suggested lower peripheral toxicity of VDS than of VCR [1, 9, 10, 38, 40, 41, 53].

The purpose of the present work was to follow the neurological evolution over time of patients treated with VDS in combined chemotherapy. The antitumoral efficacy of the protocols tested and their clear impact on survival of responders has been emphasized elsewhere [14, 19, 20].

Materials and Methods

Fifty-one patients with solid tumours (for histology see Table 1) were included in the trial (sex ratio M : F, 2 · 4; median age 62; range, 30–80). Twenty-two patients had been previously treated, nine by chemotherapy alone, two by radiotherapy alone, one by surgery alone, four by chemo- and radiotherapy, two by combined surgery, radiotherapy and hormonotherapy, one by surgery, radio- and chemotherapy, one by hormonotherapy alone, and two by immunotherapy with levamisole, following surgery in one case. The previous chemotherapeutic regimens included various agents: in particular, nine patients had received vinblastine (10–49 mg), seven, vincristine (2–25 mg) and three, both vincristine (3.2–25 mg) and vinblastine (11–49 mg).

According to a simplified Karnofsky scale [31, 60], the performance status of individuals was as follows: 0 (no clinical sign): one case; 1 (symptomatic ambulatory): 19 cases; 2

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(bedridden less than 50% of the time): ten cases; 3 (bedridden more than 50%): seven cases; 4 (bedridden 100%): 14 cases.

The chemotherapy regimens including vindesine are summarized in Table 2. Vindesine was substituted for vincristine or vinblastine in the original protocols developped in our clinics, especially those currently used for the chemotherapy of lung and breast cancers [12–14, 19, 20], or in more classic schemes as MOPP, ABVD, and CYVADIC [4, 8, 11, 17, 27, 32, 43, 44]. All these chemotherapeutic regimens were adapted so that each drug would be administered at a chosen time of day according to the circadian rhythm of tumours (i.e., for VDS during the evening or at midnight) [12, 13, 15–19]. The individual dosage of vindesine was 4 mg/m^2. The courses were generally repeated every third week.

Over the whole trial, 262 courses of chemotherapy were given (range 1–16; mean 5.2 per patient); the mean amount of vindesine per patient was 30.1 ± 3.4 mg (range 4.1–115.2 mg).

The neurotoxicity of drug(s) was evaluated as frequently as possible (ideally at each course of chemotherapy), by precise anamnesis and clinical examination and by classic electroneuromyography (EMG) including needle electrode studies and nerve stimulation studies [55]. Four degrees of severity of motor disorders were arbitrarily attributed (Table 3).

According to the cumulative dose of VDS received when the neurological evaluation was performed, the patients were divided into groups at every 5 mg VDS up to 70 mg, and at every 10 mg from 70–100 mg.

Table 1. Histology of treated tumors

1. Lung cancer	31
Oat cell	7
Squamous cell	16
Adenocarcinomas	8
2. Breast cancer	10
3. Lymphomas[a]	4
4. Others	
Sarcomas	2
Head and neck cancer	2
Seminoma	1
Hypernephroma	1

[a] Including two cases of Hodgkin's disease, one of reticulum cell sarcoma, and one of lymphoblastic lymphosarcoma

Results

The inclusion of vindesine in the chemotherapy protocols did not appear to add any general toxic effects to the combinations. The general side-effects were still of the same type and order of magnitude as we reported with the use of vincristine or vinblastine [12, 13]. Regrettably there were two deaths from Gram-negative septicaemia secondary to granulocytopenia in debilitated patients.

Neurological evaluation of toxicity related to VDS yielded the following observations. The appearance of sensory disturbances (Fig. 1) did not seem to be dose-related and they were not sufficiently

Table 2. Chemotherapy protocols including vindesine

1. Lung cancer (31 patients): MVE/VAC [12, 13, 17–19]		
A. Methotrexate 60 mg/m^2 or 5FU 750 mg/m^2	Day 1	10 a.m. to 8 p.m.
Vindesine 4 mg/m^2 + Cyclophosphamide 300 mg/m^2	Day 2	8 p.m. to 2 a.m.
B. Vindesine 4 mg/m^2	Day 1	12 p.m.
Adriamycin 40–60 mg/m^2	Day 2	8 a.m. to 8 p.m.
CCNU 120 mg per os	Day 3	Evening
Courses repeated every third week		
2. Breast cancer (ten patients): FVE/VA [12, 13, 17–19]		
A. 5FU 750 mg/m^2	Day 1	10 a.m. to 8 p.m.
Vindesine 4 mg/m^2 + Cyclophosphamide 300 mg/m^2	Day 2	8 p.m. to 2 a.m.
B. Vindesine 4 mg/m^2	Day 1	12 p.m.
Adriamycin 40–60 mg/m^2	Day 2	8 a.m. to 8 p.m.
Courses repeated every third week. These patients received also hormonotherapy		
3. Others (ten patients)		
CYVADIC regimen [43]	Chondrosarcoma (one case)	
CVP regimen [17, 27]	RS (one case)	
MVPP regimen [4, 8]	HK (one case)	
ABVD regimen [4]	HK resistant to MOPP (one case)	
V. Asp. [32]	Lymphoblastic LS resistant to all known regimens (one case)	
VABMF regimen [44]	Head and neck cancer (two cases)	
VA CB cis-DDP regimen [11]	Seminoma (one case)	
FVE regimen [12, 13, 17–19]	Hypernephroma	
Dose for single VDS injection, 4 mg/m^2. Courses repeated according to protocols described in publications referred to, or after haematological recovery		

Table 3. Vindesine peripheral neuropathy: Scale in four degrees of severity

Degree	Deep tendon reflexes	Needle electrodes recordings	Conduction speeds
1	Normal	Normal	$\geq$ 42 m/s
2	Mild depression	Moderate neurogenic signs, i.e., mild reduction of interference pattern; mild modification of morphology of motor unit potentials; mild increase in frequency of discharge	Decrease $\leq$ 15% of initial values if normal
3	Clear depression. Disappearance of ankle jerk reflex with conserved patella reflex	Impoverishment of sketching Marked increase in polyphasic potentials High frequency of discharge	Decrease > 15% of initial values if normal
4	Abolition	Simple pattern Electrical silence Very high frequency of discharge Fibrillation potentials Increase in motor unit size	Inexcitability of one or several nervous trunks

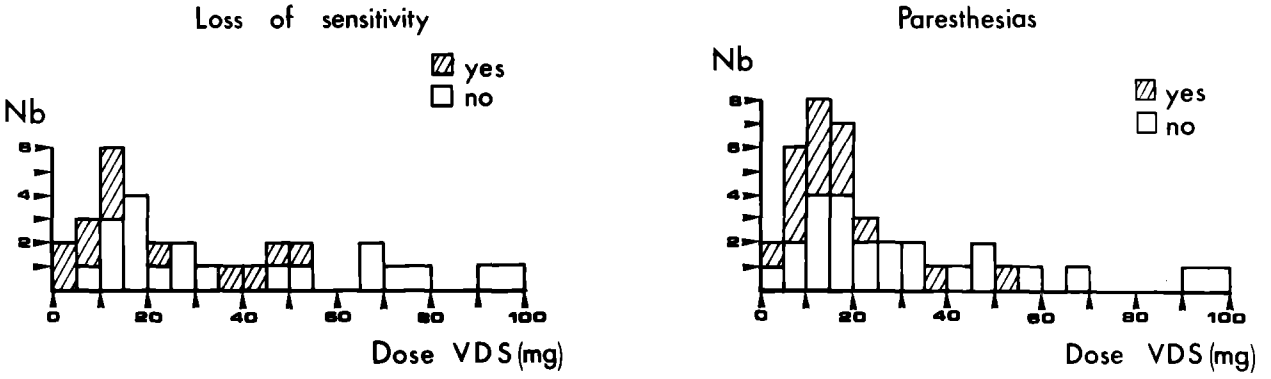

Fig. 1. Sensory disorders according to cumulative VDS dose. *Ordinate*, number of patients; *abscissa*, dose of VDS (mg)

bothersome for patients to withdraw treatment. Two patients developed jaw pain after 15.2 and 19.6 mg VDS; the VDS could be continued with reduced unit doses of up to 3 mg/m^2. The evaluation of motor toxicity had to be balanced against the frequency of abnormal electromyographic findings before any treatment in 15 cases, related to previous medication with vincristine and/or vinblastine in four cases, to diabetes mellitus in two cases (complicated by alcoholism in one case), to rheumatoid arthritis in one case, and to paraneoplastic peripheral disorders in the other cases. In all patients, the treatment was conducted as described.

After VDS, very early depression of osteotendinous reflexes, especially the ankle reflex (Fig. 2) and appearance of neurogenic pattern at EMG (Fig. 3) were observed from the first or second course of chemotherapy: as the cumulative doses increased, the deterioration of DTR and EMG recordings progressed, with disappearance of normal reflexes above 55 mg and of normal electromyographic determinations after 45 mg. In contrast (Fig. 4), despite an unquestionable cumulative effect, conduction velocities could still remain normal at high doses of vindesine: between 55 and 60 mg, 50% of measures were normal and normality or mild slowing down was still observed till above 80 mg. Three patients developed severe constipation culminating in paralytic ileus during the next course of treatment in two cases (after 14.4 and 50.4 mg VDS); VDS was withheld in the patient who had received 50.4 mg, while it was continued at a reduced dosage (2–3 mg/m^2) in the other two cases. Vindesine had to be withdrawn in three patients, because of general intolerance after 15 mg in one case (appearance of allergic reaction, constipation, severe paresis and

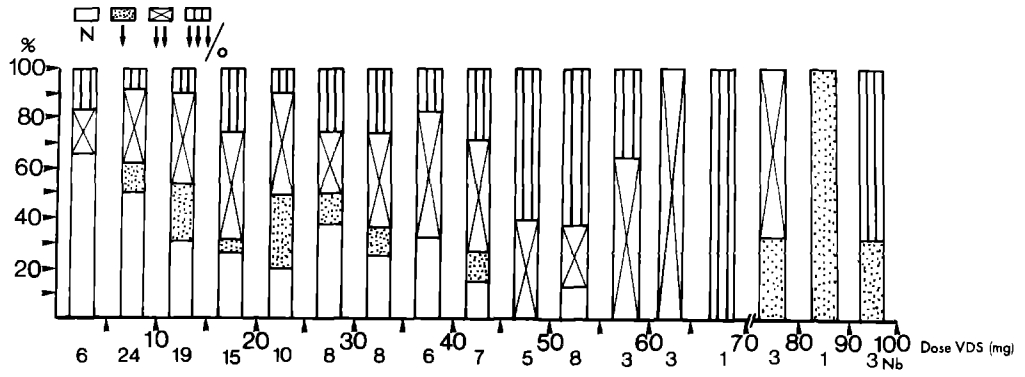

Fig. 2. Deterioration of deep tendon reflexes in four steps of severity according to cumulative VDS dose. *Ordinate*, percentage of patients; *abscissa*, dose of VDS (mg) and number of patients

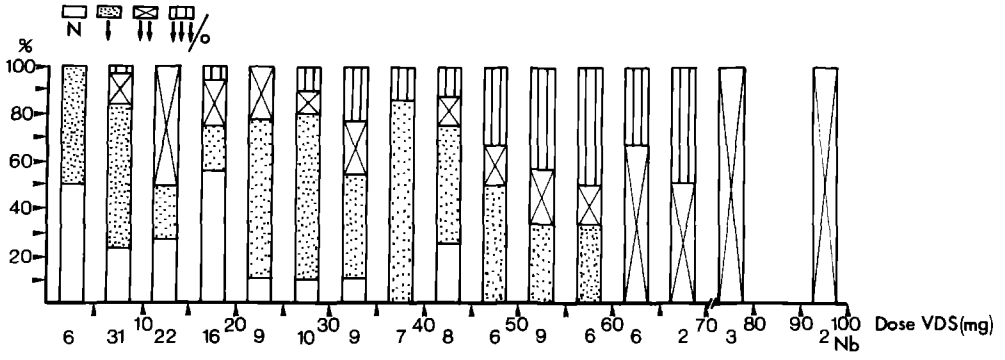

Fig. 3. Deterioration of EMG recordings in four steps of severity according to cumulative VDS dose. *Ordinate*, percentage of patients; *abscissa*, dose of VDS (mg) and number of patients

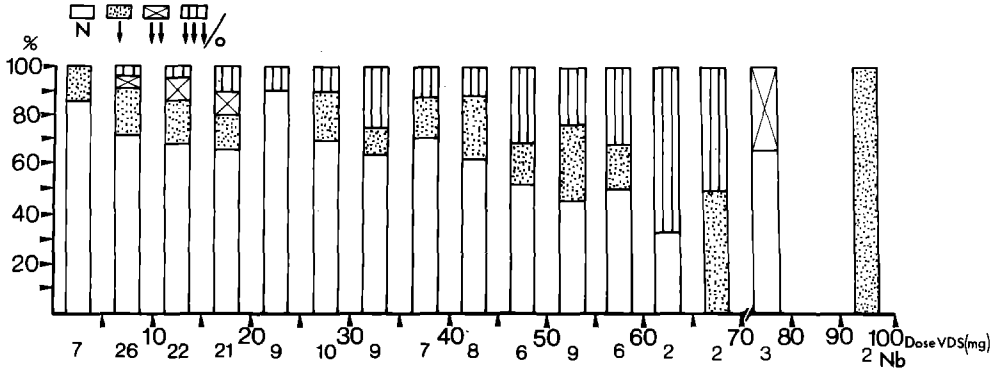

Fig. 4. Evolution of conduction velocities in four steps of severity according to cumulative VDS dose. *Ordinate*, percentage of patients; *abscissa*, dose of VDS (mg) and number of patients

paraesthesias strictly related to VDS, while it exerted an unquestionable antitumoral effect) and because of motor signs confining the patient to bed in two other cases after 12 mg (individual sensitivity) and 50.4 mg (this last patient having also exhibited a paralytic ileus).

Reducing the unit dose of VDS by 50% while maintaining the same time interval (four cases), or increasing the interval between administrations from twice a month to once a month in one case, or stopping chemotherapy with the vinca alkaloid derivative (three cases) brought about progressive

improvement of peripheral neurological disorders during therapy or even complete recovery after the end of treatment.

Discussion

The involvement of the peripheral nervous system following vindesine repeated administration appears to be of the same type that has been reported after vincristine use [6, 7, 24, 25, 28, 35, 36, 47, 49, 56, 58, 59]. As after vincristine, no dose-related sensory disorders were observed [6, 7, 25, 28, 36, 47, 56, 58, 59]. In a similar way, soon after VDS administration the first events to be recorded were the decrease of deep tendon reflexes amplitude (especially ankle reflex), and soon after, the appearance of a neurogenic pattern with needle electrode studies: the two processes are dose-related. Later on, a reduction of conduction velocity could be shown. These types of alterations have been described after VCR and reveal a toxic phenomenon expressed primarily as an axonal degeneration culminating later in an alteration of myelin sheaths [6, 7, 22, 24, 25, 28, 35, 36, 47, 49, 52, 56, 58, 59]. The early depression of deep tendon reflexes, sometimes preceding the axonal degeneration signs, has also already been reported after VCR and reflects early damage of the muscle spindle by dystrophy of the gamma-innervation, or of the annulospiral terminations, or of the very distal part of afferent fiber inside the muscle spindle, rather than an alteration of the sensitive afferent fibres [7, 28, 58, 59].

The clinical use of VDS in combination chemotherapy scheduled according to diurnal rhythms raises the question of a possible potentiation of neurological damage resulting from the other drugs and/or from the choice of the hours of administration. None of the other compounds used has exhibited neurological toxicity strictly related to its use [58, 59] and except perhaps for L-asparaginase (used in one case in this trial), which could influence the hepatic metabolism, no increase in VCR toxicity has been reported after combination chemotherapy, despite a wide clinical experience [24, 58, 59]. Moreover, in a previous randomized trial, including high doses of vinblastine (10 mg/m^2 every 3 weeks, infused from 8 p.m. to 2 a.m. or from 8 a.m. to 2 p.m.), no difference in toxicity could be assessed whatever the time of vinblastine administration [13].

As already reported after VCR use, the possibility of improvement of the peripheral neuropathy by interspacing, reducing, or withdrawing the vinca alkaloid derivative was also demonstrated [7, 28, 58, 59], but a lesser neurological toxicity of VDS is suggested by our observations. This has been predicted from comparative animal studies [1, 22, 28, 53] but also from comparative pharmacokinetics in man, showing a body clearance of VDS closer to that of VLB (short terminal half-life about 1 day as VDS) than to that of VCR (much longer terminal half-life, about 6 days) [1, 10, 38, 40, 41, 50, 51]. The pharmacological data are clinically related to the general tolerance of VDS, related not only to the unit dose in single administrations but also to the time interval between administrations. Indeed, it has been clearly stated that the neuro- and haematotoxicities of VDS could be enhanced by administration of the same dose over a more prolonged period of time (IV bolus versus 8–24 h infusions or continuous infusions during 5 days [2, 3, 39, 57]) and by increasing the single dose at fixed time intervals [39]. Therefore, it appears that if 4 mg VDS/m^2 per week induces troublesome neuropathies, a lower dose of 3 mg/m^2 can be clinically tolerated [39]; similarly, increasing the time between VDS administrations to 2 [2, 39] or 3 weeks (this study), while maintaining a single dose of 4 mg/m^2, or reducing the unit dose and/or increasing the delay between injections (as we did and as Misset et al. did in ALL, where 2 mg/m^2 every 2 weeks were used [34]), made it possible partially to overcome cumulative toxicities and to allow the patients to receive doses as high as 96–115 mg (this study) of VDS [34].

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