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Phase-II Trial with Vindesine for Regression Induction in Patients with Leukemias and Hematosarcomas

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Summary. *Vindesine (VDS) has been submitted to a phase-II trial, the results of which were assessed in terms of regression induction. VDS was given weekly IV in doses of 2 mg/m² on two consecutive days to 59 patients, 55 of whom were evaluable. A high proportion of complete (36%) and over 50% partial regressions were obtained in acute lymphoid leukemias (ALL) (overall response 63%) whatever the perceptible phase, in blastic crisis of chronic myeloid leukemia (55%), and some responses were recorded in lymphosarcoma (40%). No effect has so far been seen in acute myeloid leukemia or in Hodgkin's disease. Malignant neoplasms of the immunoblastic type seem to be particularly sensitive to VDS. Continuous 48 h IV infusion can induce a remission where an IV push administration of the same dose has failed. One remarkable characteristic of VDS is the apparent absence of cross-resistance with VCR: in acute leukemic forms, 55% of patients who failed to obtain remission induction after three weekly injections of VCR (used in combination chemotherapy) achieved a complete or partial remission with VDS. The toxicity was mainly neurologic (paralytic ileus, constipation, paresthesias, loss of reflexes) and hematologic (leukopenia and thrombopenia), and was not more significant than with the other agents: four patients died of infection or hemorrhage.*

Introduction

Vindesine (VDS) or deacetyl vinblastine amide sulfate is an analog of the vinca alkaloid family [1]. It is a semisynthetic derivative of vinblastine (VLB) and it was chosen for clinical evaluation for several reasons. First, its experimental spectrum of antitumor activity was not the same as that of its parent, VLB, but much closer to that of vincristine (VCR), particularly on Ridgeway osteosarcoma and B 16 IP melanoma, which could be predictive models for human malignancies (II). Second, it head a potentially minor neurotoxicity in animals (mice, rats, dogs, chickens, monkeys) when used at the same or higher doses as VCR given for a longer time [13]. Moreover, its preparation was sufficiently simple and reproducible [1]. VDS was thus proposed for clinical trials with the hope of enhancing the activity of the vinca alkaloid family and/or of reducing its toxicity in humans also, on the basis of the results obtained in the animal studies. VDS was shown to have about the same mechanism of action as the other two vinca alkaloids, VCR and VLB, in that it arrests the cells in mitosis at their metaphase, as we were also able to show reproducibly in the P 388 leukemic strain (M. Paintrand et al., in preparation), and binds to tubulin; there is a disruption of the microtubules not only of the spindle apparatus but also of many cells, and complete disorganization of the mitosis, as seen in electron microscopy studies, which reveal the appearance of a paracrystalline structure [5]. Phase-I trials were conducted and the dose-limiting toxicity took the form of leukopenia at the dose level of 4 mg/m² week [4]. This paper describes our experience in a phase-II trial concerning 55 evaluable patients with leukemias and hematosarcomas.

Patients, Materials, and Methods

1. Selection of Patients

The study was confined to patients having leukemias and hematosarcomas who had all been previously treated and either displayed primary resistance to all the chemotherapeutic agents available at the time of the study (VDS was given as a second-line treatment drug) or were in relapse under maintenance chemotherapy protocols and first received VDS in an attempt to induce a remission: we found it ethical to submit patients in these two different groups to a phase-II trial with VDS as a single chemotherapeutic agent.

2. Treatment

VDS was given at the dose of 2 mg/m² on two consecutive days in each week: the method of administration was by IV push over

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Table 1. Leukemia and hematosarcoma patients admitted to vindesine trial

Diagnosis	PP[a] or stage	No. of patients	Age	Sex		VCR-resistant	Unevaluable
				M	F		
ALL	1st[b]	1	12	1	0	1	
	2nd	8	8–40	5	3	4	1 (maintenance)
	≥3rd	12	4–31	8	4	9	1 (8% blast cells)
	—	—	—	—	—	—	—
			<20 >20				
	Total	21	17 4	14	7	14	2
AML	1st–2nd	5	12–72	3	2	1	1 (1 cycle)
CML, blastic crisis		11	19–69	6	5	8	
Lymphosarcoma							
Leukemic	1st–4th	9	7–33	5	4	6	1 (pleural)
Immunoblastic	IV	3	50–67	3	0	0	
Prolymphocytic	III IV	4	11–73	2	2	0	
Hodgkin's disease	III IV	4	14–57	2	2	0	
Unclassified (CLL–CML)		2	72–73	1	1	0	
Total		59	$\bar{m}=33$	36	23	29	4

[a] PP, perceptible phase [b] Immunoblastic form

Table 2. Vindesine treatment protocol for leukemias and hematosarcomas

No. of cycles[a] (interval)	No. of patients	Variation of interval duration (days)	Mean interval duration (days)
1	7		
2 (1st–2nd)	53	(4–17)	8.1
3 (2nd–3rd)	22	(4–18)	9.5
4 (3rd–4th)	4	(6–14)	9.25
5 (4th–5th)	1	(13)	13

[a] One cycle consists of 2 mg/m²/day for 2 days within 8 days (i.e., treatment-free interval is 6 days). The compound was administered IV by push (42 patients), continuous infusion (3 patients), or both (14 patients)

2–3 min, by continuous infusion over 48 h, or both modalities, beginning with IV push. Almost all the patients were in-patients, and detailed blood counts were performed each day or every 2 days. Laxatives were given daily to prevent the digestive neurologic side effects.

At least two cycles of treatment were given; if a major progression of the disease was seen, with a threat to life, and if the patients were not resistant to all the available drugs, treatment with VDS could be changed after one cycle; if no effect was seen after two cycles, treatment was discontinued; if no, or a very minor, effect was seen with the IV push treatment, some patients were switched to 48-h infusions after two cycles.

3. *Design of the Study*

VDS was supplied as sulfate in sterile vials, by Eli Lilly Laboratories. We dissolved 10 mg vindesine in a diluent containing sodium chloride with benzyl alcohol and sterile water for injection; when mixed, the solution could be stored at −4° C for 14 days. The study was initiated in January 1976 and closed in May 1977: the final analysis was made for an expert's report in June 1977. Concomitant treatment, previous therapy, particularly with VCR, it last dose and the efficacy, and toxic side effects were elicited and recorded by clinical and laboratory investigations.

4. *Evaluation of Response*

To be evaluable, patients had to have more than 10% blast cells in the bone marrow aspirate on the first day of treatment with VDS, to have a measurable tumor mass, and to receive more than two cycles of the drug being studied, unless major progression was observed after one cycle, as described above. Response was assessed by clinical (including lymph node, spleen, and liver enlargements) and laboratory (including bone marrow aspiration before each cycle of treatment with VDS BC each day or every other day and liver and renal) tests. The response was noted in terms of regression, concerning the tumor cells in the bone marrow and the blood, and in terms of remission, concerning the signs and symptoms of the disease (normalization of the BC) [9] a disappearance was considered a complete response (CR), measurable reduction was considered a partial response (PR: more than 50%; less than 50% but more than 25%: MR). Very minor regressions or stabilizations were not considered responses, but failures. The duration of the responses cannot be predicted from our data because, as soon as we obtained a complete regression, the patient was switched to reinduction or maintenance chemotherapy.

To allow evaluation of the toxic side effects, only the patients who had more than 40,000 platelets/mm³, more than 500 polynuclear cells/mm³, more than 10 g hemoglobin/100 ml at the beginning of the treatment were considered evaluable.

Resistance to VCR in combination therapy was defined as failure to obtain remission induction after three cycles of treatment with VCR (1.4 mg/m²/week), prednisone (40 mg/m²/day), and L-asparaginase (10,000 IU/m² × 2/week): therapy with VDS was initiated 1 week after the last injection of VCR (i.e., 4 weeks after the first).

Table 3. Response to vindesine in patients with leukemia or hematosarcoma

Diagnosis	No. of evaluable patients	Regression			Failure	Response rate	
		Complete	Partial			≥50%	Overall
			>50%	<50%			
ALL	19	7	6	1	5	63%	73%
AML	4	—	—	2	2	0/4	2/4
CML blastic crisis	11	5	1	1	4	55%	64%
Lymphosarcoma							
Leukemic	8	—	3	—	5	38%	38%
Immunoblastic	3	—	1	1	1	1/3	2/3
Prolymphocytic	4	—	2	1	1	2/4	3/4
	15		6	2	7	40%	53%
Hodgkin's disease	4	—	—	—	4	0/4	
Unclassified	2	—	—	2	0	0/2	
Total	55	12 (22%)	13	8	22		
			25			45%	
				33			60%

Results

1. Efficacy

Our phase-II trial with VDS involved 59 patients, 55 of whom were evaluable: four patients were rejected as nonevaluable. One was treated with VDS as maintenance chemotherapy, one had a bone marrow aspirate with less than 10% blast cells, one died after only one cycle of treatment before any evaluation, and one was ineligible because a pleural effusion was the only measurable disease.

As seen in Table 1, there were 19 evaluable patients with acute lymphoid leukemia (ALL), 4 with acute myeloid leukemia (AML), 11 with chronic myeloid leukemia (CML) in blastic crisis, 15 with lymphosarcomas, 4 with Hodgkin's disease, and 2 with a malignant hematologic disease to which we could not give a precise classification, one resembling chronic lymphoid leukemia and one resembling CML. The classification used was that of the World Health Organization [8].

The mean age was 33 years (4–72 years); there were 33 men and 22 women. Twenty-nine patients were considered resistant to VCR.

The total doses varied from 5.2 to 24 mg/m^2 in two to five cycles. Seven patients received only one cycle, because of lethal toxicity (2 patients) or major progressive disease (5 patients). The mean duration of the interval between two cycles was 8–13 days: treatment was postponed for more than 1 week in the case of intolerance or toxicity (Table 2).

The results were judged in terms of regression induction and are summarized in Table 3.

In Acute Lymphoid Leukemia. Out of 19 patients (Table 4) 36% (6 patients) achieved complete regressions, 26% of these being remissions; the response rate was 63% (CR plus PR), or 73% if the mild responses are included (these were at least disappearance of the blast cells from the blood and over 25% reduction of the blast cells in the bone marrow, which can be accepted as a response in patients who were previously resistant to therapy and had a long evolution of disease). All the patients were in relapse except one, a child 12 years of age with an immunoblastic cytologic type of leukemia in which the number of blast cells had increased after 2 weeks of VCR-PDN-ASP with major bone pains; after a single injection of VDS on two consecutive days, we observed a CR. Except for this particular type of disease, responses could be obtained whatever the cytologic type and perceptible phase.

The complete regressions were generally obtained after one (4 patients) or two cycles (2 patients). If VDS was used as the first line of treatment as soon as the relapse appeared, the number of CR plus PR was higher (5/6: 83%) than when it was used after failure of a therapy with VCR in combination with other drugs (9/13 : 64% response). These differences, however, are not statistically significant (see Table 5).

Table 4. Response to vindesine in ALL

No. of PP	No. of evaluable patients	Regression				Failure	Response rate
		Complete		Partial			
		with remission	without remission	>50%	<50%		
1st	1[a]	1	–	–	–	–	1/1
2nd	7	1	2	1	1	2	5/7
≧3rd	11	3	–	4	1	3	
Total	19	5 (26%)	2	5	2		14/19
		7					36%
		12					63%
		14					73%

[a] 12 years, Immunoblastic, resistant to VCR in first PP

Table 5. Difference in sensitivity to vindesine according to the time of administration

		No. of evaluable patients	CR	PR>50%	Response rate
ALL	Before VCR[a]	6	4	1	83%
	After VCR	13	4	5	64%
CML, blastic crisis	Before VCR[a]	6	3	2	80%
	After VCR	4	1	1	2/4

[a] VCR is used here to indicate the combination

In Acute Myeloid Leukemia. No response of more than 50% could be achieved (MR in 2 of 4 patients) (Table 6).

In Blastic Crisis of Chronic Myeloid Leukemia. Eleven patients were treated: they were either in primary blastic crisis, at first showing an acute leukemic pattern (with the Phi chromosome positive), or in a secondary one according to the classic evolution of a chronic myeloid leukemia. Five of these 11 patients entered CR (45%) which gives an overall response rate of 55% (PR plus CR). We were also able to achieve response in myeloblastic types of the disease as well as in lymphoblastic-like types and the mixed lymphoblastic and myeloblastic cytologic types. Five of the responses were in the group of patients whose ongoing blastic crisis had not been previously treated with other drugs (Tables 5 and 6).

In Lymphosarcomas. Six patients of 15 (Table 7) achieved over 50% regression; no complete regression was seen in this category, but responses could be obtained whatever the cytologic type of the disease. According to the WHO classification, there were two responsive patients out of three with prolymphocytic forms, two out of three with immunoblastic forms, and three out of five with lymphoblastic leukemic forms [7]: all these patients were resistant to the previous chemotherapy currently available for their form of the disease.

In Hodgkin's Disease. We recorded four total failures in four patients with this condition.

In the total, of 55 evaluable patients the overall response rate was 22% (CR), 45% (CR plus PR), or 60% (over 25% regression) (see Table 3).

Mode of Administration

We tried giving VDS as a 48-h continuous infusion at the same dosage as was given by the direct IV mode. Twelve patients had had primary failures or very partial regressions of less than 50% with two cycles of treatment with IV push injections, and instead of discontinuing the therapy, we switched them to 48-h infusions: six of these patients (50%) then responded to the drug. Three patients had 48-h infusions from the beginning, which is very few to draw any conclusion; and only one patient achieved a partial response. However, we observed a very high venous toxicity manifested mainly in thrombophlebitis, despite the stringent precautions taken with the infusion (in a peripheral vein, however).

Table 6. Response to vindesine in AML and in blastic crisis of CML

Diagnosis	No. of PP	No. of evaluable cases	Regression			Failure	Response rate
			Complete	Partial			
				>50%	<50%		>50%
AML	1st	3			1	2	
	2nd	1			1	–	—
Total		4			2	2	
CML blastic crisis							
Secondary disease	1st	6	2	1	—	3	
	2nd	2	1	—	—	1	
Primary disease	1st	3	2	—	1	—	55%
			5/11 (45%)				

Table 7. Response of hematosarcomas to vindesine

Diagnosis	No. of PP or stage	No. of evaluable patients	Regression			Failure	Overall response rate
			Complete	Partial			
				>50%	<50%		
Lymphosarcoma							
Leukemic	1st	1				1	1/1
	2nd	2				2	
	≥3rd	5		3 (38%)		2	3/5
Immunoblastic	IV	3		1	1	1	2/3
Prolymphocytic	III	3		1	1	1	2/3
	IV	1		1			1/1
Total		15		6 (40%)	2	7	53%
Hodgkin's disease	III	2				2	
	IV	2				2	—

Table 8. Advantages of continuous 48-h infusion over IV push

Conditions	Number	Improvement	
		CR	PR
After failure of IV push			
As initial treatment			

2. Tolerance

The main manifestations of toxicity consisted of hematologic and neurologic side effects (see Table 9).

The hematologic toxicity is detailed in Table 10. Forty-four patients were evaluable, the others being nonevaluable because of very low blood counts at the beginning of the VDS therapy.

The WBC count fell to below 2,500/mm^3 in 64% of patients, the neutrophil polynuclear cell count being lower than 1,000/mm^3 in 73%, with a mean minimum value or nadir of 200/mm^3 on day 17, generally after the second cycle, and with a mean duration of 15.4 days; there were two fatal major infections among patients affected with neutropenia. The platelet count fell to 100,000/mm^3 in 53% of cases, being under 20,000/mm^3 in one-third of these: the mean nadir was 42,000/mm^3 on day 14, and it appeared rapidly, generally after one cycle. The mean duration was 9.4 days and two patients died of meningeal hemorrhages. The fall in hemoglobin was systematically recorded. There was no thrombocytosis in this series.

The neurologic side effects, which are detailed in Table 11, consisted of paralytic ileus in three cases (5%), in whom treatment was suspended for 8 days: it regressed under medical symptomatic supportive care, but was very painful, requiring major analgesic therapy. Ileus was manifest on the third day of the first cycle of treatment and did not recur after the second cycle. No connection with the IV or infusion

Table 9. Tolerance of vindesine

	No. of evaluable patients	No. of cases	Rate (%)	Treatment delayed
Hematologic	47	36	76	
Leukopenia <1,000 Poly/mm³	45	33	69	
Thrombopenia <1,000,000/mm³	44	24	53	
Anemia <10.5 g/100 ml	43	24	55	
Neurologic				
Paralytic ileus	59	3	5	3/3
Constipation, abdominal pain	59	8	14	
Paresthesias	59	4	7	
Loss of reflexes	59	3	5	
General intolerance				
Fever (38–39 °C for 1–2 days)	59	15	25	
Pain (muscles, bones, throat)	59	8	14	
Malaise (minor)	59	5	8	
Cutaneous rash	—	1	2	
Venous phlebitis	59	5	5	
Venous cellulitis	59	3	8	
Digestive				
Epigastralgia	59	1	2	
Elevated alkaline phosphatase	59	2	3	
Hyponatremia with natriuresis	59	2	3	1
Alopecia	3	3	3/3	
Death	45	4[a]	7	

[a] Infection and meningeal hemorrhage in two cases each

Table 10. Hermatologie toxicity of vindesine

Blood cells	No. of eval. cases	With toxicity	Rate (%)	Nadir per mm³				Mean duration (days)	Lethal
				Mean	Range	Day (range)	Cycle		
White (per mm³)	44								
WBC <2,500/mm³		29	64						
Polynuclear neutrophil <1,000/mm³		33	73	200	0–1,000	17.4 (2–32)	2	15.4	2[a]
Platelets (10³/mm³)	44								
75–100		5							
50–75		7							
20–50		4							
<20		8							
<100,000 (total)		24	53	42	1–95	14 (3–36)	1	9.4	2[b]
Red; Hgb (g/100 ml)	43								
10–11		2							
8–10		15							
<8		7							
<10.5 (total)		24	55	8.1	6.6–10.3	15.4 (2–32)	2	15.3	—

[a] Infections
[b] Meningeal hemorrhage

method of administration of VDS was seen. Constipation and abdominal pains were seen in 14% of the other cases and we tried to prevent them by giving laxatives daily: these symptoms were never too troublesome. No diarrhea was observed; paresthesias involving the toes or the fingers were seen in four cases (7%), one of whom had been previously treated with VCR: two of them appeared together with an ileus. One was seen in a patient in the first perceptible phase of ALL (immunoblastic type). VDS was given the day after the third injection of VCR and was remarkably effective against the bone pains and on the bone marrow, which VCR had not previously affected: there was either a hypersensitivity to VDS or a cumulative effect of VDS given just after VCR, and we observed an ileus in the first cycle; on the first

Table 11. Neurotoxicity of vindesine

Type		Treatment			Previous therapy with VCR		Modification of treatment	Evolution	Effect of VDS
Major	Other signs	Cycle	Day	Dose (mg/m^2)	Total dose (mg)	Days from VCR to VDS admin.			
Ileus		1	1	4	4.2	1	Postponed (15 days)	Regressed (5 days)	CR
	Central facial Paralysis	2	16	6	4.2	1	Discontinued	Regressed (1 day)	CR
	Peripheral Neuropathy	2	25	6	4.2	1	—	Regressed (2 mo.)	CR
Ileus	Paresthesias	13	3	6	7.5	7	—	Regressed (3 days)	PR > 50%
Ileus		1	4	4	4.5	$1\frac{1}{2}$ mo.	—	Regressed (5 days)	Progression
Paresthesias	Distal	10	104	20			Discontinued	Decreased (3 mo.)	PR > 50%
	Distal	2	28	8		>3 mo.		Decreased (2 mo.)	MR < 50%
	Distal	2	30	8				Regressed (1 mo.)	MR < 50%

day of the second cycle or day 15, there was central facial paralysis, on account of which treatment was discontinued, with subsequent regression. Nine days later, on day 25, after a total dose of 4.2 mg VDS, peripheral neuropathy appeared with motor deficiency and without sensory impairment, which lasted 2 months and which did not reappear when VDS was used as maintenance chemotherapy. The electromyogram showed a reduction of sensory conduction rates.

All the paresthesias regressed and their appearance did not correlate with the method of treatment or with previous treatment with VCR, but only if administration of VDS was less than 1 week after VCR.

A loss of deep tendon reflexes was found on clinical examination in 5% of the evaluable cases, but this may have been underestimated. There was motor weakness in 5% of cases.

There were two syndromes of inappropriate antidiuretic hormone (ADM)-like secretions, in adults and the ADH concentration in the blood was found to be normal: there were no other neurotoxic signs at the same time, in contrast to the results seen with VCR.

General intolerance consisted of: raised body temperature of 38° – 39° C (25%) during the first and/or second day of therapy, particularly during infusion, but this was not too troublesome; diffuse pains (muscle, bone, and sometimes, curiously, throat pain with redness but no infection) in 14% of cases; minor malaise was reported in 5% of cases. Asthenia was common but was generally difficult to judge in this type of patient.

A cutaneous maculo-papular rash was seen in 2% of patients, who had previously shown asparaginase allergy: treatment was not discontinued and the rash did not reappear during the next cycle.

Venous problems were manifested as venous pain during IV injection (5%) or thrombophlebitis and/or cellulitis (8%) during infusion, which should be administered via a central catheter.

Finally, there was some digestive intolerance with epigastralgia (2%) and isolated elevated alkaline phosphatase (3%).

Alopecia was observed in three patients, in whom it was complete: other patients were bald before treatment with VDS.

Four patients died during therapy, two of infections (1 septicemia, 1 pneumonitis) and two of meningeal hemorrhage.

3. Apparent Absence of Cross-Resistance with Vincristine

Resistance to VCR has already been defined. All the 22 patients who were resistant to VCR in combination therapies were in an advanced stage of the disease, and the number of blast cells in the bone marrow aspirate was considered to be in progression or unchanged. VDS treatment was initiated 1 week after the last VCR injection. The results are detailed in Table 11: of 22 patients, six achieved CR and six PR; thus, 55% of the patients considered resistant to VCR in combination chemotherapy then responded to VDS therapy (see Table 12). On the other hand, four patients who were resistant to VDS achieved CR with the combination of VCR-PDN-ASP.

Table 12. Apparent absence of cross-resistance between vindesine and vincristine

Diagnosis	No. of resistant patients	Complete regression	Partial regression >50%	Failures	Response rate
ALL 1st PP	1	1	0	0	
2nd PP	4	1	1	2	6/13
≥3rd PP	8	2	1	5	
CML, blastic crisis	4	1	2	1	3/4
Leukemic lymphosarcoma	5	1	2	2	3/5
Total	22	6	6	10	55%

Discussion

VDS has previously been used in phase-I trials and early phase-II trials, and the dosage of 4 mg/m^2/week has been defined as the maximum tolerated dose [4]: it was given over 2 days because of the particular pharmacokinetics of VDS, which has a terminal half-life of 24 h [6, 10, 12], the advanced stage of the patients' disease, the relatively high dose used compared with that of its parent compound, VCR, and its potential toxicity.

All the patients had been previously treated and, apart from one, were in relapse: VDS showed significant activity in cases of ALL, where 36% of apparent complete regressions were obtained, which compared with the 44% – 57% rate described with VCR as first-line treatment in acute leukemias [2] is relatively high bearing in mind the patients' condition. The responses were all obtained rapidly (1 or 2 courses); at present we include VDS in our combination chemotherapies for complementary maintenance therapy in acute leukemias with poor prognosis. There is no evidence at present that VDS could cross the blood-brain barrier, and patients with meningeal relapse were excluded from the trial. In 11 cases of CML blastic crisis, 45% CR were achieved, which is a very good response rate compared with the results obtained with single agents, except peptichemio (PTC) [3], and even with combination chemotherapies: therefore, we are using VDS plus PTC in an attempt to induce remission in CML blastic crisis. In non-Hodgkin's lymphomas, except for leukemic lymphoblastic forms, in which three responses in five patients but no CR were obtained, no conclusion can be drawn because of the small number of patients. Two patients previously treated with conventional chemotherapy were responsive out of three having immunoblastic types of the disease: consideration of this together with the rapid response we previously described in an immunoblastic type of leukemia suggests that there could be a particular sensitivity of immunoblastic disease to VDS, and we are using it in a combination protocol as the first line of treatment in this indication. Another point is that VDS seems to be well tolerated in elderly patients: in one 73-year-old patient with a prolymphocytic lymphosarcoma that had not been previously treated, VDS was given in a cycle of 2 days at first and then at a dose of 2 mg/m^2 each week for 5 months as a maintenance treatment, giving a PR with minor myelosuppression. We could not achieve CR in AML or in Hodgkin's disease.

VDS administered as a 48-h infusion yielded a better response rate when used after failure or attainment of a very partial effect with direct IV administration: further studies are needed, but we should emphasize its high venous toxicity.

VDS was a little, but not significantly, more efficient if given before VCR and if used as soon as the patient was in relapse rather than after failure of VCR: it can be surmised, taking into account the condition of the treated patients, that its global efficacy was underrated and that its use in combination chemotherapy will prove its true role.

With regard to toxicity, from the hematologic point of view VDS cannot be evaluated in very advanced diseases with leukemic bone marrow involvement: however, it appears not to be more myelosuppressive than other combinations of drugs, for example. Concerning its neurologic side effects, these were generally not progressive; they did not lead to discontinuation of therapy and regressed at the end of the therapy: treatment of leukemias at the induction of remission is not a very good predictive test for the actual neurologic toxicity, particularly in view of the short period of treatment, the global percentage is about the same as with VCR, but if the dosages used (4 mg/m^2 for VDS and 1.4 mg/m^2 for VCR) are compared, VDS seems to be much less toxic at equal dosage. Alopecia is more pronounced than with VCR.

One of the most remarkable effects of VDS is that some patients were able to achieve CR during treatment when they were considered resistant to VCR in combination with PDN and ASP and/or other chemotherapeutic agents: in these cases we achieved 55% response (PR plus CR: Table 11). The apparent

absence of cross-resistance with another member of the vinca alkaloid family is of great importance if one considers that VDS is an analog.

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