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Original Articles

Vindesine Effect in Myeloid Leukemia

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Summary. *Vindesine (VDS), a semisynthetic vinca alkaloid derivative, was given weekly at a dose of 3 mg/m² as single-agent chemotherapy to seven patients with chronic myeloid leukemia (CML), 17 patients with chronic myeloid leukemia in blastic metamorphosis (CML/BM), and 12 patients with acute nonlymphocytic leukemia (ANLL). A substantial and rapid decrease of leukemic cells was obtained in 31 of 36 patients, and this was independent of cell phenotype and morphology. VDS may improve the results of polychemotherapy of ANLL, and is useful for palliative treatment of CML/BM.*

Introduction

Vindesine (deacetyl vinblastine amide sulfate; VDS) is a semisynthetic vinca alkaloid derivative with a wide spectrum of antitumor activity [4, 5, 10, 11]. Many trials of VDS have evaluated the effect of the drug in malignant lymphomas and acute lymphoblastic leukemia [1, 2, 4, 5, 8, 11, 12], i.e., in malignancies known to be very sensitive to the parent compounds, vinblastine and vincristine. A few studies have shown that VDS is also effective in chronic myeloid leukemia (CML) in blastic metamorphosis (BM) [2, 11], suggesting that chemotherapy of nonlymphocytic leukemias may be improved by the introduction of VDS. Accordingly, we evaluated the antitumor effect of VDS as single-agent chemotherapy in acute and chronic myeloid leukemias. It was found that this drug was active in 31 of 36 patients.

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Patients and Methods

The antileukemic effect of VDS was studied in 36 consecutive patients with chronic myeloid leukemia (CML), CML in blastic metamorphosis (CML/BM), or acute nonlymphocytic leukemia (ANLL).

VDS was always used alone as single-agent chemotherapy. For this reason, the period of therapy was short. The antileukemic effect of the drug was evaluated by determining the reduction of peripheral blood leukemic cells, of bone marrow cellularity, and of any other sizable tumor mass.

CML. Seven patients with Ph¹+CML at first diagnosis were studied prior to any therapy. All patients were given two to three doses of VDS at weekly interval as the only treatment. The effect on white blood cell (WBC) count, platelet count, and spleen size was monitored until 7 days after the last VDS dose.

CML/BM. Seventeen patients with Ph¹+CML/BM were studied prior to any specific therapy for BM (all patients had received treatment for CML by busulfan, dibromomannitol, or hydroxyurea). Patients received two to five doses of VDS at 7- to 15-day intervals as the only treatment. Three patients (cases 4, 5, and 14) were given two separate courses of therapy. According to the morphology, cytochemistry and terminal deoxynucleotidyl transferase (TdT) activity of peripheral blood leukocytes [9], ten patients had a myeloid BM, two a lymphoid BM, and the remaining five patients a mixed, myeloid, and lymphoid BM.

ANLL. Six patients were given a single dose of VDS at the onset of disease prior to any other therapy, and were observed thereafter for 3–5 days, before any standard induction chemotherapy was given. The remaining six patients were in first or second relapse and received one to three doses of VDS at weekly intervals before reinduction chemotherapy with other drugs was started. Subtypes of ANLL were identified by the morphological and cytochemical criteria suggested by the FAB group [3] and by serum lysozyme level.

VDS was dissolved in 10 ml sterile saline solution and administered by rapid IV injection at the standard dose of 3 mg/m² body surface area.

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Results

CML

Table 1 shows the effect of two to three doses of VDS in seven patients with Ph^1+CML. WBC count and marrow cellularity were reduced down to normal values in patients 1–5 and also decreased significantly in patients 6 and 7. Spleen volume was less rapidly affected by therapy. The decrease of WBC count was rapid (Fig. 1). Platelet count (not shown in Table 1) was not modified in five cases, and increased significantly in two cases (from 576 to 1,250 × 10^9/l and from 695 to 1.672 × 10^9/l, respectively).

Table 1. Reduction of WBC and of spleen volume after two to three doses of VDS in seven patients with Ph^1+ chronic myeloid leukemia studied prior to any other therapy

Patient	No. of doses	WBC × 10^9/l	Marrow cellularity	Spleen size[a]
		Before VDS/After VDS		
1. P. A.	3	47.8/ 3.8	++−/+−−	3/ 0
2. G. V.	3	40.9/ 6.0	++±/+−−	0/ 0
3. G. G.	3	69.0/ 9.3	+++/+−−	0/ 0
4. F. D.	2	82.2/13.0	+++/+−−	3/ 1
5. C. V.	3	86.0/10.7	+++/+−−	3/ 3
6. Z. A.	3	250.0/73.0	+++/++−	18/15
7. G. L.	2	190.0/92.0	+++/++−	18/16

[a] Centimeters below left costal margin

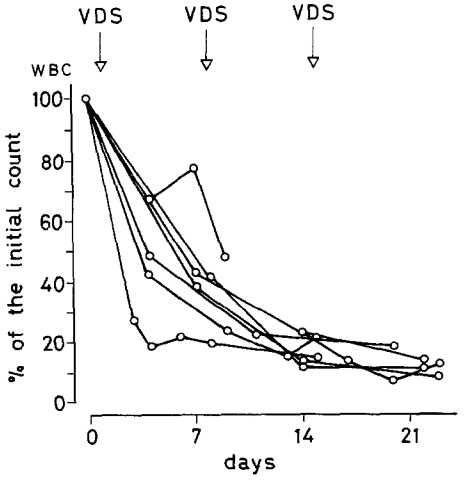

Fig. 1. VDS effect on white blood cell (WBC) count in seven patients with previously untreated chronic myeloid leukemia. The behavior of WBC count was monitored until another course of therapy was started

CML/BM

A significant decrease of peripheral blast cell count was observed in all patients but two (cases 10 and 17) (Table 2). Bone marrow became hypocellular in 13 cases, and aplastic in another 3 cases. As in patients with CML in chronic phase, the reduction of spleen volume was less important. The effect of VDS was apparently independent of CML/BM cytotype, and both myeloid and lymphoid populations were sensitive to the drug, with only one exception. In patient 14, marrow and blood cells were TdT− and were sensitive to VDS, while lymph node blast cells were TdT+ and were resistant to the drug. Figure 2 shows that in many cases the decrease of peripheral blood blast cell count occurred very quickly. The smallest decrease of peripheral blood blast cell count was recorded in one of the two patients with 'lymphoid', TdT+, cytotype.

ANLL

A sharp and quick reduction of peripheral blood blast cell count was observed in all patients but case 10 (M4 in first relapse) (Table 3 and Fig. 3). In another patient (case 9, M2 in second relapse), the effect of VDS was transient and the blast cell count increased quickly after the first and the second dose (Fig. 3). Patient 12 had M5 (monoblastic) ANLL in first relapse and achieved a complete marrow and skin remission with three doses of VDS as the only therapy.

Toxicity

Hematological toxicity could not be evaluated properly, because many patients with CML/BM and ANLL had severe granulocytopenia and/or thrombocytopenia prior to VDS administration. However, in CML/BM a granulocyte count lower than 1 × 10^9/l was observed in seven of 17 courses, and three patients died of infection. The nadir of the granulocyte count was reached 8–28 days after the first dose of VDS (median 13 days). A decrease of platelet count to below 50 × 10^9/l was recorded in seven cases of CML/BM.

Nonhematological toxicity included febrile reaction (after 8 of 76 injections), vomiting and diarrhea (once each), constipation (4 patients), paresthesia (14 patients), and hyporeflexia (8 patients).

Table 2. Antitumor effect of VDS in 17 cases of chronic myeloid leukemia in blastic metamorphosis

Patient	Cytotype[a]	TdT	No. of doses	Peripheral blood blast cell count ($\times 10^9$/l)	Marrow cellularity	Spleen size[b]
				Before VDS/After VDS	Before VDS/After VDS	Before VDS/After VDS
1. S. P.	M	ND	1	6.5/ 1.0	+++/+−−	2/ 1
2. R. P.	M	ND	1	32.4/ 0.3	Fibrosis	16/ 8
3. G. L.	M	ND	4	22.1/ 0	+++/+−−	6/ 3
4. I. D.	M	−	2	69.9/ 0	+++/−−−	0/ 0
4. I. D. (2)[c]	M	−	2	53.5/ 0.9	+++/±−−	0/ 0
5. R. O.	M	ND	4	74.1/ 0	+++/+−−	14/ 2
5. R. O. (2)[c]	M	ND	4	21.5/ 1.4	+++/+±−	12/ 8
6. C. S.	M	ND	4	25.3/ 0.1	+++/+−−	1/ 1
7. P. G. P.	M	−	3	3.9/ 1.0	+++/+−−	12/ 6
8. M. G.	M	−	3	14.5/ 1.3	+++/+−−	11/ 9
9. P. C.	M	−	4	99.0/ 1.7	+++/+−−	(Splenectomized)
10. L. C. S.	M	−	3	52.4/27.9	+++/++±	24/18
11. M. M.	M/L	+	2	2.5/ 1.0	+++/±−−	14/ 9
12. V. E.	M/L	+	5	104.4/ 3.2	+++/+−−	0/ 0
13. C. L.	M/L	ND	2	1.2/ 0	+++/−−−	6/ 0
14. M. E. M.	M/L	+	3	136.0/ 0	+++/±−−	0/ 0
14. M. E. M. (2)[c]	M/L	+	3	246.5/ 0	+++/±−−	0/ 0
15. Z. A.	M/L	+/−[d]	2	31.5/ 0.2	+++/±−−	(Splenectomized)
16. M. F.	L	+	2	215.2/ 0	+++/−−−	4/ 0
17. S. M.	L	+	3	136.3/50.6	+++/+++	4/ 4

[a] Cytotype: M, myeloid; L, lymphoid; M/L, myeloid and lymphoid (mixed)
[b] Spleen: centimeters below left costal margin
[c] Patients 4, 5, and 14 each had two separate courses of therapy
[d] Blast cells were TdT − in peripheral blood, but TdT + in involved lymph nodes. ND, not done

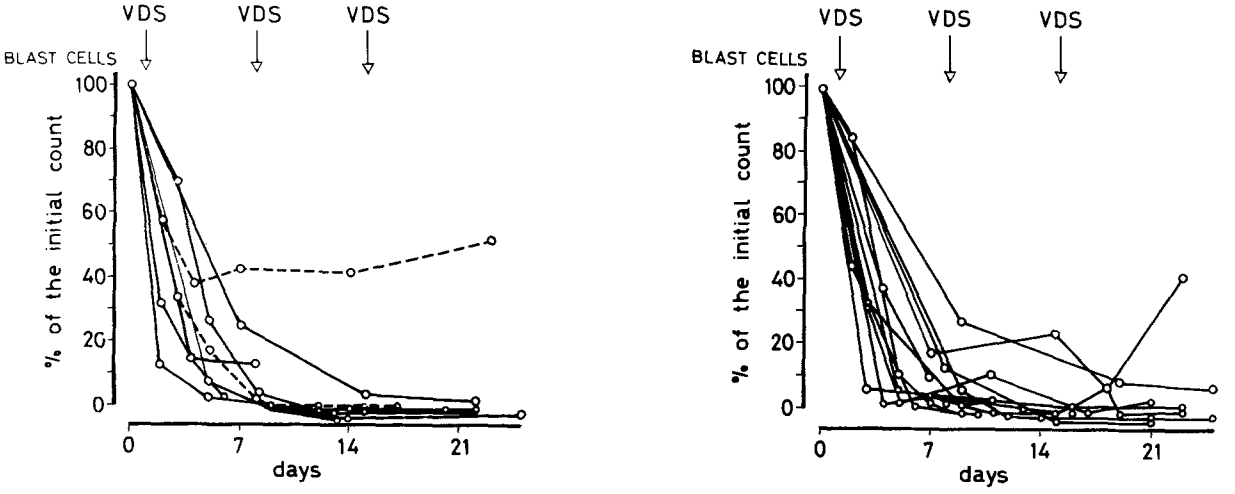

Fig. 2. VDS effect on peripheral blood blast cell count in 17 patients with chronic myeloid leukemia in blastic metamorphosis (three patients had two separate courses of VDS)

Discussion

The aim of this study was to investigate the effect of VDS in nonlymphoid leukemias. For a proper evaluation, it was necessary to give VDS alone, as single-agent chemotherapy, and to study previously untreated cases, as heavily pretreated patients may provide less valuable information. Patients with CML and CML/BM were suitable for this study, as in CML standard chemotherapy could be postponed without any drawback, and in CML/BM the usefulness of current chemotherapy was so low [9] as to allow a trial

Table 3. Effect of VDS on peripheral blood blast cell count in 12 cases of acute nonlymphocytic leukemia

Patient	Morphological FAB subtype	No. of doses	Peripheral blood blast cell count ($\times 10^9$/l)	Marrow cellularity[b]
			Before VDS/After VDS	Before VDS/After VDS
1. B. F.	M1 (onset)	1	20.9/ 8.4	NE
2. I. L.	M1 (onset)	1	52.2/ 6.4	NE
3. M. K.	M2 (onset)	1	1.5/ 0.5	NE
4. L. G.	M2 (onset)	1	41.4/13.3	NE
5. F. A.	M4 (onset)	1	44.8/14.2	NE
6. B. S.	M4 (onset)	1	13.6/ 3.7	NE
7. Z. G.	M1 (relapse)	3	35.2/ 0.6	+++/±−−
8. Z. V.	M2 (relapse)	2	62.9/ 1.3	+++/+−−
9. C. T.	M2 (relapse)	2	3.9/ 0.4	+++/+−−
10. P. C.	M4 (relapse)	1	9.7/28.1	+++/+++
11. P. G.	M4 (relapse)	2	34.6/ 0.8	+++/+−−
12. A. D.	M5 (relapse)	3	1.9/ 0[a]	+++/CR[a]

[a] Complete remission after three doses of VDS
[b] NE, not evaluated

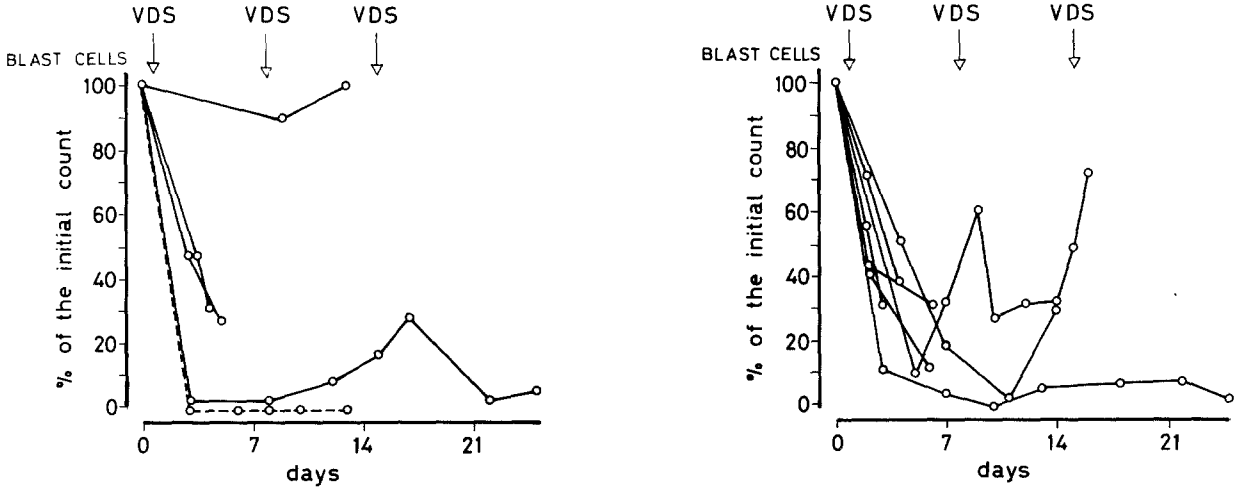

Fig. 3. Antileukemic effect of VDS in 12 cases of acute nonlymphocytic leukemia. Six patients were studied at diagnosis, prior to any other therapy, and the reduction of peripheral blood blast cell count could be evaluated for 3–5 days only. These patients subsequently received standard induction chemotherapy with other drugs

of a new promising drug [2]. Patients with ANLL were less suitable, as standard induction chemotherapy could not be refused to patients at the onset of disease or in their first relapse. Therefore, in most cases of ANLL it was possible to evaluate only the short-term effect of one to two doses of VDS before giving other appropriate drugs, and for these reasons it was difficult to evaluate the effect of VDS in ANLL in the usual term of remission. On the other hand, the definition of a complete remission is hardly applicable in CML and to CML/BM [9]. The antileukemic effect of the drug was therefore evaluated by determining the reduction of peripheral blood leukemic cells, of bone marrow cellularity (and differential, whenever appropriate), and of any other sizable tumor mass. In consequence, the ability of VDS to induce a complete remission in myeloid leukemias cannot be extrapolated from these data. This study provides information only on the number of myeloid leukemias that are sensitive to VDS, and on the rapidity of its antileukemic effect. Such information is of value for planning new polychemotherapy regimens.

The preliminary observation of the activity of VDS in CML/BM [2, 11] was confirmed and extended. It was important to show that VDS was effective not only in lymphoid, TdT^+, CML/BM, but also in myeloid CML/BM. This finding was recently confirmed by Hellriegel [6]. The efficacy of VDS on

leukemic granulocytopoiesis was also proven by the rapid decrease of WBC count in patients with CML in chronic phase. On the basis of this finding, we continued to treat these CML/BM patients with VDS alone (3 mg/m^2 every 2–3 weeks) for several months, showing that this single-agent chemotherapy provided satisfactory control of the disease without recourse to a more intensive and more toxic polychemotherapy [9]. We suggest that most patients with CML/BM may benefit from VDS as long as treatment of CML/BM is palliative.

The efficacy of VDS in CML/BM and in 10 of 12 patients with ANLL (including myelomonoblastic and monoblastic subtype) suggested that the introduction of VDS in polychemotherapy of ANLL is warranted. In fact, VDS was able to kill a large number of leukemic cells very quickly, and this could help to raise the rate and extend the duration of complete remission.

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