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Phase II trial of vincristine infusion in acute leukemia

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Summary. *A phase II trial of prolonged IV infusions of vincristine was conducted in 21 patients with refractory acute leukemia. Patients received 0.25–0.50 mg/m² by infusion daily for 5 days after an initial 0.5-mg bolus. A partial response was observed in one of two patients with acute lymphoblastic leukemia. Of 14 patients with acute nonlymphoblastic leukemia, a complete response lasting for 2.5 months occurred in one patient and a partial response lasting 1.3 months was observed in a second. No objective responses were noted in five patients with blast crisis of chronic granulocytic leukemia. Nonhematologic toxicity was minimal and, when present, generally consisted of a feeling of weakness; constipation, mucositis, and areflexia were also observed. Hematologic toxicity consisted mainly of mild to moderate reduction of platelets in most patients; marked thrombocytopenia (< 50,000/mm³) occurred in two patients whose pretreatment platelet count was > 100,000/mm³. Although generally well tolerated, prolonged infusion of vincristine appears to have limited activity in the treatment of refractory acute nonlymphoblastic leukemia and blast crisis of chronic granulocytic leukemia; further evaluation is needed in acute lymphoblastic leukemia refractory to conventional bolus injection.*

Introduction

Typically the antitumor agent vincristine has been given as a rapid IV bolus injection. Prolonged infusions have been investigated in our institution for two major reasons: (1) pharmacokinetic analyses have demonstrated a rapidly falling serum concentration after bolus injection, to levels below those found to be cytotoxic for mammalian cells in vitro [6, 7]; and (2) the cytotoxicity of this agent appears to be critically dependent on both drug concentration and exposure interval [6]. Five-day infusions of vincristine during a phase I trial resulted in steady-state serum concentrations within a potentially cytotoxic range, and objective responses were observed in a small number of patients with refractory acute leukemia [7, 8]. The current phase II trial was undertaken to explore this therapy further in such patients.

Patients and methods

Between 9/80 and 2/83, 21 patients with refractory acute leukemia were entered on study. Patient characteristics are given in Table 1. Patients were generally heavily pretreated; the median number of prior drugs was five (range 1–8). All but 1 patient had previously received an anthracycline, and 19 had prior exposure to vincristine. All patients gave informed consent before entry on the study; all procedures and the consent form were approved by the clinical research practices committee of our institution.

Patients each received a 0.5-mg IV bolus of vincristine, immediately followed by a 5-day continuous infusion of vincristine. The infusion dose prior to 4/82 was 0.25 mg/m²/day, which was increased to 0.5 mg/m²/day in the four patients subsequently entered on study in an attempt to increase the responsiveness to the regimen. Because of lack of correlation of infusion dosage with areas under the serum concentration curve in a previous pharmacologic evaluation [7], a lower dosage (0.25 mg/m²/day) than previously investigated in the phase I trial [8] was initially used in the current investigation. Serum concentrations attained during infusion in one of the patients (no. 11) are shown in Fig. 1; the levels are similar to those previously observed during infusion of larger doses [11].

The infusate consisted of the appropriate daily dose of vincristine in 1,000 ml 5% dextrose and water to which was added 3,000 units of heparin and 50 mg hydrocortisone to reduce phlebitis. The stability of vincristine in this solution has been previously demonstrated [8].

Infusions could be repeated every 3 weeks in patients with responsive disease, but there was no mandatory maintenance therapy. Bone marrow aspirations were done prior to each

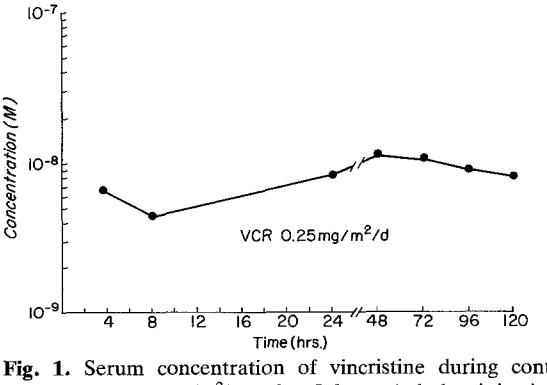

Fig. 1. Serum concentration of vincristine during continuous IV infusion of 0.25 mg/m²/day for 5 days. A bolus injection (0.5 mg) immediately preceded the infusion. These results were obtained in a single patient (No. 11) using a radioimmunoassay described in detail elsewhere [11]

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Table 1. Patient characteristics

Patient	Diagnosis[a]	Age	Sex/Race	Performance status[b]	Best prior response[c]	Prior vincristine	No. prior drugs	Interval (months) from diagnosis to treatment
1	ALL	22	M/W	2	CR	Yes	6	53.3
2	ALL	19	F/W	1	CR	Yes	5	37.5
3	ANLL	46	F/W	2	CR	Yes	5	21.8
4	ANLL	56	F/W	1	Prog	No	5	2.8
5	ANLL	40	F/W	1	Prog	No	4	2.7
6	ANLL	56	M/W	2	CR	Yes	5	17.2
7	ANLL	18	M/W	1	CR	Yes	5	6.6
8	ANLL	51	F/W	1	CR	No	3	6.5
9	ANLL	44	M/W	1	CR	No	5	25.9
10	ANLL	64	F/B	2	Prog	No	2	1.1
11	ANLL	49	F/W	2	CR	No	3	8.4
12	ANLL	37	M/B	2	CR	Yes	5	13.0
13	ANLL	44	M/W	2	CR	No	4	40.5
14	ANLL	39	F/W	2	Prog	No	2	5.0
15	ANLL	58	F/W	2	PR	No	2	4.0
16	ANLL	48	F/W	2	CR	Yes	7	27.0
17	BC	15	F/W	2	CR	Yes	8	5.0
18	BC	56	F/B	3	–[d]	No	1	1.0
19	BC	52	M/W	2	Prog	No	4	2.0
20	BC	45	F/W	2	Prog	Yes	6	3.3
21	BC	63	M/W	2	–[e]	No	2	1.0

[a] ALL = acute lymphoblastic leukemia; ANLL = acute nonlymphoblastic leukemia; BC = blast crisis of chronic granulocytic leukemia
[b] Performance status: 1) ambulatory with symptoms; 2) bedridden $\leqq$ 50% of the time; 3) bedridden $\geqq$ 50% of the time but capable of self-care
[c] CR = complete response; PR = partial response; Prog = progression
[d] Patient had previously received only busulfan for treatment of chronic granulocytic leukemia
[e] Hydroxyurea and busulfan had previously been given during the chronic phase of the granulocytic leukemia

course in such patients. Objective responses (complete and partial remission) were documented using both peripheral blood count and marrow criteria [4]. Patients were considered to have had an adequate trial if they completed one 5-day infusion. Patients were immediately removed from study when progressive disease was obvious with increasing blasts in the peripheral blood. No cytotoxic agents other than vincristine were administered during treatment.

Results

Response and toxicity are listed in Table 2. Of two patients with refractory acute lymphoblastic leukemia, one had progressive disease and the other had a partial response lasting 2.5 months, during which time three infusions (0.50 mg/m^2/day) were given. In the latter patient, the marrow cellularity decreased from 100% to 10% with complete clearance of blasts, but the platelet count, although improved, never normalized. Relapse was heralded by a falling platelet count.

Among 14 patients with refractory acute nonlymphoblastic leukemia, progressive disease was observed in 12 and objective responses occurred in 2 patients (1 partial and 1 complete response). A partial remission was observed after three courses of vincristine infusion (0.25 mg/m^2/day), during which time blasts were cleared from the peripheral blood and marrow blasts decreased from 49% to 7%. Relapse occurred after a fourth course. A complete response occurred after a single 5-day infusion of vincristine (0.25 mg/m^2/day) in a patient whose pretreatment white blood cell count of 47,500/mm^3 fell to 1,500/mm^3 the day after completion of the 5-day infusion. One week after infusion the white blood cell count and differential were normal; at this time a bone marrow sample showed 10% cellularity with no blasts. A pretreatment marrow contained 84% blasts, with a cellularity of 90%. The platelet count normalized slowly over a 1-month period after infusion; the pretreatment level was 13,000/mm^3. No maintenance therapy was administered. After a 2.5-month period of remission, relapse was noted with a rapidly increasing white blood cell count and falling platelet count. A second infusion of vincristine was administered. The white blood cell count and the percentage of blasts fell from pretreatment levels of 72,700/mm^3 and 76%, respectively, to 1-day posttreatment levels of 3,700/mm^3 and 13%, respectively. A third infusion was met with relentless progression.

Progressive disease occurred in all patients with blast crisis of chronic granulocytic leukemia. However, a reduction of marrow blasts to 27% associated with improvement in symptomatology occurred in a 15-year-old girl (patient no. 17) with two courses of infusion (0.25 mg/m^2/day).

Nonhematologic toxicity was either nonexistent or mild; a sense of weakness and easy fatiguability or depression occurred in four patients. Constipation without ileus and mucositis occurred in one patient each. No nausea or vomiting was observed. Neurotoxicity (areflexia) occurred in only one case, despite multiple infusions in some patients. Neurologic toxicity was not dose-limiting but most patients received only one course as a consequence of failure to control the leukemia.

Thrombocytopenia was the major hematologic toxicity and was generally mild. A marked fall in platelets occurred in only two patients, but in both cases it was associated with progressive disease, as manifested by a rapidly rising white blood cell and blast count.

Table 2. Response and toxicity

Patient	VCR[a] infusion dose (mg/m^2/day)	Clearance of peripheral blasts	Response[b]	Toxicity	Comments
1	0.25	–	Prog	–	–
2	0.50	–	PR (2.5 mo)	–	Marrow cellularity decreased from 100% to ≦ 10% with complete clearance of blasts after three courses.
3	0.25	No	Prog	Fatigue, depression	
4	0.25	No	Prog	Weakness	
5	0.25	No	Prog	–	
6	0.25	No	Prog	Fatigue	
7	0.25	No	Prog	Lethargy, depression	
8	0.25	No	Prog	–	
9	0.25	No	Prog	–	
10	0.25	Yes	PR (1.3 mo)	Constipation	Marrow blasts decreased from 49% to 7% after three courses.
11	0.25	Yes	CR (2.5 mo)	–	Marrow cellularity decreased from 40% to 10% with complete clearance of blasts after one course.
12	0.25	No	Prog	Marked thrombocytopenia	
13	0.25	No	Prog	–	
14	0.25	No	Prog	–	
15	0.50	No	Prog	–	
16	0.50	No	Prog	–	
17	0.25	No	Prog	areflexia, marked thrombocytopenia	Marrow blasts decreased from 83% to 27% after two courses.
18	0.25	No	Prog	–	
19	0.25	No	Prog	–	
20	0.25	No	Prog	Mucositis	
21	0.50	No	Prog	–	

[a] VCR = vincristine; infusions in all patients were preceeded by a 0.5 mg rapid bolus injection
[b] Prog = progression; PR = partial response; CR = complete response; response criteria are those of CALGB(4)

Discussion

Vincristine given as an IV bolus injection has been an extremely active antitumor agent in the treatment of childhood leukemia for nearly two decades. Its effectiveness as a single agent in the treatment of acute lymphoblastic leukemia refractory to such agents as 6-mercaptopurine, steroids, and methotrexate was clearly demonstrated in large multicenter trials in the early 1960s [3, 9]. An objective response rate of 40%–70% was obtained in over 200 such patients, many of whom obtained complete remission.

However, the data concerning the activity of vincristine as a single agent in the treatment of acute nonlymphoblastic leukemia is much more limited, and confined almost exclusively to children with disease refractory to agents such as 6-mercaptopurine, steroids, and methotrexate (Table 3). Among 46 such patients involved in five clinical trials, the overall objective response rate was about 40%, with a complete response rate of about 25% (1, 3, 5, 9, 10). Most patients received weekly IV bolus injections with a dose range of 0.01–0.06 mg/kg or 1.0–2.5 mg/m^2. Responses were generally described as 'short', although an occasional response exceeded 6 months.

Vincristine given as an infusion rather than conventional bolus injection has been tested in a limited number of patients with refractory acute leukemia [2, 8, 12]. Ferreria [2] reported two complete responses among ten patients, one of whom had lymphoblastic leukemia and the other an undifferentiated leukemia. Remission duration was described as 'short-lived'. The dosage was 2 mg/m^2 daily for 1–2 days. Weber et al. [12] reported 'regression' in one of two patients with lymphoblastic leukemia following a dose of 0.5 mg/m^2 infused over 1 day. Another patient, who had an undifferentiated leukemia, improved following infusion of 1.2 mg/m^2 over 1 day.

Of 11 patients with refractory acute leukemia in a phase I trial in our institution, complete responses were observed in three (one patient each with promyelocytic leukemia, myeloblastic leukemia, and blast crisis of chronic granulocytic leukemia) [8]. Only one patient with lymphoblastic leukemia was treated; marrow aplasia and a rapid fall in peripheral blasts (to 0 by day 4) associated with disseminated candidiasis occurred after administration of vincristine 1.0 mg/m^2/day by infusion for 5 days. In this trial infusion doses of 0.75 and 1.0 mg/m^2/day for 5 days were generally too toxic (neurotoxicity) to recommend them for further investigation; 0.5 mg/m^2/day for 5 days was well tolerated [8].

In the current study an objective response to infusion of vincristine was observed in three of 21 patients (14%) with refractory acute leukemia. The combined results of the phase I and II trials of vincristine infusion in our institution include four complete and two partial responses in 32 patients, giving an overall objective response rate of 19%. Among 19 patients with acute nonlymphoblastic leukemia (excluding blast crisis of chronic granulocytic leukemia), three complete and one partial

Table 3. Previous results of vincristine treatment of ANLL[a]

Authors	No. of patients	Age (years)	Previous therapy[b]	Response	Comments
Karon et al. [9]	14	≦ 20	Yes	5 CR; 1PR	Duration of CR + PR 2.3 months; maintenance with VCR not helpful
Heyn et al. [3]	14	≦ 15	Yes	1 CR; 4PR	Duration of CR + PR 'short'
Martin and Compston [10]	4	34, 60[c], 62, 65	Yes (2/4)	? 1 CR	Duration of CR 9 + months; three others improved; thrombocytopenia in two
Howard [5]	7	≦ 15	Yes	3 CR; 3PR	Duration of CR + PR ?; maintenance with other agents given
Evans et al. [1][d]	7	≦ 15	Yes	1 CR	Duration of CR 6.7 months
Total	46	Range 1–65; most ≦ age 15	Yes[e]	11 CR; 8PR	Duration generally short; dose range 0.01–0.06 mg/kg or 1.0–2.5 mg/m^2 weekly

[a] Single-agent IV bolus injection; repeated injections given weekly in most patients; ANLL, acute nonlymphoblastic leukemia
[b] Agents other than vincristine, usually 6-mercaptopurine, steroids, and methotrexate
[c] Patient with blast crisis of chronic granulocytic leukemia
[d] Two patients received steroids in addition to vincristine
[e] All but two of the patients (Martin et al.) received previous therapy

responses (21%) were observed. However, in all patients but one who remained in remission for 20 months, responses were of short duration. In 10 patients with blast crisis of chronic granulocytic leukemia there was only one objective response, which was also short in duration. Only three patients with acute lymphoblastic leukemia have been evaluated; one attained a partial response and a rapid cytoreduction to marrow aplasia occurred in another. Both had previously received vincristine by bolus injection, which suggests the possibility of infusions of vincristine being effective salvage therapy for acute lymphoblastic leukemia.

In summary, a historical review of trials using vincristine given by IV bolus injection has shown some single-agent activity in the treatment of acute nonlymphoblastic leukemia. These trials were conducted mostly in children using a variety of doses, some of which would be considered excessively large by conventional standards. The current trial has demonstrated the tolerability of continuous infusion of vincristine for 5 days in patients with refractory acute leukemia. However, objective responses in refractory acute nonlymphoblastic leukemia, including blast crisis of chronic granulocytic leukemia, were infrequent and usually of short duration. Further evaluation in larger numbers of patients will be required to assess the activity of vincristine infusion as a potential salvage therapy for acute lymphoblastic leukemia refractory to conventional bolus injection of this agent.

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