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A study of toxicity and comparative therapeutic efficacy of vindesine-prednisone vs. vincristine-prednisone in children with acute lymphoblastic leukemia in relapse

A Pediatric Oncology Group study

Tribhawan Vats[1], George Buchanan[2], Paulette Mehta[3], Abdal Ragab[4], Eva Hvizdale[5], Ruprecht Nitschke[6], Michael Link[7], G. Peter Beardsley[8], David Maybee[9] and Jeffrey Krischer[10]

[1]*University of Kansas Medical Center, Kansas City, KS, USA;* [2]*Southwestern Medical School, Dallas, TX, USA;* [3]*University of Florida, Shands Teaching Hospital, Gainesville, FL, USA;* [4]*Emory University School of Medicine, Atlanta, GA, USA;* [5]*University of South Florida, Tampa, FL, USA;* [6]*Oklahoma University Health Sciences Center, Oklahoma City, OK, USA;* [7]*Stanford University Medical Center, Palo Alto, CA, USA;* [8]*Yale University School of Medicine, New Haven, CT, USA;* [9]*Walter Reed Army Medical Center, Washington, DC, USA;* [10]*Pediatric Oncology Group Statistical Office, Gainesville, FL, USA*

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Summary

Vindesine (des-acetyl Vinblastine) is a synthetic derivative of vinblastine, and was produced with the hope that it would have less neurotoxicity and hematopoietic toxicity than other vinca alkaloids.

Phase I and II studies also demonstrated significant activity in lymphoid malignancies, especially Acute Lymphoblastic Leukemia (ALL). The present study was designed to compare therapeutic effectiveness of twice weekly vindesine (2 mg/M²/dose) plus Prednisone (60 mg/M²/dose) (Treatment 1) to weekly Vincristine (2 mg/M²/dose) plus Prednisone (60 mg/M²/day) (Treatment 2). All patients were less than 21 years of age, and had documented bone marrow relapse (blast count > 25%). In 39 patients presumed sensitive to vincristine, there were 11 complete responses out of 20 patients (55%) randomized to receive vindesine/prednisone and 7 complete responses out of 19 patients (37%) treated with Vincristine/Prednisone. In 37 patients resistant to vincristine, there were 7 complete responses (19%). Vindesine was more toxic than Vincristine. Major toxicities of vindesine included paraesthesias, peripheral neuropathy and ileus. Vindesine hematological toxicity appeared greater, but such toxicity is hard to assess in patients with bone marrow disease. In this study, vindesine and vincristine had similar efficacy, but vindesine use was associated with more toxicity.

Vindesine (des-acetyl vinblastine), a synthetic derivative of the vinca alkaloid vinblastine, was produced with the hope that it would have less neurotoxicity than vincristine and less hematopoietic toxicity than vinblastine. Vindesine, like other vinca alkaloids, binds to tubulin and produces mitotic arrest. Vindesine has a shorter half life and a more rapid clearance than vincristine, and it seemed logical that a more frequent dosing schedule might prove to be more effective [1].

An anti-tumor effect of vindesine was seen in L1210 leukemia, P-388 leukemia and various solid tumors [2]. Phase I and II studies in man demonstrated significant activity in lymphoid malignancies, especially acute lymphoblastic leukemia (ALL) [3,4,5]. Vats *et al.*, reported 4 complete remissions (CR) and 4 partial remissions (PR) using weekly vindesine and prednisone in 16 patients with

Table 1. Summary and analysis of clinical response

	Group A		Group B
	Vincristine/ prednisone	Vindesine/ prednisone	Vindesine/ prednisone
Total patients registered	21	22	43
Fully evaluable	19	20	37
Not evaluable	2	2	6
Early death	1	1	4
Protocol violation	0	1	0
Refusal of treatment	0	0	1
Response of fully evaluable patients			
Complete response	7	11	7
Partial response	0	1	2
No response	12	8	28

ALL who had previously failed vincristine-prednisone induction [6]. The Children's Cancer Study Group (CCSG) reported 3 complete remissions and 13 partial remissions using vindesine-prednisone in 35 patients with advanced ALL who were previously treated with multi-agent therapy including vincristine [7]. In a prospective phase III study conducted by CCSG, the efficacy of vincristine and vindesine was compared in patients with relapsed ALL. Response rates were equivalent and some degree of cross resistance was seen between the two agents utilizing a cross over study [8].

Vindesine has been given weekly as an IV bolus, as a 24–28 hour continuous infusion, or twice weekly on two consecutive days. Weekly doses of vindesine have ranged from 3 mg/M^2 to 10 mg/M^2. Neurotoxicity and hematotoxicity have been dose limiting. Side effects have been more frequent at doses of greater than 4.0 mg/M^2 week.

The present study was designed to compare, as induction agents, the effectiveness and toxicity of twice weekly vindesine in combination with oral prednisone to weekly vincristine and oral prednisone in children with relapsed ALL. We also examined the response of vindesine as induction agent in patients known to be resistant to vincristine-prednisone.

Material and methods

Patients were less than 21 years of age and had ALL in second or subsequent bone marrow relapse (> 25% blasts). Patients had received no prior vindesine and had recovered from all previous toxicity. Written informed consent, in accordance with FDA and institutional guidelines, was obtained prior to enrollment.

Group A

These patients had not failed prior vincristine treatment and were in their second bone marrow relapse. They were randomized to treatment with vindesine-prednisone or vincristine-prednisone. Patients failing vincristine or vindesine after four weeks of treatment were to be crossed over to the alternative agent.

Group B

The patients had failed vincristine treatment in the past. Failure of treatment was defined as no remission following four weeks of an induction regimen containing weekly vincristine. These patients were treated from the outset with vindesine-prednisone.

Table 2. Comparative toxicity of vindesine and vincristine

Toxicity	Degree					
	Mild		Moderate		Severe	
Frequency	Vincristine	Vindesine	Vincristine	Vindesine	Vincristine	Vindesine
Peripheral neuropathy	0	5	2	8	0	0
Ileus/constipation	1	1	1	3	0	2
Nausea/vomiting	1	1	0	0	0	0
Hepatic (enzyme)	0	0	0	2	0	0
Hepatic (bilirubin)	0	0	0	1	0	0
Mucositis/ulcers	0	1	0	2	0	0
Venous sclerosis	0	1	0	1	0	0
Skin necrosis	0	0	0	1	0	0

Treatment

Group A patients were randomized between Treatment I (vindesine-prednisone) and Treatment II (vincristine-prednisone). Vindesine was given at a dose of 2 mg/M^2 on days 1 and 4 each week, for 4 weeks by IV bolus. Prednisone was given at a dose of 60 mg/M^2 orally in four divided doses everyday for 28 days. Treatment II consisted of vincristine (2 mg/M^2/week for 4 weeks as IV bolus) and prednisone as above. Patients in group B were assigned to vindesine regimen. Patients in both groups were assessed at 2 weeks with bone marrow examination. Patients in group A who showed progressive disease at 2 weeks or no remission at 4 weeks were switched over to the alternate treatment. Patients in group B showing progressive disease at 2 weeks were taken off study. Standard response criteria were utilized for evaluating patients and toxicity was graded according to the Pediatric Oncology group toxicity guidelines.

Results

The study details are depicted in Table 1. Eighty-six patients were registered on the study carried out between 1980–1983. In group A, 39 of the 43 patients were fully evaluable, 20 on Treatment I and 19 on Treatment II. Of the 20 patients treated on the vindesine arm, 11 achieved CR (55%) and 7 patients out of 19 (37%) achieved CR on the vincristine arm. In group B, 37 of the 43 patients registered were fully evaluable and CR was achieved in 7 (19%). The cross over portion of the protocol was closed as there were very few entries and no response was seen with either agent after cross over. Toxicity was more pronounced in the vindesine arm (Treatment I) as compared to the vincristine arm (Treatment II). The major toxicity in patients was pancytopenia but this toxicity is hard to assess in patients with bone marrow disease. There were twenty episodes of other moderate to severe toxicities with vindesine compared to three such episodes with vincristine. Major non hematological toxicity of vindesine included paraesthesias, peripheral neuropathy, severe ileus and rise in liver enzymes (Table 2).

Discussion

In several phase II studies vindesine has elicited a 15–20% response rate in children with ALL in advanced relapse who are refractory to vincristine [3,4,6]. We found vincristine resistant patients (group B) to have an overall complete response rate of 19%, which is consistent with these earlier reports. Unlike prior studies, we directly assessed the comparative efficacy and toxicity of vindesine and vincristine in patients with ALL in second marrow relapse who presumably were not resistant to

vincristine. Moreover, we were able to more accurately compare these two agents since the only other medication used along with the vinca alkaloid was prednisone. Among the group A patients, the complete response rate in the vindesine arm was 55% compared to 37% in the vincristine arm. This difference was not statistically significant ($p = 0.28$). Vindesine caused more neurotoxicity than vincristine, and although it was difficult to assess in a quantitative fashion, myelotoxicity was more frequent with this agent. Therefore, vindesine failed to live up to its expected potential as a therapeutic agent in ALL in relapse.

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Address for offprints: T. Vats, Pediatric Oncology Group, 4949 West Pine Boulevard, Suite 2A, St. Louis, MO 63108, USA