Cancer Chemother. Pharmacol. 2, 267–270 (1979)

Cancer Chemotherapy and Pharmacology

Short Communication

An Initial Report of a Phase-III Trial Comparing Vindesine and Vincristine for Acute Lymphocytic Leukemia of Childhood

W. Krivit, R. Chilcote, A. Pyesmany, J. Anderson, and D. Hammond

Children's Cancer Study Group[1]

Summary. *The initial results from the Children's Cancer Study Group (CCSG) study on vindesine are the subject of this report. Vindesine was shown to be active in the treatment of acute lymphocytic leukemia (ALL) in children in a phase-II clinical trial conducted by the CCSG. A phase-III trial is now in progress. The aim of this is to compare the use of vincristine and of vindesine with reference to induction rate, toxicity, and cross-resistance.*

Introduction

In 1977 CCSG conducted a phase-II clinical trial of vindesine in ALL [1, 2]. Vindesine (4 mg/m^2, IV bolus injection) was used alone on a weekly basis. Complete remissions were obtained in three of 35 patients who had received prior multiple-agent or repeated chemotherapeutic regimens. Partial remissions were noted in 12 of the 35 patients. As a result of these positive responses, several questions were posed concerning the value of vindesine in the armamentarium of agents used for ALL. The CCSG phase-III protocol was developed specifically to determine whether or not vincristine and vindesine are cross-resistant. Another purpose of the phase-III protocol was to determine whether vindesine is superior to vincristine when used at the standard dose and according to the standard schedule for the reinduction of patients in relapse with ALL. An additional evaluation in the phase-III trial was a comparison of the quality of myelotoxicity of vincristine versus vindesine.

[1] The Children's Cancer Study Group investigators, institutions, and grant numbers are listed in the appendix to this paper

Reprint requests should be addressed to: Children's Cancer Study Group Operations Office, 1721 Griffin Avenue, Los Angeles, CA 90031, USA

Materials and Methods

Patients. The patients entering the study had ALL were less than 21 years old, and had M_3 marrow ratings with more than 25% blasts. The majority of these patients were studied in their initial relapse period following a previous CCSG study.

Resistance to Vincristine. Resistance to vincristine was defined arbitrarily as failure to achieve a remission during *induction* of an excerbation in which vincristine was used in combination with other agents. This definition, therefore, requires that there be a failure with vincristine during an induction period. Relapse while receiving monthly maintenance doses of vincristine was not considered a sufficient criterion of resistance.

Non-resistance to Vincristine. Patients who did not meet the above requirements of resistance were randomized to receive either vincristine or vindesine.

Crossover Study. If the patient failed on one regimen, the other regimen was instituted. Figure 1 outlines the schema used for this study.

Maintenance Study. The pharmacologic question relating to maintenance concerned the relative merits of giving either vinca alkaloid at the same time as, or 24 h before, cyclophosphamide injection. These maintenance data are not available for this report.

Chemotherapy. The chemotherapy given consisted of either vincristine (1.5 mg/m^2 IV weekly) or vindesine (4 mg/m^2, IV weekly) L-asparaginase (6,000 units IM × 9 over 3 – 4 weeks), and prednisone (40 mg/m^2 per day, PO) for 28 days.

Results

Vincristine-Resistant Patients. Of 14 vincristine-resistant patients who completed induction on the pilot and open phases of the study, 11 achieved an M_1 or M_2 marrow when vindesine was given in conjunction with L-asparaginase and prednisone. The marrow ratings were performed on day 28 (Table 1).

0344-5704/79/0002/0267/$ 01.00

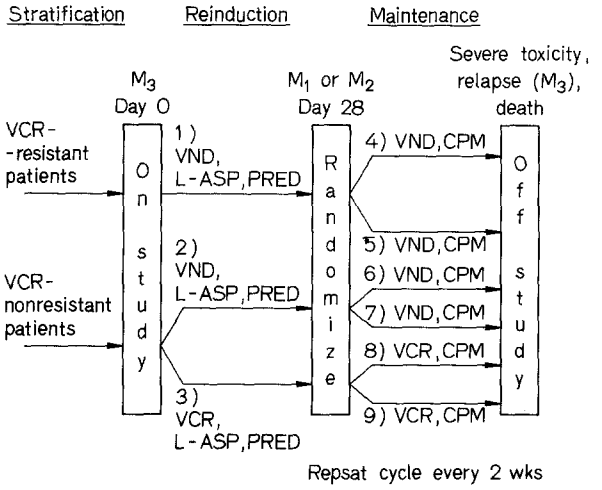

Fig. 1. Schema for reinduction therapy for patients with acute lymphocytic leukemia with vindesine or vindesine versus vincristine, each plus L-asparaginase and prednisone. *VCR*, vincristine; *VND*, vindesine; *L-asp*, L-asparaginase; *PRED*, prednisone; *CPM*, cyclophosphamide. At day 28, patients with M_1 or M_2 continue on the study; M_3 patients receiving Regimen 1 are withdrawn from the study; in M_3 patients receiving Regimen 2 or 3, reinduction with the other regimen is attempted.

Table 1. Induction in vincristine-resistant patients treated with vindesine, L-asparaginase, and prednisone in the phase-III study

Study phase	Marrow rating			Total completing induction	Died during induction	Total
	M_1	M_2	M_3			
Pilot	2	2	2	6	3	9
Open	5	2	1	8	4	12
Total	7	4	3	14	7	21

Non-Vincristine-Resistant Patients. Of 11 non-vincristine-resistant patients who were randomized to the vindesine regimen of the phase-III study, eight achieved an M_1 or M_2 marrow. Three of six patients who were randomized to the vincristine regimen and who completed induction achieved an M_2 marrow (Table 2).

Direct Crossover Study. Two non-vincristine-resistant patients entered on the vincristine, L-asparaginase, and prednisone regimen of the phase-III study had an M_3 marrow at day 28. When switched to vindesine plus L-asparaginase and prednisone at the same dosage, both achieved complete remission.

Discussion

Until recently the family of vinca alkaloids contained only vincristine and vinblastine. The vinca alkaloid spectrum has now been enlarged to include vindesine. The conceptual thinking in the development of this last compound was to maintain the good qualities of both vincristine and vinblastine, while reducing the toxicity problems. Myelosuppression, to the point of severe neutropenia and thrombocytopenia, is a regular accompaniment of vinblastine therapy and is seen occasionally with vincristine. A comparison of the vindesine regimen with the vincristine regimen, as noted above, will be evaluated in this study to determine whether or not vindesine has similar properties to vincristine.

The results to date are preliminary. But, as defined by our protocol, 11 of 21 vincristine-resistant patients obtained an M_1 or M_2 marrow by day 28. Similar results were presented at the Frankfurt meeting and have been published by other members of CCSG [3]. These combined results show that vincristine and vin-

Table 2. Induction in non-vincristine-resistant patients randomized to treatment with vincristine or vindesine plus L-asparaginase and prednisone in the phase-III study

Regimen randomization	Marrow rating			Total completing induction	Died during induction	Still in induction	Total
	M_1	M_2	M_3				
Vincristine prednisone L-asparaginase	0	3	3	6	2	10	18
Vindesine prednisone L-asparaginase	6	2	3	11	0	10	21
Total	6	5	6	17	2	20	39

desine are not totally cross-resistant. Further data will be needed from our ongoing CCSG protocol to determine the degree of cross-resistance. A comparison of toxicity, as measured by myelosuppression and neurotoxicity, is under continued surveillance.

The relative values of regimens containing vincristine or vindesine in non-vincristine-resistant patients has been studied. Our preliminary results indicate some superiority of the vindesine regimen. However, the number of patients admitted to this study at the time of the Frankfurt meeting was too small to allow an adequate evaluation.

Acknowledgements: Grant support for this work was received from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Eduction and Welfare.

References

1. Krivit, W.: Minutes of the New Drug Liaison Committee Meeting; February 17th–18th, 1977, pp. 31–73. National Cancer Institute, Division of Cancer Treatment, Cancer Therapy Evaluation Program (1977)
2. Krivit, W., Hammond, D.: Vindesine: A phase-II study by the Children's Cancer Study Group. Curr. Chemother. **2**, 1331–1334 (1978)
3. Mathé, G., Misset, J., Vassal, F. de, et al.: Phase-II clinical trial with vindesine for remission induction in acute leukemia, blastic crisis of chronic myeloid leukemia, lymphosarcoma, and Hodgkin's disease: Absence of cross-resistance with vincristine. Cancer Treat. Rep. **62** (5), 805–809 (1978)

Received September 25, 1978/Revised October 2, 1978

Appendix

Principal investigators in Children's Cancer Study Group

Institution	Investigator(s)	Grant No.
Group Operations Office University of Southern California Comprehensive Cancer Center Los Angeles, CA	Denman Hammond, M.D. John Weiner, Dr. P.H. Richard Honour, Ph.D. Harland Sather, Ph.D. James Anderson, Ph.D.	CA 13539
University of Michigan Medical Center Ann Arbor, MI	Ruth Heyn, M.D.	CA 02971
Children's Hospital National Medical Center George Washington University Washington, DC	Sanford Leikin, M.D.	CA 03888
Memorial Sloan-Kettering Cancer Center Cornell University New York, NY	Denis R. Miller, M.D.	CA 14557
Children's Hospital of Los Angeles University of Southern California Los Angeles, CA	Gussie Higgins, M.D.	CA 02649
Babies' Hospital Columbia University New York, NY	James Wolff, M.D.	CA 03526
Children's Hospital of Pittsburgh University of Pittsburgh Pittsburgh, PA	Vincent Albo, M.D.	CA 07439
Children's Hospital of Columbus Ohio State University Columbus, OH	William Newton, M.D.	CA 03750
Children's Orthopedic Hospital and Medical Center University of Washington Seattle, WA	Ronald Chard, M.D.	CA 10382
University of Wisconsin Hospitals Madison, WI	N. Shahidi, M.D.	CA 05436

(Continued)

Institution	Investigator(s)	Grant No.
University of Minnesota Health Sciences Center Minneapolis, MN	Mark Nesbit, M.D.	CA 07306
Children's Memorial Hospital Northwestern University Chicago, IL	George Honig, M.D.	CA 07431
University of Utah Medical Center Salt Lake City, UT	Eugene Lahey, M.D.	CA 10198
Princess Margaret Hospital University of Toronto Toronto, ONT, Canada	Marilyn Sonley, M.D.	Ontario Cancer Treatment and Research Foundation Grant No. 41-17
Strong Memorial Hospital University of Rochester Rochester, NY	Martin Klemperer, M.D.	CA 11174
Children's Hospital University of Louisville Louisville, KY	Donald R. Kmetz, M.D.	—
University of British Columbia Vancouver, BC, Canada	Mavis Teasdale, M.D.	Vancouver
Children's Hospital of Philadelphia University of Pennsylvania Philadelphia, PA	Audrey Evans, M.D.	CA 11796
James Whitcomb Riley Hospital for Children Indiana University Indianapolis, IN	Robert Baehner, M.D.	CA 13809
New Jersey College of Medicine and Dentistry Newark, NJ	Leonard Vitale, M.D.	CA 12637
Harbor General Hospital University of California Los Angeles Torrance, CA	Jerry Finklestein, M.D.	CA 14560
University of California Medical Center San Francisco, CA	Arthur Ablin, M.D.	CA 17829
Rainbow Babies and Childrens Hospital Case Western Reserve University Cleveland, OH	Samuel Gross, M.D.	CA 20320
Children's Hospital Medical Center University of Cincinnati Cincinnati, OH	Beatrice Lampkin, M.D.	—
Vanderbilt University School of Medicine Nashville, TN	John Lukens, M.D.	—
University of Oregon Health Sciences Center Portland, OR	Robert Neerhout, M.D.	—
University of Texas Health Science Center San Antonio, TX	Thomas Williams, M.D.	—
University of California Medical Center Los Angeles, CA	Stephen Feig, M.D.	—
University of Iowa Hospitals and Clinics Iowa City, IA	C. Thomas Kisker, M.D.	—