Cancer Chemother Pharmacol (1983) 10: 224–226

Cancer Chemotherapy and Pharmacology

Short Communication

Vindesine, Prednisone, and Daunomycin in Acute Lymphoblastic Leukemia in Relapse*

Guy Garay, Jörge Milone, Eduardo Dibar, Santiago Pavlovsky, Rita Kvicala, Federico Sackmann Muriel, Dolores Montres Varela, and Mariana Eppinger-Helft

Oncohematology Departamento, Instituto de Investigaciones Hematológicas, P. de Melo 3081, 1425 Buenos Aires, Argentina, and the Grupo Argentino de Tratamiento de la Leucemia Aguda (G.A.T.L.A.)

Summary. *Patients with resistant or recurrent acute lymphoblastic leukemia were treated with vindesine 3 mg/m²/IV weekly × 4, daunomycin 25 mg/m²/IV weekly × 4, and prednisone 40 mg/m²/PO daily × 28.*

Seventeen (44%) of 38 evaluable patients achieved complete remission. Fifty-one percent of 31 patients in first relapse achieved complete remission, while only one of five in second or third relapse and neither of two resistant to first induction achieved complete remission. The major toxicity was hematologic. The median duration of complete remission was only 6 weeks and median survival from start of the study, 3 months, with 22% patients remaining alive at 10 months.

We conclude that the vindesine, prednisone, and daunomycin combination is no more effective than vincristine, prednisone, and daunomycin in achieving remission of relapsed acute lymphoblastic leukemia patients, and is more toxic than the latter regimen.

Introduction

The combination of vincristine and prednisone produces a remission rate of more than 95% in previously untreated acute lymphoblastic leukemia (ALL) patients. The combination of daunomycin, vincristine, and prednisone produces higher rates of complete remission only in children with WBC count greater than 50,000 and in adults [9, 10]. However, 40%–60% of the patients who achieve complete remission will have bone marrow relapse [10].

Vietti et al. [13], using the combination of daunomycin, vincristine, and prednisone in patients in relapse, obtained a 78% complete remission rate. Each of their patients had received prior therapy with vincristine-prednisone and/or daunomycin, but none had received all three agents concurrently. Information about new agents or new schedules is therefore urgently required for a more effective treatment of ALL. For this reason, we chose to study vindesine. Vindesine is a semisynthetic derivative of the vinca alkaloid vinblastine sulfate. Phase I and II studies of vindesine showed activity against ALL [2, 4, 6, 11, 12].

This report describes the results of combination therapy with vindesine-daunomycin and prednisone in ALL patients in relapse; al had been previously treated with daunomycin-vincristine and prednisone.

Materials and Methods

This study was opened for the entry of ALL patients in June 1981 and ended in March 1982. Diagnosis in all cases had been established by peripheral blood and bone marrow examination using standard procedures. Leukemic cells were classified by cytochemical studies using PAS, peroxidase, and Sudan Black B reactions. In addition, the FAB and immunological classifications in T, B, null, and common groups were routinely employed from January 1981 onward.

All patients in relapse as evidenced by a bone marrow aspirate containing > 25% lymphoblast cells were consecutively admitted. The relapse did not have to be the patient's first one. All the patients had been previously admitted to a phase III trial conducted by the Argentine Group for the Treatment of Acute Leukemia (G.A.T.L.A.), in which therapy consisted of: daunomycin, vincristine, and prednisone induction therapy; 6-mercaptopurine and methotrexate as maintenance with periodic pulses of vincristine-prednisone [9, 10]. CNS prophylaxis was performed in one patient with cranial radiotherapy and five doses of IT methotrexate and in the remaining patients with IT methotrexate-dexamethasone alone given during induction and periodically during maintenance. The ages of the patients ranged from 2 to 33 years, with a median age of 9 years (31 children ≤ 14 years and 9 adults).

The duration of illness ranged from 3 months to 104 months, with a median of 24 months.

Patients were treated as follow: vindesine 3 mg/m²/IV weekly × 4; daunomycin 25 mg/m²/IV weekly × 4; and prednisone 40 mg/m²/PO daily × 28. The treatment for remission maintenance was: 6-mercaptopurine 100 mg/m²/PO daily; methotrexate 15 mg/m² twice a week PO. Every 30 days pulses of vindesine 3 mg/m²/IV × 1 and prednisone 40 mg/m²/PO daily × 7 were also given.

CNS prophylaxis consisted of: intrathecal methotrexate (6, 8, 10, and 12 mg for patients aged < 1, 1, 2, and ≥ 3 years, respectively) and dexamethasone (1, 2, and 4 mg for patients

Reprint requests should be addressed to G. Garay

* This study was conducted in the following institutes by the following investigators: (1) Instituto de Investigaciones Hematológicas (Buenos Aires): S. Pavlovsky, G. Garay, C. Scaglione, J. Dupont, N. Roizman, J. Milone; (2) Hospital Nacional "A. Posados" (Haedo): E. Dibar, I. Freitas, A. Picón, D. Montes Varela; (3) Hospital Escuela "José de San Martín" (Buenos Aires): E. Bugnard, R. Kvicala, E. Pirotta Ucha; (4) Hospital de Niños (Buenos Aires): F. Sackmann Muriel, J. L. Braier, B. Diez; (5) Instituto Municipal de Hematologia, Hospital Ramos Mejía (Buenos Aires): M. Eppinger-Helft, V. Birman

aged ≤ 1, 2, and ≥ 3 years). These doses were given every month for 5 months during maintenance therapy.

Bone marrow examination was performed after 14 and 28 days of therapy. If the patient had not achieved complete remission within that time, therapy could be extended for 2 weeks more. Administration of at least one dose of combination chemotherapy was considered an adequate trial.

Complete marrow remission (M1) was attained when there were 5% or fewer leukemic cells in the marrow; partial marrow remission (M2) was present when there were 5.1%–25% blasts in the marrow. When there were more than 25% blasts the patient was considered to have had no response.

CBC with differential and quantitative platelet count was performed every week, while bilirubin, SGOT, SGPT, alkaline phosphatase, BUN, uric acid, and creatinine were checked at the beginning of the trial and every other week during induction, or more frequently if it was considered necessary. All the patients started treatment as out-patients and were only admitted to the hospital in case of fever or severe bleeding.

Results

Remission Induction

During the 9 months of the study, 40 patients were entered on this trial. Two patients were not evaluable because they were lost to follow-up. Thirty-eight patients were therefore evaluable for analysis of remission induction. Seventeen (45%) achieved complete remission, none achieved partial remission, 18 had no response, and three died before completing induction therapy. Fourteen (48%) of 29 children and three (33%) of nine adults achieved complete remission. Results of remission induction were analysed with reference to number of previous relapses (Table 1). Fifty-one percent of the patients in first relapse achieved complete remission, while only one of five in second or third relapse achieved complete remission. Six patients achieved complete remission at 14 days and 11 patients at 28 days. Only 10% of the patients were admitted to hospital during induction therapy.

Table 1. Complete remission as % of number of relapses

	No. of patients	No. of CR	% CR
Resistant to induction	2	0	0
First relapse	31	16	57
Second relapse	4	1	25
Third relapse	1	0	0
Total	38	17	44

Table 2. Toxicity. Patients evaluated: 39

	No.	%
Myelosuppression (leukopenia $< 2{,}000/mm^3$)	22	56
Nausea and vomiting	4	10
Alopecia	6	15
Neurotoxicity (paresthesia)	3	0.7
Anorexia	3	0.7
Phlebitis	1	0.2

Toxicity

The toxicities encountered with this regimen are listed in Table 2. The major toxicities were leukopenia and anemia, which were observed in 56% of the patients. The nadir of the leukocyte count ranged from 300 to 18,500 and the nadir of the hemoglobin level ranged from 5.20 g/dl to 12 g/dl.

Twenty-six patients started reinduction with more than 100,000 platelets/mm^3 and in nine patients the number decreased below 100,000, with a range of 15,000–95,000/mm^3.

Ten percent experienced mild nausea and vomiting. None of the patients had abdominal pain or oral ulceration. Three patients developed paresthesiae of both lower extremities. Alopecia was seen in six patients and phlebitis in one. No episodes of anaphylaxis or hypotension were observed. No renal or hepatic toxicity was seen.

Remission Duration and Survival

Median remission duration was 6 weeks. Sixteen of 17 patients relapsed, with 15% of them still in remission at 6 months. One patient was in continuous complete remission for 16 months. The median survival from start of the protocol was 3 months; 29 patients have died and 22% remain alive at 10 months.

Discussion

In this study, the combination of vindesine, daunomycin, and prednisone gave a complete remission rate of 44%. For patients treated in first relapse the complete remission rate was 57%. For those treated in subsequent relapse the complete remission rate was 20% (Table 3). These figures indicate a similar remission rate to that obtained in a previous study by our group using daunomycin, vincristine, and prednisone. Of 266 patients treated in first relapse, 141 (53%) achieved complete remission, as against 14 (23%) of 61 patients treated in subsequent relapse [7]. The difference in the rate of complete remission between first and subsequent relapses was significant ($P < 0.0005$).

In a randomized study of ALL patients in relapse, the Children's Cancer Study Group [1] compared either vindesine or vincristine, in combination with prednisone and L-asparaginase. Complete remission rates were 57% for both regimens and were significantly greater for first relapses (69%) than for subsequent relapses (43%). No significant difference in response rates was observed between these regimens. Patients treated with vindesine experienced a significantly greater hematologic toxicity. Other groups report that the combination of vincristine, prednisone and L-asparaginase produces a complete remission rate in ALL patients in relapse, which ranges from 68% to 74% [3, 5]. Vietti et al. [13], using vincristine, prednisone, and daunomycin, obtained 39 (61%) complete remissions in 64 evaluable patients in relapse. Only two of them had received daunomycin previously. Reaman et al. [8] report a 91% complete remission rate in 56 patients in first relapse treated with a four-drug reinduction regimen consisting of L-asparaginase, vincristine, daunomycin, and prednisone. The rates of remission induction for second and third reinduction attempts were 89% and 90%, respectively.

The results described in this report indicate no advantage in terms of remission rate, when vindesine rather than vincristine is used in combination with daunomycin and prednisone to treat patients with relapsed acute lymphoblastic leukemia. Since the vindesine combination regimen is more

Table 3. Complete remission in ALL during first or subsequent relapses and with different combination therapies

Therapy	First relapse			2nd–3rd relapse			References
	No. of patients	No. of CR	%	No. of patients	No. of CR	%	
DNM-VCR-PRED	266	141	53	61	14	23	[7]
VCR-PRED-LASA	47	33	70	31	11	35	[1]
VND-PRED-LASA	37	25	68	38	19	50	[1]
VCR-PRED	42	33	79				[3]
VCR-PRED-LASA	38	28	74				[3]
VND-PRED	–	–	–	13	4	31	
VCR-PRED-LASA	69	47	68				[5]
VCR-PRED-LASA-CTX	63	48	76				[5]
VCR-PRED-DNM	48	34	71	14	5	36	[13]
VCR-PRED-DNM-LASA	56	51	91	69	63	91	[8]
VND-PRED-LASA	31	16	57	5	1	20	Present study

toxic it cannot be recommended for the treatment of children with ALL in relapse.

Acknowledgements. This study was supported in part by a grant from FUNDALEU (Fundación para Combatir la Leucemia) and in part by Eli Lilly Laboratories, who supplied vindesine.

The authors would like to thank Daniel Goldar and Susana Cotlar for performing the statistical analysis and Isabel Kabat for preparing the manuscript.

References

1. Anderson J, Krivit W, Chilcote R, Pyesmany A, Chard R, Hammond D (1981) Comparison of the therapeutic response of patients with childhood acute lymphoblastic leukemia in relapse to vindesine versus vincristine in combination with prednisone and L-asparaginase. A phase III trial. Cancer Treat Rep 65: 1015–1019
2. Ettinger LJ, Brecher M, Coleman M, Smithson WA, Patterson R, Russell EC, Necheless T, Jones B, Ohnuma T (1982) Vindesine: A phase II study in childhood malignancies. A report for Cancer and Leukemia Group B. Med Pediatr Oncol 10: 35–43
3. Herson J, Starling KA, Dyment PG, Humphrey GB, Pullen J, Vats T (1979) Vincristine and prednisone vs vincristine, L-asparaginase and prednisone for second remission induction of acute lymphocytic leukemia in children. Med Pediatr Oncol 6: 317–323
4. Krivit W, Hammond D (1978) Vindesine: A phase II study by the Children's Cancer Study Group. In: Siegen Thaler W, Luthy R (eds) Current chemotherapy, vol II. Proceedings of the Tenth International Congress of Chemotherapy. American Society of Microbiology, Washington, pp 1331–1334
5. Kung FH, Nyhan WL, Cuttner J, Falkson G, Lanzkowsky P, Del Duca V et al. (1978) Vincristine, prednisone and L-asparaginase in the induction of remission in children with acute lymphoblastic leukemia following relapse. Cancer 41: 428–434
6. Mathé G, Misset JC, De Vassal F, Gouveia J, Hayat M, Machover D, Belpomme D, Pico JL, Schwarzenberg L, Ribaud P, Musset M, Jasmin C, De Luca L (1978) 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: 805–809
7. Pavlovsky S, Sackmann Muriel F, Eppinger-Helft M, Bustelo P, Garay G, Giuntoli JM, Kvicala R, Divito J, Picon A (1983) Daunomycin, vincristine and prednisone for induction of remission in patients with acute lymphoblastic leukemia in relapse. (in press)
8. Reaman GH, Ladisch S, Echelberger C, Poplack OG (1980) Improved treatment results in the management of single and multiple relapses of acute lymphoblastic leukemia. Cancer 45: 3090–3094
9. Sackmann Muriel F, Pavlovsky S, Peñalver JA, Hidalgo G, Cebrian Bonesana A, Eppinger-Helft M, Macchi GH, Pavlovsky A (1974) Evaluation of induction of remission, intensification and central nervous system prophylactic treatment in acute lymphoblastic leukemia. Cancer 34: 418–426
10. Sackmann Muriel F, Svarch E, Eppinger-Helft M, Braier JL, Pavlovsky S, Guman L, Vergara B, Ponzinibbio C, Failace R, Garay GE, Bugnard E, Ojeda FG, De Bellis R, Sijvarger SR, Saslavsky J (1978) Evaluation of intensification and maintenance programs in the treatment of acute lymphoblastic leukemia. Cancer 42: 1730–1740
11. Sklaroff RB, Arlin Z, Young CW (1979) Phase II trial of vindesine in patients with acute leukemia. Cancer Treat Rep 63: 2063–2065
12. Vats TS, Mehta P, Trueworthy RC, Smith SD, Klopovich P (1981) Vindesine and prednisone for remission induction in children with acute lymphocytic leukemia. Cancer 47: 2789–2792
13. Vietti TJ, Starling K, Wilbur JR, Lonsdale D, Lane DM (1971) Vincristine, prednisone and daunomycin in acute leukemia of childhood. Cancer 27: 602–607

Received September 6, 1982/Accepted March 16, 1983