Cancer Chemother Pharmacol (1982) 9:89–92

Cancer Chemotherapy and Pharmacology

Prednimustine and Vincristine Compared with Cytosine Arabinoside and Thioguanine for Treatment of Elderly Patients with Acute Nonlymphoblastic Leukemia

Berit Lönnqvist[1], Börje Andersson[3], Magnus Björkholm[2], Lars Engstedt[4], Gösta Gahrton[1], Robert Hast[3], Göran Holm[7], Andreas Killander[6], Bo Lantz[3], Dieter Lockner[1], Håkan Mellstedt[8], Jan Palmblad[4], Christer Paul[1], Curt Peterson[9], Bengt Simonsson[6], Ann-Marie Stalfelt[5], Ann-Mari Udén[4], Bengt Wadman[5], and Gunnar Öberg[6]

[1] Department of Medicine, Huddinge Hospital, S-141 86 Huddinge
[2] Danderyds Hospital, S-141 86 Stockholm
[3] Karolinska Hospital, S-141 86 Stockholm
[4] South Hospital Stockholm
[5] Regional Hospital, S-141 86 Örebro
[6] University Hospital Uppsala
[7] Department of Clinical Immunology, Huddinge Hospital, S-141 86 Huddinge
[8] Radiumhemmet, Karolinska Hospital, S-141 86 Stockholm
[9] Department of Pharmacology, Karolinska Institute, S-141 86 Stockholm, Sweden

Summary. *Sixty-seven patients with acute nonlymphoblastic leukemia (ANLL) and above the age of 60 years were randomly allocated to treatment with either prednimustine + vincristine or cycles with cytosine arabinoside and thioguanine. Of the 67 patients, 13 (19%) entered a complete remission and four a partial remission. Of 33 patients randomized to prednimustine and vincristine (15 adequately treated), three entered a complete remission and one a partial remission. Four further patients went into complete remission after a switch to other treatment modalities. Of 34 patients randomized to cycles of ARA-C and thioguanine (22 adequately treated), four entered a complete remission and three a partial remission with the correct program. One patient entered a remission with intermittent cytosine arabinoside + thioguanine (wrong program) and one further patient entered a complete remission after a switch to prednimustine and vincristine. Prednimustine + vincristine did not appear to be superior to treatment with cytosine arabinoside thioguanine cycles for elderly patients with ANLL.*

Introduction

Prednimustine is a chlorambucil ester of prednisolone [19] which is highly effective for the treatment of several animal tumors [18]. The therapeutic index appeared high when the survival of L1210 leukemia cells was compared with that of normal hematopoietic cells [10]. Several investigations have shown that the drug is effective against human tumors, particularly lymphoproliferative malignancies [4, 12, 16, 22, 24, 26], but also against other tumors such as lung cancer [15] and breast cancer [25]. In a pilot study in 1977 Brandt and Könyves [2] reported that prednimustine was effective in acute nonlymphoblastic leukemia (ANLL), which was later confirmed in 37 patients [3]. The lack of severe bone marrow depression indicated that the drug might be particularly suitable for the treatment of elderly patients. Preliminary observations by Brandt et al. (personal communication) also suggested that vincristine might increase the response to prednimustine. This was the background for including both drugs on one arm in a randomized treatment program for elderly patients. This treatment was compared with another drug combination previously reported to induce a relatively high frequency of remissions with moderate bone marrow depression [11], i.e., cycles of cytosine arabinoside (ARA-C) and 6-thioguanine (TG).

Reprint requests should be addressed to Berit Lönnqvist

Materials and Methods

Sixty-seven patients (27 males, 40 females) above the age of 60 and with newly diagnosed untreated acute nonlymphoblastic leukemia (ANLL) entered the study. They were all consecutively admitted to one of the hospitals in the Leukemia Group of Central Sweden during the 3-year-period 1976–1979. These hospitals cover a defined area with a population of about 1.8 million inhabitants. All acute leukemia patients from the area enter one of these hospitals.

The patients were randomly allocated to one of two treatment regimens (group 1 and group 2). In group 1 prednimustine was given at a dose of 1 mg/kg/day in three divided dosages. An increase to 1.5 mg/kg/day was instituted after 2 weeks if the patient had not responded. As seen in the *Results,* protocol violations were frequent at this point, i.e., the dose was not increased. Instead treatment was switched to ARA-C + TG, as in group 2. Treatment was withdrawn or the prednimustine dose was reduced to 0.5 mg/kg/day if treatment-induced granulocytopenia and thrombocytopenia was severe. Vincristine 0.04 mg/kg/week was given IV with a maximum dose of 2 mg/week. Patients who entered complete remission continued to receive prednimustine 0.5 mg/kg/day and vincristine at the same dose level once monthly.

Group 2 patients were treated according to a cyclic schedule with ARA-C and TG (ARA-C 80 mg/m^2/day IV on days 1–5, no treatment on days 6–7, 6-TG 70 mg/m^2/day PO on days 8–12, no treatment on days 13–21, restart on day 22). Dose reduction was allowed or intervals prolonged during treatment-induced severe granulocytopenia or thrombocytopenia. The same program was continued during remission.

Patients were not considered to have had an adequate treatment trial if (a) they died during the first week (5 patients in group 1, 7 patients in group 2); (b) the prednimustine dosage was not increased after 2 weeks in nonresponding patients (8 patients from group 1); or (c) other protocol violations were made within the first month of treatment (5 patients in group 1, 4 patients in group 2).

Patients with smouldering leukemia were excluded according to the program. However, retrospectively it was found that one patient in group 1 and two patients in group 2, although

0344-5704/82/0009/0089/$ 01.00

included in the study, had this diagnosis. None entered remission.

The mean age of the patients in the two treatment groups was the same, 70.0 years in group 1 and 69.5 years in group 2. There were 14 males and 19 females in group 1 and 13 males and 21 females in group 2.

Results

Three of 33 patients in group 1 entered complete remission with prednimustine and vincristine (Table 1). One further patient went into partial remission. Sixteen patients were switched to other chemotherapy 7–35 days (median 14 days) from the start of prednimustine and vincristine (13 after inadequate trial). Fourteen of these were switched to ARA-C + TG cycles (the same program as in group 2) and two to other treatment programs (daunorubicin and ARA-C or VAMP). Four of these 16 patients entered a complete remission. Survival data are seen in Table 2. Of the 25 patients who did not enter remission, five died within the first week. The median survival in this group was 39 days. Only 10 of the patients who did not enter remission received an adequate trial with prednimustine and vincristine. Altogether only 15 patients were considered to have had an adequate trial with vincristine and prednimustine.

Of the 34 patients randomized to treatment group 2 (ARA-C + TG cycles), four went into complete remission and three into partial remission with the correct program. One further patient went into remission after she was switched to prednimustine and vincristine and one patient went into remission after having received a different treatment from the start (intermittent ARA-C + TG) (Table 1). Survival data are seen in Table 2. The median survival of the patients who did not enter remission was 27 days. Seven patients died within 1 week. Twenty-two patients were adequately treated according to the program. Five patients were switched to other chemotherapy, three of them to prednimustine and vincristine (the same program as in group 1) and two to other chemotherapeutic combinations. One of these patients went into complete remission with prednimustine and vincristine.

A comparison between the two programs shows that there was no significant difference in the frequency of remissions or in survival (Table 2), although the median survival of the four patients in group 2 in complete remission following ARA-C + TG cycles tended to be longer than in the three patients in group 1 who attained complete remission with prednimustine and vincristine. A similar tendency was found if patients in complete remission plus partial remission were compared. Patients in group 1 were more rapidly switched to other therapy than in group 2. Therefore group 2 had a higher

Table 1. Remissions with correct program or after switch to other chemotherapy

	Total patients	Adequate trial	CR with correct program	PR with correct program	CR after switch	PR after switch	Total	
							CR	CR+PR
Group 1 (Prednimustine + vincristine)	33	15	3	1	4	0	7	8
Group 2 (ARA-C + thioguanine)	34	22	4	3	2[a]	0	6	9

CR, complete remission; PR, partial remission

[a] One patient received a different treatment from the start (protocol violation)

Table 2. Survival of patients in remission with correct program or after switch to other chemotherapy

	Type of remission	Program correct/switch	Survival
Group 1	CR	Correct	209
Prednimustine + vincristine	CR	Correct	305
	CR	Correct	108
	PR	Correct	152
	CR	Switch to DR + ARA-C	391
	CR	Switch to ARA-C-TG cycles	446 +
	CR	Switch to ARA-C-TG cycles	396 +
	CR	Switch to ARA-C-TG cycles → VAMP	542 +
Group 1	CR	Correct	621
ARA-C – thioguanine (TG) cycles	CR	Correct	261
	CR	Correct	948
	CR	Correct	429
	PR	Correct	282
	PR	Correct	247
	PR	Correct	358 +
	CR	Switch to prednimustine + vincristine	201
	CR	Wrong program (ARA-C + thioguanine in combination)	435

CR, complete remission; PR, partial remission

Table 3. Bone marrow toxicity

			Decrease in platelet count during treatment to $< 10 \times 10^9$/l Number of patients/ total patients	Mean amount of transfused platelets (units)	Decrease in granulocyte count during treatment to		Mean number of days with granulocytes $< 0.5 \times 10^9$/l
					$< 0.5 \times 10^9$/l	$< 0.1 \times 10^9$/l	
					Number of patients/total patients		
No remission	Pr + Vc	(1)	8/20	10	2/20	0/20	5
	TG + ARA-C	(2)	11/21	38	7/21	6/21	25
Remission	Pr + Vc	(1)	0/4	1	1/4	1/4	30
	TG + ARA-C	(2)	7/7	26	7/7	7/7	32

number of adequately treated patients. The overall complete remission rate was 19% and complete + partial remission was achieved in 25%.

Side-Effects

Side-effects during induction treatment were studied adequately in 52 patients (78%) (24 in group 1 and 28 in group 2). There was less bone marrow toxicity in patients treated with vincristine and prednimustine than in those treated with thioguanine and ARA-C (Table 3). This was judged by the number of patients with a decrease in platelet count to less than 10×10^9/l or decrease in granulocyte count to less than 0.5×10^9/l or less than 0.1×10^9/l, and by the need for platelet transfusions. Other side-effects were mild and there was no clear difference between the groups.

Discussion

The present study confirms previous reports that the frequency of remissions in elderly patients with ANLL is low irrespective of treatment [1, 5, 7, 8, 9, 21, 23, 27, 28, 29, 30]. Although only 19% of the patients entered complete remission, our study does not compare unfavorably with other reports. The combination of prednimustine with vincristine was not better than other drug combinations used in this age group (> 60 years). Unfortunately adherence to the program with prednimustine and vincristine was poor. In 13 of 33 patients the treatment was switched to other chemotherapeutic agents before an adequate trial had been given. This was probably due to low confidence in the effectiveness of the drug (since there was no clear difference in side-effects). In the patient group treated with ARA-C and TG no patient was switched to other treatment modalities before an adequate trial had been made. Whatever the reason only 9% of the patients randomized to prednimustine and vincristine entered complete remission with the initial therapy (3 of 33). Four went into complete remission after a switch to other therapy, two of them to ARA-C and TG cycles (as in group 2). In group 2, 12% (4 of 34 patients) went into complete remission with ARA-C + TG. Only one complete remission was obtained after switching to prednimustine + vincristine. Thus, although our results with prednimustine and vincristine compare favorably with those published by Juul et al. [16], who reported that only one of 18 patients with ANLL entered remission on prednimustine, we cannot confirm the reports by Brandt and Könyves [3] that 17% of elderly ANLL patients enter remission. It is, however, worth noting that three of 15 patients who had an adequate trial went into complete remission (20%).

ARA-C and TG are well-known effective drugs in ANLL. In addition to the seven patients who entered a complete or partial remission in group 2, two patients went into complete remission and one into partial remission in group 1 after a switch from prednimustine + vincristine (inadequate trials) to ARA-C + TG cycles. However, it is also interesting that one patient who did not respond to an adequate trial with ARA-C + TG responded to prednimustine and vincristine. The reason for the varied and generally poor response to prednimustine is unclear. ANLL blast cells generally have a high content of steroid receptors [6, 13, 14, 17]. The variation in receptor content between patients is wide, but there appears to be no clear correlation between receptor content and in vitro response of blast cells to treatment with corticosteroids [6, 14, 17]. Clinical studies correlating response to treatment with corticosteroids in ANLL and receptor content are lacking. However, it is well-known that responses to corticosteroids are few in ANLL. Thus, in view of the high receptor content on ANLL blast cells and the poor response of this disease to either corticosteroids or prednimustine it is not likely that the receptor content plays any decisive role in the response to treatment with either of these two drugs. Other unknown factors must be of greater importance.

Bone marrow depression appears to be less severe in patients treated with prednimustine and vincristine than in those treated with ARA-C + TG. This indicates that it would perhaps have been possible to intensify the treatment with prednimustine and vincristine. Whether this would have increased the frequency of remissions cannot be adequately answered. It is still clear that the combination prednimustine and vincristine results in a poor frequency of remission and is not superior to other drug combinations in elderly patients with ANLL. Our view is that it does not merit use as first choice for their treatment.

Acknowledgements. The skilful technical assistance of Åsa Johansson and Irene Blennby is gratefully acknowledged. This work was supported by grants from the Swedish Cancer Society.

References

1. Bodey GP, Coltman CA, Freireich EJ, et al. (1974) Chemotherapy of acute leukemia. Comparison of cytarabine alone and in combination with vincristine, prednisone, and cyclophosphamide. Arch Intern Med 133: 260
2. Brandt L, Könyves I (1977) Therapeutic effect of prednimustine (Leo 1031) in various types of leukaemia. Eur J Cancer 13: 393
3. Brandt L, Könyves I (1979) Prednimustine in adult acute leukaemia. Cancer Chemother Pharmacol 2: 133

4. Brandt L, Könyves I, Möller TR (1975) Therapeutic effect of Leo 1031, an alkylating corticosteroid ester in lymphoproliferative disorders. I. Chronic lymphocytic leukaemia. Acta Med Scand 197: 317
5. Burge PS, Richards JDM, Thompson DS, et al. (1975) Quality and quantity of survival in acute myeloid leukaemia. Cancer 2: 621
6. Crabtree GR, Smith KA, Munck A (1978) Glucocorticoid receptors and sensitivity of isolated human leukemia and lymphoma cells. Cancer Res 38: 4268
7. Crosby WH (1968) To treat or not to treat granulocytic leukemia. Arch Intern Med 122: 79
8. Crosby WH (1974) Grounds for optimism in treating acute granulocytic leukemia. Arch Intern Med 134: 177
9. Crosby WH (1976) Acute granulocytic leukemia (AGL) in the elderly. Arch Intern Med 136: 493
10. Evenaar AH, Wins EHR, Van Putten LM (1973) Cell killing effectiveness of an alkylating steroid (Leo 1031). Eur J Cancer 9: 773
11. Guyer RJ, Winfield DA, Shahani RT, Blackburn EK (1971) Combination chemotherapy in acute myeloblastic leukemia. Br Med J 1: 231
12. Håkansson L, Könyves I, Lindberg LG, Möller T (1978) Continuous treatment of non-Hodgkin's malignant lymphoma with Prednimustine (Leo 1031). Oncology 35: 103
13. Hansson L-A, Gustafsson SA, Carlstedt-Duke J, Gahrton G, Högberg B, Gustafsson J-Å (1982) Glucocorticoid receptor content in leukemia cells. (in manus)
14. Ho AD, Hunstein W, Schmid W (1981) Glucocorticoid receptors and sensitivity in leukemias. Blut 42: 183
15. Jensen HS, Hansen HH, Dombernowsky P (1980) Phase II trial of Prednimustine (NSC-124087) in the treatment of small-cell anaplastic carcinoma of the lung. Cancer Chemother Pharmacol 4: 259
16. Juul K, Sørensen P, Pedersen-Bjergaard J, Krogh-Jensen M (1979) Phase II trial of Prednimustine, Leo-1031 (NSC-134087) in acute non-lymphocytic leukaemia. Scand J Haematol 23: 388
17. Kontula K, Andersson LC, Paavonen T, Myllylä G, Teerenhovi L, Vuopio P (1980) Glucocorticoid receptors and glucocorticoid sensitivity of human leukemic cells. Int J Cancer 26: 177
18. Könyves I, Liljekvist J (1976) The steroid molecule as a carrier of cytotoxic groups. Excerpta Medica, Amsterdam, p 98 (Int Congress Series no. 375)
19. Könyves I, Fex H, Högberg B (1974) Novel corticosteroid esters with alkylkating properties. In: Daikos GK (ed) Antineoplastic chemotherapy, vol III. Proc 8th Congr Chemotherapy, Athens, p 791
20. Lippman ME, Perry S, Thompson EB (1975) Glucocorticoid binding proteins in myeloblasts of acute myelogenous leukemia. Am J Med 59: 224
21. Mandelli F, Amadori S, Fabiani F, Grignani F, Liso V, Martelli M, Neri A, Petti MC, Tonato M (1979) Treatment of acute nonlymphocytic leukemia (ANLL) in elderly patients. Results of a multicenter study. Haematologica 64: 331
22. Mattsson W, von Eyben F, Turesson I, Wahlby S (1978) Prednimustine (NSC-134087, Leo 1031) treatment of lymphocytic and lymphocytic-histocytic lymphomas. Cancer 41: 112
23. Medical Research Council's Working Party on Leukaemia in Adults (1974) Treatment of acute myeloid leukaemia with daunorubicin, cytosine arabinoside, mercaptopurine, L-asparaginase, prednisone and thioguanine – Results of treatment with five multiple-drug schedules. Br J Haematol 27: 373
24. Möller TR, Brandt L, Könyves I, Lindberg LG (1975) Therapeutic effect of Leo 1031, an alkylating corticosteroid ester in lymphoproliferative disorders. II. Lymphocytic lymphoma. Acta Med Scand 197: 323
25. Mouridsen HT, Kristensen D, Halskov-Nielsen J, Dombernowsky P (1980) Phase II trial of Prednimustine, L-1031 (NSC-134087) in advanced breast cancer. Cancer 46: 253
26. Pedersen-Bjergaard J, Mørk-Hansen M, Geisler CM, Nissen NI (1980) Clinical trial of Prednimustine, Leo 1031 (NSC-134087), in patients with non-Hodgkin lymphomata and chronic lymphocytic leukaemia previously treated with steroid and alkylating agents. Acta Med Scand 207: 215
27. Petersen BA, Bloomfield CD (1977) Treatment of acute nonlymphocytic leukemia in elderly patients. A prospective study of intensive chemotherapy. Cancer 40: 647
28. Rubio LF Jr (19609) Acute leukemia in patients past the age of 50. J Am Geriatr Soc 8: 644
29. Udén A-M, Brenning G, Engstedt L, et al. (1975) L-Asparaginase and prednisolone pretreatment followed by rubidomycin and cytosine arabinoside for induction of remission in adult patients with acute myeloblastic leukaemia. Scand J Haematol 15: 72
30. Wiernik PH, Serpick AA (1970) Factors effecting remission and survival in adult acute nonlymphocytic leukemia (ANLL). Medicine (Baltimore) 49: 505

Received March 18, 1982/Accepted July 21, 1982