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Risk Groups in a Multicenter Pilot Study for Treatment of Acute Lymphoblastic and Acute Undifferentiated Leukemia in Adults*

D. Hoelzer, E. Thiel, H. Löffler, H. Bodenstein, T. Büchner, R. Engelhardt, A. Ganser, D. Messerer, H. Rühl, and T. Zwingers

A. Introduction

The German Multicenter Trial for Adult Acute Lymphoblastic (ALL) and Acute Undifferentiated (AUL) Leukemia was undertaken to improve remission duration by using a modified form of an intensified induction regimen successful in childhood ALL (Riehm et al. 1980). The results from the pilot study, with a total of 162 patients and a median observation time of 4½ years, now allow some conclusions regarding prognostic factors which influence the achievement of complete remission or the length of remission.

B. Treatment

The concept of this therapeutic trial was to eradicate as much as possible of the initial tumor cell load by an eight-drug induction therapy and a similarly intensive early consolidation therapy after 3 months, whereas the maintenance therapy is conventional with 6-mercaptopurine and methotrexate. The 8-week induction regimen consists of two phases: In the first 4 weeks prednisone 60 mg/m² PO daily, vincristine 1.5 mg/m² IV once weekly, daunorubicin 25 mg/m² IV once weekly, and l-asparaginase 5000 units/m² IV on days 1–14; and in the second 4 weeks cyclophosphamide 650 mg/m² IV 3 doses at 2-week intervals, cytosine arabinoside 75 mg/m² IV on 4 days per week for 4 weeks, and 6-mercaptopurine 60 mg/m² PO daily for 4 weeks. CNS prophylaxis consists in methotrexate 10 mg/m² intrathecally each week and CNS irradiation with 24 Gy. A 6-week reinduction course is given after 3 months and is similar to the induction regimen, adriamycin being substituted for daunorubicin, dexamethasone for prednisone, and thioguanine for 6-mercaptopurine; L-asparaginase is omitted. Maintenance therapy with 6-mercaptopurine 60 mg/m² PO daily and methotrexate 20 mg/m² PO or IV once weekly is continued for 2 years. Further details of the therapy and of the diagnostic procedure have been described previously (Hoelzer et al. 1984).

C. Results

From October 1978 to June 1981 a total of 162 adult patients from 25 hospitals entered the study, and 126 (77.8%) achieved complete remission. At the evaluation date, 30 November 1983, the median survival time for all patients was 23.4 months and that for complete remitters was 34 months. Median remission duration was 20.5 months. The probability of being in complete remission at 4½ years is 0.397. Cell marker analysis identified c-ALL in 56.4%, null-AL (defined as being non-B-ALL, non-T-ALL, cALLA⁻) in 25.6%, T-ALL in 15.4%, B-ALL in 0%, and mixed leukemia in 2.6%. The best results were achieved in patients with T-ALL, for whom the prob-

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Table 1. Prognostic factors for remission duration: Pilot study

Factor		*n* (126)	MRD (months)	In continuous CR	P-value
Age	≦35 years	98	24.9	42.9%	0.0150
	>35 years	28	12.7	28.6%	
Leukocyte count	≦30 000/μl	85	28.0	44.7%	0.0314
	>30 000/μl	41	14.8	29.3%	
Time to achieve CR	Within 4 weeks	94	28.2	42.6%	0.0285
	After 4 weeks	32	11.8	31.3%	
Immunological subtype	c-ALL	32	23.4	48.8%	0.0143
	T-ALL	11	m.n.r.[a]	63.6%	
	null-AL	16	12.7	12.5%	
Low-risk group		19	m.n.r.[a]	79.0%	0.0000
High-risk group		40	11.8	20.0%	

[a] Median not reached

ability of being in continuous complete remission at 4½ years is 0.636.

D. Prognostic Factors and Risk Groups

Regarding the complete remission rate, none of the initial laboratory or clinical features, such as age, leukocyte count, hepatosplenomegaly, mediastinal tumor, CNS involvement, or other organ infiltration, had an unfavorable influence on the achievement of complete remission. The adverse effect of older age, high initial leukocyte count, and hepatosplenomegaly, which have been shown in other studies to have an unfavorable influence on the achievement of complete remission, could not be confirmed in the large number of patients in this study (Hoelzer et al. 1984).

I. Prognostic Factors

Prognostic factors for remission duration (Table 1) were time required to achieve remission, initial leukocyte count, immunological subtype, and age.

Age. The difference in remission duration for patients above and below 35 years of age was evident. In earlier studies (Hoelzer 1984) higher age was also found to exert an unfavorable influence on the survival time and remission duration. This multicenter ALL/AUL study has proved that results for older patients who did not require any essential omissions or reductions in the therapy program were similar to those for younger patients. The main problem is that for many of the older patients it is not possible to carry out the complete therapy schedule.

Leukocyte Count. In this therapy study, as in other ALL studies in adults (Schauer et al. 1983) or children, a high initial leukocyte count was found to be unfavorable for a long remission.

Immunological Subtype. The best prognosis in this study was for the subtype T-ALL, for which the median remission duration has not yet been reached. This finding is remarkable, since up to now patients with T-ALL, who frequently have a high initial leukocyte count, a mediastinal tumor, or CNS involvement, have had a poor prognosis. The worst prognosis, in keeping with findings from another study (Lister et al. 1979), was for patients with null-AL, who had a median remission duration of 13 months. Of the patients with c-ALL, 44% were disease-free at the evaluation date.

Time Required to Achieve Complete Remission. The length of treatment required to achieve complete remission had the

strongest influence on remission duration. Late response to therapy probably reflects a primarily more resistant population of leukemic cells. Other adult ALL therapy studies have also shown that of a total of 70% remission patients, only 50% achieved remission within 4 weeks (Hoelzer 1984). In childhood ALL the proportion of patients who reach complete remission after prolonged treatment is very low (< 5%). For them, it is also true that late response to therapy is correlated with a very poor prognosis (Frei and Sallan 1978).

II. Definition of Risk Groups

On the basis of these factors found to have prognostic significance for remission duration in the pilot study, it was possible to define groups of patients exposed to different degrees of risk. Those defined as low-risk patients are the ones who have none of the four risk factors, in comparison to high-risk patients who have one or more of the four risk factors. At the last evaluation date of 30 November 1983, 79% of the low-risk patients were still in first remission, whereas only 20% of the high-risk patients were still free of disease.

E. Risk-Adapted Therapy Protocol

The study group has developed a new risk-adapted therapy protocol based on the results of the pilot study, which was activated on 1 July 1983. According to this, in addition to the intensive induction therapy and consolidation therapy, high-risk patients will receive further cycles of consolidation therapy with VM-26 and cytosine arabinoside, to improve results in this group. In addition, the high-risk patients are to be considered for allogeneic bone marrow transplantation in first remission if a suitable donor is available. After establishment of the method, autologous bone marrow transplantation also appears to be useful for these patients. The low-risk patients will be treated according to the present protocol with no essential changes. It is to be expected that in this group, even with chemotherapy alone, more than 50% will reach the 5-year limit without disease and might thereby be considered as cured.

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