Haematology and Blood Transfusion Vol. 26
Modern Trends in Human Leukemia IV
Edited by Neth, Gallo, Graf, Mannweiler, Winkler

Different Therapy Protocols for High Risk and Standard Risk ALL in Childhood

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Children with acute lymphocytic leukemia can be apparently cured today. The subclassification of ALL in childhood as "high risk" and "standard risk" ALL by means of a determination of immunologic and clinical parameters is of increasing importance. This classification could become the basis for a risk-oriented individual therapy. We present here the current results attained in the treatment of childhood ALL by our Pediatric Hematology and Oncology working group involving 13 treatment centers of the German Democratic Republic.

A. Patients and Methods

I. Study IV

From January 1976 to December 1977 111 previously untreated patients were entered in this study. The outline of therapy is shown in Fig. 1. There were two different treatment groups based upon the presence or absence of high risk factors at the time of diagnosis. The criteria for high risk factors were defined as:

1. Leukocyte count above 20,000 cells/mm^3,
2. Age under 2 years and over 10 years,
3. Mediastinal mass,
4. Generalized enlargement of lymph nodes or enlargement of one or more lymph nodes by 3 cm or more,
5. Tumor of other organs,
6. Enlargement of liver or spleen by 5 cm or more, and
7. CNS leukemia at diagnosis.

In the presence of one or more high risk criteria the patients received a consolidation therapy with Ara-C and L-asparaginase.

Of the 111 patients 67 were classified as high risk and 44 as standard risk patients.

As CNS prevention therapy – regardless of their prognostic factors – all children received combined intrathecal injections of methotrexate and prednisolone during induction therapy, early in remission, and periodically throughout the continuation treatment. In addition, 41 patients received preventive cranial irradiation (2400 rad telecobalt) and 68 received intrathecal application of macrocolloidal radiogold (198 Au, 2,5 mCi) (Metz et al. 1977).

II. Study V and LSA_2L_2 Protocol

As of January 1978 treatment was given by two other protocols: study V (Fig. 2) for standard risk patients and LSA_2L_2 protocol for high risk patients (Fig. 3). This latter group also included children with non-Hodgkin lymphomas who had 25% or more tumor cells in the bone marrow. In this study high risk criteria differed from the previous study and was limited to:

1. Leukocyte counts 50,000 per cu mm and more,
2. Mediastinal mass,
3. T-ALL (blast cells form spontaneous rosettes with sheep erythrocytes and/or give a positive reaction with antithymocyte serum),
4. Positive acid phosphatase reaction of the blast cells, and
5. CNS leukemia at diagnosis.

III. Statistical Analysis

The results of each of the three studies were analysed as of 31 December 1979 and the statistical analysis was performed according to the life table method of Cutler and Ederer (1958).

B. Results

I. Study IV

Table 1 depicts the clinical course of the 111 patients entered on study IV. As shown in Fig. 4, no statistical difference could be detected in

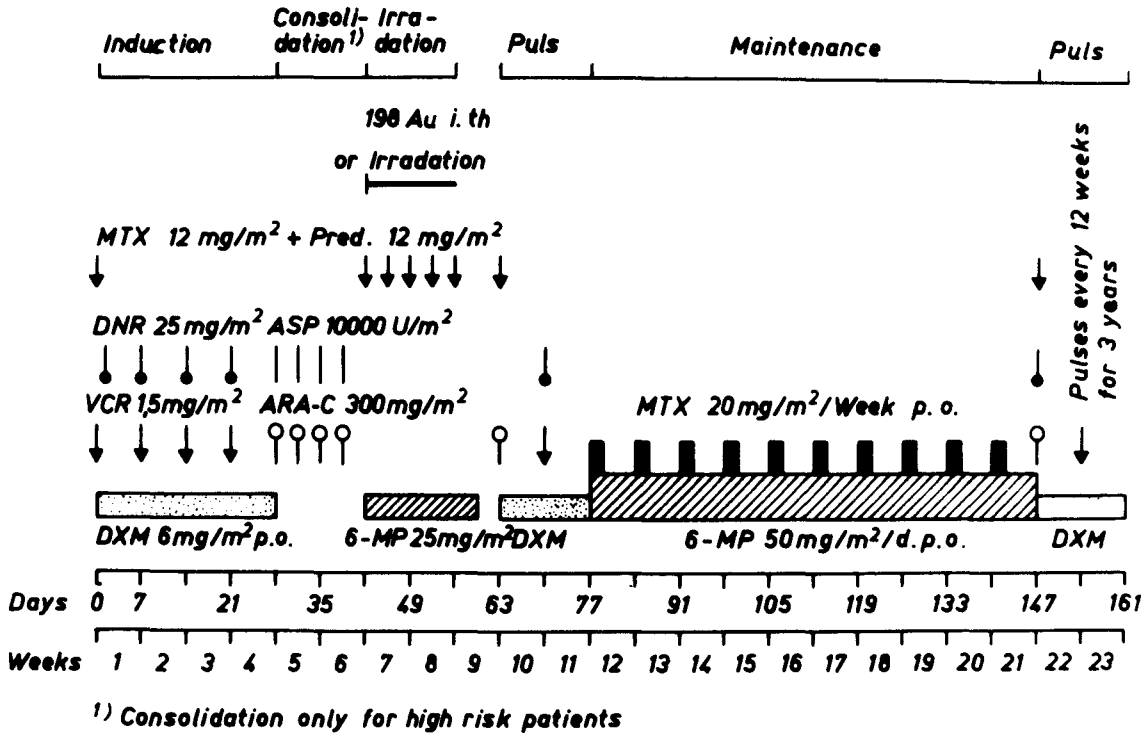

Fig. 1. Outline of therapy for study IV (1976–77)

the outcome of standard and high risk patients entered on study IV. At 3 years the cumulative complete remission rate was 0.56 ± 0.11 for the standard risk group and 0.44 ± 0.07 for the high risk group. Thirty nine patients are still receiving chemotherapy and in 15 treatment has recently been stopped (median time off therapy was 3 months).

II. Study V and LSA_2L_2 Protocol

New treatment programs were introduced in 1978 with the objective of improving these results. The LSA_2L_2 protocol developed by Wollner et al. (1976) for patients with non-Hodgkin lymphoma was used for a newly defined group of high risk patients as described

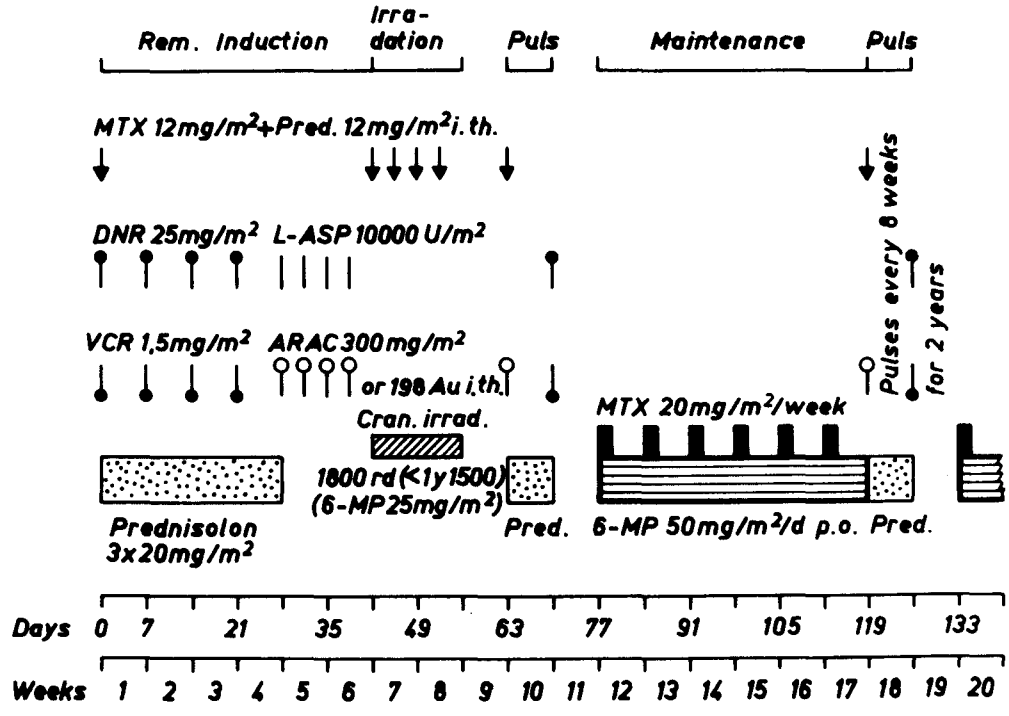

Fig. 2. Outline of therapy for study V (1978–79)

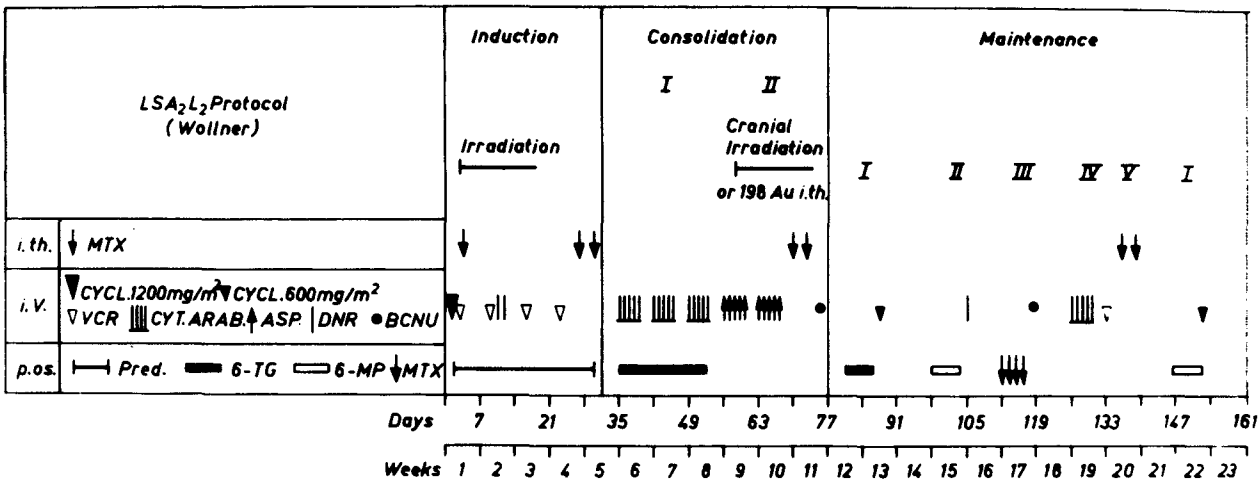

Fig. 3. Outline of therapy for study LSA_2L_2 (Wollner et al.)

above. At this time only preliminary results are available for these studies. The cumulative complete remission rate at 2 years is 0.79 for 111 standard risk patients and 0.50 for 58 children with high risk leukemia. Thus far the outcome has been significantly worse for patients with leukocyte counts exceeding 100,000 cells/mm³ (Fig. 6), with mediastinal masses (Fig. 7), and in children under the age of 2 and above the age of 10 years (Fig. 8). The significance of T-cell lymphoblasts and of initial CNS leukemia could not be calculated.

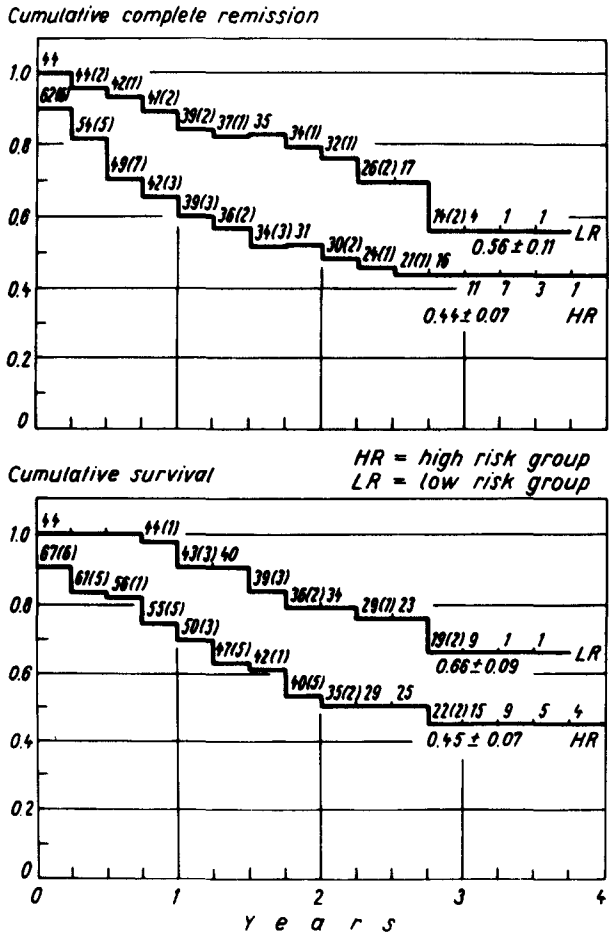

Fig. 4. Survival and relapse-free survival in childhood acute lymphocytic leukemia, study IV

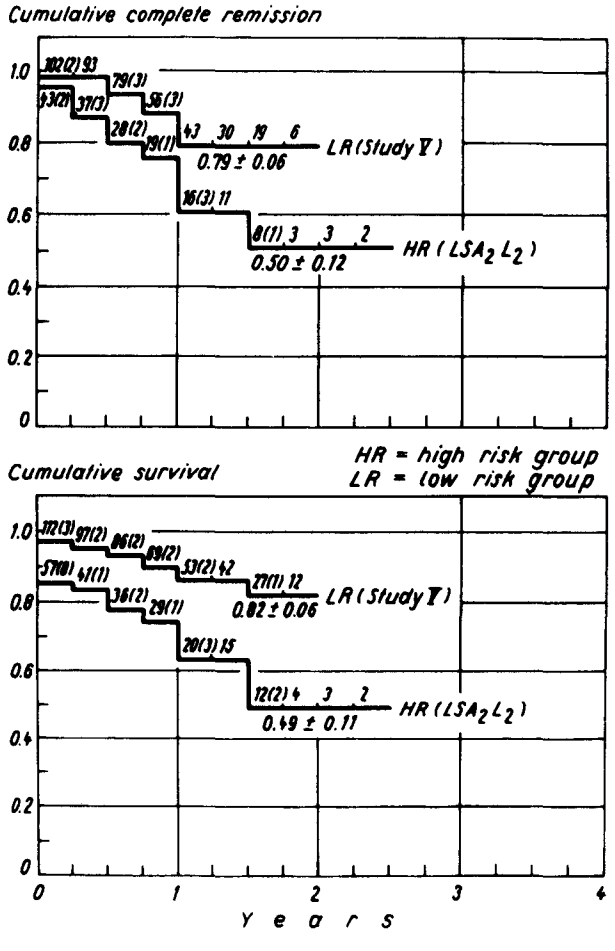

Fig. 5. Survival and relapse-free survival in childhood acute lymphocytic leukemia, studies V and LSA_2L_2

	High risk	Standard risk	Total
Number of patients	67	44	111
Early deaths	5	0	5
Complete remission	62	44	106
Number of relapses	34	14	48
Marrow	28	9	37
Marrow+CNS	0	3	3
CNS	4	2	6
Testes	2	0	2
Remission deaths	2	2	4
Cumulative complete remission	0.44±0.07	0.56±0.11	0.50±0.06

Table 1. Clinical course in study IV (1976–1977)

C. Discussion

The therapeutic value of intensive early therapy for ALL remains controversial. Pinkel has reported that this treatment phase does not reduce the incidence of relapses (Pinkel 1979), while Riehm et al. have concluded that intensified induction treatment definitively improves the final outcome (Riehm et al. 1977). Because of the recognized poor prognosis in patients with high risk leukemia we decided to use more intensive initial therapy in these patients. However the 2 week consolidation therapy with cytosine arabinoside and L-asparaginase

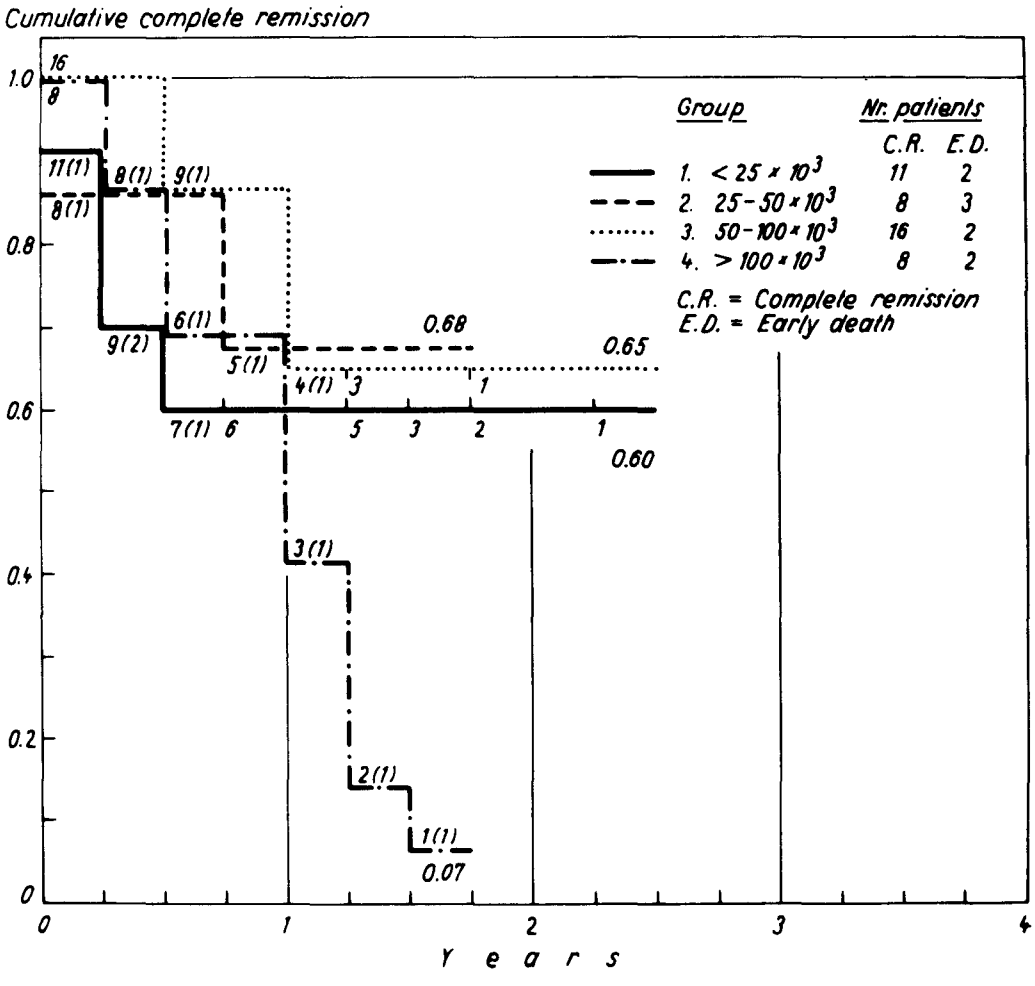

Fig. 6. Relationship of initial WBC to relapse-free survival in childhood acute lymphocytic leukemia, study LSA_2L_2

	Study V Standard risk patients)	LSA_2L_2 (Wollner) (High risk patients)
Number of patients	111	58
Early deaths	4	9
Complete remission	102	44
Number of relapses	12	12
Marrow	7	7
Marrow + CNS	0	0
CNS	4	4
Testes	1	1
Remission deaths	2	2
Cumulative complete remission	0.79±0.06	0.50±0.12

Table 2. Clinical course in study V and LSA_2L_2 (1978–1979)

used in study IV did not prove to be more effective when important features such as leukocyte count over 100,000 cells/mm^3, mediastinal mass, or age under 2 or over 10 years were present. Since different criteria were used to define high risk patients in studies IV and LSA_2L_2, results cannot be readily compared among both treatment groups. Current information, however, favors the results attained in the LSA_2L_2 study when single factors are comparatively analyzed, i.e., mediastinal mass, leukocyte count up to 100,000 cells/mm^3, and acid phosphatase reaction by lymphoblasts. For patients with leukocyte counts over

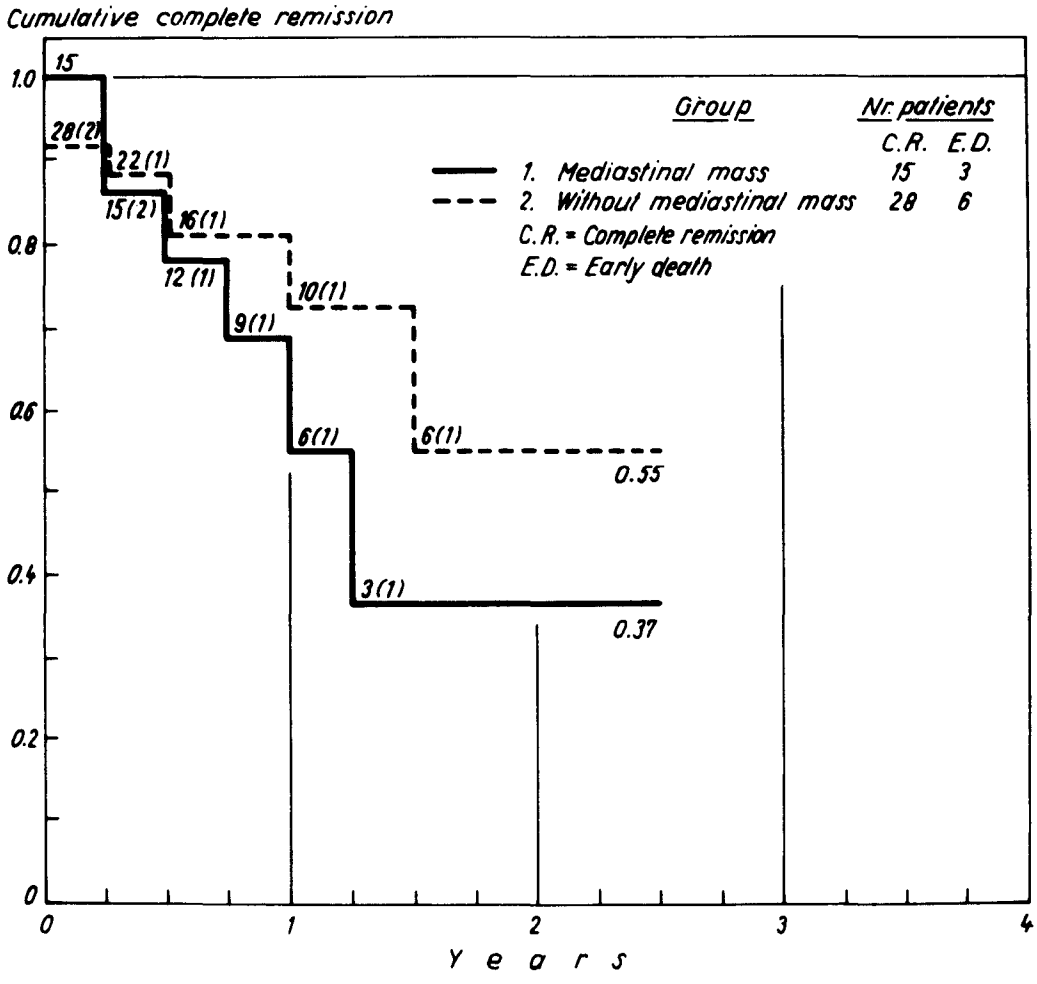

Fig. 7. Relationship of mediastinal mass to relapse-free survival in childhood acute lymphocytic leukemia, study LSA_2L_2

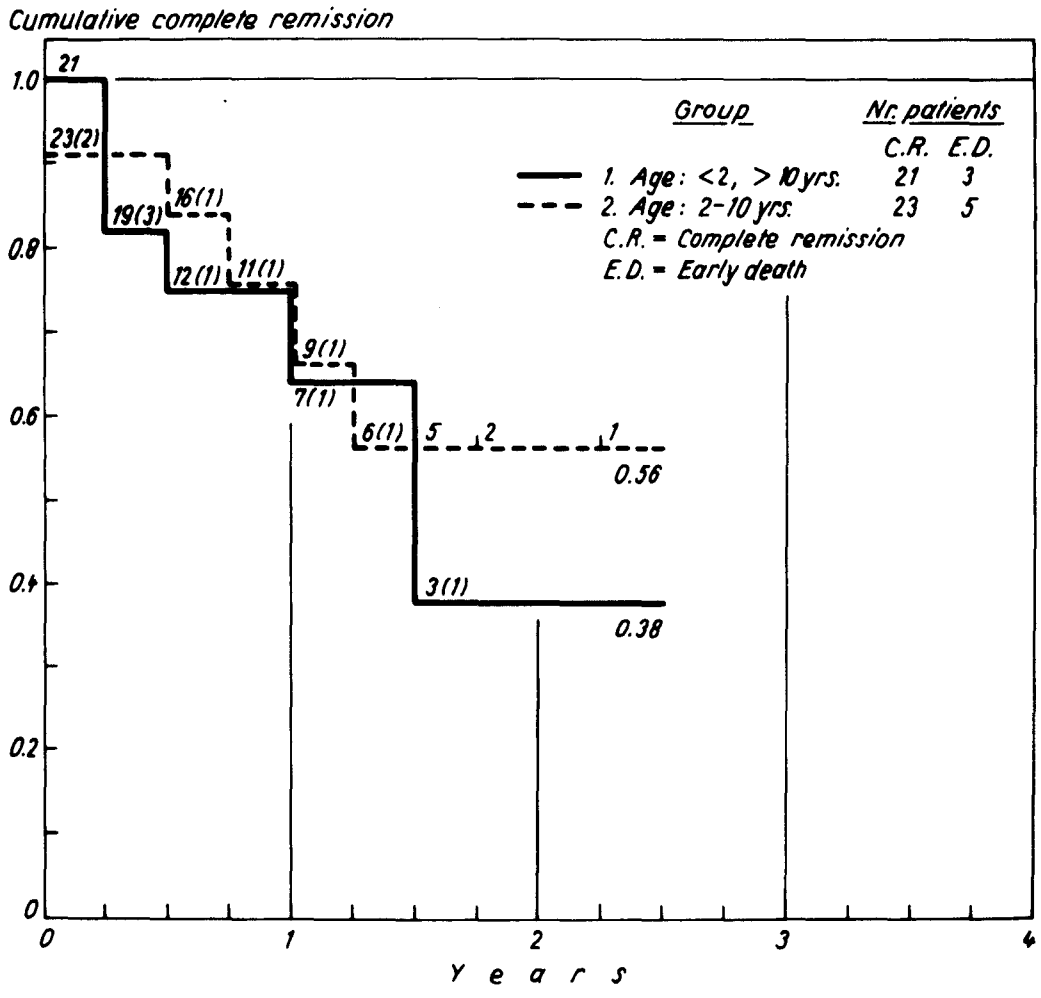

Fig. 8. Relationship of age to relapse-free survival in childhood acute lymphocytic leukemia, study LSA_2L_2

100,000 cells/mm^3 the results have not been influenced by this latter therapy.

The division into high and standard risk patients is based on empirical clinical observations. Little is known about the biologic behaviour of the different ALL forms that are responsible of the sensitivity of resistance to cytostatic drugs (Pinkel 1979).

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