Haematology and Blood Transfusion Vol. 28
Modern Trends in Human Leukemia V
Edited by Neth, Gallo, Greaves, Moore, Winkler

Results of LSA_2-L_2 Therapy in Children with High-Risk Acute Lymphoblastic Leukemia and Non-Hodgkin's Lymphoma *

F. Zintl, J. Herman, D. Katenkamp, H. Malke, and W. Plenert

In the early seventies, overall survival in patients with childhood non-Hodgkin's lymphomas (NHL) was less than 30% at 5 years. The majority of long-term survivors were patients with very limited disease. Subsequently a dramatic improvement in the end results of therapy for children with NHL has been reported. The best overall disease-free survival curves were reported by Wollner and her colleagues using the LSA_2L_2 protocol [4]. In 1978 we adopted this protocol for treatment of childhood NHL in our group. Independently of the stage of disease all children were treated in the same way. At the same time a study was started to evaluate the efficacy of the LSA_2L_2 protocol only for patients with high-risk acute lymphoblastic leukemia.

A. Materials and Methods

I. Non-Hodgkin's Lymphoma

From January 1978 to December 1981, a total of 44 consecutive previously untreated children with NHL were treated with the LSA_2L_2 protocol [4]. No patients were excluded from this therapy.

1. Staging

Prior to the initiation of therapy the stage of disease was assigned according to the Wollner staging system [4]. Retrospectively the patients were restaged according to the staging system used by Murphy et al. [3]. The primary location of tumor and the stage for the 44 children on study are shown in Table 1. Stage IV NHL was defined as less than 25% replacement of the marrow cells by blast cells. ALL was defined by complete or at least more than 25% replacement of the marrow with blasts.

2. Histology

Histology confirmation was obtained in all cases except one. In the 44th patient the diagnosis was established by a typical mediastinal presentation. Cases were classified according to the Kiel classification [1].

3. Treatment

Children with high-risk ALL and NHL all received the same cytostatic therapy ac-

Table 1. Stage and location of primary tumor

Primary sites	No. of pts	Stage I	II	III	IV
Intra-abdominal	16	–	7	9	–
Mediastinal	16	–	–	14	2
Peripheral-nodal	4	1	1	1	1
Naso-pharyngeal	4	1	3	–	–
Extranodal	4	1	1	2	–
Total	44	3	12	26	3

* A Report from the Working Group for Pediatric Hematology and Oncology of the GDR

Table 2. ALL therapy study LSA_2L_2: patient characteristics and results

	n	%	CCR (after 42 months)
ALL patients	82	100	0.389±0.06
Sex:			
Boys	49	60	0.427±0.08
Girls	33	40	0.325±0.09
Age:			
2 – 10 yrs	49	60	0.440±0.08
<2 and >10 yrs	33	40	0.329±0.09
Thymic mass:			
Negative	55	67	0.394±0.08
Positive	27	33	0.370±0.09
WBC:			
$<50\times10^3/mm^3$	29	35	0.402±0.10
$>50\times10^3/mm^3$	53	65	0.375±0.07
CNS involvement:			
Negative	74	90	0.417±0.06
Positive	8	10	–
E-Rosettes:			
Negative	30	57	0.377±0.10
Positive	23	43	0.413±0.10
Acid phosphatase:			
Negative	57	71	0.374±0.07
Positive	23	29	0.432±0.10

cording to the LSA_2L_2 protocol [4]. Laparotomy was done in all NHL children with their primaries in the abdomen. In eight children the intra-abdominal tumor had been completely resected primarily. Eight children had presented with nonresectable tumor. Thirty-five of 44 children received radiation therapy to the involved field. The dose range varied from 11 to 45 Gy. In cases of widespread abdominal disease the whole abdomen was treated to 20 Gy, and second-look laparotomy in the 4th to 5th week of the induction phase was performed. Thirty-five children (stages I–IV) achieving a complete remission received prophylactic treatment of the CNS (10 MTX only, 14 cranial irradiation with 18 Gy and MTX, 11 radiogold intrathecal and MTX).

II. High-Risk Acute Lymphoblastic Leukemia

Eighty-two consecutive children with high-risk acute lymphoblastic leukemia were entered into the nonrandomized LSA_2L_2 study between January 1978 and April 1981. Patient characteristics are given in Table 2. Children with non-Hodgkin's lymphomas who had 25% or more tumor cells in the bone marrow were included.

The criteria for high-risk factors were defined as:

1. Leukocyte counts of 50,000 per/mm^3 and more.
2. Mediastinal mass.
3. T-ALL (blast cells from spontaneous rosettes wich sheep erythrocytes).
4. Positive acid phosphatase reaction of the blast cells.
5. CNS leukemia at diagnosis.

As CNS prevention therapy all children received combined intrathecal injections of methotrexate and prednisolone during induction and consolidation therapy and periodically throughout the continuation treatment. In addition, 30 children received preventive cranial irradiation (18 Gy) and 34 received intrathecal application of macrocolloidal radiogold (range 1.5–6.5 mCi).

B. Definitions

Complete remission (CR) is defined by the absence of all symptoms and signs of lymphoma. The duration of CR is the time from the end of the induction phase and the first sign of relapse. Children who died during remission are considered to be therapeutic failures and counted as relapses. Calculation of actuarial estimates of remission has been performed by the Life Table Method [2].

C. Results and Conclusions

I. Non-Hodgkin's Lymphoma

Forty of the 44 children could be evaluated for their response to induction therapy. Four patients were still not in remission at the cut-off date (31 December 1981). The complete remission frequency was 35 out of 40 (88%). The overall actuarial estimate of

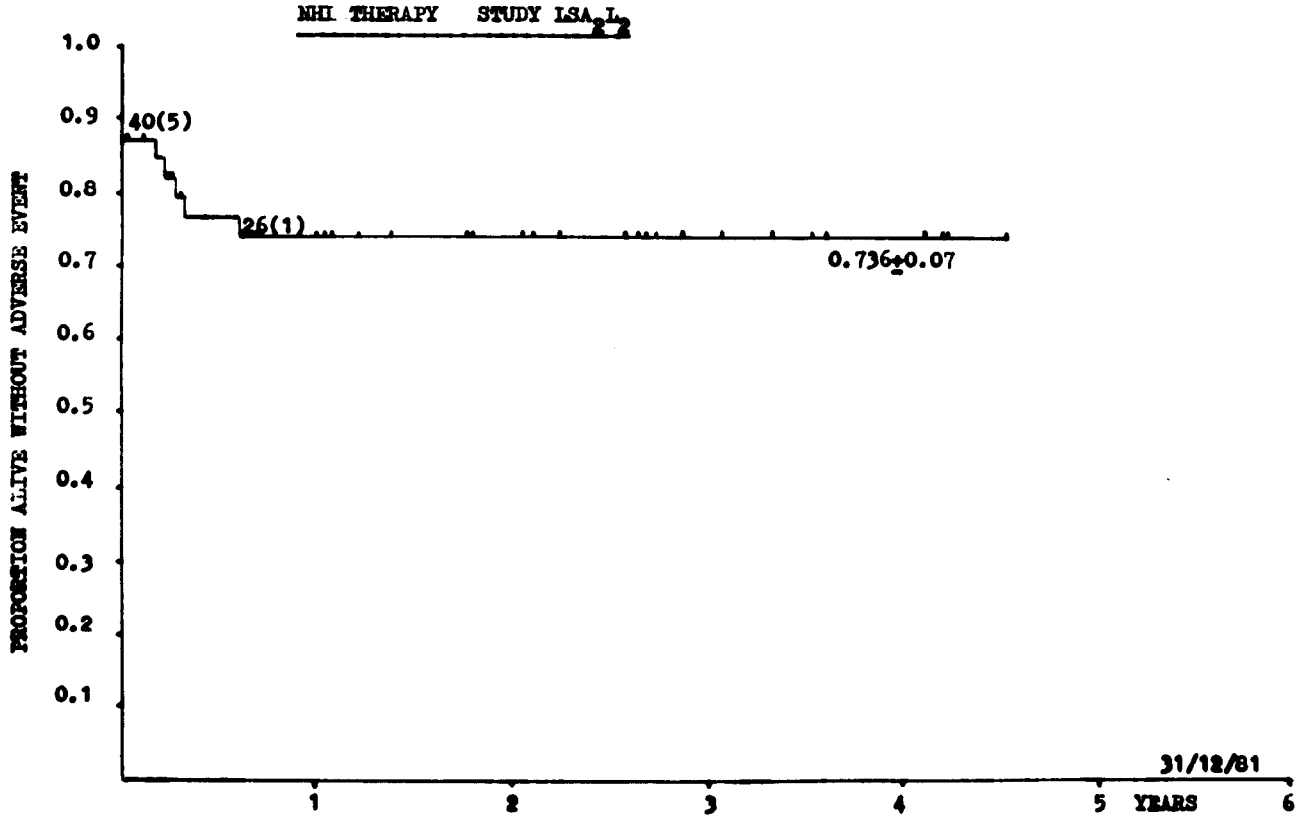

Fig. 1. Actuarial disease-free survival for the total NHL patient population

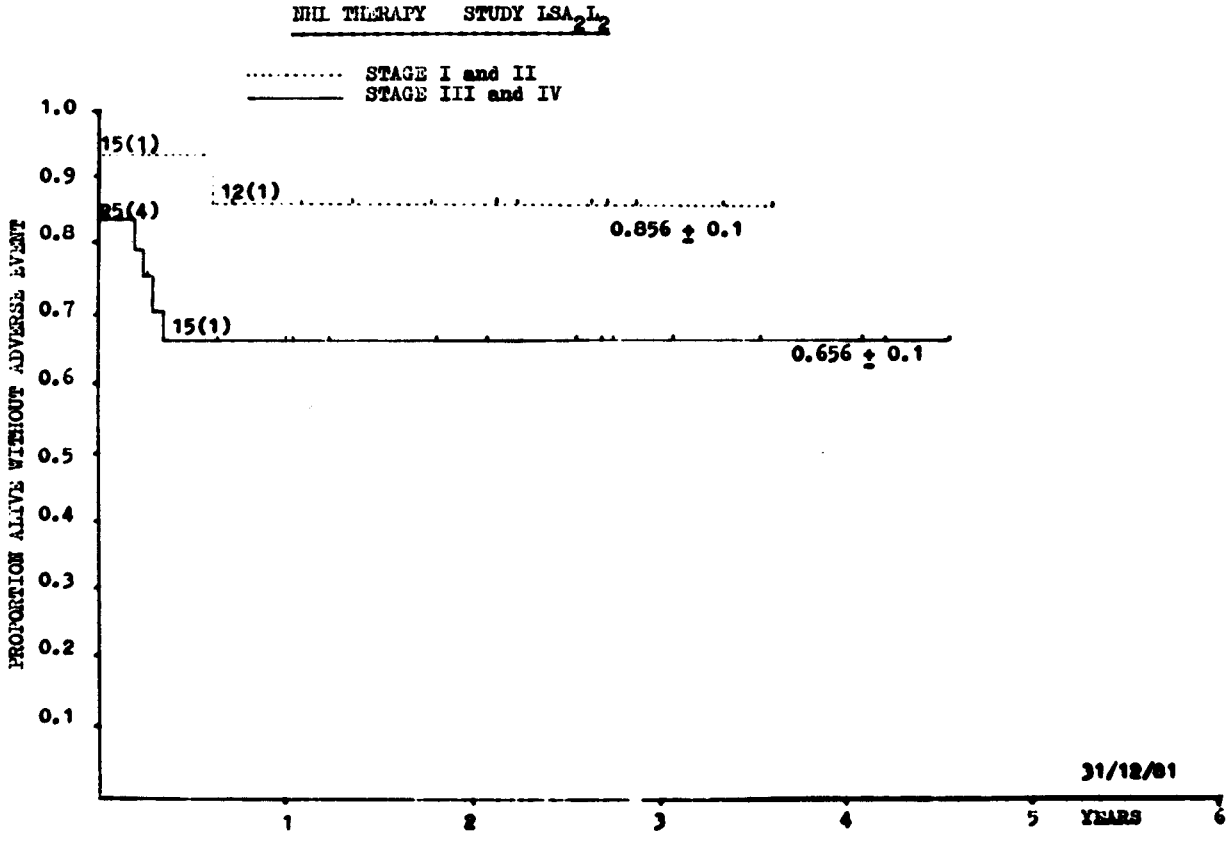

Fig. 2. Actuarial disease-free survival for NHL children with stage I–II disease and stage III–IV disease

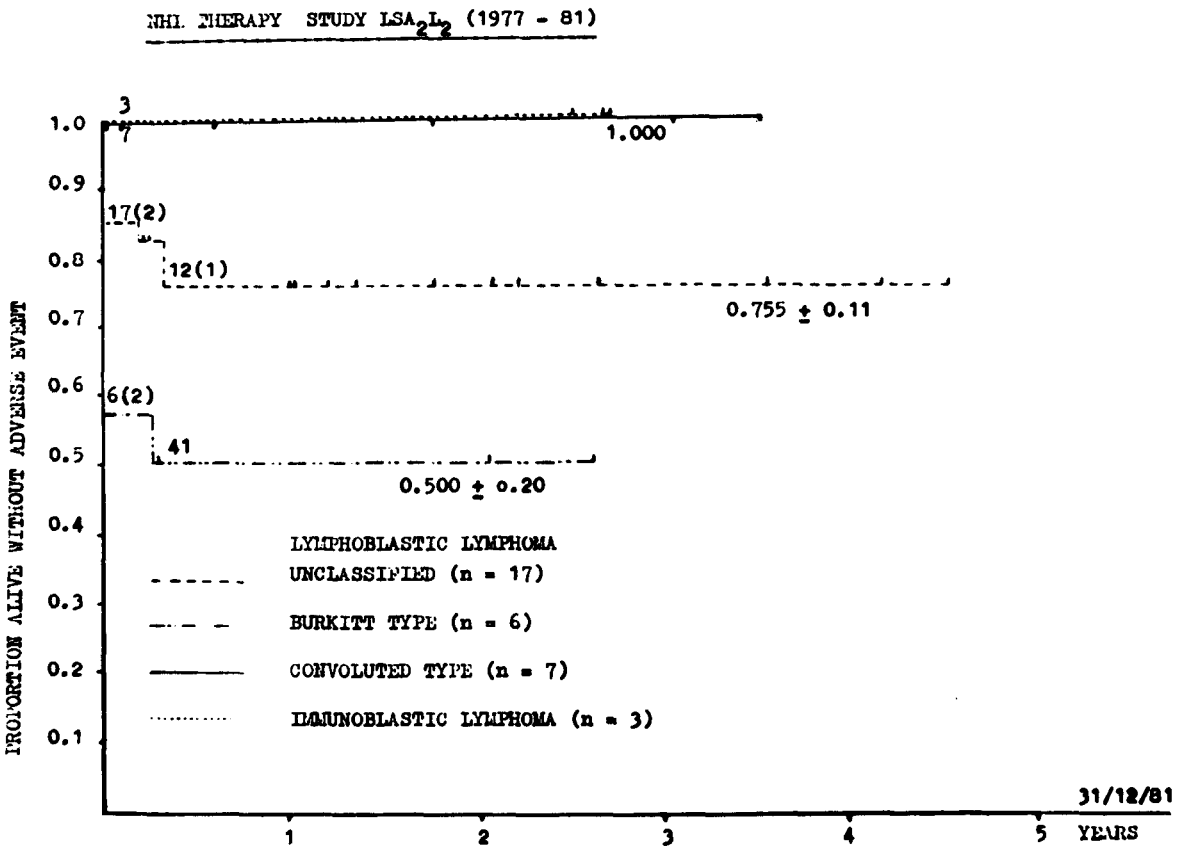

Fig. 3. Actuarial disease-free survival for NHL children with different histology (Kiel classification)

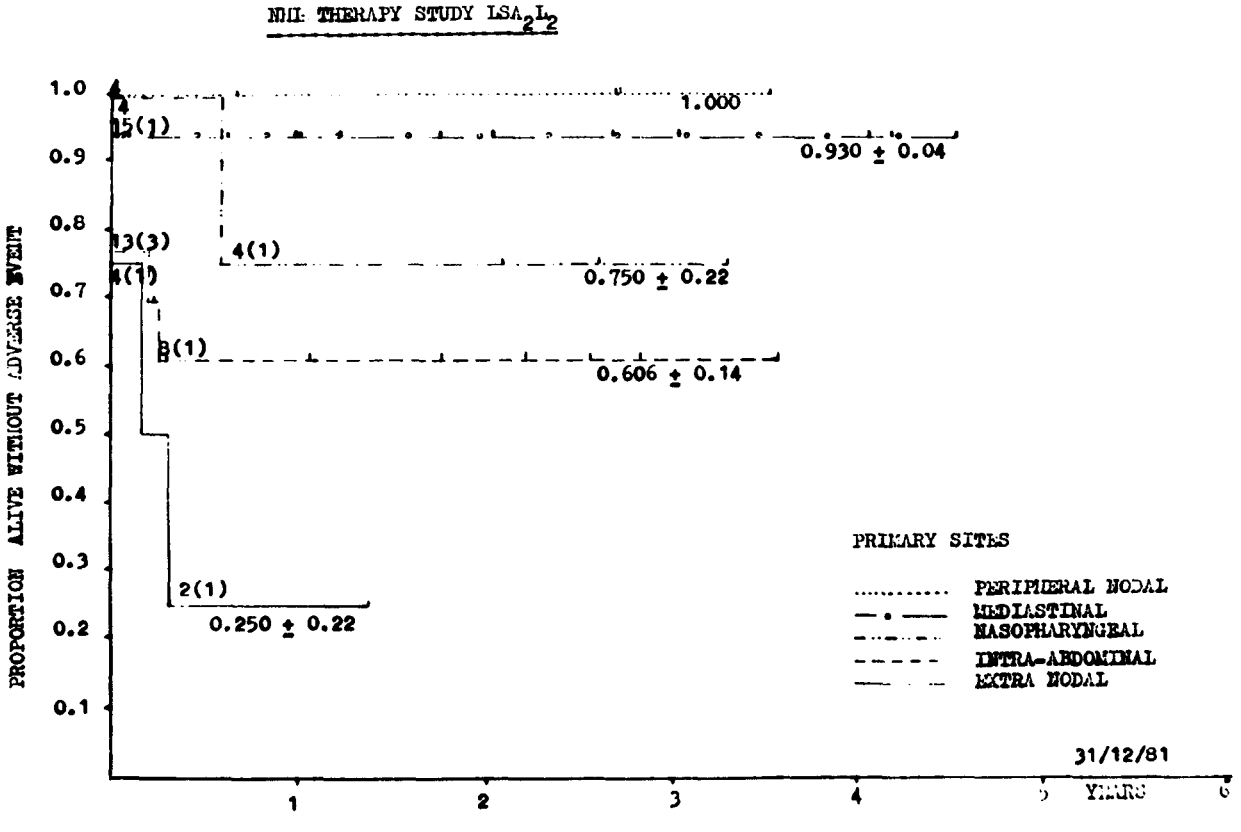

Fig. 4. Actuarial disease-free survival for NHL children with different primary sites of disease

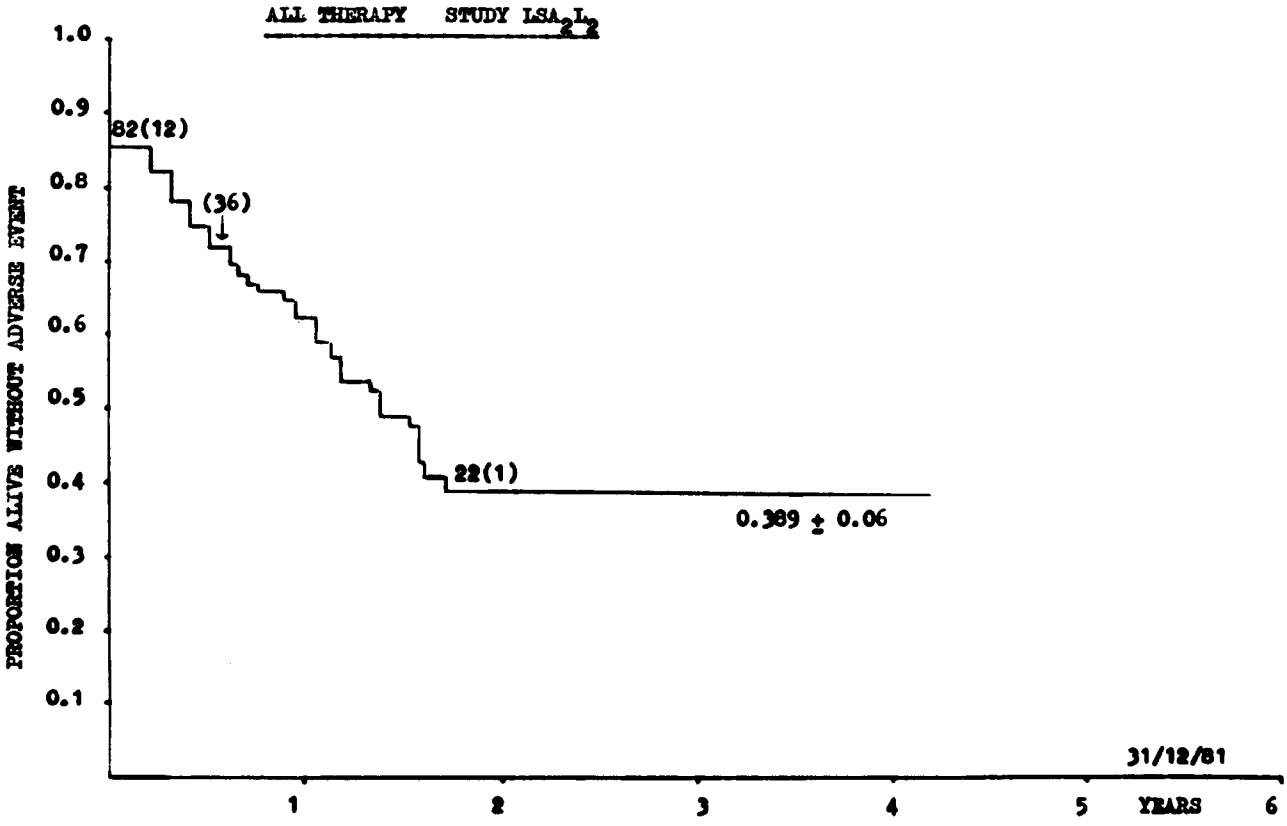

Fig. 5. Actuarial disease-free survival for total high-risk ALL patient population

disease-free survival for complete responders is 73.6% (Fig. 1). Children with stage I and II disease had significantly superior disease-free survival than did children with stages III–IV (Fig. 2). The influence of histological type and the location of the primary tumor on the outcome of treatment is shown in Figs. 3 and 4.

II. High Risk Acute Lymphoblastic Leukemia

The results are summarized in Fig. 5 and Table 2. Seventy of the 82 (85%) attained complete remission after 4 weeks of therapy. Twelve children died during the induction phase. Another three children died during maintenance therapy. The cumulative proportion in continuous complete remission is 0.39 (SD = 0.06) (Fig. 5). ALL relapses [31] occurred during the first 2 years, 12 of them concerning patients with WBC above 100,000/mm³. Patients with thymic involvement did no worse than those who had no mediastinal mass. Five of eight children with initial CNS involvement died during induction therapy phase or relapsed. CNS relapses occurred only in the radiogold group (8 of 34).

We found the LSA_2L_2 protocol was highly effective for children with lymphoblastic lymphoma (73% relapse-free survival), but inferior (39% relapse-free survival) for patients with high-risk lymphoblastic leukemia.

Patients with stage I or II NHL have similar survival rates irrespective of treatment with the LSA_2L_2 protocol or less-aggressive therapy. A less-aggressive treatment should be used for these children to avoid therapeutic complications and late sequelae.

References

1. Gerard-Marchant R, Hamlin J, Lennert K, Rilke F, Stansfiels AG, van Unnik JAM (1978) Classification of non-Hodgkin's lymphomas. Lancet II:406–408
2. Kaplan EL, Meier P (1980) Nonparametric estimation from incomplete observation. J Am Statist Assoc 53:457–481
3. Murphy SB, Hustu HO (1980) A randomized trial of combined modality therapy of childhood non-Hodgkin's lymphoma. Cancer 45:630–637
4. Wollner N, Burchenal JH, Lieberman PH, Exelby P, D'Angio G, Murphy ML (1976) Non-Hodgkin's lymphoma in children. Cancer 37:123–134