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

Multicentre Pilot Study for Therapy of Acute Lymphoblastic and Acute Undifferentiated Leukemia in Adults*

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In 1978 a study group was formed in the Federal Republic of Germany for the treatment of acute lymphoblastic leukemia (ALL) und acute undifferentiated leukemia (AUL) in adults. A modified form of an intensive induction and consolidation regimen successful in children with ALL [1] was used. The objective was to determine whether a prolonged remission induction and the addition of the drugs cyclophosphamide, cytosine-arabinoside and 6-mercaptopurine to the more conventional drugs for induction therapy of ALL, vincristine, prednisone, daunorubicin and L-asparaginase would improve the long-term results. It was hoped that a large number of hospitals would participate and that, with a sufficient number of patients uniformly treated, it would be possible to determine prognostic factors and to identify risk groups. This report concerns the design of the study, the toxicity of the therapeutic regimen and the first results.

I. Design of Study

In this multicentre, prospective, non-randomised study, patients between 15 and 65 years of age with ALL or AUL were treated according to the protocol. Excluded from the study were patients with previous intensive chemotherapy or severe pre-existing somatic or psychiatric disease.

* Supported by the Bundesministerium für Forschung und Technologie, Förderungs Nr. 01 ZW 450

II. Diagnostic

The aim was to have central diagnosis for all participating insitutes including morphology and cytochemistry, cell surface marker studies and determination of terminal deoxynucleotidyl transferase (TdT). This central execution of the diagnostic required a considerable amount of organisation and expense and could thus be only partially achieved during the pilot study.

The *morphological* diagnosis was made on the basis of Giemsa staining of blood and bone marrow smears and the cytochemical reactions PAS, peroxidase, naphthyl acetate esterase. To avoid delay, therapy was commenced according to the diagnosis made locally and, in addition, blood and bone marrow smears were stained and reviewed in one centre (H. Löffler, Kiel). Considered as ALL were cases with PAS-positive blasts and as AUL cases with blasts negative in all cytochemical reactions and without signs of granulopoietic differentiation [2].

The *immunological* diagnosis by cell surface marker analysis of blood and bone marrow cells was made in Munich (E. Thiel) for all participating institutions. According to methods already described [3], ALL should be classified into subtypes (c-ALL, c/T-ALL, pre-T-ALL, T-ALL, B-ALL) and morphological AUL identified either as a subtype of ALL, as unclassifiable "Null"-ALL or possibly as myeloid or erythroid leukemia. Furthermore, the enzyme terminal deoxynucleotidyl transferase was determined centrally by a biochemical and immunofluorescence assay (H. Bodenstein, Hannover).

III. Therapy

The treatment comprises induction therapy with CNS-prophylaxis, consolidation therapy and continuous maintenance therapy over 2 years. The 8-week *induction* regime (Fig. 1) consists of two phases: *Phase I* prednisone, 60 mg/m² p.o., days 1–28, vincristine 1.5 mg/m² i.v. weekly, days 1, 8, 15, 22, daunorubicin 25 mg/m² i.v. weekly, days 1, 8, 15, 22, L-asparaginase 5,000 u/m² i.v., days 1–14; *Phase 2*, cyclophosphamide 650 mg/m² i.v., days 29, 43, 57, cytosine-arabinoside 75 mg/m² i.v. for 4 days × 4, days 31, 38, 45, 52, 6-mercaptopurine 60 mg/m² p.o., days 29–57. The *CNS-prophylaxis,* following achievement of complete remission, consists of methotrexate 10 mg/m² i.th., days, 31, 38, 45, 52 and CNS-irradiation with 24 Gy. A 6-week *consolidation* course (Fig. 2) is given after 3 months similar to the induction regime but with dexamethasone and adriamycin instead of prednisone and daunorubicin and without L-asparaginase. *Maintenance* therapy comprises 6-mercaptopurine 60 mg/m² p.o. daily and methotrexate 20 mg/m² p.o. or i.v. weekly for a period of 2 years.

Patients with a leucocyte count over 25,000 cells/µl and/or large tumour masses may receive a pre-phase therapy with vincristine and prednisone. A 1- to 2-week interval may be inserted between phase 1 and phase 2 of the induction therapy when the blood values or the clinical status require it. Since it was expected that drug toxicity would be higher for adolescents and adults than for children, the induction therapy of the West Berlin scheme was modified by reducing L-asparaginase in dose and duration and the other drugs in dose. In the consolidation therapy, L-asparaginase was omitted altogether as was also the intrathecal methotrexate and the dose reduced for the other drugs. Furthermore, in view of the greater risk of bleeding, particularly of cerebral haemorrhage, in patients over 35 years, it was recommended

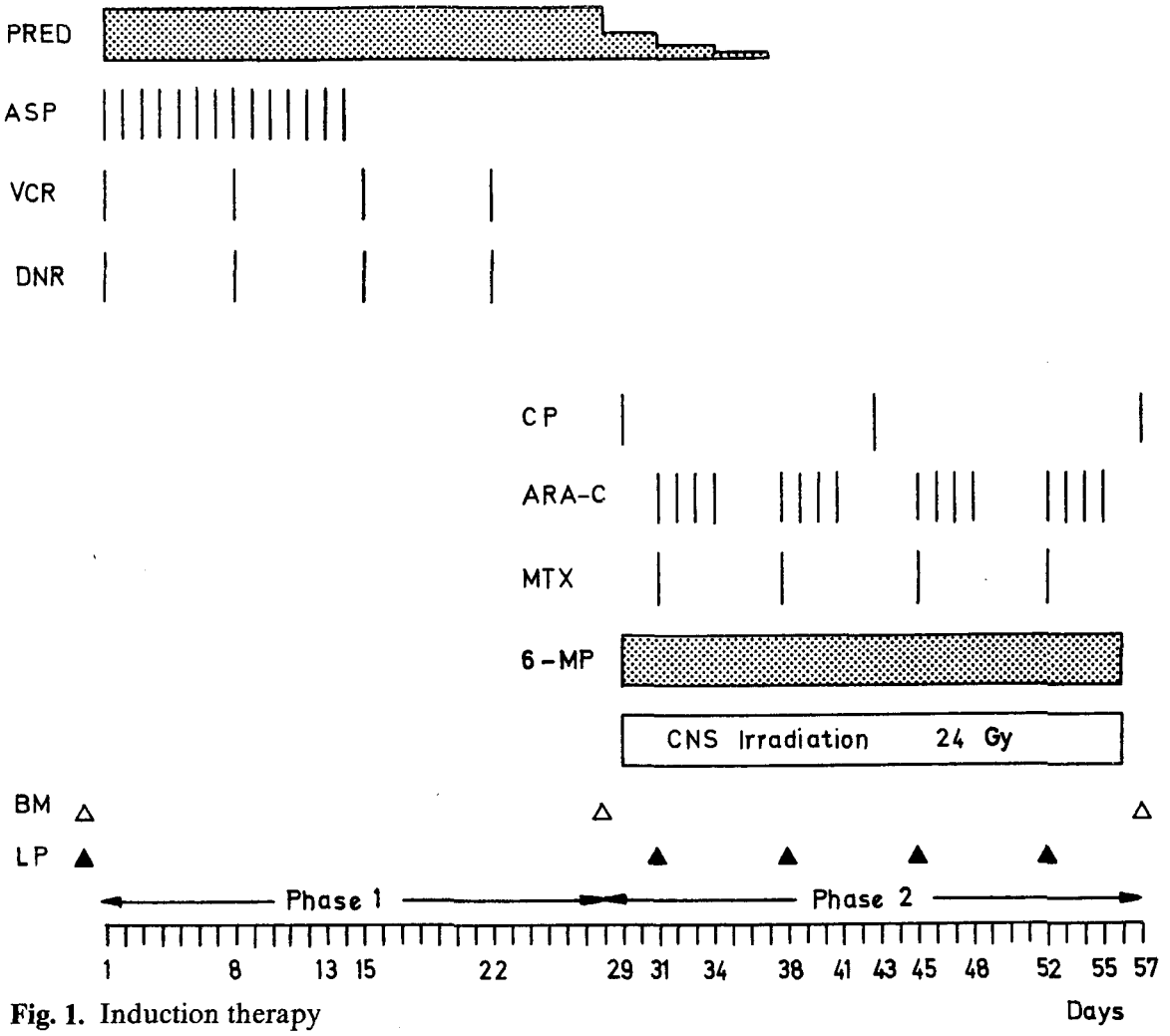

Fig. 1. Induction therapy

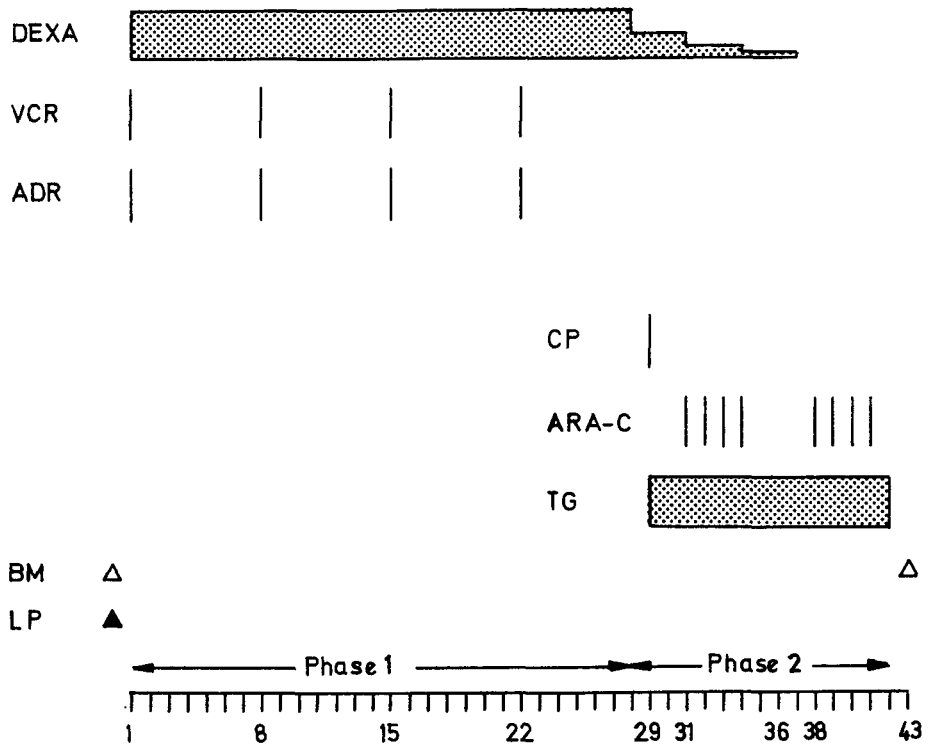

Fig. 2. Consolidation therapy

that in the induction therapy L-asparaginase should only be started when platelets were above 50,000/µl following the initial therapy. In addition, the dose of drugs in phase 2 was reduced to 2/3 in patients of this age group.

IV. Statistical Evaluation

Collection of data and its statistical evaluation was carried out at the Biometrical Centre for Therapy Studies (D. Messerer and T. Zwingers) in Munich. To assess therapeutic results, bone marrow samples were taken after phase 1 and phase 2 of the induction therapy (Fig. 1). Complete remission (CR) rate was the percentage of patients in complete remission after phase 2 of induction therapy, remission duration was timed from the first M_0 or M_1 bone marrow to relapse, death or last follow-up in CR and survival time from diagnosis to death or last follow-up. The Kaplan-Meier [4] method was used to calculate curves for remission duration and survival time.

V. Recruitment of Patients

Participation in the therapy study was open to all hospitals in the Federal Republic of Germany that had sufficient experience in the treatment of malignant disease and the means to provide adequate supportive therapy. The pilot study started in October 1978 and closed at the end of June 1981. During this time, 170 patients from 25 hospitals were recruited, 162 of whom were eligible. The closing date for this analysis was May 30, 1982.

The main phase was activated on July 1, 1981, and up to May 30, 1982, 101 additional patients accrued but are not considered in this evaluation.

A. Results

A complete remission was attained by 77.8% (126/162) of the patients, a partial remission by 3.7% and 18.5% were failures

Table 1. Results of induction therapy

		CR	PR	F
Total		77.8% (126)	3.7% (6)	18.5% (30)
Age	≦35 J.	81.0%	3.3%	15.7%
	>35 J.	68.3%	4.9%	26.8%
Diagnosis	ALL	77.3%	4.1%	18.6%
	AUL	78.5%	3.2%	18.5%

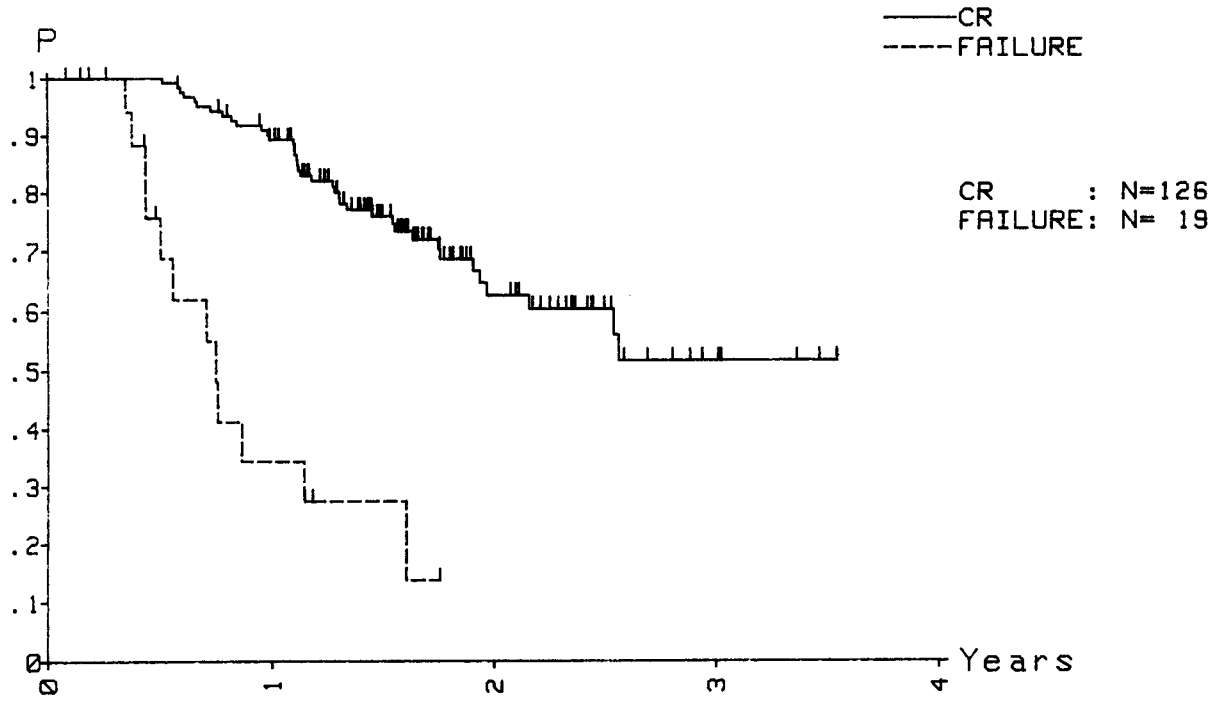

Fig. 3. Survival time (cumulative proportion alive) of patients with complete remission or failure to respond

(Table 1). The complete remission rate for patients under 35 years was 81.0%, for those over 35 years 68.3%. Regarding the morphological and cytochemical diagnosis of ALL or AUL, there was no difference between the remission rates of 77.3% and 78.5%. The median duration of remission for the 126 patients who reached CR was 20 months (confidence limits, 19–21 months). The median survival time for all 145 patients who completed the induction therapy was 31 months. For the 126 patients with CR, the median survival time (Fig. 3) has not yet been reached (last observation 43 months); for the non-responders (without death during the induction period) the median was 9 months.

Table 2. Toxicity during induction therapy

	Moderate	Severe
Infection	17%	9%
Sepsis	7%	5%
Haemorrhage	6%	6%
Stomatitis	1%	–
Gastrointestinal side effects	9%	2%
Hepatotoxicity	11%	2%
Pulmonary toxicity	1%	1%
Cardiotoxicity	1%	–
Neurotoxicity	8%	1%
Psychosis (steroid)	3%	–
Other	7%	6%

I. Toxicity

The frequency of moderate and severe toxicity is given in Table 2. The most common complications were infection, including sepsis, and haemorrhage. Gastrointestinal side effects and hepatotoxicity were most probably drug related as well as the neurotoxicity induced by vincristine. Pulmonary toxicity and cardiotoxicity were seldom observed. Seventeen (10.5%) of the 162 patients died during induction therapy. The most frequent causes of death were haemorrhage, particularly cerebral and gastrointestinal, and resistant infections, particularly pneumonia and sepsis. Death occurred mainly (15/17) in phase 1 and correspondingly seldom (2/17) in phase 2 of the induction therapy.

B. Discussion

The observation time for this study was too short to provide any conclusive information on the long-term results of the intensified induction and consolidation regimen. However, a reasonable number of 170 ALL/

AUL patients could be recruited and together with the 101 patients from the first 11 months of the main phase study a total of 271 patients entered the trial, which is a substantial proportion of patients with that disease in the Federal Republic of Germany.

The success of the intensified induction regime is demonstrated by the complete remission rate of 77.8%, which is relatively high compared to other multicentre trials (literature summarised by Esterhay et al. [5]), especially when the large number of participating institutes is considered. A better response rate was seen for younger patients as in other trials. However, except for hepatomegaly, no other clinical and laboratory features had any statistically significant influence on the achievement of complete remission. Also for the morphologically defined acute lymphoblastic and acute undifferentiated leukaemia the CR rate was very similar.

The protocol seems tolerable with regard to toxicity and manageable even in patients over 35–65 years. The main complications were, as in other studies, bleeding and infection. Pulmonary toxicity and cardiotoxicity were seldom seen, the latter probably because of the low dosage of daunorubicin. The frequency of death during induction is of a similar order as in other adult ALL trials, and the main causes of death were bleeding and infection. Since only two patients died during the intensive phase 2 of the induction therapy with the drugs cyclophosphamide, cytosine-arabinoside and 6-mercaptopurine, whereas the majority of patients died in phase I, it seems reasonable to assume that death was due not only to drug toxicity but also to the advanced stage of the disease.

Regarding the long-term results, the median remission duration (MRD) of 20 months (confidence limits, 19–21 months) is one of the longest observed in large trials [5], apart from the superior results in a monocentric study where the very intensive L10/L10M protocol was used [6]. The survival time for the complete responders reflects the MRD. Preliminary analysis gave as possible prognostic factors: the time needed to achieve CR (i.e. the number of therapy courses required), age, initial leucocyte count and the immunological subtype. The observation time was, however, as yet too short to provide a reliable assessment of their significance.

Reference

1. Riehm H, Gadner H, Henze G, Langermann H-J, Odenwald E (1980) The Berlin childhood acute lymphoblastic leukemia therapy study, 1970–1976. Am J Pediatr Hematol Oncol 2:299–306
2. Loeffler H (1975) Biochemical properties of leukemia blast cells revealed by cytochemical methods: their relation to prognosis. In: Fliedner TM, Perry S (eds) Prognostic factors in human acute leukemia. Advances in the biosciences, vol 14. Pergamon Press, Vieweg & Sohn, Braunschweig, pp 163–173
3. Thiel E, Rodt H, Huhn D, Netzel B, Grosse-Wilde H, Ganeshaguru K, Thierfelder S (1980) Multimarker classification of acute lymphoblastic leukemia: evidence for further T subgroups and evaluation of their clinical significance. Blood 56:759–772
4. Kaplan EL, Meier P (1978) Nonparametric estimation for incomplete observations. J Am Stat Assoc 53:457–481
5. Esterhay RJ, Wiernik PH, Grove WR, Markus SD, Wesley MN (1982) Moderate dose methotrexate, vincristine, asparaginase, and dexamethasone for treatment of adult acute lymphocytic leukemia. Blood 59:334–345
6. Clarkson B, Schauer P, Mertelsmann R, Gee T, Arlin Z, Kempin S, Dowling M, Dufour P, Cirrincione C, Burchenal JH (1981) Results of intensive treatment of acute lymphoblastic leukemia in adults. In: Cancer. Achievements, challenges and prospects for the 1980s, vol. 2. Grune & Stratton, New York, London, pp 301–317