Haematology and Blood Transfusion Vol. 29
Modern Trends in Human Leukemia VI
Edited by Neth, Gallo, Greaves, Janka

Clinical Experiences with a Modified BFM Protocol in Childhood Acute Lymphoblastic Leukemia *

F. Zintl, H. Malke, and W. Plenert

A. Introduction

The most important problem in current therapy of childhood acute lymphoblastic leukemia (ALL) is a failure in over one-half of patients. We were unable to increase the failure-free survival of children with high risk ALL by a ten-drug regimen (modified LSA_2L_2) above 30% at 6 years [1].

The results of the West Berlin therapy study between 1970 and 1976 confirmed the hypothesis that intensification and prolongation of remission induction produce a higher percentage of disease-free long-term survivors [2]. We decided in 1981 to adopt a modified BFM protocol for ALL therapy in our group [3]. This paper presents preliminary results of this multicenter randomized study.

* Universitäts-Kinderklinik Jena, Abt. Hämatologie/Onkologie/Immunologie, Kochstraße 2, 6900 Jena, GDR

B. Materials and Methods

I. Patients

A total of 208 consecutive, previously untreated children with ALL were entered in-

Table 1. Characteristics of patients in the study

Characteristics	Total		SR		MR		HR	
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)
Patients	208	100	133	100	60	100	15	100
Median age at diagnosis (years)	5	3/12	5	1/12	5	3/12	9	10/12
2 years	13	6	5	4	5	8	3	20
10 years	49	24	31	23	12	20	6	40
Boys	111	53	79	59	23	38	9	60
Median age at diagnosis (years)	5	10/12	5	5/12	5	4/12	11	0/12
Girls	97	47	54	41	37	62	6	40
Medianage at diagnosis (years)	4	9/12	4	10/12	5	2/12	3	10/12
Leukocytes 25 000/mm³	55	26	11	8	34	57	10	67
50 000/mm³	32	15	2	2	20	33	10	67
100 000/mm³	16	8		0	7	12	9	60
CNS involvement	9	4	5	4	2	3	2	14
Mediastinal mass	17	8	10	7	2	3	5	33
Liver 5 cm	67	32	15	11	37	62	15	100
Spleen 5 cm	57	27	9	7	33	55	15	100
Acid phosphatase positive	46	22	26	20	15	25	5	33

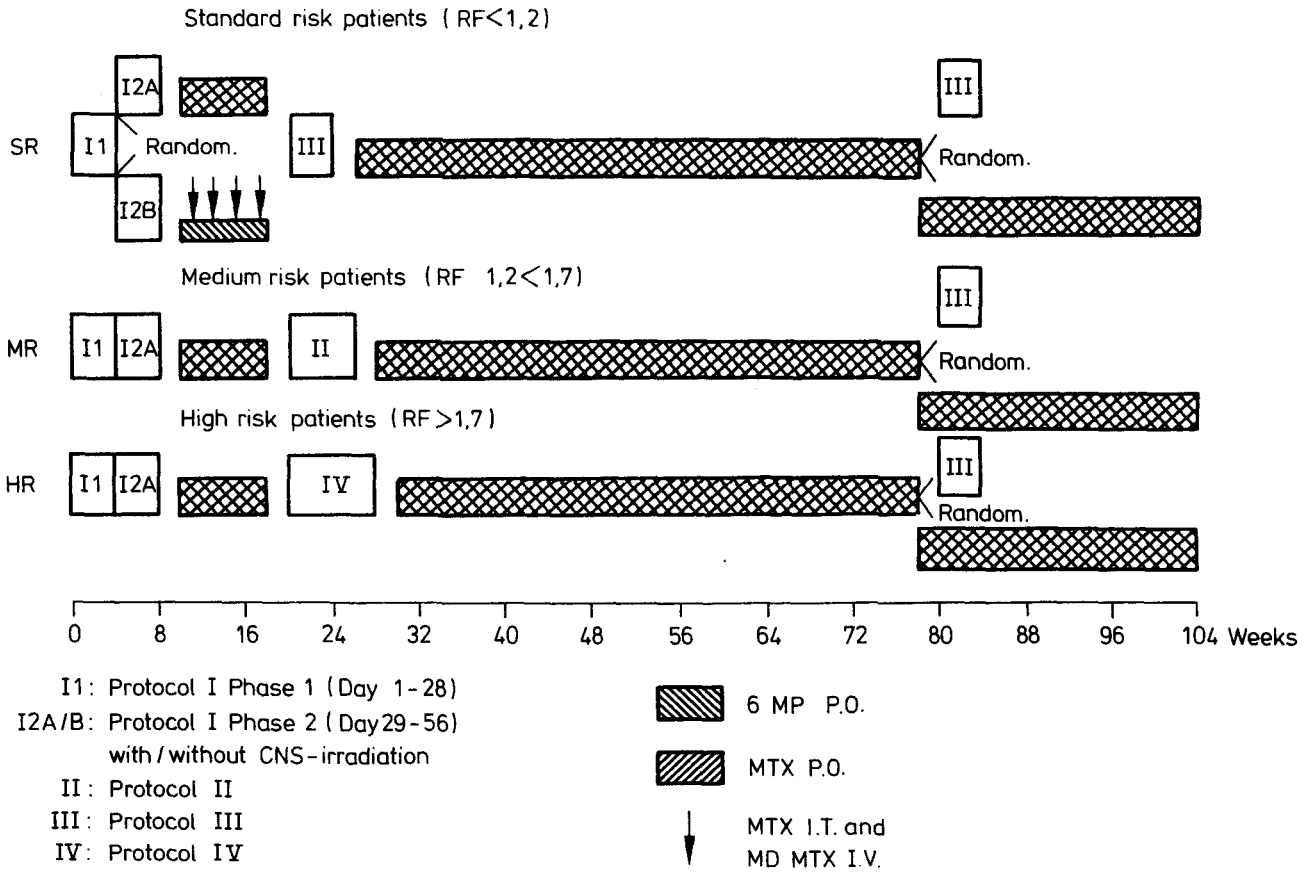


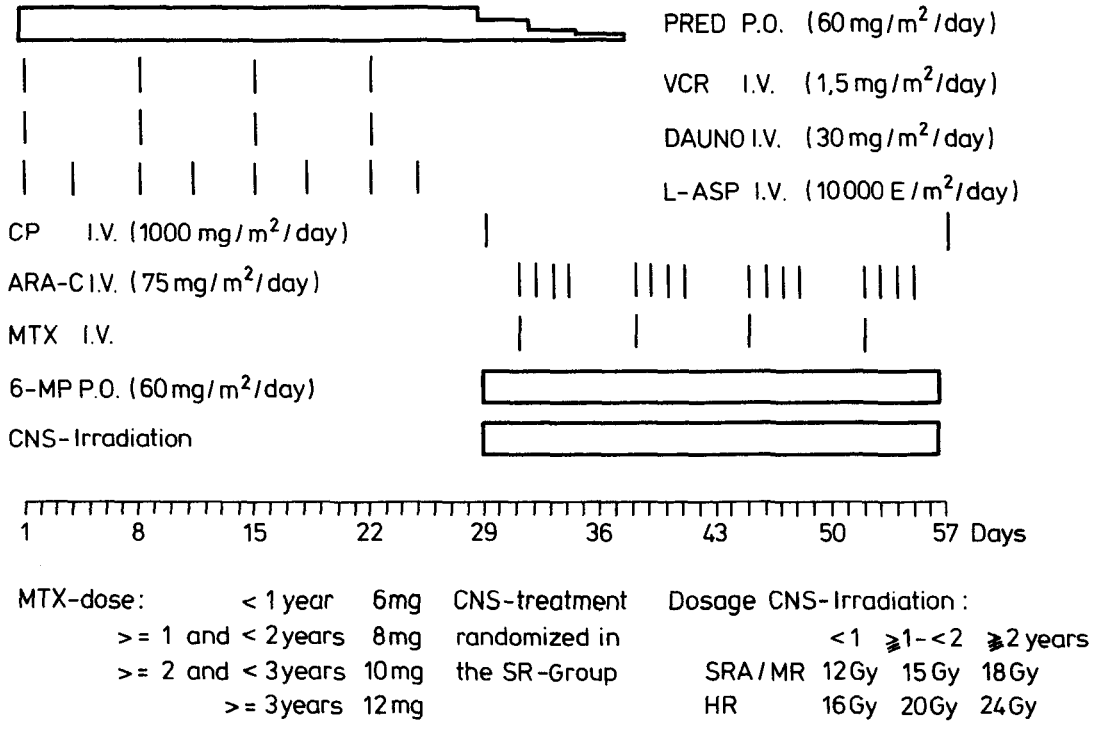
Fig. 1. Schedule for the modified BFM-protocol (ALL study VII/81)

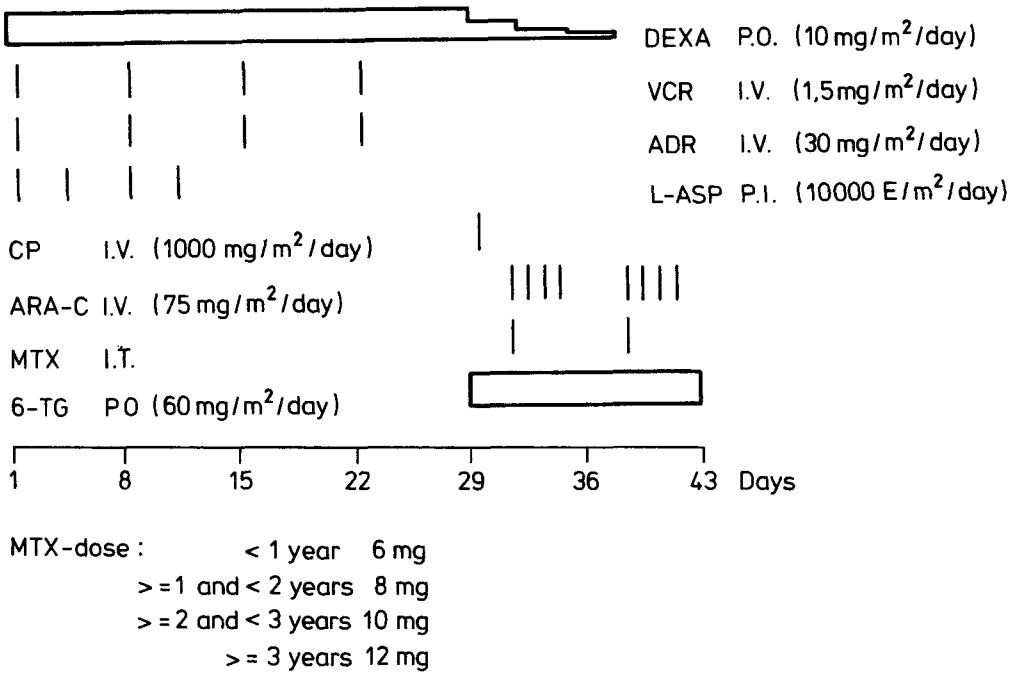
to the study (VII/81) between September 1981 and March 1984. Patients' characteristics are given in Table 1. Patients were divided into three risk groups according to the initial leukocyte count and liver and spleen enlargement: standard (SR), medium (MR), and high risk (HR) groups [4].

II. Treatment

The treatment comprises induction therapy with CNS prophylaxis, reinduction therapy, and continuous maintenance therapy (Figs. 1–5). The induction protocol I, con-

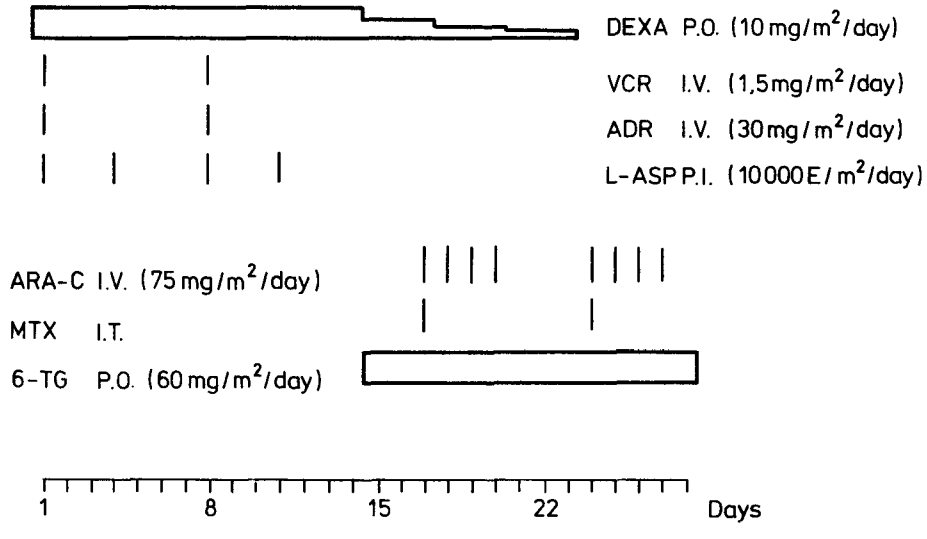
Fig. 2. Outline for the induction protocol





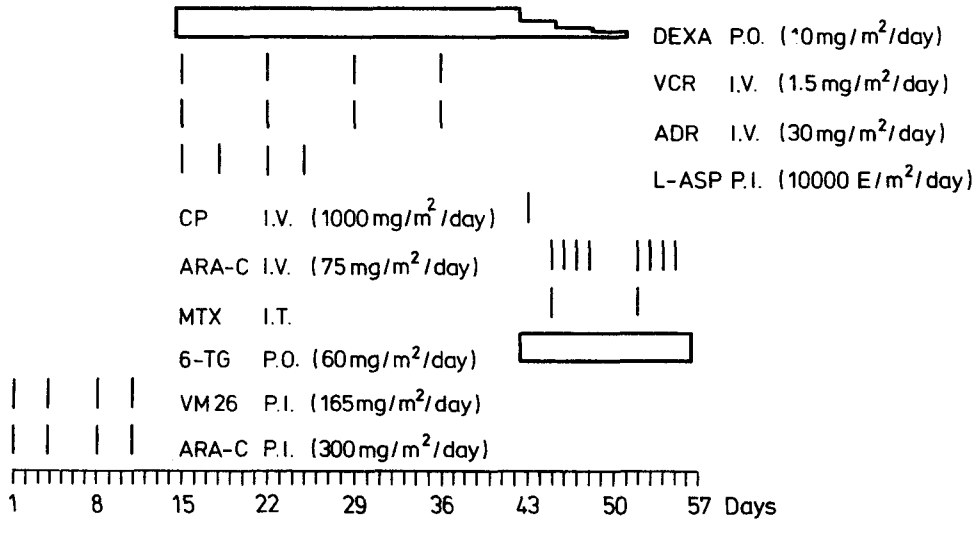
MTX-dose :
< 1 year 6 mg
>= 1 and < 2 years 8 mg
>= 2 and < 3 years 10 mg
>= 3 years 12 mg

Fig. 3. Outline for the re-induction protocol II (MR patients)



MTX-dose :
< 1 year 6 mg
>= 1 and < 2 years 8 mg
>= 2 and < 3 years 10 mg
>= 3 years 12 mg

Fig. 4. Outline for the re-induction protocol III (SR patients)



MTX-dose :
< 1 year 6 mg
>= 1 and < 2 years 8 mg
>= 2 and < 3 years 10 mg
>= 3 years 12 mg

Fig. 5. Outline for the reinduction protocol IV (HR patients)

sisting of two phases, was identical for each risk group. The reinforced reinduction protocols were risk adjusted: protocol III for SR, protocol II for MR, and protocol IV for HR patients. For prophylactic CNS therapy in the SR group, patients were randomized to receive cranial irradiation and intrathecal methotrexate (MTX) or medium dose methotrexate (500 mg/m^2) and intrathecal methotrexate (Fig. 1). For the duration of maintenance therapy, patients were randomized after 78 weeks to receive MTX and 6-MP for another 6 months or protocol III. The induction therapy of the BFM scheme was modified by reducing L-asparaginase in dose and duration. The reinduction with protocol III before stopping therapy was the second modification to the BFM protocol.

III. Statistical Analysis

Complete remission (CR) was defined as less than 5% bone marrow and no evidence of extramedullary leukemia. Kaplan-Meier analysis were performed for survival and continuous CR. Failure is defined as induction failure, initial relapse at any site, death during induction, or death during initial CR.

C. Results

Preliminary results are summarized in Table 2. It was found that 93% of patients attained CR after 4 weeks of therapy. The cumulative proportion in continuous CR is 0.77 ± 0.04 for the total group of 195 patients (Fig. 6). No significant difference was found between the treatment groups SR (0.83 ± 0.04) and MR (0.78 ± 0.07) (Fig. 7). Of 14 HR patients, 11 (79%) attained CR. One died in CR and four relapsed (three bone marrow relapses, one CNS relapse). Thus, the proportion in continuous CR was 0.19 ± 0.16. Of the total number of children, 12 relapsed. Eight patients had isolated marrow relapse. Isolated CNS relapses occurred in two children. One patient had a simultaneous marrow and CNS relapse and one patient had an isolated relapse in the eye. Patients with

Table 2. Summary of results

Results of therapy (0–30 months)	Total		SR		MR		HR	
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)
Patients	195	100	124	100	57	100	14	100
Not yet in remission	13		9		3		1	
Early deaths	9	5	5	4	1	2	3	21
Deaths in initial stage	5	3	3	3	2	4	0	
Complete remission	181	93	116	94	54	95	11	79
Deaths in remission	8	4	5	4	2	4	1	7
Relapses	12	6	4	3	4	7	4	29
BM	8	4	2	2	3	5	3	21
CNS	2	1	1	1	–	–	1	7
BM + CNS	1	1	–	–	1	2	–	–
Testes	–	–	–	–	–	–	–	–
Others (eye)	1	1	1	1	–	–	–	–
In first remission	161	82	107	86	48	84	6	43
Alive	168	86	109	88	50	88	9	64
Proportion in continuous complete remission	0.77±0.04		0.83±0.04		0.78±0.07		0.19±0.16	
Median time of remission (months)	12		12		12		12	

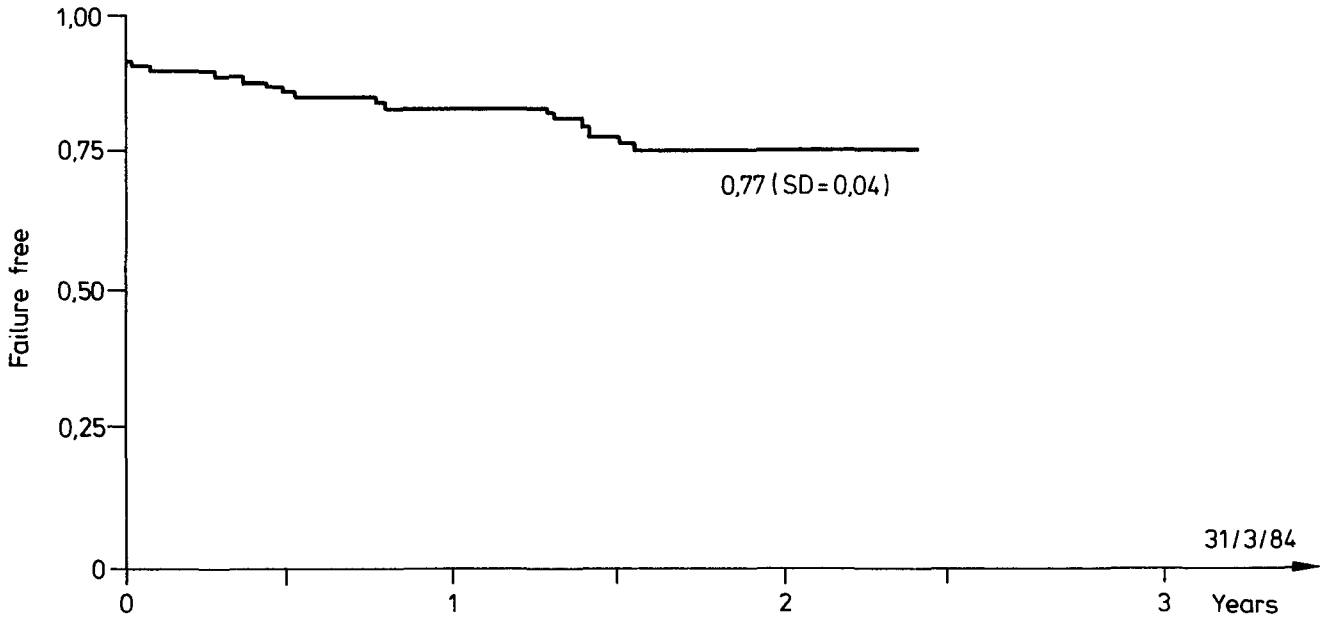


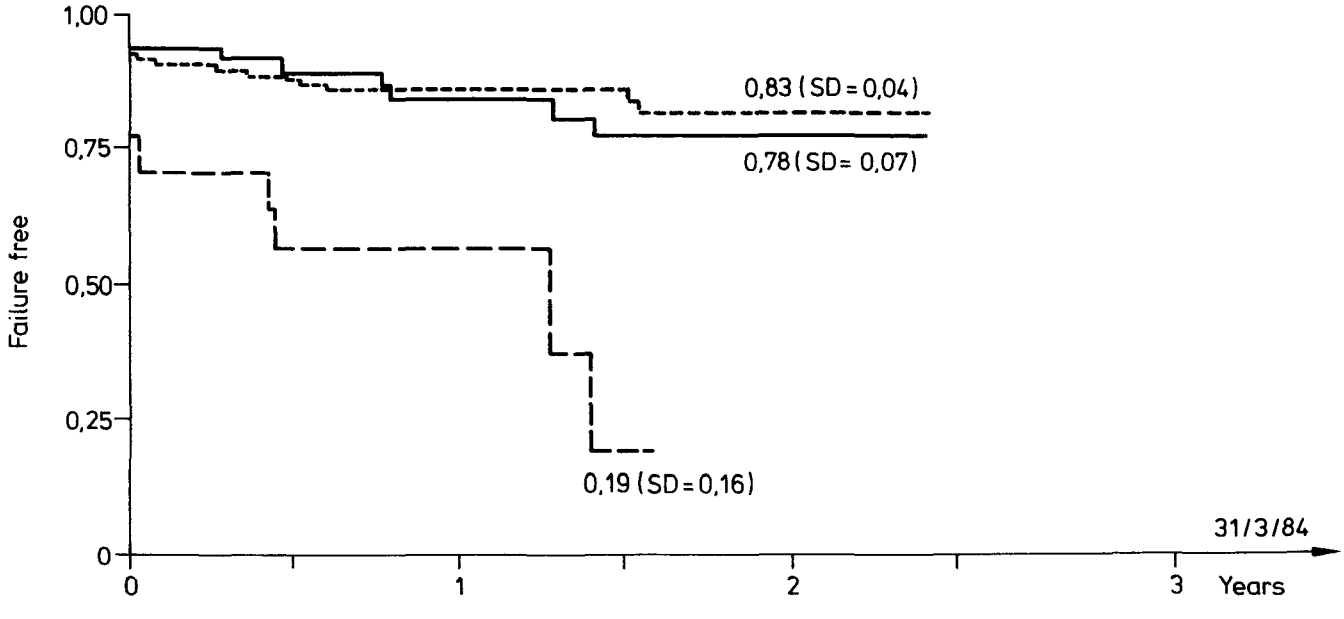
Fig. 6. Probability of continuous complete remission (195 patients, 161 in continous complete remission). Failure = end of remission by relapse or death for any reason

initial WBC above 50 Gpt/l did worse than those who had WBC below 150 Gpt/l (Fig. 8). There were no significant differences in failure-free survival in SR and MR patients with WBC greater or less than 125 Gpt/l. Within the groups of SR and MR patients, mediastinal mass was not significantly related to outcome. The differences over the total group for the parameters thymic involvement and age are closely related to high WBC in HR patients.

Fig. 7. Difference in the duration of continous complete remission (CCR) of the three risk groups. *Dotted line* standard risk (124 patients, 107 in CCR); *full line* medium risk (57 patients, 48 in CCR); *dashed line* high risk (14 patients, 6 in CCR)

D. Discussion

Kaplan-Meier life table analysis of failure-free survival data for 195 patients with ALL of different risk estimates that 77% ± 8% of patients will be in continuous CR 30 months after diagnosis. Although the median time of remission in our study is just 12 months, these results represent a marked improvement compared with former studies. Our results support the hypothesis of



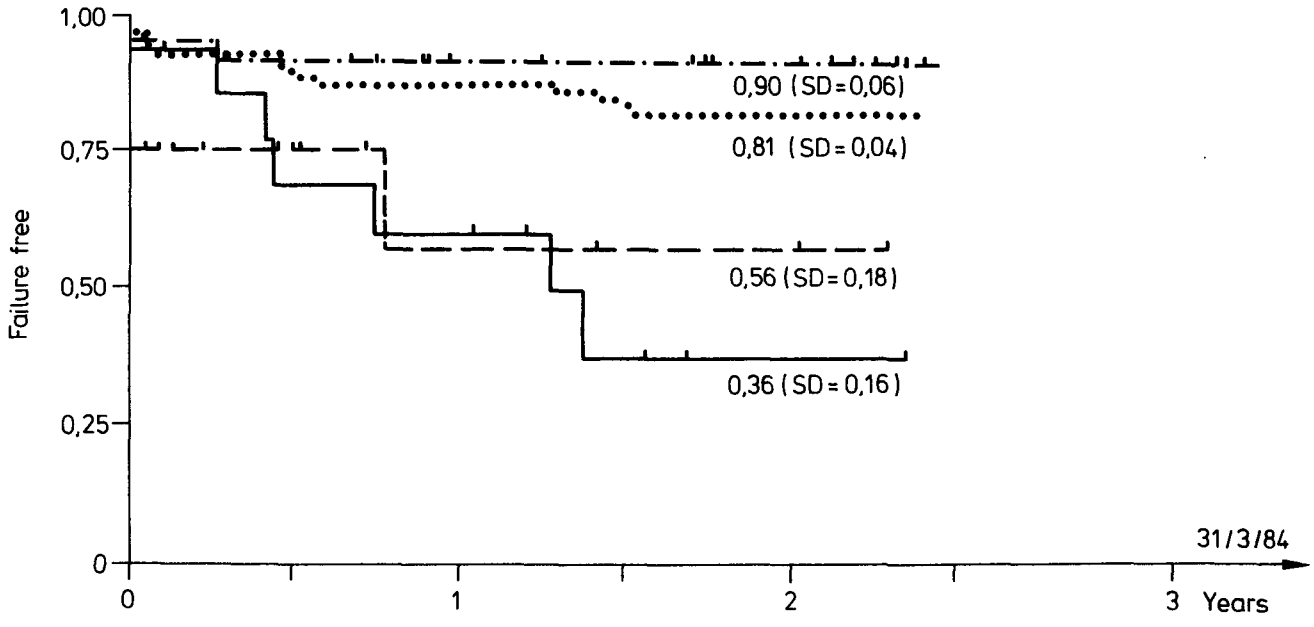


Fig. 8. Probability of continuous complete remission (CCR) in patients with different initial white blood cell counts. *Dotted line* <25 Gpt/l (142 patients, 122 in CCR); *dashed-dotted line* 25–50 Gpt/l (22 patients, 18 in CCR); *dashed line* 50–100 Gpt/l (16 patients, 11 in CCR); *full line* >100 Gpt/l (15 patients, 8 in CCR)

the BFM group that intensification and prolongation of remission induction produce a higher percentage of disease-free long-term survivors [2, 5]. Patients in the HR group (risk factor > 1.7) did worse than those in the SR and MR groups. This is in marked contrast to the results reported by the BFM group [5].

References

1. Zintl F, Hermann J, Katenkamp D, Malke H, Plenert W (1983) Results of LSA_2L_2 therapy in children with high risk acute lymphoblastic leukemia and non-Hodgkin's lymphoma. In: Neth R, Gallo RC, Greaves MF, Moore MAS, Winkler K (eds) Modern trends in human leukemia, vol V. Springer, Berlin Heidelberg New York Tokyo, pp 62–66
2. Riehm H, Gadner H, Henze G, Langermann HJ, Odenwald E (1980) The Berlin childhood acute lymphoblastic leukemia therapy study, 1970–1976. Am J Ped Hematol Oncol 2:299–306
3. Riehm H, Henze G, Langermann HJ (1981) Multizentrische Therapiestudie BFM 81 zur Behandlung der akuten lymphoblastischen Leukämie im Kindes- und Jugendalter. Studienprotokoll, 1981
4. Langermann HJ, Henze G, Wulf M, Riehm H (1982) Abschätzung der Tumorzellmasse bei der akuten lymphoblastischen Leukämie im Kindesalter: prognostische Bedeutung und praktische Anwendung. Klin Pädiatr 194:209–213
5. Henze G, Langermann HJ, Fengler R et al. (1982) Therapiestudie BFM 79/81 zur Behandlung der akuten lymphoblastischen Leukämie bei Kindern und Jugendlichen: intensivierte Reinduktionstherapie für Patientengruppen mit unterschiedlichem Rezidivrisiko. Klin Pädiatr 194:195–203