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Treatment Strategy for Different Risk Groups in Childhood Acute Lymphoblastic Leukemia: A Report From the BFM Study Group*

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A. Introduction

Development of effective treatment programs for childhood acute lymphoblastic leukemia (ALL) has led to marked improvement of prognosis. The proportion of patients remaining in first remission for at least 5 years is generally estimated to be in the range of 50% once remission is achieved (Frei and Sallan 1978; Riehm et al. 1980; Robison et al. 1980). Since remission rates have been shown to be 90%–95% with currently used induction therapy, successful induction of remission is no longer an essential problem. Nevertheless, the quality of remission is apparently unsatisfactory in about one-half of the patients, eventually resulting in recurrence of the disease. Predictors of outcome have been defined and include white blood count (WBC), sex, thymic involvement, central nervous system disease at diagnosis, immunologic markers, unfavorable age, and blast cell morphology (Dow et al. 1977; Henze et al. 1979; Mathé et al. 1971; Sallan et al. 1978; Simone et al. 1975; Wagner and Baehner 1979; Working Party on leukemia in Childhood 1978); but attempts to adapt the therapeutic strategy to the presence of factors associated with a poor prognosis have not been able to enhance significantly therapeutic results. The approach of the BFM study group with the concept of intensive multidrug remission induction gives hope for an overall 75% relapse-free survival in childhood ALL.

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B. Patients and Methods

Between October 1970 and March 1979, 277 children and adolescents were enrolled in sequence in two BFM acute lymphoblastic leukemia therapy studies. The treatment plans of study BFM 70/76 (Oct. 1970–Sept. 1976) and study BFM 76/79 (Oct. 1976–March 1979) are outlined in Figs. 1 and 2. All patients received Protocol I (Fig. 3) for remission induction. In study BFM 76/79 a risk index (RI) was established for definition of high risk patients (Table 1). Children with RI ≥ 3 received a reinforced reinduction protocol (Protocol II, Fig. 4) within the first 6 months after diagnosis. These patients were randomly allocated to either limb B1 or B2.

Diagnosis of ALL was made by morphologic analysis of stained bone marrow smears. Only children with a least 25% blasts in the bone marrow aspirate were diagnosed as having ALL; patients with less than 25% lymphoblasts were considered to be cases of non-Hodgkin's lymphoma and not included in this series. Relapse was diagnosed by the appearance of leukemic cells at any site. Patients who failed to achieve complete remission after 4 weeks of therapy were considered therapeutic failures and counted as relapses as were patients who died during remission induction or in continuous complete remission (CCR).

Methods of statistical analysis were the life table algorithm (Cutler and Ederer 1958) and Cox's regression model (Cox 1972). The date of evaluation for this report was 4 June 1980.

C. Results

Remission rates were comparable in both studies. Two patients with B-cell leukemia, one in study BFM 70/76 and one in study BFM 76/79, did not respond to therapy. Deaths during remission induction (five children in study BFM 70/76 and four children in study

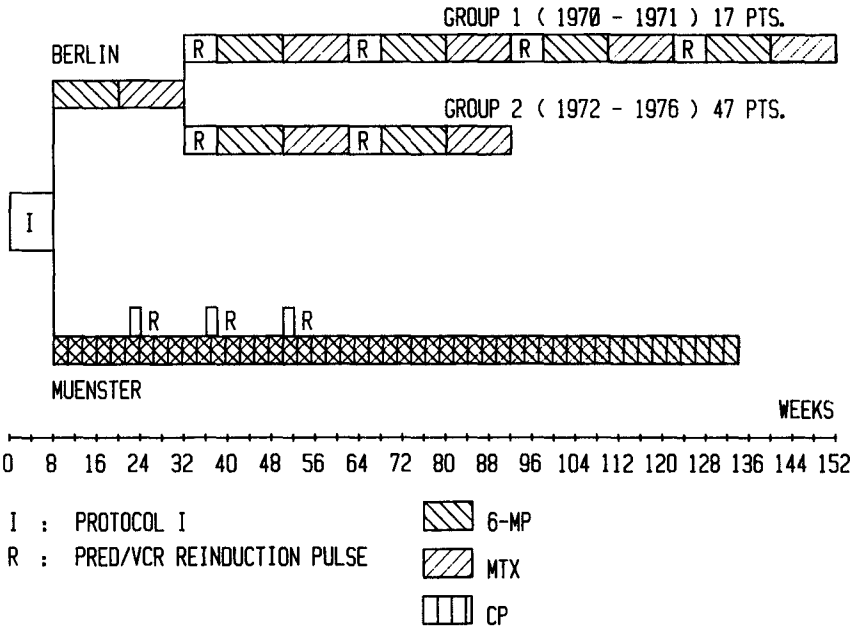

Fig. 1. Outline of study BFM 70/76. *PRED*, prednisone; *VCR*, vincristine, *6-MP*, 6-mercaptopurine; *MTX*, methotrexate; *CP*, cyclophosphamide

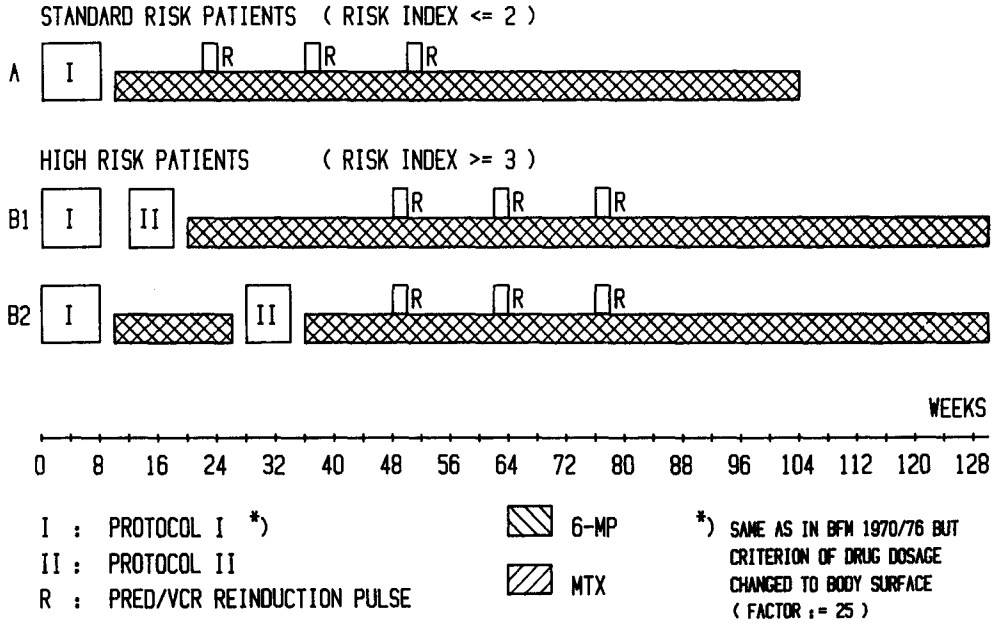

Fig. 2. Outline of study BFM 76/79. Abbreviations as in Fig. 1

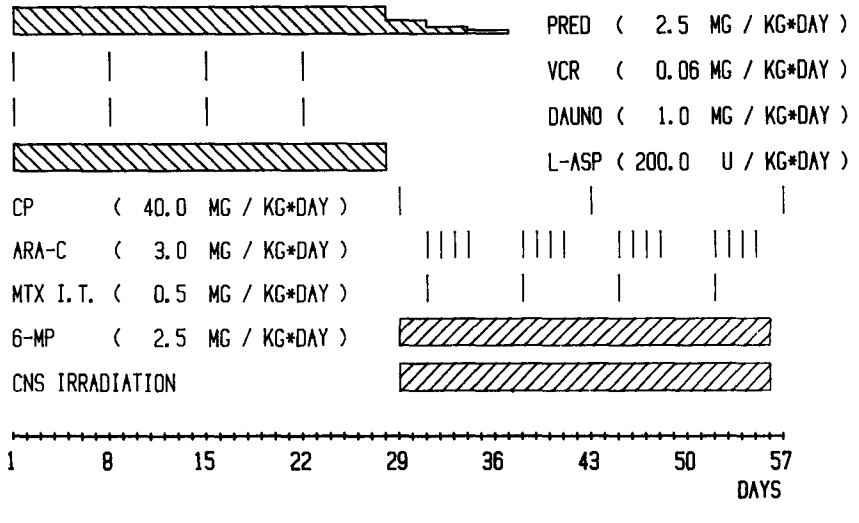

Fig. 3. Induction therapy: Protocol I, *PRED*, prednisone; *VCR*, vincristine; *DAUNO*, daunorubicin; *L-ASP*, asparaginase; *CP*, cyclophosphamide; *ARA-C*, cytarabin; *MTX*, methotrexate; *6-MP*, 6.mercaptopurine

Table 1. Determination of the risk index according to findings at diagnosis

Findings at diagnosis	Score
White blood count≥25E9/L	3
Leukemic cells in the spinal fluid	2
Thymic enlargement	1
Positive acid phosphatase and/or rosette formation test	1
Negative perjodic acid Schiff reaction (PAS reaction) Age<2 years or age≥10 years	1
Significant extranodal mass	1
	Risk index: = Score sum

BFM 76/79) were mainly due to infectious complications.

Fourteen patients (eight in study BFM 70/76, six in study BFM 76/79) died during remission. In 11 children death was related to infectious complications. Another three patients died of toxic side effects of therapy (pulmonary fibrosis caused by methotrexate, vincristine induced encephalopathy, and brain stem necrosis of unknown origin).

The probability of continuous complete remission (life table analysis) for patient groups with regard to initial clinical features is summarized in Table 2. Cox regression was used to estimate the influence of commonly

Table 2. Patient characteristics of studies BFM 70/76 and BFM 76/79 with corresponding probability of continuous complete remission (p-CCR) calculated by the life table method after 117 and 44 months, respectively

	BFM 1970/76		BFM 1976/79	
	No. (%)	p-CCR After 117 MTHS	No. (%)	p-CCR After 44 MTHS
Boys	78 (65.5)	0.55 ±/± 0.06	89 (56.3)	0.74 ±/± 0.06
Girls	41 (34.5)	0.57 ±/± 0.08	69 (43.7)	0.78 ±/± 0.06
Age < 2 yrs	10 (8.4)	0.50 ±/± 0.16	15 (9.5)	0.80 ±/± 0.10
Age 2–10 yrs	88 (73.9)	0.57 ±/± 0.06	107 (67.7)	0.85 ±/± 0.04
Age ≥10 yrs	21 (17.6)	0.52 ±/± 0.11	36 (22.8)	0.41 ±/± 0.14
Thymic mass	15 (12.6)	0.47 ±/± 0.13	14 (8.9)	0.74 ±/± 0.14
WBC< 25,000/mm³	79 (66.4)	0.63 ±/± 0.06	107 (67.7)	0.77 ±/± 0.05
WBC≥ 25,000/mm³	40 (33.6)	0.40 ±/± 0.08	51 (32.3)	0.72 ±/± 0.07
Risk index≤2	76 (63.9)	0.65 ±/± 0.06	103 (65.2)	0.77 ±/± 0.05
Risk index≥3	43 (36.1)	0.39 ±/± 0.08	55 (34.8)	0.75 ±/± 0.07
Total	119	0.55 ±/± 0.05	158	0.76 ±/± 0.04

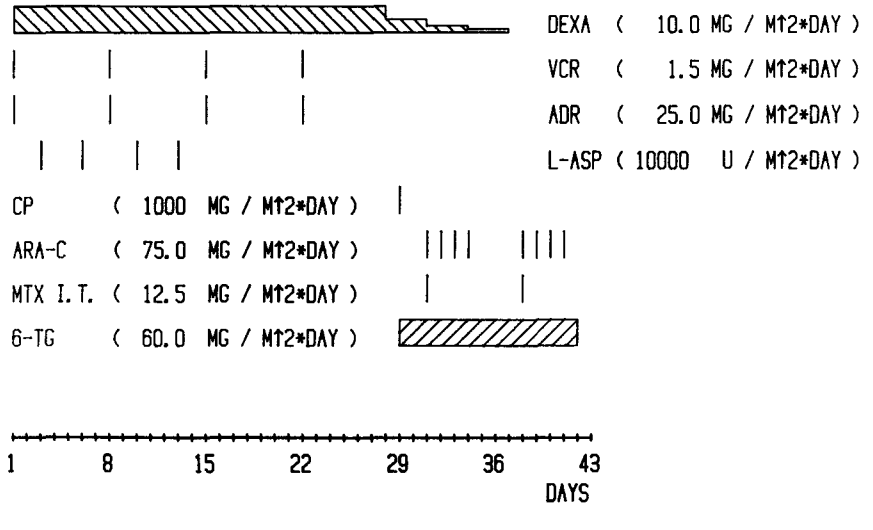

Fig. 4. Reinforced reinduction therapy: Protocol II. *DEXA*, dexamethasone; *VCR*, vincristine; *ADR*, adriamycin; *L-ASP*, asparaginase; *CP*, cyclophosphamide; *ARA-C*, cytarabin; *MTX*, methotrexate; *6-TG*, 6-thioguanine

Table 3. Influence of initial features on prognosis in study BFM 70/76 obtained by Cox regression analysis

Initial features	*P*-values for significance
Peripheral blast cell count	<0.001
Spleen enlargement (cm)	<0.001
Liver enlargement (cm)	<0.001
PAS reaction	0.17
Thymic enlargement	0.20
Hemoglobin (g/dl)	0.31
Platelet count	0.31
Age: 0–2, 2–10, ≥10 years	0.44
Acid phosphatase reaction	0.46
Sex	0.65

reported risk factors on prognosis. In study BFM 70/76 one-parametric analysis (Table 3) as well as multiparametric analysis revealed the peripheral blast cell count and enlargement of the liver and spleen to be significant. In study BFM 76/79 only an age over 10 years was found to influence prognosis ($P<0.01$), even when adjustment was made for the remaining features.

Remarkably, prognosis is independent of the presence of T-cell characteristics. In study BFM 76/79 the probability of CCR is exactly the same for T-ALL patients as for non-T-ALL cases (Fig. 5). Of note, however, is that 17/22 patients with T-cell characteristics received therapy B1 or B2 because of their high concomitant WBC.

The main reason for allocating patients to the high risk group (RI≥3) was the initial WBC of ≥25,000/mm^3. Combination of initial features other than WBC ≥25,000/mm^3 caused a score sum ≥3 in only three patients of study BFM 70/76 and in four patients of study BFM 76/79.

Life table curves correspond well for low risk patients (RI≤2) in both studies after comparable periods of time (Fig. 6). In study BFM 76/79 prognosis could be markedly improved for high risk patients by the addition of Protocol II early in remission (Fig. 7). No significant difference was found between limb B1 and B2. Figure 8 supports the assumption that relapses in high risk patients are really prevented rather than postponed. The probability of any first event was reduced by more than 50% in BFM 76/79 compared to BFM 70/76 in every yearly interval up to 4 years after onset of treatment.

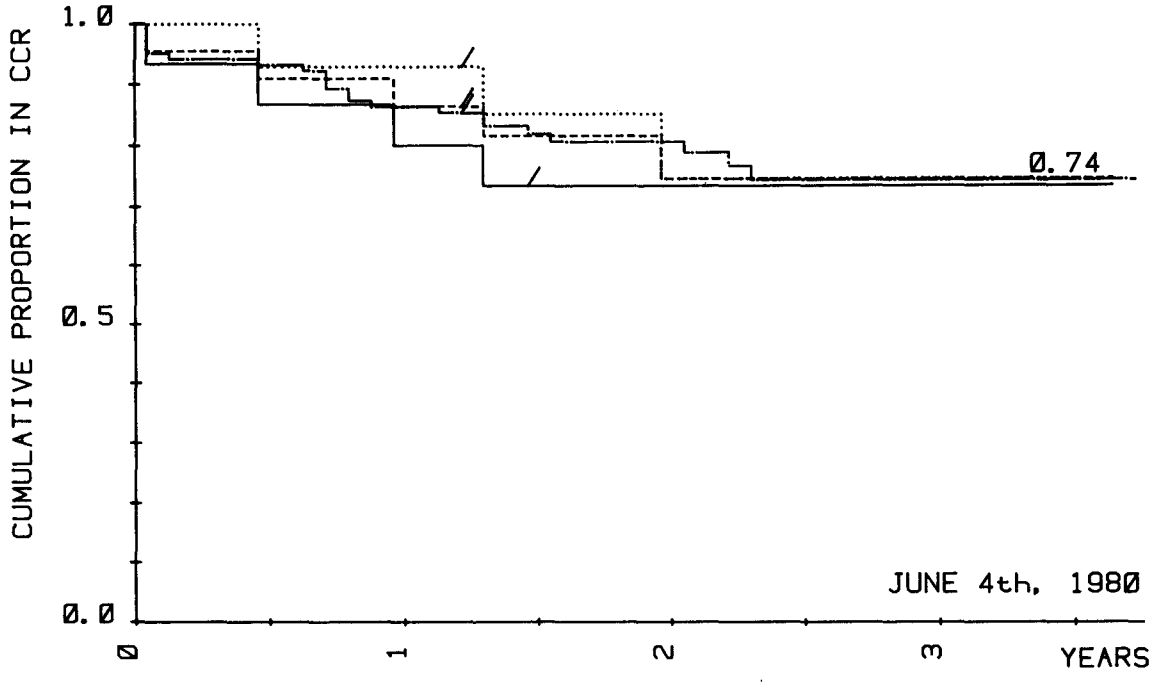

Fig. 5. Study BFM 76/79: Probability of continuous complete remission;/, Last patient of the group; ——, rosette formation test positive (n=15); ....., mediastinal mass (n=14); – – – –, mediastinal mass and/or positive E-rosette formation (n=22); and –.–.–, no mediastinal mass and E-rosette formation negative (n=102). Thirty-four patients not investigated

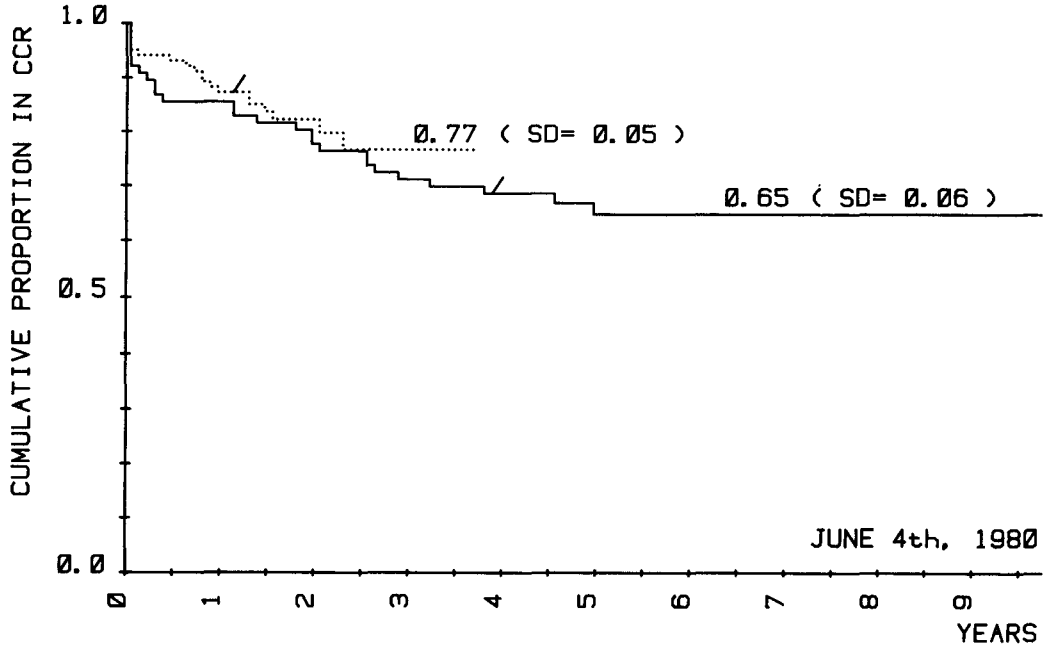

Fig. 6. Comparison of probability of continuous complete remission for low risk patients (RI≤2). ———, study BFM 70/76 (n=76); . . . . ., study BFM 76/79 (n=103)

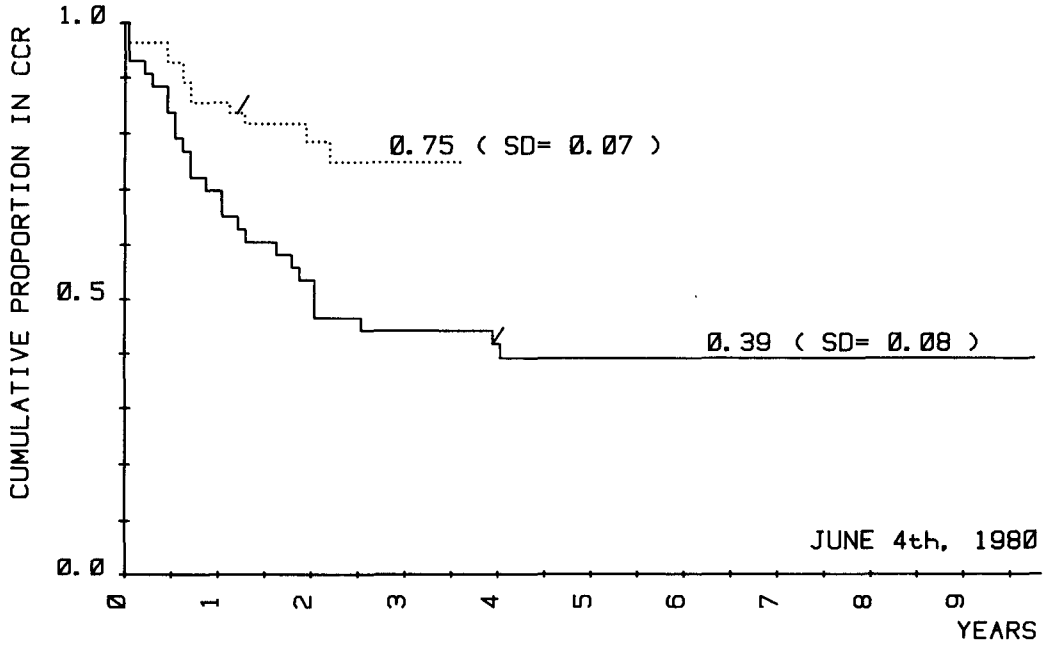

Fig. 7. Comparison of probability of continuous complete remission for high risk patients (RI≥3). ———, study BFM 70/76 (n=43); . . . . . ., study BFM 76/79 (n=55)

D. Discussion

Currently used induction therapy for childhood ALL is capable of producing complete remission in about 90%–95% of patients after several weeks. However, complete remission is a very poorly defined condition with respect to prediction of final outcome, since it merely indicates that leukemic cells can no longer be detected. The number of residual leukemic cells that might eventually cause recurrence of the disease is unknown. Combination therapy with vincristine and prednisone, for example, produces remission rates that are similar to but in a large series significantly lower than those obtained with vincristine, prednisone, and asparaginase (Ortega et al. 1977). There is little doubt that multidrug combination che-

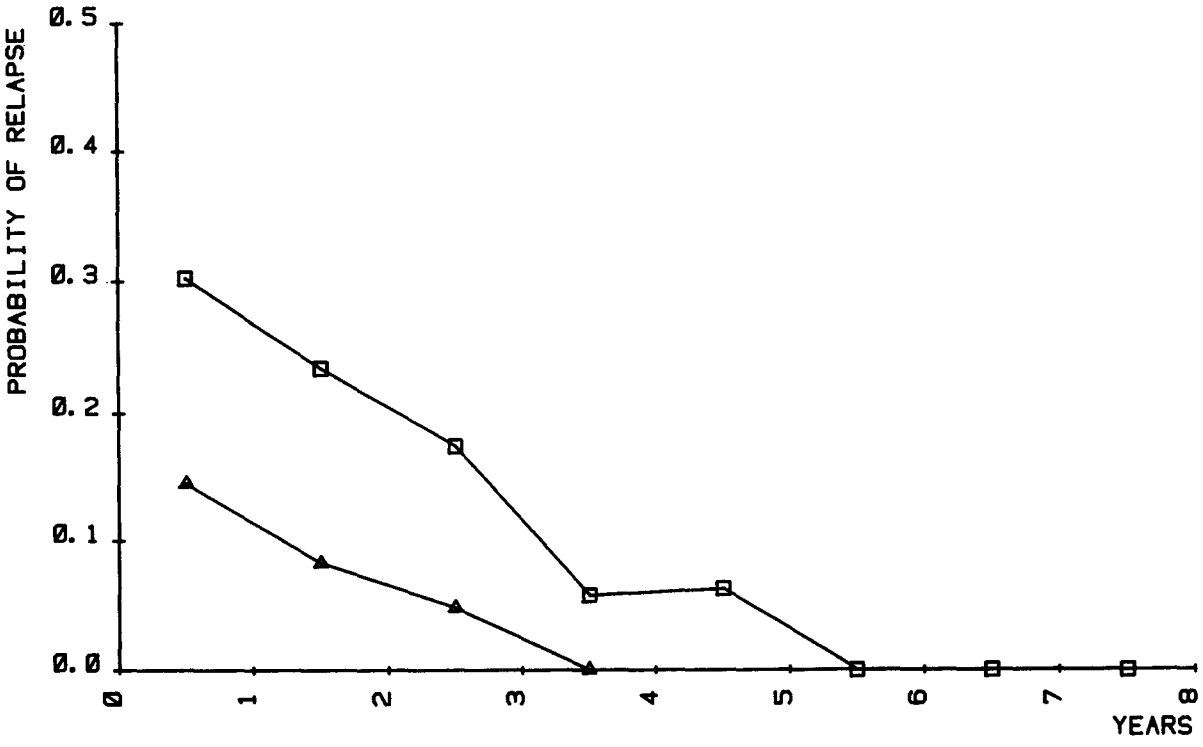

Fig. 8. Probability of any first event during yearly intervals after onset of treatment estimated by life table analysis (induction deaths, deaths in remission, and all sites of relapse included) for high risk patients. □, study BFM 70/76 ($n=43$), Protocol I plus maintenance therapy; △, study BFM 76/79 ($n=55$), Protocol I and Protocol II plus maintenance therapy

motherapy is superior to single or two drug combination therapy, because rapid cytoreduction lessens the chance for persistent leukemic cells to develop drug resistance. It is more likely, therefore, that the remission status established after 4 weeks of intensive therapy is "more complete".

Even though results with the original West Berlin protocol were promising, it was evident in 1976 that therapy was insufficient for patients with high initial WBC, a strong indicator of the total leukemic cell burden. About 60% of these patients relapsed, most during the 1st year after onset of treatment. Since conventionally administered reinduction pulses of prednisone and vincristine failed to prevent early relapses, it seemed to be reasonable to introduce a second intensive phase of induction therapy at a time when the proliferating residual leukemic cells were not detectable by currently available methods. Hitherto existing results in high risk patients support this concept.

An unexpected finding was the compartatively unfavorable result obtained in children over 10 years of age in study BFM 76/79. Despite a shorter observation period and improved therapeutic strategy in this group, prognosis is worse than in the previous study. One possible explanation might be that the drug dosage was changed from body weight to body surface area. For older patients the calculated surface area dosages are distinctly lower, making up only about 75% of the dosage calculated according to body weight. Since in most therapy protocols drug dosage is based on body surface the question arises whether the significance of age as an adverse prognostic factor might be partially corrected.

Results of study BFM 76/79 indicate that the overall prognosis in childhood ALL is 75% with respect to long-term disease-free survival. We conclude that intensification of chemotherapy early in remission is capable of significantly reducing the relapse rate in high risk patients. Further improvement of prognosis in low risk patients may be achieved by remission induction intensification as was done in the current study BFM 79/81. Future efforts should be aimed at the development of more sensitive methods to determine the individual risk for relapse at diagnosis and to detect residual leukemic cells. This would enable us to design individual and appropriate therapeutic regimens and evaluate the efficacy of therapy early in treatment.

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