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Treatment Results in Childhood AML, with Special Reference to the German Studies BFM-78 and BFM-83 *

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A. Introduction

The number of children with acute myelogenous leukemia (AML) who achieve remission and the number of long-term survivors have increased in the last 10 years owing to intensified chemotherapy and better supportive care. This report reviews nine pediatric studies, particularly the German AML studies BFM-78 and BFM-83.

A total of 294 children with AML under 17 years of age entered the AML studies BFM-78 ($n=151$) and BFM-83 ($n = 143$) between December 1978 and January 1986. The second study is still open for patient entry. The treatment in the first study consisted of a seven-drug regimen over a period of 8–10 weeks, together with prophylactic cranial irradiation, and was followed by maintenance therapy with 6-thioguanine and cytosine arabinoside (Ara-C) for 2 years and additional Adriamycin during the 1st year [1]. In the BFM-83 study an 8-day induction with Ara-C, daunorubicin, and VP-16 precedes the BFM-78 protocol.

The initial patient data of the two studies are in general comparable – age: median 9.11 and 9.3 years; sex: boys 54% and 52%; WBC: median ($\times 10^3/\mu l$) 24.0 and 28.5; initial CNS involvement: 9% and 7%, respectively. Extramedullary organ involvement (excluding liver and spleen enlargement) was seen more often in the BFM-83 study (32%); it accounted for only 18% of patients in the BFM-78 study. But the involvement of bone, orbits, and kidney (7% in the BFM-83 study) was not evaluated in the BFM-78 study. The distribution of the FAB subtypes [2] shows a higher proportion of the FAB M5 type (28%) in the BFM-83 study (only 21% in BFM-78). In both studies the myeloblastic subtypes M1 and M2 account for 20%–24% of patients, whereas the M3 and the M6 subtypes were rarely seen (2%–4%).

The overall results are presented in Table 1. In the BFM-78 study, 54 relapses (8 with CNS involvement) occurred after a median follow-up time of 5.3 years (range 3.3–7.0 years). The life table estimations for an event-free survival (EFS, total group) and an event-free interval (EFI, remission group) after 7.0 years are 38% (SD 4%) and 47% (SD 5%), respectively (Fig. 1). In the BFM-83 study, 25 relapses occurred (4 with CNS involvement) after a median follow-up of 1.8 years (range 0.2–3.0 years). The life table estimations are EFS 48% (SD 5%) and EFI 62% (SD 6%) (Fig. 1).

Risk factor analysis shows that hyperleukocytosis (WBC $\geqq 100 \times 10^3/\mu l$) is the main risk factor for early hemorrhage and/or leukostasis ($p<0.001$, X^2 test), for nonresponse ($p<0.05$, X^2 test), and also for relapse ($p=0.08$, log rank test). In addition, in the monocytic subtypes M4 and M5, extramedullary organ involvement was a risk factor for early hemorrhage and/or leukostasis ($p<0.001$) and also for relapse ($p=0.07$, log rank test). The M1 subtype has the best prognosis: EFS 55% (SD 7%) and EFI 66% (SD 7%) after 7 years.

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Table 1. Results of the AML studies BFM-78 and BFM-83, January 1986

	BFM-78	BMF-83
Patients	151	143
Death before onset of therapy	2	9
Death during induction		
Hemorrhage/leukostasis	12	7
Other complications	5	2
Partial/nonresponder	13	21
Complete remission achieved	119 (80%)	104 (78%)
Death in remission	6	4
Withdrawals (BMT)	5 (2)	6 (6)
Relapses (with CNS involvement)	54 (8)	25 (4)
In continuous complete remission	54	69
Alive	66	88
Event free survival (%)[a]	38 (SD 4)	48 (SD 5)
Event free interval (%)[a]	47 (SD 5)	62 (SD 6)

BMT, bone marrow transplantation.
[a] Kaplan-Meier estimated after 7.0 years in BMF-78 and 3.1 years in BFM-83.

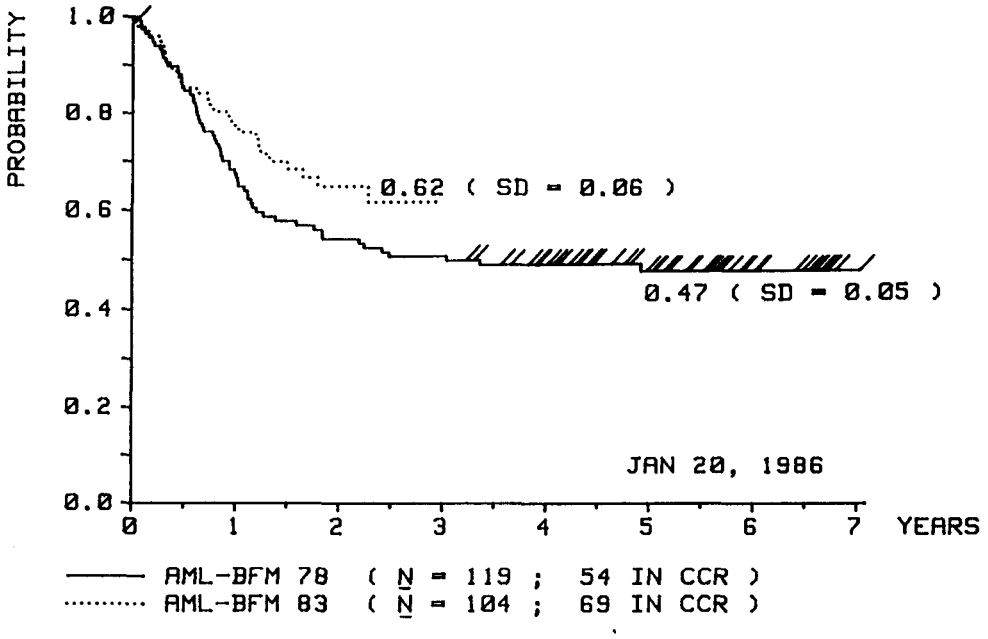

Fig. 1. Probability of event-free interval in AML studies BFM-78, and BFM-83. /, patients in CCR (all patients of BFM-78 study, last patient entered the BFM-83 study group). *CCR*, continuous complete remission

B. Discussion

In most pediatric trials starting before 1976, the median duration of complete remission was short – less than 12 months; after 3 or 4 years, life table estimation for EFI was about 30% and for survival 20% in the best studies [3].

Eight recent pediatric chemotherapy protocols with high remission rates and good results are presented in Table 2, together with one bone marrow transplantation (BMT) trial. Even though the induction/consolidation regimens with two to seven drugs differ considerably, they all include one of the anthracyclines and Ara-C. Vincristine and

Table 2. Design and results of nine AML trials in patients <20 years of age

Study institute	Start of trial	Induction/ consolidation	CNS prophylaxis	Intensification/maintenance	No. patients	No. in CR	No. relapses	No. CNS relapses	EFI[a] %
VAPA	1976	VAPA 1–7, 1–5	–	12 months, intensive sequential chemotherapy	61	45 (74%)	22	8	48 \ 5 years
80-035 (4)	1980	DA 3+7, 2+5	Ara-C i. th.		64	45 (70%)	20	3	40 / 5 years
St. Jude's (5)	1976	D, V, AZA, A×2–5	MTX i. th.	30 months maintenance	95	68 (72%)	50	6	29 \
	1980	DA 3+7, 2+5	–	12 months intensive sequential chemotherapy (or BMT)	87	65 (75%) (15)	33 (7)	5	35—3 years (53) /
UK–MRC (6)	1982	DAT 3+10×2	–	MAZE / melphalan \ DAT/MAZE/HD-Ara-C (BMT)	66	60 (91%) (15)			35 \ 2.5 years (70) /
Norway (7)	1981	DAT (modified)	–	HD-Ara-C 2–4 courses +retinol	12	12	1		70—3 years
BFM (1)	1978	V, P, A, A, T, CTX (8 weeks)	Cranial irradiation (18 Gy) MTX i. th.	24 months A, A, T	149	119 (80%)	54	8	47—7 years
BFM	1983	ADE 8+3+3 followed by 8 weeks induction/consolidation	Cranial irradiation (18 Gy) Ara-C i. th.	24 months A, A, T	134	104 (78%)	25	4	62—3 years
Seattle (8)	1978			BMT		23	7		70—6 years

V, vincristine; P, prednisone; A, Ara-C (in VAPA and BFM, second A= Adriamycin); AZA, azauridine; D, daunorubicin; MTX, methotrexate; T, thioguanine; MAZE, amsacrine, AZA, etoposide; CTX, cyclophosphamide; E, etoposide; BMT, bone marrow transplantation.

[a] Event-free interval, Kaplan-Maier estimation.

prednisone were also administered in the VAPA [4] and BFM [1] studies. The first St. Jude's study [5] combined Ara-C with 6-azauridine. In consolidation of the BFM studies, cyclophosphamide was given at least twice.

In most studies, remission was induced by relatively short and intensive therapy with a seven-plus-three regimen (Ara-C plus daunorubicin), with or without thioguanine, which induced a complete myelosuppression and was followed by a therapy pause of approximately 3 weeks. In contrast, the BFM-78 study used a prolonged induction/consolidation regimen for 8 weeks, which also caused severe bone marrow hypoplasia, but in most cases the necessary therapy pauses were short.

A new strategy in intensive post-remission therapy – called intensification – was initiated with the VAPA-10 protocol [4] and is now part of most of the new studies presented in Table 2. Lie et al. [7] reported excellent results with high-dose Ara-C as post-remission therapy in a small group of children. The results of BMT, which is another way of intensification in remission, are very encouraging, especially in young patients [8].

In conclusion, new therapy strategies including intensive induction regimens together with consolidation and intensification or intensive maintenance with non-cross-resistant drugs will improve the treatment results in childhood AML and increase the proportion of patients in long-term remission to 50%. The low incidence of CNS relapses in the BFM studies indicates that prophylactic CNS treatment early in remission can prevent CNS disease, and the increasing number of long-term survivors emphasizes the need for effective prevention of CNS relapse in pediatric patients. It still remains to be seen whether prophylactic cranial irradiation together with intrathecal methotrexate or Ara-C is necessary or whether systemic treatment with Ara-C infusion or especially HD-Ara-C would produce an effective liquor level.

Although some results favor BMT, this therapy is currently limited to patients with HLA-compatible donors, and the long-term effects are unknown. Prospective comparisons of BMT with chemotherapy intensification or maintenance are necessary.

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