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Improved Results in Treatment of Acute Myelogenous Leukemia in Children – Report of the German Cooperative AML Study BFM-78*

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Recently the treatment programs for childhood acute myeloid leukemia (AML) have become more effective, not only in achieving a higher percentage of induction responses but also in the improvement of duration of the first remission [7, 9, 12]. Because AML in children is rare – about 80 new cases per year are expected in West Germany and West Berlin – it is necessary to cooperate in multicenter trials to gain experience and to establish the value of new therapies.

A. Patients and Methods

Between December 1978 and May 1982, 138 children aged less than 17 years with AML entered the protocol of the childhood AML study BFM 78, which is a cooperative prospective trial of 31 German hospitals.

The initial treatment consists of an induction regimen (Fig. 1) with two intensive 4-week cycles, which resembles in design the West Berlin ALL Protocol [8]. Before starting the protocol reduction of the cell mass in patients with high leukocyte counts is attempted by using low doses of 6-thioguanine (6-TG) per os and cytosine arabinoside (ara-C) i.v. daily. Prednisone therapy should not be started as long as the danger of severe bleeding exists.

Seven different drugs and prophylactic irradiation to the skull are given over a period of 2½ months, with a recovery period of 1–2 weeks between phase 1 and 2. Maintenance therapy lasts for 2 years. 6-TG (40 mg/m² per os) is given daily and ara-C (40 mg/m² s.c.) every 4 weeks for 4 days and in addition adriamycin (Adr) (25 mg/m² i.v.) every 8 weeks but only in the first year. The diagnosis AML is based upon the morphological and cytochemical criteria of the FAB classification [2].

Patients who failed to achieve complete remission (CR) after the induction regimen were classified as nonresponders. Relapse was diagnosed on appearence of more than 5% of blasts in the bone marrow or of leukemic cells at any other site. Methods of

Table 1. Characteristics of 138 protocol patients of the AML therapy study

	n	(%)
Total	138	
Boys	73	(53)
Initial CNS involvement	10	(8)
Initial extraordinary organ manifestation	26	(19)
Liver ≧ 5 cm below costal margin	33	(24)
Spleen ≧ 5 cm below costal margin	36	(27)
Leukocyte count $< 5 \times 10^9$/liter	28	(21)
Leukocyte count $> 100 \times 10^9$/liter	31	(23)
Platelet count $< 10 \times 10^9$/liter	16	(12)
Platelet count $10 - 20 \times 10^9$/liter	23	(17)
Hemoglobin <60 g/liter	18	(13)

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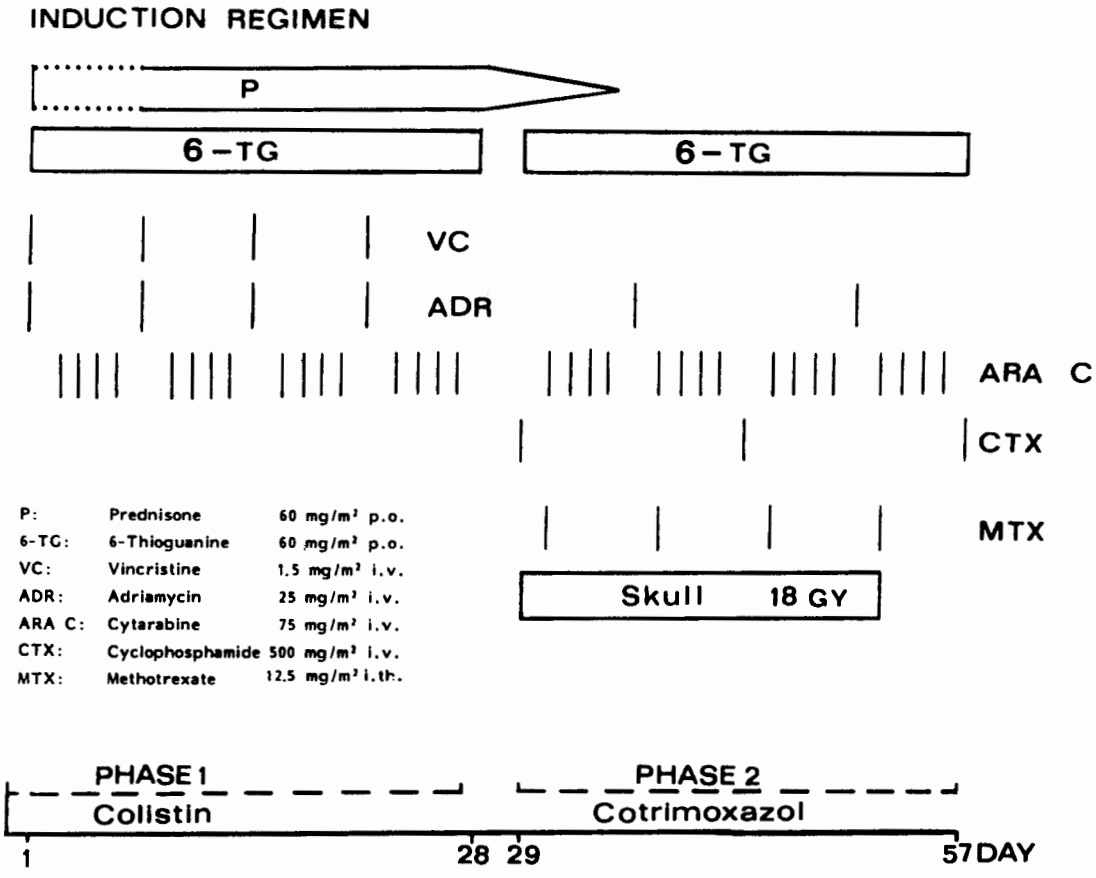

Fig. 1. Induction regimen of the cooperative AML study BFM-78

statistical analysis were the life table algorithm [5] and Cox's regression model [4]. Date of analysis was 1 May 1982.

Patient characteristics are given in Table 1. The median age is 9.8 years. Initial extraordinary organ manifestations were mainly skin involvement or infiltration of the tonsils, submandibular glands, or testes. The classification according to the FAB criteria is:

M 1 and M 2	acute myeloblastic leukemia	(AMBL):	64 (46%)
M 3	acute promyelocytic leukemia	(APL):	6 (4%)
M 4	acute myelomonocytic leukemia	(AMML):	37 (27%)
M 5	acute monoblastic-monocytic leukemia	(AMOL):	28 (20%)
M 6	acute erythroleukemia	(EL):	3 (2%)

B. Results

The results after 41 months are shown in Table 2. Seventy-eight percent of the children achieved CR during induction regimen in median after 43 days. Thirteen children died of cerebral bleeding within the first 12 days, two of them before onset of therapy. Five more patients died of therapy complications or infections and six children died later on in remission. Twelve patients (9%) were classified as non-responders; two of them achieved CR after starting maintenance therapy. For sites of relapses see Table 2. Twenty-four of the total of 33 relapses occurred in the bone marrow only. There was only one isolated CNS relapse.

Sixty-seven children have been in continuous complete remission (CCR) for 1–41 months. In addition, two children have been in first remission for 2 years, although further treatment was refused after the induction regimen. The life table analysis indicates that the probability for CCR for the total group of 138 patients after 41 months is 0.40 ± 0.05 (Fig. 2). The

probability of CCR for the remission group (nonresponders and early deaths during induction therapy are excluded) is 0.57 ± 0.07 after 41 months. Death during remission induction as well as poor response to therapy occurred more frequently in AMML and AMOL patients. Long-term results are not significantly different among these subgroups.

The analysis of risk factors indicates that fatal hemorrhage is more common in AMOL patients than in other subgroups (descriptive P value $= 0.009$). The analysis of hemostasiological factors in 34 patients showed that the plasminogen levels were low in those five patients who died of early cerebral bleeding, whereas the other patients had normal plasminogen levels [11]. In general the risk of relapse is not predictable. Only in the subgroup of AMML do initial extraordinary organ manifestation ($P = 0.03$) and high initial leukocyte count

Table 2. Treatment results in 138 patients of the AML therapy study BFM-78

	n		
Patients	138		
Death before onset of therapy	2		
Death during induction therapy			
Bleeding	11		
Infection	3		
Therapy	2		
Nonresponders	12		
Complete remission achieved	108 (78%)	*Relapse sites*	
Death in remission	6	BM (bone marrow)	24
Relapses	33	CNS	1
In CCR (1 – 41 month)	67	Testes	1
Alive	79	Skin	2
		BM/CNS	3
		BM/testes	2

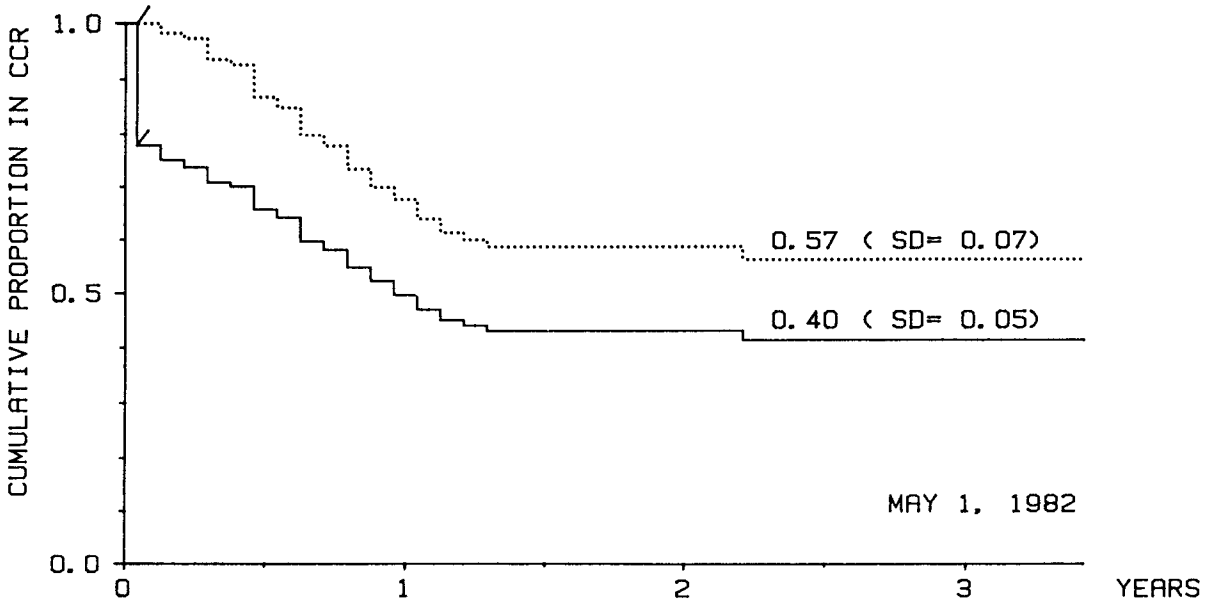

Fig. 2. Probability of continuous complete remission; /, last patient of the group; —, total group (*n*, 138; 67 in CCR). · · · · ·, remission group (*n*, 108; 67 in CCR); patients who died in the first remission were censored at the date of expiry

($P=0.01$) correlate with increased risk of relapse.

C. Discussion and Conclusions

The preliminary results of the German AML study BFM 78 make the following conclusions possible:

1. A prolonged intensive induction therapy using seven drugs and preventive cranial irradiation produces a high proportion of remission (78%) in childhood AML and – in combination with a continuous maintenance therapy over a period of 2 years – a 57% rate of CCR after 3.5 years.

2. The results of the German AML study are in general comparable to those of the VAPA-10 study in Boston, concerning only the children [12]. However, the localization of recurrences is markedly different. In the BFM study only 1/33 relapses was an isolated CNS infiltration (in a patient with initial CNS involvement) compared to 7/14 in the VAPA-10 study (children only). Therefore we conclude that prophylactic cranial irradiation has become a very important factor in childhood AML, since the duration of the remission period has been prolonged considerably.

3. In contrast to childhood ALL, high initial leukocyte counts generally do not seem to be a risk factor for recurrences with BFM therapy. Only the combination of AMML with large tumor mass, which is more frequent in this subgroup than in the others, indicates a high risk of relapse.

4. It is remarkable that the portion of children with AMOL in the BFM study (20%) is higher than in adults. Sultan et al. [10] found 31/250 adult patients with AMOL (12%) and Economopoulos et al. [6] 8/75 (11%). So far only few data exist on the percentage of AMOL patients in childhood AML. The range is 9%–16% ([1, 3]; Weinstein, personal communication at Wilsede Joint Meeting 1982).

There are no reports of other pediatric groups about early fatal bleeding in AMOL subtype. Chessels et al. [3] found that early death from leukostasis occurred in AMML and AMOL patients. In the VAPA-10 study the reason for the low incidence of fatal cerebral bleeding (1/61) might be the effectiveness of therapy with hydroxyurea before starting the protocol. Our analysis of hemostasiological factors has shown a low plasminogen level even before onset of bleeding in those children who died of cerebral hemorrhages. Future efforts should be directed toward avoiding this complication in AML children, especially in those with AMOL.

5. In general the results of the German AML study as well as the data of the VAPA-10 study support the hope that childhood AML will no longer be an incurable disease if treated with suitable aggressive chemotherapy programs.

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