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Improved Treatment Results in Childhood Acute Myelogenous Leukemia: An Update of the German Cooperative Study AML-BFM-78*

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A. Introduction

Major progress in the treatment of children with acute myelogenous leukemia has occurred in the past decade. Advances in chemotherapy and supportive care have been associated with an increase in the complete remission (CR) rate, and more important, an increase in the duration of first remission [1, 5]. In addition, bone marrow transplantation in first remission may provide a new approach for a selected group of patients to improve further on treatment results for AML [3, 4]. In 1978 the AML-BFM-78 chemotherapy protocol was initiated by the German cooperative group with encouraging early results [1, 2]. This report is an update of the trial.

B. Patients and Methods

A total of 151 children with AML from 30 German pediatric centers entered the cooperative study AML-BFM-78 between December 1978 and October 1982. Induction therapy consisted of vincristine, adriamycin, prednisone, cytosine arabinoside (Ara-C) and 6-thioguanine for the first 4 weeks. After a treatment-free interval of 1–2 weeks, a combination of cyclophosphamide, Ara-C, 6-thioguanine, and adriamycin was administered for an additional 4 weeks, together with CNS prophylaxis consisting of four intrathecal methotrexate injections and cranial irradiation. For remission maintenance, daily 6-thioguanine was given together with monthly cycles of subcutaneous Ara-C for 4 days. In the first year, patients also received one dose of adriamycin every 8 weeks. In children with CCR, maintenance was stopped after 2 years [1].

The diagnosis AML was based upon the morphological and cytochemical criteria of the FAB classification. Patients who failed to achieve CR after the induction regimen were classified as nonresponders. Relapse was diagnosed on appearance of more than 5% of blasts in the bone marrow or of leukemic cells at any other site. Methods of statistical analysis were the life table method according to the Kaplan-Meier and Cox regression model. Date of analysis was 1 May 1984.

C. Results

In all, 119 (79%) children achieved CR. After a median follow-up time of 40 (17–62) months, 52 relapses have occurred. Two late relapses occurred after 40 and 58 months, whereas all the other relapses were within the first 30 months. The results for the major morphological subtypes according to the FAB classification are given in Table 1. Life table analysis – influenced by the two late relapses – reveals a probability for remaining in CR of 42% ± 10% at 62 months for patients having achieved CR and of 31 ± 7% for all patients entered into the trial. No risk factors for relapse could be identified so far, whereas early fatal hemorrhage occurred predominantly in

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Table 1. AML-BFM-78 results by morphological subtypes

	M1	M2	M3	M4	M5	M6	All patients
Patients	36	34	6	40	32	3	151
Early deaths	3	0	3	4	9	0	19
Nonresponders	4	1	0	5	3	0	13
Complete remission	29 (80%)	33 (97%)	3	31 (77%)	20 (62%)	3	119
Relapses	10	17	0	16	6	3	52

children with the M5 subtype and in children with initially high WBC. An initially high WBC and liver enlargement were unfavorable parameters for achieving CR.

D. Discussion and Conclusions

The update of the German AML-BFM-78 study reveals:

1. A prolonged intensive induction therapy produces a high proportion of remissions in childhood AML and, in combination with maintenance therapy over a period of 2 years, an estimated CCR rate of 42% after more than 5 years.
2. Late relapses may occur after intensive induction therapy, even after 60 months of CR, further follow-up of the trial is needed before definite conclusions can be drawn.
3. The number of children achieving CR is relatively low in the monocytic subtypes M4 and M5; the number of early deaths, mainly because of early fatal hemorrhage was highest in the M5 subgroup.
4. The localization of relapses is markedly different in this study as compared with the VAPA-10 study from Boston: in the BFM study, the CNS was involved in 8/52 relapses, whereas in the VAPA-10 study, where CNS prophylaxis was not included in the treatment, the CNS was a primary site of relapse in 8/19 [6]. In our study most relapses occurred in the bone marrow.
5. Based on these findings, a new trial of the BFM group was started in 1983 with an initial intensive 8-day chemotherapy consisting of Ara-C, VP-16,213, and daunorubicin. After recovery of the bone marrow, a slight modification of the BFM-78 remission induction protocol is given as consolidation therapy. So far, 66 patients have entered this protocol, the CR rate being 85%.
6. The results of the AML-BFM-78 trial emphasize the probability of cure for a significant proportion of children with AML as a consequence of intensive remission induction and postremission multidrug treatment.

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