Improved outcome of children with acute myeloid leukemia treated on 2 consecutive protocols

Taha M. Khattab, MD, PhD, Ayad A. Atra, MD, FRCP, Najla A. Elimam, MD, Ahmed Kassar, BSc, Abdullah Zayed, MD, Abdullah Baothman, MD.

The outcome of childhood acute myeloid leukemia (AML) has improved over the last 10 years with a long-term overall survival of approximately 60%.[1] Response to initial chemotherapy and leukemia karyotype emerged as the most important prognostic factors.[1] Relapse of underlying leukemia and treatment related mortality (TRM) are the main causes of treatment failure.[2] In this single center study, we assess the outcome and causes of treatment failure of children with AML treated at our center with 2 consecutive chemotherapy regimens over the last 20 years.

We retrospectively reviewed the files of all children with AML diagnosed at King Abulaziz Medical City, Jeddah, Kingdom of Saudi Arabia from January 1986 to November 2005. Between 1986 and 1995 (first era), Berlin-Frankfurt-Munchen (BFM) (German protocol)-type chemotherapy was used,[3] and in the second era extending from 1996 to 2005, UK AML-type treatment was used.[1] Three patients with acute promyelocytic leukemia (APL) in the second group received all-trans retinoic acid for 12 months in addition to standard chemotherapy. There were no facilities to carry out bone marrow cytogenetics during the first era. Survival rates were calculated according to Kaplan-Meier analysis, and compared by log-rank test.

Fifty-four patients with AML (23 boys) were included in the study. Ages at diagnosis ranged from 0.5-14 years (median 5). Twelve patients (21%) had white blood cell count >50,000/cm^{2,} and 5 (9%) had central nervous system leukemia at diagnosis. Patients' characteristics, details of treatment, and outcome are shown in **Table 1**. Between 1986 and 1995, 22 patients were treated with BFM-type chemotherapy,[3] and the remaining 32 patients received UK AML-type protocol.[1] Four patients had matched sibling bone marrow transplantation (BMT) in first remission. Two are alive in remission, and 2 died of relapsed AML post-BMT. Eight/22 (36%), and 5/32 (16%) died of bacterial and fungal infections in the first and second era. Nine/11 (81%) with favorable karyotype[1] survive in remission and 2 died, one with inversion chromosome (16) from Pseudomonas sepsis, and the other with translocation chromosone (8;21) from relapse of AML. Twelve patients (54%) relapsed in the first era while still on treatment, all died. Nine patients (28%) relapsed in the second era, 6 on therapy and died, and the remaining 3 responded to second line chemotherapy of Fludarabine and high-dose cytarabine, and went into second remission. Two died of toxicity after matched sibling BMT, and one survived with extensive chronic graft versus disease after a matched unrelated BMT. With a median follow up of 3 years (range 0.5-10), the overall survival is 9% (95% confidence interval 0.53-3.14) in the first era, and 59% (95% confidence interval 42.88-68.04), in the second era (p<0.5) (**Figure 1**).

The prognosis of childhood AML has improved over the last decade due to increasing intensity of systemic chemotherapy and advances in supportive care.[1] In this study, we aimed to assess the outcome and causes of treatment failure in children with AML

Table 1 - Patients' characteristics, details of treatment, and outcome.

Characteristics	1st era	2nd era
Gender		
Male	10	11
Female	12	21
Age at diagnosis (in years)		
0-2	7	7
3-10	11	19
11-14	4	6
WBC's >50 x 10^9/L	9	3
WBC's <50 x 10^9/L	9	16
WBC's not available	4	13
CNS positive	2	3
CNS negative	18	23
CNS unknown	2	6
Cytogenetics		
translocation (8;21)	-	4
Inversion (16)	-	4
translocation (15;17)	-	3
Others	-	5
Normal	-	2
UK AML - chemotherapy	-	29
BFM- type chemotherapy	22	-
Toxic death	8/22 (36%)	5/32 (16%)
AML- related death	12/22 (54%)	8/32 (25%)
Overall survival	2/22 (9%)	19/32 (59%)

WBC - white blood cell, CNS - central nervous system, UK AML - United Kingdom acute myeloid leukemia, BFM - Berlin-Frankfurt-Munchen, AML - acute myeloid leukemia

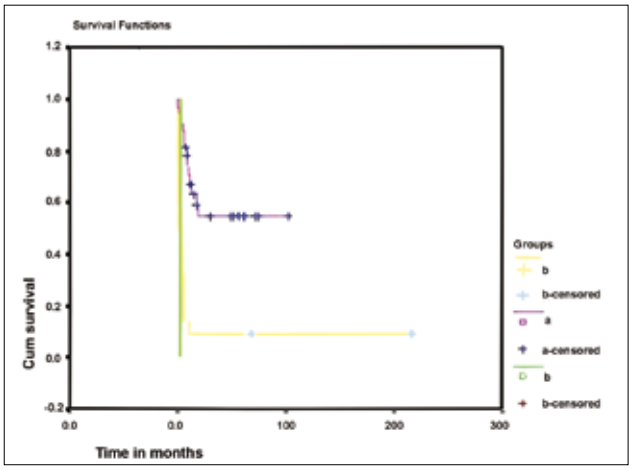

Figure 1 - The first era survival was 9% (yellow line), and 57% on the second era of survival (pink line).

treated at our center over the last 20 years. This study has its limitations. The number of patients is small, some important data are missing, and there were no facilities to carry out cytogenetic analysis in the first period of the study. Besides, significant advances in supportive care were made during the study period, which might have affected the results. We used 2 chemotherapy regimens with different dose intensity. The UK AML-based regimen[1] contained 3.5 times the cytarabine dose, twice the dose of Adriamycin, and 2/3 the dose of Etoposide when compared to the BFM 78 protocol used in the first era.[3] Response to induction chemotherapy and karyotypic abnormalities are important prognostic markers.[1] Response criteria were not clearly documented in all patients' files, however, 11 patients with favorable karyotype had 81% overall survival rate, which is very encouraging and compares well with published results.[1] Relapse of underlying leukemia is the main cause of treatment failure, and is associated with a poor outcome.[4] In this study, all relapsed patients in the first period died while in the second era one patient survived after second line of chemotherapy and unrelated donor BMT. By increasing the intensity of chemotherapy, the relapse rate was reduced from 54% in the first era to 25% in the second era, and the overall survival was significantly improved. There is general agreement that AML in patients with Down Syndrome (DS) is very sensitive to cytarabine and have a better outcome than other patients.[5] In our study, we treated 2 patients with DS who received reduced chemotherapy by 25%. Both survive in complete remission. Treatment-related mortality is the second most common cause of treatment failure, and bacterial and fungal infections predominate among other causes.[2] The TRM in our study was high (36%) in the first era, however, it was significantly reduced to 16% in the second era.

In conclusion, AML is a complex disease and optimal facilities are required for its diagnosis, treatment, and follow-up. This single center study confirmed that the outcome of children with AML has improved over the last decade. Increasing local experience, advances in supportive care and chemotherapy have contributed to this improvement.

Acknowledgment. *We would like to express our special thanks to Dr. Sami Felimban, and all the medical staff of the National Guard Hospital, Jeddah, Kingdom of Saudi Arabia for their help.*

Received 19th January 2008. Accepted 18th March 2008.

From the Department of Pediatric Oncology/Hematology, Princess Noorah Oncology Center, King Abdulaziz Medical City, Jeddah, Kingdom of Saudi Arabia. Address correspondence and reprint requests to: Dr. Taha Khattab, Department of Pediatric Oncology/Hematology, Princess Noorah Oncology Center, King Abdulaziz Medical City, PO Box 9515, Jeddah 21423, Kingdom of Saudi Arabia. Tel. +966 (2) 6240000 Ext. 24000. Fax. +966 (2) 6240000 Ext. 24287. E-mail: khattabt@hotmail.com

References

1. Wheatley K, Burnett AK, Goldstone AH, Gray RG, Hann IM, Harrison CJ, et al. A simple, robust and highly predictive prognostic index for the determination of risk directed therapy in acute myeloid leukaemia derived from the MRC AML 10 trial. ***Br J Haematol*** 1999; 107: 69-79.
2. Creutzig U, Zimmermann M, Reinhardt D, Dworzak M, Stary J, Lehmbecher T. Early deaths and treatment-related mortality in children undergoing therapy for acute myeloid leukemia: analysis of multicenter clinical trials AML-BFM 93 and AML-BFM 98. ***J Clin Oncol*** 2004; 22: 4384-4393.
3. Creutzig U, Ritter J, Zimmerman M, Langermann HJ, Henze G, Kabisch H, et al. Improved treatment results in childhood acute myelogenous leukemia: a report of the German cooperative study AML-BFM-78. ***Blood*** 1985; 65: 298-304.
4. Webb DKH, Wheatley K, Harisson G, Hann IM. Outcome for children with relapsed acute myeloid leukemia following initial therapy in the Medical Research Council (MRC) AML 10 trial. ***Leukemia*** 1999; 13: 25-31.
5. Gamis AS, Woods WG, Alonzo TA, Buxton A, Lange B, Barnard DR, et al. Increased age at diagnosis has a significantly negative effect on outcome in children with Down syndrome and acute myeloid leukemia: a report from the Children's Cancer Group Studies 2891. ***J Clin Oncol*** 2003; 21: 3415-3422.