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Infant Leukemia, Single-Center Eight Years' Experience

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Abstract

Objectives: The aim of this study is to evaluate the clinical course, laboratory findings and treatment outcomes of the infant patients diagnosed with leukemia treated in our center.

Design: This is a retrospective study of all the patients below one year old who diagnosed with leukemia and treated in King Fahd specialist hospital in Dammam, pediatric hematology/ oncology department between 1st January 2011 and 1st December 2018, our study included 14 cases.

Setting: It is a single center study at King Fahad Specialist Hospital in Dammam which is 400 beds tertiary referral hospital with 27 beds pediatric oncology Ward, 2 beds bone marrow transplant and 18 bed pediatric oncology day care services.

Methods and Results: All data and information of patients including laboratory results were retrieved from patients' files and electronic medical records. Data analysis was done by using Statistical Package for the Social Sciences (SPSS) program version.

Results: Within our study period we diagnosed 13 cases with infantile leukemia out of 202 cases of childhood leukemia in 8 years period (incidence of 6.4%) with overall survival of 61.5%.

Conclusion: The incidence of ALL in infants is significantly lower than in other groups of children it tends to be presented with aggressive clinical features at diagnosis, including hyper leukocytosis, massive organomegaly, and central nervous system (CNS) involvement. The management particularly challenging, the outcome is inferior with tendency towards refractory course and increased relapse rates. In our study the survival rate was 61.5% which is minor better than what was reported in some centers for theses group of patients probably masked by the small number of patients in our study. More studies with larger patient numbers are needed to reevaluate HSCT's eligibility criteria in this group of patients, in addition to studying some new strategies such as CAR-T cell, targeted therapies, improving conditioning regimens, and maximize the supportive care should all be considered to improve the prognosis.

Keywords: Leukemia • Childhood leukemia • Infantile leukemia • Leukemia of infancy

Introduction

Acute leukemia in early infancy is defined by a group of leukemia's characterized by acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) during the first years of life. The term infant acute leukemia (IAL) is usually applied when the diagnosis is made within the first twelve months after birth [1]. Acute leukemia is the second most common malignancy in the first year of life; although neuroblastoma is the most common neoplasm in infants, leukemia is the leading cause of death caused by neoplastic disease in this age group [1].

In one study from the United States of America, 160 new patients are diagnosed with leukemia during the infancy period annually; 90 of them are ALL while the other 70 cases are AML [2]. The incidence of ALL in infants is significantly lower than in children aged 1 to 14 years old and approximately the same as adolescents; in contrast, the incidence of AML in infants is roughly twice that of older children and adolescents. Interestingly, females have a higher risk of developing infant leukemia than males but a lower risk of developing leukemia beyond the first birthday [3]. Infants with leukemia tend to present with aggressive clinical features at diagnosis, including hyper leukocytosis, massive organomegaly, and central nervous system (CNS) involvement at diagnosis; that make initial management particularly challenging, and this difficulty is amplified by the vulnerability of infants to complications and toxicity of the necessary procedures and treatments [2]. A high proportion of acute leukemia's occurring in infants are characterized cytogenetically by balanced chromosomal translocations involving the mixed lineage leukemia (MLL) gene at chromosome 11q23. MLL rearrangements (MLL-r) occur in 5% of childhood ALL cases overall, but in 70% to 80% of ALL in infants. In childhood AML, MLL-r is more common overall (15%- 20%), but is also particularly common in the infant age group (50%) [3]. virtually all cases of ALL in this population are of an early pre-B phenotype; infants with this disease have the worst prognosis of pediatric patients with leukemia. Specific adverse prognostic features in this population include age younger than three months, white blood cell (WBC) count greater than 200,000 per mL, and MLL gene rearrangement, especially t(4;11). Many studies have analyzed the clinical and biological criteria influencing the outcome of infant AML without exact results. Favorable cytogenetic and a blast percentage after induction therapy <5% are the most potent predicting factor for the outcome of infant AML [4,5]. Males with leukocytosis were associated with poorer prognosis in children with AML aged 12 months or less in one study. Nevertheless, these data have not been confirmed in other studies.

An analysis of 299 children with AML treated in four consecutive clinical trials between 1980 and 1997 showed that FAB M4 or M5 was an independent prognostic factor predicting better outcomes in children younger than two. This finding was confirmed, although at a non- statistically significant level, in other experiences [6]. (3-year event-free survival EFS of 80.8% reported by the Japanese group *vs*. 56.1%, P = 0.105) [7]. while in infant AML, MLL-r is not a significant risk factor,but the presence of MLL-r in infant acute leukemia has different prognostic implications in ALL than in AML. In infant ALL, MLL-r is clearly associated with poorer outcome. In the Children's Cancer Group protocol CCG-1953, the 5-year EFS for MLL-r infants was 34% compared with 60% with germline (wild-type) MLL (MLL-g) [7]. In Interfant-99, the 4-year EFS in MLL-r and MLL-g infants were 37% and 74%, respectively [8]. In a combined analysis of AMLBFM-98 and AML-BFM-2004, the 5-year EFS were 43% and 52% for MLL-r and MLL-g infants, respectively (P-0.59) [9]. Perhaps most importantly, the eventual outcomes for infants with leukemia in terms of relapse- free survival are poor compared with leukemia in older children despite the use of maximally intensified standard therapies (chemotherapy with or without hematopoietic stem cell transplantation [HSCT]) [10]. The largest infant ALL trial to date, the Interfant-99 study, included 482 infants, ALL patients from 22 countries, and had a 4-year event-free survival (EFS) of 47% and 55% survival. This is showing how important it is to study infant leukemia

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biology and treatment. This study intended to retrospectively evaluate the clinical and laboratory findings with treatment outcomes of our infant leukemia patients.

Material and Methods

202 patients were diagnosed with acute leukemia between 1st January 2011 and 1st December 2018, at king Fahd specialist hospital in Dammam, pediatric hematology/ oncology department.13 out of them were under one year of age and diagnosed by morphology, cytochemistry, and flow cytometric immunophenotyping of bone marrow aspirate. The age, gender, signs, and symptoms, laboratory assessment at diagnosis including blood counts, CNS involvement; immunophenotype, clinical course, response to the treatment; hematopoietic stem cell transplant (HSCT); relapse rate, and time of follow-up were analyzed. IRB approval was obtained and data were collected from electronic and hard medical records and analyzed by help of SPSS.

Results

The incidence of infant leukemia in our hospital was 6.4% (13/202) among leukemia patients diagnosed in this period. We found nine boys (69%) and four girls (30%) with a median age of 10 months (range 0-12 months), and 11 out of 13 (84%) were at six months of age or older at the initial diagnosis. Physical examination revealed significant hepatosplenomegaly in 7 out of 13 patients (53.8 %), 6 of the patients had B cell ALL (42.8%), out of them 4 had MLL rearrangement (66%), However, 2 cases (33%) were diagnosed as T cell ALL with none of both had MLL rearrangement, AML was diagnosed in the rest of 5 cases (38.46%), 2 out of them had MLL rearrangement (40%).

So, the overall Cytogenetic analysis showed MLL positivity in total of 6 (46%) patients. Cerebrospinal Fluid was positive with blasts in 2 (15.3%) of the patients. The 5 patients with AML were treated with MRC 15 protocols, In the rest they were given Interfant 06 protocol and one patient received Modified St. Jude Total XV protocol. Relapse was observed in 6 (46%) patients, 3 of them received HSCT, and the rest were not fit to proceed with transplant due to severe morbidities (1 had cardiac dysfunction, 1 had typhlitis complicated with severe sepsis, 1 had no suitable donor).However, HSCT was performed in 3 patients. Unfortunately, all of them experienced second relapse after HSCT within 3 and 4 months post-transplant; one of them managed to be given second stem cell transplantation but unfortunately died later with a third relapse. In our study the mortality rate was 38% as we had five patients (38%) died after a median of 2 months (range 3- 91 months) follow-up period, all of them had relapse disease, one case develop severe refractory sepsis with pseudomonas infection just before death, and another case complicated with severe typhlitis and perforated gut. Eight patients (61.5%) were alive and in remission by the time of study; one of them received CAR-T cell therapy abroad with resultant secondary immunoglobulin deficiency.

DISCUSSION

Childhood leukemia is more commonly observed in boys, while infant leukemia is more common among girls [2], unlike in our study, in which we had around 70% of cases were males. It is known from the studies that the biological and clinical features of patients diagnosed earlier under the age of 6 months are more aggressive [11,12]. We had 3 (22%) of our cases diagnosed at the age of six months or under, all of them presented with very high WBC counts to more than 150,000 x 109 per liter (L), one deceased after a very stormy course of fulminant refractory sepsis. Infant leukemia patients characterized by significant hepatosplenomegaly and extramedullary involvement [2]. In our study, a Physical examination in 50% of the patients revealed important hepatosplenomegaly. Leukemia in infants usually presents with hyperleukocytosis. White blood cell count (WBC)> 50000/mm accounts for 66% of cases and WBC>100000/mm^3 accounts for 34% patients [13,14]. Our study showed 61% (8/13) of our patients had WBC>50000/mm^3, while 53% (7/13) of our patients had WBC>100000/mm^3 at the time of diagnosis of acute leukemia.

Though the incidence of CNS involvement (CNS2,3) at the time of diagnosis in childhood ALL is 1.5%, they reported much more CNS involvement in infant leukemia as It is documented up to14% in the BFM group and 9% in Interfant 99 protocol [15] and that higher frequency of CNS involvement is considered as a poor prognostic indicator for the outcome [16] In our study, two patients were CNS positive; one of them died from relapse disease (50%). Most of the infant leukemia patients tend to have precursor B cell phenotype than other types of leukemia. (10), similarly, our study showed that precursor B cell phenotype occurred in 6 out of 13 patients, while only two patients had T cell-derived blast cells. T cell phenotype is associated with more aggressive figures in EFS and overall survival (OS) [17]. By the time of our study analysis, only one patient with T-cell leukemia was alive and still in remission at the end of the follow-up period of 56 months after diagnosis; however, unfortunately, the other case with T-cell leukemia died of fatal chemotherapy toxicity (typhlitis) and perforated gut. MLL rearrangement is associated with poor prognosis [2,3] six patients (46%) were found to have MLL in our study; one of them died of relapse, and two died with treatment toxicities. Despite the fact that patients with infant leukemia can respond to chemotherapy initially, but it seems that they tend not to maintain their remission status for a long period, with relapse occurs for almost half of them in one year. Relapses involve most frequently bone marrow (in 80% of cases), the CNS in 30%, and the testes in 8% [2,3]. In contrast to our study, disease relapse occurred in 6 (46%) of our patients, 2 of them had combined CNS and bone marrow relapse, and the other four were isolated bone marrow relapses. As they all agreed about HSCT is indicated in all patients with infant ALL with disease status beyond CR1, COG did not show a difference in EFS for HSCT and chemotherapy in a group of patients with low-risk and very high-risk infants (younger children with high WBC), however, The Interfant99 demonstrated the advantage of HSCT for high-risk patients in CR1 [18] Three patients received HSCT in our study, and 2 of them were treated with Interfant 06 protocol before HSCT and 1 with MRC 15 protocol; also, we found 2 of them were t(4;11) positive. Unfortunately, all of our bone marrow transplanted patients died with relapse. One patient relapsed after HSCT and had a second HSCT and died with relapse. Thus, it is crucial to sensitively determine the group of patients who will benefit from HSCT without relapse. Generally, the prognosis of infants' leukemia is poor, and some international collaborative studies reported that four-year EFS rates were between 28-54%. [18]. In our patient, despite the small number of patients, yet the survival rates among patients who reached the stage of HSCT is extremely poor (0%), unlike those who did not have HSCT(8/10) (80%), so in this study, we found that bone marrow transplantation did not improve the survival rate of infants with leukemia. The overall survival rate in this study was 61.5%.

Conclusion

Infant leukemia is one of the most challenging clinical situations encountered in pediatric hematology/oncology. HR infant leukemia still remains a candidate to HSCT in CR1 in some studies, despite unsatisfying results so far. The preparative regimen should be carefully evaluated and adjusted to avoid long-term morbidities. More studies with larger patient numbers are needed to assess and optimize the recommendation for the HSCT's this group of patients. New strategies such as CAR T-cell, targeted therapies started to be promising, and great efforts in maximizing the supportive care for those groups should be considered to avoid fatal toxicities related to therapy.

References

1. Emerenciano M, Koifman S and Pombo-de- Oliveira MS. Acute leukemia in early childhood. *Braz J Med Biol Res* 40(2007): 749-60.

2. Brown P. Treatment of infant leukemias: Challenge and promise. *Hematology Am Soc Hematol Educ Program* 2013: 596-600.

3. Creutzig U, Zimmermann M, Bourquin JP, Dworzak MN and Kremens B, et al. Favorable outcome in infants with AML after intensive first and second-line treatment: An AML- BFM study group report. *Leukemia* 26(2012): 654-61.

4. Masetti R, Rondelli R, Fagioli F, Mastronuzzi A and Pierani P, et al. Infants with acute myeloid leukemia treated according to the associazione italiana di ematologia e oncologia Pediatrica 2002/01 protocol have an outcome comparable to that of older children. *Haematologica* 99(2014): 127-9.

5. Mann G, Attarbaschi A, Schrappe M, Lorenzo PD and Hann I, et al. Interfant-99 Study Group. Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with mixed-lineage leukemia (MLL)-rearranged acute lymphoblastic leukemia: Results from the Interfant-99 Study. *Blood* 116 (2010): 2644-2650.

6. Masetti R, Vendemini F, Zama D, Giagi C and Pession A. Acute myeloid leukemia in infants: Biology and treatment. *Front Pediatr* 2015: 3.

7. Hilden JM, Dinndorf PA and Meerbaum SO. Analysis of prognostic factors of acute lymphoblastic leukemia in infants: report on CCG 1953 from the Children's Oncology Group. *Blood* 108(2006): 441-451.

8. Pieters R, Schrappe M, De Lorenzo P, Hann I and Rossi G, et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. *Lancet* 370(2007): 240-250

9. Creutzig U, Zimmermann M, Bourquin JP, Dworzak MN and Kremens B, et al. Favorable outcome in infants with AML after intensive first- and second-line treatment: An AML-BFM study group report. *Leukemia* 26(2012): 654- 661.

10. Ibagy A, Silva DB, Seiben J, Winneshoffer APFF and Costa TEJB, et al. Acute lymphoblastic leukemia in infants: 20 years of experience. *J Pediatr (Rio J)* 89(2013): 64-69.

11. Bueno C, Montes R, Catalina P, Rodríguez R and Menendez P. Insights into the cellular origin and etiology of the infant pro-B acute lymphoblastic leukemia with MLL-AF4 rearrangement. *Leukemia* 25(2011): 400-410.

12. Tomizawa D, Koh K, Hirayama M, Miyamura T and Hatanaka M, et al. outcome of recurrent or refractory acute lymphoblastic leukemia in infants with MLL gene rearrangements: A report from the Japan Infant Leukemia Study Group. *Pediatr Blood Cancer* 52(2009): 808-813.

13. Silverman LB. Acute lymphoblastic leukemia in infancy. *Pediatr Blood Cancer* 49(2007): 1070-1073.

14. Pui CH, Gaynon PS, Boyett JM, Chessells JM and Baruchel A, et al. outcome of treatment in childhood acute lymphoblastic leukemia with rearrangements of the 11q23 chromosomal region. *Lancet* 2002; 359: 1909-1915.

15. Doerrenberg M, Kloetgen A, Hezaveh K, Wössmann W and Bleckmann K, et al. T-cell acute lymphoblastic leukemia in infants has distinct genetic and epigenetic features compared to childhood cases. *Genes Chromosomes Cancer* 56(2017): 159-167

16. Koh K, Tomizawa D, Moriya Saito A, Watanabe T and Hirayama M, et al. Early use of allogeneic hematopoietic stem cell transplantation for infants with MLL gene-rearrangement-positive acute lymphoblastic leukemia. *Leukemia* 29(2015): 290-296.

17. Sison EAR and Brown P. Does hematopoietic stem cell transplantation benefit infants with acute leukemia? *Hematology Am Soc Hematol Educ Program* 2013: 601-604.

18. Zweidler- McKay, PA and Hilden JM. The ABCs of infant leukemia. *Curr Probl Pediatr Adolesc Health Care* 38(2008): 78-94.

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