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Original Research Article

Treatment results of children with the diagnosis of acute myeloid leukemia. Is trisomy 21 an important cause of mortality?

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ABSTRACT

Background: Acute myeloid leukemia (AML) is the second most common leukemia accounts for 20% of childhood leukemia. Intensive chemotherapy and hematopoietic stem cell transplantation (HSCT) improve outcomes. In this study, it was aimed to present the clinical features and treatment results of patients diagnosed with pediatric AML in the last three years.
Methods: It is an observational clinical study, patients who received chemotherapy and HSCT with the diagnosis of AML between 2018 and 2020 were retrospectively evaluated. Age, gender, AML subtype, genetic characteristics, laboratory findings, treatment responses, febrile neutropenia and fungal infection frequencies of the patients were evaluated. HSCT indications, pre-transplant bone marrow aspiration results, transplant type, donor characteristics, and post-transplant complications of patients who underwent HSCT were recorded. Post-treatment status and treatment success rates of the patients were evaluated.
Results: Of the 46 patients included in the study, 26 were female and 20 were male. The mean age was 8.2 ± 5.75 years. The most common subtypes were AML M4 and M5 with 9 patients. Total of 201 febrile neutropenia attacks were observed. Suspicious or definite proven Aspergillus infection was detected in 20 of the patients. HSCT was applied to 27 of the patients. Four patients were Down syndrome-myeloid leukemia (DS-ML) and FLT3-ITD mutation was detecetd in 5 patients.
Conclusions: FLT3-ITD mutation, relapse disease, and pre-HSCT M2 bone marrow were found to be highly correlated with progressive disease and mortality. In addition, patients with Down syndrome had a high mortality due to additional comorbidity and drug adverse effects.

Keywords: AML, Down syndrome, HSCT, FLT3-ITD

INTRODUCTION

Pediatric acute myeloid leukemia (AML) is the second most common pediatric leukemia characterized by clonal expansion of abnormally differentiated myeloid lineage blasts, accounts for 20% of childhood leukemia. The use of intensive chemotherapy and hematopoietic stem cell transplantation (HSCT) improve outcomes of pediatric AML.[1,2] Associations between cytogenetic changes and patient outcomes have since shifted the focus toward cytogenetic classification to distinguish between types of AML and allow for risk-stratified therapy.[3] Risk stratification based on genetic abnormalities is a critical determinant for predicting outcomes of the pediatric AML.[4]

Advances in supportive care have also contributed to improving the survival rates of patients with pediatric AML. In the literature, results were reported that complete remission (CR) rates of 80-90%, relapse rates

of 30-40%, event-free survival (EFS) rates of 50%, and overall survival (OS) rates of nearly 70%.[2] Much of this improvement is due to better supportive care, optimization of intensity of treatment including employment of HSCT in 1st complete remission (CR1) and better salvage in 2nd complete remission (CR2). Whilst the majority of children (>90%) achieve CR, the relapse rate (RR) in CR1 remains unacceptably high at 30-35%.[3,4] In this study, it was aimed to present the clinical features and treatment results of patients diagnosed with pediatric AML in the last three years.

METHODS

This is an observational retrospective clinical study; patients who received chemotherapy and HSCT with the diagnosis of AML in Istanbul Yeni Yuzyil university Gaziosmanpasa hospital pediatric hematology and oncology Service between 2018 and 2020 were evaluated. Age, gender, AML subtype, genetic characteristics, laboratory findings, treatment responses, febrile neutropenia and fungal infection frequencies of the patients were evaluated. The AML-Berlin Frankfurt Munster (AML-BFM) 2004 protocol or AML-BFM 2013 protocol was applied to the first diagnosis patients according to the year of diagnosis and the experience of the physician. Bone marrow (BM) aspiration results on day 28 and day 42 in response to treatment were evaluated. In the AML BFM 2004 protocol, the 15th day bone marrow aspiration results were also evaluated. Two cycles of FLAG-IDA (fludarabine, ARA-C, idarubicin) regimen was used in relapsed or refractory AML. Treatment response was evaluated with the results of BM aspiration before chemotherapy courses. M1: <5% blast in assessment of BM; M2: 5-20% blast; M3: evaluated as> 20% blast. HSCT indications, pre-transplant bone marrow aspiration results, transplant type, donor characteristics, and post-transplant complications of patients who underwent HSCT were recorded. Post-treatment status and treatment success rates of the patients were evaluated. The results obtained were evaluated in the light of the literature.

The patients included in the study consisted of patients with a diagnosis of AML. Patients with other leukemia types were not included in the study. Patients who were lost at the stage of diagnosis or before treatment could be started were excluded from the study. Because of an observational retrospective data evaluation, the data were evaluated with the consent of the relatives of the patients and permission from the institution management.

Statistical analysis

Case characteristics, including diagnosis, age, and gender were calculated. The incidence as a percentage of datas were calculated. All analyses were conducted with the use of Statistical Product and Service Solutions (SPSS 22.0) software.

RESULTS

Of the 46 patients included in the study, 26 were female and 20 were male. The mean age was 8.2±5.75 years. The general characteristics of the patients are given in Table 1. The most common subtypes were AML M4 and M5 with 9 patients. AML M2 subtype followed with 7 patients. Translocation t (8;21) was detected in 6 patients diagnosed with AML M2 in morphological and immunophenotypic examination. In 6 patients diagnosed with acute promyelocytic leukemia (APL), t (15;17) translocation was detected and all-trans retinoic acid (ATRA) treatment was applied. Four patients were Down syndrome-myeloid leukemia (DS-ML). While monosomy 7 and monosomy 8 were detected in 3 patients, 5 patients had FLT3-ITD mutations. Two of the patients with FLT3-ITD mutations were continuing their chemotherapy before HSCT, while the response of one to induction treatment was good, the response of the other patient on day 28 and day 42 was found to be poor. One patient is being followed up in remission after HSCT, and when the treatment process was examined, it was seen that the bone marrow examination on the 28th day was M2. Two of 5 patients with FLT3-ITD mutations died as a result of relapse and refractory disease after HSCT. It was observed that these patients had poor responses to induction therapy and were compatible with M2 bone marrow before HSCT.

Hyperleukocytosis was detected in 18 patients. Diagnostic laboratory mean values of the patients are shown in Table 2. At the first admission, 23 of the patients had bleeding symptoms. Two patients did not have hepatosplenomegaly on physical examination. Gingiva hypertrophy was present in four patients, according to available information. While one patient had chloroma, two patients had central nervous system involvement. Treatment-related myeloid leukemia developed in 4 of the patients. Two patients developed myeloid leukemia while being followed up with a diagnosis of myelodysplastic syndrome (MDS) and Fanconi aplastic anemia (FAA). In the treatment, AML-BFM 2004 protocol was applied in 8 of the patients, while the AML-BFM 2013 protocol was given to 24 patients. FLAG-IDA chemotherapy protocol was applied to 14 patients with relapse or poor response to treatment. When all patients were evaluated, a total of 201 febrile neutropenia attacks were observed. Suspicious or definite proven Aspergillus infection was detected in 20 of the patients.

HSCT was applied to twenty seven of the patients. In order of frequency, HSCT indications were relapse AML, high risk mutations, poor response to treatment, and secondary AML. In 4 patients who underwent HSCT, M2 bone marrow was detected before transplantation. After HSCT, twenty three patients had febrile neutropenia, four had BK virus hemorrhagic cystitis, and four had cytomegalovirus (CMV) reactivation. Veno-occlusive disease (VOD) developed in two patients. When graft

versus host disease is evaluated in patients who underwent HSCT; skin involvement in 8 patients, gastrointestinal system involvement in 4 patients, pulmonary involvement in one patient, and liver involvement in one patient.

Considering the final status of the patients, 29 patients are being followed up in remission and 11 patients are still being treated. The characteristics of six patients who were lost due to disease progression or treatment complications are shown in Table 3.

Table 1: General characteristics of the patients.

Variables		N (%)
Age (mean ± SD), (Years)	8.2±5.75	
Gender	Male	20 (43)
	Female	26 (57)
Subtype	AML M0	4 (8)
	AML M1	2 (4)
	AML M2	7 (15)
	AML M3	6 (13)
	AML M4	9 (19)
	AML M5	9 (19)
	AML M6	3 (6)
	AML M7	6 (13)
Genetic disorders	T (15;17)	5
	T (8;21)	6
	Inv (16)	2
	FLT3-ITD	5
	T (4;11)	1
	Monosomy 7	2
	Monosomy 8	1
	Trisomy 21	4
Physical examination / involvement	Hepatomegaly	44
	Splenomegaly	44
	CNS involvement	2
	Chloroma	1
Secondary AML, familial or acquired causes	Neuroblastoma	1
	Retinoblastoma	1
	Osteosarcoma	1
	ALL	1
	MDS	1
	FAA	1
	Down syndrome	4
Chemotherapy protocol	AML-BFM 2004	8
	AML-BFM 2013	24
	FLAG/FLAG-IDA	14
Number of febrile neutropenia	1-3	16
	4-6	24
	7-9	6
Total number of febrile neutropenia		201
Number of patients with *Aspergillus* infection (definitive evidence/ suspect)		20
Number of patients who underwent HSCT		
HSCT type	Allogeneic	27
	MSD	11
	MFD 10/10	1
	MUD 9/10	8
	MUD 10/10	3
	Haploidentic	4
HSCT indication	Poor response to treatment	5
	High risk mutations	6
	Relapsed disease	11
	Seconder AML	5

Continued.

Variables		N (%)
Pre-HSCT bone marrow	M1	23
	M2	4
Post-HSCT complication	Febrile neutropenia / sepsis	
	GVHD	23
	Skin	8
	Gastrointestinal	4
	Liver	1
	Pulmoner	1
	BKV-HC	4
	CMV reactivation	4
	VOD	2
Final situation	In remission	29
	Continue treatment	11
	Death	6

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; BKV-HC: BK virus-hemorrhagic cystitis; CMV: Cytomegalovirus; CNS: Central nervous system; FAA: Fanconi aplastic anemia; GVHD: Graft-versus-host disease; HSCT: Hematopoietic stem cell transplantation; MDS: Myelodysplastic syndrome; MFD: Matched familial donor; MSD: Matched sibling donor; MUD: Matched unrelated donor; VOD: Veno-occlusive disease.

Table 2: Laboratory values of patients.

Variables	Mean ± SD
Leukocyte (/mm^3)	35983±46569.413
Hemoglobin (g/dL)	7.9±1.929
MCV	86±8.66
Platelet (/mm^3)	63456±103994.595
Urea (mg/dL)	21± 8.78
Creatinine (mg/dL)	0.4±0.26
AST (U/L)	51±56.31
ALT (U/L)	40±3.19
Uric acid (mg/dL)	3,5±1.23
LDH (U/L)	878±830.621
CRP (mg/L)	36±52.95

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRP: C-reactive protein; LDH: lactate dehydrogenase; MCV: Mean corpusculer volume

Table 3: Characteristics of the cases resulting in mortality.

Patient	Subtype	Genetic mutation	Familial/acquired predisposing factor	Relapsed disease	HSCT	Pre-HSCT bone marrow
1	AML M5	Monosomy 7 /FLT3-ITD	MDS	X	X	M2
2	AML M7	Trisomy 21	Down syndrome / myelofibrosis			
3	AML M6	Trisomy 21	Down syndrome			
4	AML M4	FLT3-ITD		X	X	M2
5	AML M7	Trisomy 21	Down syndrome			
6	AML M2			X	X	M2

AML: Acute myeloid leukemia; HSCT: Hematopoietic stem cell transplantation; MDS: Myelodysplastic syndrome

DISCUSSION

AML in children consists of a heterogenous group; and it is classified according to morphology using the French-American-British (FAB) classification. Immunophenotyping is used in order to determine AML FAB subtypes. The minimal diagnostic requirements in childhood AML are morphology with the cytochemistry, immunophenotyping, karyotyping, fluorescence *In situ* hybridization (FISH), and specific molecular genetics in the bone marrow. AML is characterized by specific chromosomal abnormalities, especially translocations. Also, these abnormalities help to both classify subtypes as well as to serve as important prognostic markers.[5] In the study by Song et al.[4] patients with adverse cytogenetics showed significantly poorer outcomes than

those with favorable cytogenetics, including t (8;21) or inv (16). Mutations frequently seen in AML were determined at the rate of 20% for t (8;21) and inv (16), and 12% for t (15;17). MLL rearrangement seen especially under the age of 2 is seen at 18%.[6] In this study, favorable cytogenetics features such as t (8;21), inv (16), t (15;17) were found in 13 patients.

Acute promyelocytic leukemia is one of the subtypes accountings for 5%-10% of pediatric AML. Children with APL have the highest cure rates of AML, with an average overall survival (OS) 95% and event-free survival (EFS) of 90% due to the combined use of ATRA and arsenic trioxide (ATO). Increased bleeding risk must be closely monitored and aggressively treated with transfusion support in APL. Serious bleeding events were reported in 15% of pediatric APL patients with up to 10% of children in literature.[7-10] With close follow-up of coagulation values and early treatment, no fatal situation due to bleeding was observed in patients. Differentiation syndrome following the treatment with ATRA and ATO was reported in 20% of children. Patients develop fever, respiratory distress, hypotension, and renal failure due to excessive numbers of maturing myeloid cells leading to endothelial damage and edema. The early recognition and treatment of differentiation syndrome is important to prevent fatalities, and patients should be closely monitored after the initiation of therapy. Steroids and hydroxyurea are used for differentiation syndrome, leukapheresis is not recomended as it does not affect outcomes and subjects' patients to unnecessary bleeding risk.[11,12] One of the patients developed respiratory distress, deterioration in liver function tests and fever on the second day of ATRA treatment. ATRA treatment was discontinued and steroid therapy was started. ATRA treatment was continued after the symptoms disappeared in the patient whose complaints regressed with steroid therapy. No additional findings were observed during follow-up.

Different inherited clinical conditions have been defined that predispose individuals to develop AML, constitutional chromosomal abnormalities constitute a large part of them. Trisomy 21, monosomy 7, and trisomy 8 are important causes of AML development, and trisomy 21 has a different significance, especially considering its prevalence in the population. In addition to this, children oncology group (COG) reported that presence of trisomy 21 was the primary risk factor for the development of leukemia and not associate with the presence of congenital anomalies.[13,14] In the study, when DS-myeloid leukemia patients were evaluated, 3 of 4 patients were lost due to DS-related additional comorbidities and chemotherapy adverse effects.

Association between FLT3-ITD and a high risk of relapse in childhood AML has been known from the recent studies.[15,16] One of the first reports in the literature showed that FLT3-ITDs were present in 15 of 91 childhood AML cases and were associated with an 8-year EFS estimate of only 7%.[17] In this study, the results of multivariate analysis indicated that FLT3-ITD was the most important prognostic factor. Meshinchi et al reported the poor outcome of patients with FLT3-ITD in a study of 630 patients.[16] Recent studies suggest that the outcome of these patients can be improved by HSCT.

Several genetic alterations in AML, including FLT3-ITD, are associated with constitutive activation of tyrosine kinases, aberrations in downstream signaling pathways, and a poor prognosis.[17,18] Therefore, sorafenib (tyrosine kinase inhibitor) is a potentially therapeutic option in AML. In a study; sorafenib, which inhibits multiple intracellular kinases, including FLT3, alone or in combination with cytarabine and clofarabine, in 12 children with refractory or relapsed leukemia. In this study, 7 days of treatment with single agent sorafenib decreased blast percentages in 10 of 11 patients with AML.[19] Sorafenib is currently being evaluated in newly diagnosed patients with AML and FLT3-ITD in the St Jude AML08 and the COG AAML1031 trials. FLT3-ITD mutation was found in 5 patients. Although one of these patients was after HSCT, 2 of them had relapsed AML and were lost due to progressive disease during treatment. Sorafenib was used in these patients.

The limitation of this study was that it was a single-center study. We think that multicenter and larger number of patient analyzes can give more precise results.

CONCLUSION

In conclusion; when a general evaluation is made to results, parallel to the literature, FLT3-ITD mutation, relapse disease, and pre-HSCT M2 bone marrow were found to be highly correlated with progressive disease and mortality. In addition to these, patients with Down syndrome also had a high mortality due to additional comorbidity and drug adverse effects. Therefore, we want to emphasize that Down syndrome is an important and risky situation because of comorbidities and mortality rate in AML.

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REFERENCES

1. Gamis AS, Alonzo TA, Perentesis JP, Meshinchi S. Committee, C.O.G.A.M.L. Children's oncology group's 2013 blueprint for research: Acute myeloid leukemia. Pediatr Cancer. 2013;60:964-71.
2. Rubnitz JE. Current management of childhood acute myeloid leukemia. Paediatr Drugs. 2017;19:1-10.
3. Creutzig U, Zimmermann M, Reinhardt D, Rasche M, von Neuhoff C, Alpermann T, et al. Changes in cytogenetics and molecular genetics in acute myeloid

leukemia from childhood to adult age groups. Cancer. 2016;122:3821-30.
4. Song TY, Lee SH, Kim G, Baek HJ, Hwang TJ, Kook H. Improvement of treatment outcome over 2 decades in children with acute myeloid leukemia. Blood Res 2018;53:25-34.
5. Pui CH, Carroll WL, Meshinchi S, Arceci RJ. Biology, risk strafication, and therapy of pediatric acute leukemias: an update. J Clin Oncol. 2011;29(5):51-65.
6. Taga T, Tomizawa D, Takahashi H, Adachi S. Acute myeloid leukemia in children: Current status and future directions. Pediatr Int. 2016:58;71-80.
7. Iland H.J, Collins M, Bradstock K, Supple SG, Catalano A, Hertzberg M et al. Use of arsenic trioxide in remission induction and consolidation therapy for acute promyelocytic leukaemia in the Australasian Leukaemia and Lymphoma Group (ALLG) APML4 study: A non-randomised phase 2 trial. Lancet Haematol. 2015;2:357-66.
8. Rajpurkar M, Alonzo TA, Wang YC, Gerbing RB, Gamis AS, Feusner JH et al. Risk Markers for Significant Bleeding and Thrombosis in Pediatric Acute Promyelocytic Leukemia; Report From the Children's Oncology Group Study AAML0631. J Pediatr Hematol Oncol. 2019;41:51-5.
9. De Azevedo AC, Matsuda E, Cervellini JY, Prandi LR, Omae C, Jotta PY et al. Early Mortality in Children and Adolescents with Acute Promyelocytic Leukemia: Experience of the Boldrini Children's Center. J Pediatr Hematol Oncol. 2020;42(7):641-6.
10. Zhang Y, Wang L, Zhang R, Qi P, Xie J, Shi H et al. Long-term follow-up of children with acute promyelocytic leukemia treated with Beijing Children's Hospital APL 2005 protocol (BCH-APL 2005). Pediatr Hematol Oncol. 2019;36:399-409.
11. Stahl M, Tallman MS. Differentiation syndrome in acute promyelocytic leukaemia. Br J Haematol. 2019;187:157-62.
12. Jin B, Zhang Y, Hou W, Cao F, Lu M, Yang H et al. Comparative analysis of causes and predictors of early death in elderly and young patients with acute promyelocytic leukemia treated with arsenic trioxide. J Cancer Res Clin Oncol. 2020;146(2):485-92.
13. Linabery AM, Arico M, Basso G, Olshan AF, Heerema NA, Ross JA. Congenital abnormalities and acute leukemia among children with Down syndrome: a Children's Oncology Group study. Cancer Epidemiol Biomarkers Prev. 2008;17(10):2572-7.
14. Ross JA, Spector LG, Robinson LL, Olshan AF. Epidemiology of leukemia in children with Down syndrome. Pediatr Blood Cancer 2005;44(1):8-12.
15. Staffas A, Kanduri M, Hovland R, Rosenquist R, Ommen HB, Abrahamsson J et al. Presence of FLT3-ITD and high BAALC expression are independent prognostic markers in childhood acute myeloid leukemia. Blood. 2011;118(22):5905-13.
16. Meshinchi S, Alonzo TA, Stirewalt DL, Zwaan M, Zimmerman M, Reinhardt D et al. Clinical implications of FLT3 mutations in pediatric AML. Blood. 2006;108(12):3654-61.
17. Meshinchi S, Appelbaum FR. Structural and functional alterations of FLT3 in acute myeloid leukemia. Clin Cancer Res. 2009;15(13):4263-9.
18. Kornblau SM, Womble M, Qiu YH, Jackson CE, Chen W, Konopleva M et al. Simultaneous activation of multiple signal transduction pathways confers poor prognosis in acute myelogenous leukemia. Blood. 2006;108(7):2358-65.
19. Inaba H, Rubnitz JE, Coustan-Smith E, Li L, Furmanski BD, Mascara GP et al. Phase I pharmacokinetic and pharmacodynamic study of the multikinase inhibitor sorafenib in combination with clofarabine and cytarabine in pediatric relapsed/refractory leukemia. J Clin Oncol. 2011;29(24):3293-300.

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