Association of cytogenetics and immunophenotype in prognosis of children with acute lymphoblastic leukemia: Literature Review

Abdollah Banihashem (MD), Ali Ghasemi (MD)*, Lueisa Tavasolian (MD)

Department of Pediatrics, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

ARTICLE INFO

ABSTRACT

Acute lymphoblastic leukemia (ALL) is the most common type of neoplastic disorder diagnosed in childhood. It is the cause of one third of all pediatric malignancies. ALL is characterized by the abnormal production and proliferation of immature lymphoblasts in bone marrow (BM). It seems that ALL occurs due to a genetic mutation in DNA structure producing white blood cell (WBC) stem cells. Because ALL is a systemic disease, its primary management is based on chemotherapy.

There are important risk factors responsible for the poor prognosis of ALL in children less than 1 year old and greater than 10 years old, such as: high WBC, mature T cell ,mature B cell, central nervous system (CNS) involvement, DNA index < 1 (hypodiploid), triploidy, tetraploidy, Mixed-Lineage Leukemia (MLL) gene re-arrangement on 11q23, the Philadelphia chromosome t(9;22), reduction in platelet count, hemoglobin>10 at diagnosis, no remission at the end of induction therapy and Minimal residual disease at the end of consolidation therapy. Complications might appear during the treatment including tumor lysis syndrome, bleeding, renal failure, sepsis, seizure, thrombosis, etc. Some consequences might identify after a long-term follow-up such as learning impairment, growth retardation, and secondary malignancies. It is estimated that up to 90% of pediatric ALL cases are curable.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common type of neoplastic disorder diagnosed in childhood. It is the cause of one third of all pediatric malignancies. It is

Corresponding author: Ali Ghasemi.
Department of Pediatrics, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
E-mail: Ghasemial@mums.ac.ir
*Tel:*0511-7273943

estimated that about 3000 children develop ALL in USA each year. White children are at higher risk compared to black ones and males have a slight superiority (1). Children with chromosomal disorders like Down syndrome or cases with congenital immune deficiency syndromes such as ataxia telangectasia and Wiskott-Aldrich syndrome might be affected more (2). ALL is a heterogeneous disorder which can occur in childhood and adolescence. The peak age-specific incidence of disease in children is between 2 and 5 and its other peak incidence is in old ages. It is characterized by abnormal production and proliferation of immature lymphoblasts in bone marrow (BM), accumulation of lymphoblasts in lymphoid tissues and peripheral blood (3).

It seems that ALL occurs due to a genetic mutation in DNA structure producing white blood cell (WBC) stem cells. The two-hit theory has been proposed for ALL, which means that few children might be born with an inherent potential for ALL and if they are exposed to another trigger factor (e.g. environmental factors) they would develop ALL. Other possible causes of childhood ALL might be electromagnetic or nuclear radiation, infections and some chemical agents (4).

Children with acute lymphoblastic leukemia present bone marrow destruction or extramedullary signs and symptoms. Fever, fatigue, growth retardation, petechiae, liver and spleen enlargement, and lymphadenopathy are some of the most common signs in ALL. Central nervous system and testicular involvement are rare. ALL might be suspected in children with abnormal complete blood cell count and impaired peripheral blood smear. Biochemistry or coagulation test might be helpful. Chromosome and cryptogenic studies and immunophenotyping provide data for ALL classification. Although

there are not any specific imaging tests to diagnosis the ALL, chest radiography might display mediastinal mass and ultrasonography could be helpful in testicular involvement condition. Bone marrow aspiration and biopsy confirm ALL diagnosis (5,6). Because ALL is a systemic disease, its primary management is based on chemotherapy. There are various drugs and methods prescribed in leukemic children. Some patients require blood components or antibiotics after complication occurrence. Nutritional supplementations and intravenous fluids might be needed in children with ALL (4). Complications might appear during treatment such as tumor lysis syndrome, bleeding, renal failure, sepsis, seizure, thrombosis, etc. Some consequences might be identified after a long-term follow-up such as learning impairment, growth retardation and secondary malignancies (7). Chromosome changes and translocation are the main pathology in acute lymphoblastic leukemia. Translocation (8;14) (q11.2;q32) is associated with Down syndrome and it is a rare condition. Its prevalence in childhood ALL is 0.7% (4). CD10, 19, 20, 21, 22, 24, 79 are suggestive of B-lineage ALL and CD3 is specific for T-lineage ALL.

It is estimated that up to 90% of pediatric ALL cases are curable. Traditional prognostic factors in ALL include: age, WBC count, cytogenesis and response to treatment (2-9).

Discussion

Patient long-term remission depends on clinical manifestation, laboratory results, treatment response and method (10). It has been confirmed that children aged younger than 1 year have a poor prognosis. Although recent advantages lead to a significant raise in 5-year survival rates of pediatric ALL, outcomes are not encouraging in developing

and poor countries due to delayed diagnosis (8). New adventures in flow cytometric assessment and invention of lineage-associated monoclonal antibodies lead to promote ALL diagnosis and determination of its prognosis.

In 2005, the Mayo Clinic leukemia database published a list of cryptogenic risk factors such as hypodiploidy, triploidy, Mixed-Lineage Leukemia (MLL) translocations, t (5;14), t (17;19) and t (1;19) in ALL. Poor diagnostic performance, reduction in platelet count and MRD (minimal residual disease) might influence the patient prognosis. Nowadays, more than 50 genetic abnormalities have been detected in ALL, which are associated with lymphoid developing or signaling proteins

Table1. Prognostic factor in ALL

Author	Publication year	Prognostic factor	Result
Bhojwani (11)	2009	Ph chromosome	Poor prognosis in Ph+ and T-cell ALL
Braoudaki (4)	2013	CLUS, CERU, APOE, APOA4, APOA1, GELS, S10A9, AMBP, ACTB, CATA	Increase aggressiveness
Khalid (3)	2010	Age and ALL phenotype	_____
Matutes (12)	1997	Hybrid or biphenotypic acute leuke-(mia (BAL	Poor prognosis
McGregor (13)	2012	MRD	_____
Mi (14)	2012	CRLF2, IKZF1	Detecting the prognosis of Ph-negative ALL
Assumpção (5)	2013	*MRD	Relapse is 8.5 times higher
Kiyokawa (6)	2013	CD66c	No prognostic effect
Patkar (15)	2012	CD20, CD10, CD45 and CD19	Useful to diagnosis of MRD
Settin (16)	2006	L2, organomegally, male, younger than 5 years old	Better prognosis
Hilden (17)	2006	Negative CD10 and MLL/11q23	Poor prognosis
Hashemi (18)	2008	Male	Better prognosis
Moorman (19)	2007	iAMP21	Poor prognosis

Minimal residual disease *

such as IKZF1, EBF1, PAX5 and CD200, etc. NR3C1 has been identified as drug responsiveness determinant factor. Table1 shows some prognostic factors in ALL (8).

Cytogenetic and molecular measures are important to predict the patient survival and prognosis. They also play a crucial role in choosing the best treatment method. Bhojwani (11) showed that negative CD10 has a great impact on the outcome of infant with ALL. Rituximab might be more effective in CD20 or Ph-positive (Philadelphia-positive) ALL cases (8). Early CD34 presentation occurs in B-lineage ALL (15).

WBC count over 50000 increases the death risk about 22 times (18). Patients who are positive for iAMP21 should be considered as bone marrow transplant candidates in first remission (19). Age is a crucial element for ALL prognosis, but 11q23 translocation does not have a prognostic value (17). It seems that cytogenetic and molecular analysis could open a new window to predict ALL outcomes in children.

Conclusion

With appropriate performing of cytogenetic and molecular tests for ALL diagnosis, treatment strategies might be modified and specified for each patient and the efficacy of new therapeutic strategies could be evaluated accurately. Genetic polymorphism affects drug metabolism and leads to different effective levels and drug toxicity.

Acknowledgement

Conflict of Interest

The authors declare no conflict of interest.

References

1. H Ronald Hoffman BF, Philip McGlave, Leslie ES, Sanford JS, Edward JB Jr, Helen H. Hematology: Basic Principles and Practice, 5th ed. Philadelphia: Churchill Livingstone; 2009.
2. Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: Results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood. 2010;115:3206–3214.
3. Khalid S, Moiz B, Adil SN, et al. Retrospective review of pediatric patients with acute lymphoblastic leukemia: a single center experience. Indian J Pathol Microbiol. 2010; 53:704-710.
4. Braoudaki M, Lambrou GI, Vougas K, et al. Protein biomarkers distinguish between high- and low-risk pediatric acute lymphoblastic leukemia in a tissue specific manner. J Hematol Oncol. 2013;6:52.
5. Assumpção JG, Paula FD, Xavier SG, et al. Gene rearrangement study for minimal residual disease monitoring in children with acute lymphocytic leukemia. Rev Bras Hematol Hemoter. 2013;35:337-342.
6. Kiyokawa N, Iijima K, Tomita O, et al. Significance of CD66c expression in childhood acute lymphoblastic leukemia. Leuk Res. 2014;38:42-48.
7. Vitale A, Guarini A, Ariola C, et al. Absence of prognostic impact of CD13 and/or CD33 antigen expression in adult acute lymphoblastic leukemia. Results of the GIMEMA ALL 0496 trial. Haematologica. 2007;92:342-348.
8. Zhao Y, Huang H, Wei G. Novel agents and biomarkers for acute lymphoid leukemia. J Hematol Oncol. 2013; 18;6:40.
9. Niedzielska E, Węcławek-Tompol J, Matkowska-Kocjan A, et al. The influence of genetic RFC1, MS and MTHFR polymorphisms on the risk of acute lymphoblastic leukemia relapse in children and the adverse effects of methotrexate. Adv Clin Exp Med. 2013; 22:579-584.
10. Mazloumi SH, Madhumathi DS, Appaji L, et al. Combined study of cytogenetics and fluorescence in situ hybridization (FISH) analysis in childhood acute lymphoblastic leukemia (ALL) in a tertiary cancer centre in South India. Asian Pac J Cancer Prev. 2012;13:3825-3827.
11. Bhojwani D, Howard SC, Pui CH. High-risk childhood acute lymphoblastic leukemia. Clin Lymphoma Myeloma. 2009;9:S222-230.
12. Matutes E, Morilla R, Farahat N, et al. Definition of acute biphenotypic leukemia. Haematologica. 1997;82:64-66.
13. McGregor S, McNeer J, Gurbuxani S. Beyond the 2008 World Health Organization classification: the role of the hematopathology laboratory in the diagnosis and management of acute lymphoblastic leukemia. Semin Diagn Pathol. 2012;29:2-11.
14. Mi JQ, Wang X, Yao Y, et al. Newly diagnosed acute lymphoblastic leukemia in China (II): prognosis related to genetic abnormalities in a series of 1091 cases. Leukemia. 2012;26:1507-1516.
15. Patkar N, Alex AA, B B, Ahmed R, Abraham A, George B, et al. Standardizing minimal residual disease by flow cytometry for precursor B lineage acute lymphoblastic leukemiain a developing country. Cytometry B Clin Cytom. 2012;82:252-258.
16. Settin A, Al Haggar M, Al Dosoky T, et al. Prognostic cytogenetic markers in childhood acute lymphoblastic leukemia: cases from Mansoura, Egypt. Hematology. 2006;11:341-349.

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

18. Hashemi A, Manochehri MA, Eslami Z, et al. Evaluation of Prognostic and Predictive Factors in Pediatric Acute Lymphoblatic Leukemia Patients Admitted to ShahidSadoughi Hospital.

Journal of Shaheed Sadoughi University of Medical Sciences and Health Services Yazd. 2008;16:14-15.

19. Moorman A, Richards S, Robinson H, et al. Prognosis of children with acute lymphoblastic leukemia (ALL) and intrachromosomal amplification of chromosome 21 (iAMP21). Blood.2006;2326-2330.