The Relationship between Immunological Markers, Disease Free Survival and Overall Survival in Acute Myeloid Leukemia in North-West of Iran

Zohreh Sanaat,[1] Yashar Amizadeh,[1] Akbar Movasagpour Akbari,[1] Roya Dolatkhah[1]

[1]Hematology- Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Corresponding Author: Zohreh Sanaat, MD; Assistant Professor of Hematology and Medical Oncology
-Hematology- Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
-Daneshgah Street, Shahid Ghazi Tabatabai Hospital, Tabriz, Iran
PO Box: 5166614731
Tel/Fax: +98 (411) 3343844
Mobile: 09131140602
E-mail address: sanaatz2000@yahoo.com, sanaatz@tbzmed.ac.ir

Abstract

Introduction: Acute myeloid leukemia (AML) is a clonal disease characterized by heterogeneous involvement of hematopoietic bone marrow cell populations. In AML patients, a variety of clinical and biologic parameters, including surface markers, have been examined for potential value in predicting treatment response and survival. By checking the myeloid, lymphoid and nonspecific markers on the blasts, we tested the hypothesis which the disease free survival and overall survival in AML could correlate with the expression of them.

Methods: The immunophenotype was performed by multiparameter flow cytometry (FACS Caliber flow cytometry, Becton Dickinson). The prognostic significance of 16 antigens is taken separately in 207 adult AML patients. We applied statistical software of SPSS-13. In this analysis, we compared DFS and OS with each of the surface markers existence.

Results: We could just find significant correlation in 4 of these markers. Those patients possessed CD3 blasts, had better overall survival (P=0.027). In contrast in CD33 patients, this parameter was worse (P=0.002). Disease free survival in CD15 patients was higher (P=0.036) but in CD34 cases, it was significantly lower (P=0.001).

Conclusions: This study suggests that dependent role of surface markers in the prognosis and response to treatment in AML is a fact which should be paid much more attention and applied it in the management of these patients.

Keywords: Acute Myeloid Leukemia, Disease Free Survival, Overall Survival, Surface Markers

Introduction

Acute myeloid leukemia (AML) is defined as a malignant, marrow-based neoplasm of the blood, bone marrow, and other tissue by neoplastic cells of the hematopoietic system.(1) Immunophenotype is a widely used method to diagnose and classify acute leukemia.(2, 3) A variety of clinical and biologic parameters, including immunophenotype, have been examined for potential value in predicting treatment response and survival. Some reports have suggested a relationship between some antigens (e.g. CD7, CD9, CD11b, CD13, CD14, CD15, CD33, and CD34) and AML prognosis.(4, 5)

Leukemic myeloblasts express a variety of CDs, which reflect commitment to the myeloid lineage as well as a level of maturation.(2, 3) Many studies were accomplished to find whether there is a relation in survival of AML and markers or not and some of them have produced conflicting results. We attempted to evaluate the prognostic significance of different immunophenotypic subgroups and especially to examine the significance of CD34 to response to treatment, because previous studies have suggested a negative effect of this surface marker on therapy failure.(6) Blast cells from 207

AML patients were analyzed with a uniform panel of monoclonal antibodies (mAbs).

Methods and materials

A retrospective cohort study, From March 2001 through February 2009, 207 untreated AML patients were selected who were diagnosed in Shahid Ghazi Tabatabaei Hematology and Oncology ward of Tabriz University of medical sciences Tabriz–Iran. We recovered our data from medical records. None of the patients had a history of prior therapies with anti-neoplastic drugs or a diagnosis of myelodysplastic syndrome. All patients of this study recovered a combination of cytosine arabinoside (Ara-C) and an anthracyclin. Patients received 100 mg/m^2 Ara-C per day for 7 days and either 45 mg/m^2 daunorubicin (DNR) or 10 mg/m^2 idarubicin per day in first 3 days of treatment (7+3 regimen). Those patients who achieved Complete Remission (CR), consolidation therapy were received with 100 mg/m^2 Are-C per day for 5 days and either 45 mg/m^2 daunorubicin or 10 mg/m^2 idarubicin per day in first 2 days of treatment (5+2 regimen). Complete Remission is defined by, absolute neutrophil count of 1500 per millimeters square or more Platelet count of 100000 per millimeters square or more, no blast in circulation, hematopoietic cell population of bone marrow more than 20% with major three lineage proliferation, blasts of bone marrow less than 5% without Auer rod, no extramedullary leukemia foci.(3) In M3 subtype of AML, an extra treatment with ATRA (All Trans Retinoic Acid) was done for 45 days.(3) The immunophenotype was performed before chemotherapy by multiparameter flow cytometry (FACSCalibur flow cytometry, Becton Dickinson, California, US). Flow cytometry was performed on blast cells of bone marrow gated on their abnormal light scatter characteristics using mAbs for the following 16 antigens: CD13, CD14, CD15, CD33, CD11bCD19, CD20, CD2, CD3, CD7, CD10,D34, CD45, HLA-DR and Glycophorin-A.

A membrane marker was considered positive when more than 15% of the blast cells expressed it.

In this study, we applied statistical software of SPSS-13. We used Cox-Regression for relationship between Immunological markers, disease free survival (DFS) and overall survival (OS). DFS and OS were estimated by Kaplan–Meier method. P<0.005 was considered significant.

Results

In this study, 207 patients with AML were included. 113 patients (54.6%) were male and 94 (45.4%) female. Age ranged from 11 to 81 years, with a median age of 40 years.

Among different markers, the most positive markers were the following: the myeloid lineage antigens CD13 (81%), CD33 (84.9%), and CD11b (42.5%), and the hematopoiesis progenitor cell markers HLA-DR (46.1%), and CD34 (55.9%). CD7 was positive in 26.8% of the patients. We were have been detected the T-cell markers CD2 in 28.1% of patients, and CD3 in 20.3%, whereas the B-cell markers CD19 in 12.4%, CD10 in 2.6%, and CD20 in 15%. CD45 and Glycophorin-A were positive in 88.9% and 10.6% of the patients, respectively.

We compared the disease free survival and overall survival of AML patients whose leukemic blasts disclosing different surface markers. Figure- 1 show OS of patients.

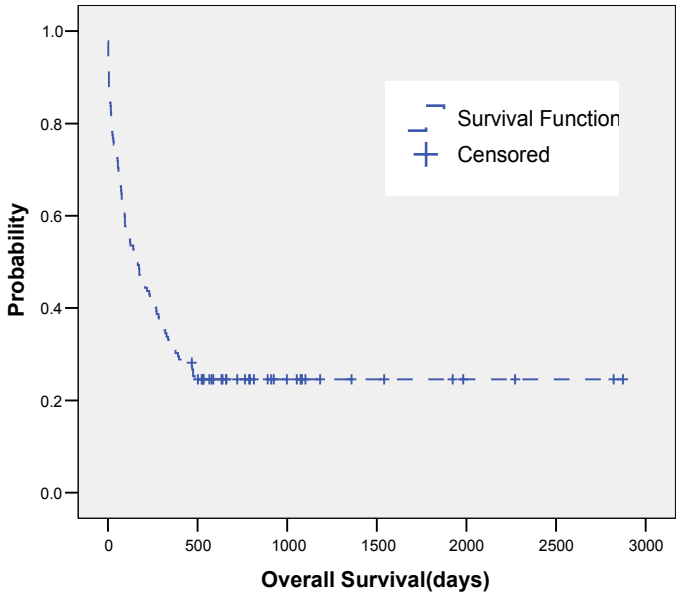

Figure -1 Kaplan-Meier analysis of Overall Survival ,in 207 patients with AML in North-West of Iran

OS patients were 24.6%, and DFS was 31.3% during this period. Those patients possessed CD3 blasts, had better overall survival (P=0.027). In contrast in CD33 patients, this parameter was worse (P=0.002). Disease free survival in CD15 patients was higher (P=0.036) but in CD34 cases, it was significantly lower (P=0.001). Disease Free Survival (DFS) was significantly worse in patients found positive for CD33 (P=0.034).

Discussion

The results concerning the prognostic value of surface antigen expression in AML. Our study involved immunophenotype examinations in a large number of adults with newly diagnosed AML.

Our results indicate that the expression of even 1 antigen can be applied for risk stratification in adult

AML at diagnosis. Several studies reported a poor response to induction chemotherapy in patients with CD34 and/or CD7 AML.(5, 9- 11) In our study, CD34+ patients were associated with shorter DFS and this is compatible with many other studies.(5, 6, 9- 11) This finding can be linked to drug resistance in these patients. The high frequency of CD34 on more immature myeloblasts would be a possible reason for this event.(12)

In the study of Perea G. et.al (2005), CD2+ and CD36+ patients had a very poor OS and lower CR in normal genotype background but it was not found in this study.(13) In some of the prior investigations, presence of CD33 was considered a favorable prognostic factor,(9,11) but our study revealed that CD33 had a significant associated with shorter DFS and OS.

In spite of finding prognostic significance of CD33 and CD34 in this study, no correlation was found for any of the surface markers, in some of the others.(14, 15) In a study of pediatric AML in the US, no prognostic significance was observed in any of the surface markers.(15)

The results of this study will be used to develop treatment strategies which are based on the specific pattern of surface marker presentation in an individual patient. Intensive therapies may be used to improve outcome in the poorer prognosis groups, while for patients with a better prognosis, reduced toxicity with standard effective therapy can be replaced by unnecessary high dose treatment.

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Conflicts of interest

The authors have no conflicts of interest to declare for this study.

References

1. Kumar V, Cotran RS, Robbins SL. Basic Pathology. 7th edition. WB Saunders, 2003:p.436.

2. Roitt I, Brostoff J, Male D. Roitt Immunology, 6th ed. London (UK): Mosby; 2002. P. 437-46.

3. Wetzler M, Byrd JC, Bloomfield CD. Acute and Chronic Myeloid Leukemia. In: Fauci AS , Kasper DL, Longo DL, Braunwald E, Hauser SL. Harrison's Internal Medicine, 17th ed. New York (US): McGraw Hill Medical; 2008. P. 677-686.

4. Hatano Y, Miura I, Horiuchi T, Hoshi N, Nanjou H, Masuda H, et al. Cerebellar Myeloblastoma Formation in CD7- positive, Neural Cell Adhesion Molecule (CD56) -positive Acute Myelogenous Leukemia(M1). Ann Hematology, 1997; 75:125-128.

5. Chianese R, Brando B, Gratama JW; European Working Group on Clinical Cell Analysis. Diagnostic and Prognostic Value of Flow Cytometric Immunophenotyping in Malignant Hematological Diseases. J Biol Regul Homeost Agents. 2002; 16: 259-69.

6. Slobinas A, Matuzevieienae R. The Immunophenotype of Adult with Acute Myeloid Leukemia Proposal of Prognostic Value. Acta Medica Lituanica, 2005; 12: 54-59.

7. Bene MC, Castoldi G, Knapp W, Ludwig WD, Matutes E, Orfao A, van't Veer MB. Proposal for the Immunological Classification of Acute Leukemias. European Group for the Immunological Characterization of Leukemias(EGIL). Leukemia, 1995; 9: 1783-6.

8. Bene MC, Bernier M, Casasnovas RO, Castoldi G, Knapp W, Lanza F, et al. The Reliability and Specificity of c-kit for the Diagnosis of Acute Myeloid Leukemias and Undifferentiated Leukemias. The European Group for the Immunological Classification of Leukemias (EGIL).Blood. 1998;92:596-9.

9. Repp R, Schaekel U, Helm G, Thiede C, Soucek S, Pascheberg U. et al. Immunophenotyping is an Independent Factor for Risk Stratification in AML. Cytometry B Clin Cytom. 2003; 53: 11-9.

10. Casasnovas RO, Slimane FK, Garand R, Faure GC, Campos L, Deneys V et.al. Immunological Classification of Acute Myeloblastic Leukemias; Relevance to Patient Outcome. Leukemia. 2003; 17: 515- 27.

11. Lanza F, Rigolin GM, Moretti S, Latorraca A, Castoldi G. Prognostic Value of Immunophenotypic Characteristics of Blast Cells in Acute Myeloid Leukemia. Leuk Lymphoma. 1994; 1: 81-5.

12. Pollard JA, Alonzo TA, Gerbing RB, Woods WG, Lange BJ, Sweetser DA. et.al. FLT3 Internal Tandem Duplication in $CD34^{+}/CD33^{-}$ Precursors Predicts Poor Outcome in Acute Myeloid Leukemia. Blood, 2006; 108: 2764- 9.

13. Perea G, Domingo A, Villamor N, Palacios C, Juncà J, Torres P, et.al. Adverse Prognostic Impact of CD36 and CD2 Expression in Adult de novo Acute Myeloid Leukemia Patients. Leuk Res; 2005; 29: 109- 16.

14. Legrand O, Perrot JY, Baudard M, Cordier A, Lautier R, Simonin G, et.al. The Immunophenotype

of 177 Adults with Acute Myeloid Leukemia: Proposal of a Prognostic Score. Blood, 2000; 96: 870-877.
15. Kuerbitz SJ, Civin CI, Krischer JP, Ravindranath Y, Steuber CP, Weinstein HJ, et.al. Expression of Myeloid-associated and Lymphoid-associated Cell surface Antigens in Acute Myeloid Leukemia of Childhood: a Pediatric Oncology Group Study. J Clin Oncol. 1992; 10: 1419- 29.