

IDENTIFICATION OF MOLECULAR MARKERS FOR DIAGNOSIS OF ACUTE LEUKEMIA IN ADULT AND PEDIATRIC PATIENTS.

*Stefania Dorobantu¹, Rodica Talmaci^{2,3},
Mihaela Dragomir³, B. Ionescu³, Anca Colita^{3,4},
D. Jordan⁵, D. Coriu^{2,3}*

¹Faculty of Biology, University of Bucharest, Bucharest, Romania

²Fundeni Hematology Department, University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania

³Center of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, Bucharest, Romania

⁴Department of Pediatrics-Fundeni, University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania

⁵Medlife SA

INTRODUCTION

In acute leukemia (AL), was identified a growing number of molecular genetic changes, highlighting biological heterogeneity of this disease. Moreover, the characterization of specific molecular abnormalities provides the basis for targeted therapies, such as using of all-trans retinoic acid (ATRA) and arsenic trioxide in the treatment of acute promyelocytic leukemia or using of tyrosine kinase inhibitors in the treatment of acute myeloid leukemia with FLT3 mutations. A detailed evaluation of molecular markers at diagnosis is crucial for risk stratification groups of patients with LA. This allows the earlier identification of patients at high risk of relapse eligible for allogeneic stem cell transplantation. Finally, molecular markers are important for detecting minimal residual disease after initial therapy and during long-term follow-up. These allow a more tailored treatment approach for each patient and are the premises of personalized medicine.

MATERIALS AND METHODS

The most common fusion genes identified in acute myeloid leukemia (AML) are: MLL - AF4, BCR - ABL1, AML1 - ETO, PML - RAR α , CBF β - MYH11 and MLLAF9. In acute lymphoblastic leukemia (ALL), the most common gene changes are: MLL - AF4, BCR - ABL1, TEL - AML1, E2A - PBX1 and SILTAL1. Detection of these genetic markers in AL was performed by using Multiplex PCR method on complementary DNA. Identifying these fusion genes allowed us to stratify the patients into risk groups. Molecular monitoring of minimal residual disease by quantitative detection (RQ-PCR) and Nested PCR allow of early prediction of relapse.

RESULTS

272 patients with suspected acute leukemia at presentation were investigated in 2014-2015, 179 (66%) - adults and 93 (34%) - children. In adults patients, 73% were diagnosed with AML and 27% with ALL. For the diagnosis of AML fusion genes were identified as following: FLT3-ITD - 45%, PML-RAR α - 29%, CBF β -MYH11 - 13%, AML1-ETO - 13%, and MLL-AF9 - 0%. For the diagnosis of ALL were identified: BCR-ABL - 70%, MLL-AF4 - 17%, E2A-PBX - 7%, TEL-AML - 6% and SIL-TAL - 0%.

In pediatric patients, 17% were diagnosed with AML and 83% with ALL. For the diagnosis of AML were identified: PML-RAR α - 62%, MLL-AF9 - 25%, AML1-ETO - 13%, CBF β -MYH11 - 0% and FLT3-ITD - 0%.

For the diagnosis of ALL have been identified: TEL-AML1 - 74%, BCR-ABL - 13%, E2A-PBX - 9%, MLL-AF4 - 4% and SIL-TAL - 0%. Observing these two groups, there is a clear majority frequency of cases of AML in adults and ALL in pediatric patients. According to publications in the literature, ITD mutation-FLT3 (Internal Tandem Duplication in FLT3) is one of the most common mutations found in adult AML. Detection of FLT3-ITD is associated with resistance to chemotherapy, early relapse, and the progression of the disease. The data identified in this study with 45% prevalence of FLT3-ITD in adult AML, may partially explain why adult AML has a poorer clinical outcome than pediatric AML. The association of FLT3-ITD tandem duplications in PML-RAR α translocation is frequently described in the literature. In the study group we have analyzed, three patients with FLT3-ITD showed PML-RAR α translocation also.

CONCLUSIONS

For acute leukemia, the most common in adults is acute myeloid leukemia and the most common in pediatric patients is acute lymphoblastic leukemia.

Detection of minimal residual disease in acute leukemia is a useful and effective method for identifying patients at high risk of relapse. Early detection and treatment can improve clinical outcome molecular relapse in acute promyelocytic leukemia with PML-RAR α positive. FLT3 gene with tandem duplication is a negative prognostic indicator for AML.

From all analyzed markers in adults we did not find any patient with TEL-AML fusion in ALL and no MLL-AF9 in AML. In children no FLT3-ITD and CBF β -MYH11 cases were identified.