

# **CORRELATIONS BETWEEN BCR-ABL LEVEL AND HEMATOLOGICAL ONSET OF CHRONIC MYELOID LEUKEMIA AT DIAGNOSIS.**

*Violeta Dan<sup>1</sup>, Rodica Talmaci<sup>2,3</sup>, Iulia Ursuleac<sup>2,3</sup>,  
Manuela Crisan<sup>2,3</sup>, Adriana Vulpe<sup>3</sup>,  
Mihaela Dragomir<sup>3</sup>, D. Coriu<sup>2,3</sup>*

<sup>1</sup>Faculty of Biology, University of Bucharest,  
Bucharest, Romania

<sup>2</sup>Fundeni Hematology Department, University of  
Medicine and Pharmacy "Carol Davila", Bucharest,  
Romania

<sup>3</sup>Center of Hematology and Bone Marrow  
Transplantation, Fundeni Clinical Institute, Bucharest,  
Romania

## **INTRODUCTION**

A rapid research development of chronic myeloid leukemia (CML) were made for a fully understanding of the mechanisms underlying these diseases.

Inhibition of the BCR-ABL tyrosine kinase activity is the most efficient way for silencing this oncoprotein. The development of tyrosine kinase inhibitors (TKI) for chronic phase CML patients was revolutionized the treatment of this disease and profoundly transformed its evolution from a fatal disease to a chronic condition. The amount of leukemic cells that remain in the patient's body during treatment with TKI can be monitored accurately by using 3 ways: examination of peripheral blood (hematologic response), cytogenetic examination of metaphase analysis in bone marrow (cytogenetic response) and quantification of BCR-ABL transcripts (molecular response).

## **MATERIALS AND METHODS**

Diagnosis and monitoring of CML patients in chronic phase was performed on peripheral blood samples, processed to obtain cell lysates and TRIzol preservation. Detection of BCR-ABL transcripts was achieved by Multiplex PCR of cDNA. Real Time Quantification of BCR-ABL transcript level was achieved by the Hybridization Probes detection method on the LightCycler 1.5 Instrument.

## **RESULTS**

The study included 222 patients in 2014-2015. In patients positive for BCR-ABL fusion gene, the most frequently identified transcripts were b3a2 - 28% and b2a2 detected in 11% of cases. Rare cases of atypical transcript b3a3 were identified in 2% of cases, and the presence of both transcripts b3a2 + b2a2 was detected in 2% of cases at presentation.

In this study we have investigated the correlation between the BCR-ABL transcript type and hematological parameters at diagnosis: hemoglobin, hematocrit, leukocyte and platelet counts. Regarding the hemoglobin and hematocrit levels, there was not a significant difference between the main two types of transcripts. A significant difference in BCR-ABL expression at diagnosis was observed regarding leukocyte levels, where in the case of transcript b2a2, we have found the average of 107,383 (103/ $\mu$ l), compared with patients with b3a2 transcript - 76,832 (103/ $\mu$ l).

Regarding platelet levels, a significant difference was identified: patients with transcript b2a2 have an median average of 740 (103/ $\mu$ l) and patients with b3a2 transcript have a lower average of 473 (103/ $\mu$ l) platelet count at diagnosis.

This observation suggests that BCR-ABL with b2a2 transcript has a lower expression, is less aggressive and thus the time from symptomatic onset to the diagnosis is prolonged. Patients with b2a2 transcript would have milder symptoms and faster response to treatment.

In patients with b3a2 transcript, symptoms can be more aggressive and thus, the time from symptomatic onset to diagnosis is shorter.

The average of BCR-ABL level (BCR-ABL1 IS%) at diagnosis was found to be slightly different. In patients with b2a2 transcript, the average of BCR-ABL was 22.6% and 35.2% for patients with b3a2 transcript.

The next aspect of the work is related to the importance of achieving major molecular response (MMR) as soon as the start of imatinib mesylate. Getting an MMR at 12 months of treatment initiation was associated with an optimal response to imatinib mesylate therapy.

## **CONCLUSIONS**

For patients enrolled in this trial, the transcript b3a2 type was more frequently identified than those with b2a2 and there were identified patients with atypical transcripts and patients with both types b3a2+b2a2. High levels of leukocytosis and thrombocytosis at diagnosis for patients with b2a2 transcript suggests a lower gene expression of BCR-ABL and thus a longer time from first signs of illness until diagnosis. The molecular response to TKI therapy was faster than those with b3a2 type.

In patients with b3a2 transcript, symptoms can be more aggressive and thus, the time from symptomatic onset to diagnosis is shorter and molecular response to treatment with TK inhibitor is delayed.