JBUON 2021; 26(3): 1165-1168
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

SHORT COMMUNICATION

# Clinico-laboratory pertinences and management of relapsed and refractory chronic myeloid leukemia

Vasile Musteata

State University of Medicine and Pharmacy "N. Testemitanu", Institute of Oncology

## Summary

***Purpose:*** *The purpose of this study was to assess the biological significance of lactate dehydrogenase (LDH), T315I mutation and treatment options in newly diagnosed and relapsed patients with chronic myeloid leukemia (CML).*

***Methods:*** *Our clinical-analytical and descriptive study enrolled 27 patients with different phases of CML, who were followed up and treated at the Institute of Oncology between 1995-2020. Venous blood samples were taken for LDH measurement, molecular screening and detection of T315I mutation of the ABL gene in order to investigate the biological significance of the increased LDH values and T315I mutation. CML patients underwent chemotherapy with alkylating agents, antimetabolites and tyrosine kinase inhibitors (TKIs).*

***Results:*** *The patient age ranged from 20 to 67 years (mean 51.3±2,14). The diagnosis of CML was established in the late chronic phase in 25 (92.6%) patients. The quantitative real-time PCR revealed p210 transcript of the BCR-ABL chimeric gene in all cases, with the range of 23.17-100% and median value of 74.73±3.21%. LDH at diagnosis ranged between 169-1609.4 U/L and was increased in 14 (63.6%) patients, especially in those with leukocytosis over 100×10$^9$/l. The complete cytogenetic and complete or major molecular responses were recorded under treatment with different generations of TKIs in 16 (59.3%) cases, including 3 cases with T315I mutation. Relapses occurred in 10 (71.4%) patients with initially increased LDH values and in 5 of 6 patients with T315I mutation. One (3.7%) patient with T315I mutation evolved into the acute phase disease, and achieved the complete hematological response after treatment with ponatinib, a 3$^{rd}$ generation TKI. The survival of patients from the disease onset till the last monitoring visit ranged between 21 and 234.8 months (median 93.97±4.52).*

***Conclusions:*** *The increased LDH values may indicate the activity at diagnosis and relapse of CML. In our study T315I mutation of the ABL gene and the increased values of LDH were associated with a higher rate of relapses and resistance to imatinib. Notwithstanding the treatment line and in relapses TKIs improve considerably the survival and ECOG-WHO score of CML patients.*

***Key words:*** *chronic myeloid leukemia, lactate dehydrogenase, p210 transcript of the BCR-ABL chimeric gene, relapse, tyrosine kinase inhibitors, T315I mutation*

## Introduction

Chronic myeloid leukemia (CML) is a clonal neoplasm of the hematopoietic system with primary bone marrow involvement, which results from the malignant transformation of the pluripotent stem cell, while maintaining the ability of differentiation intoall cell lines [1-5]. CML morbidity increases with age, with a maximum between 35 and 65 years (median 53 years), that includes the predominant involvement of workable population. CML morbidity varies between 1.0–2.0 cases per 100,000 of the population [6-10]. The clinico-evolutional, hematological and molecular-cytogenetic patterns of CML comprise splenomegaly, myeloid hyperplasia of the bone marrow, hypercatabolic

*Corresponding author:* Vasile Musteata, MD, PhD, MPH. Testemita nust.no. 30, MD-2025, Chisinau, Republic of Moldova.
Tel: +37322 852635, Email: vasile.musteata@usmf.md
Received: 26/12/2020; Accepted: 18/01/2021

symptoms,balanced genetic translocation [t(9;22)(q34;q11.2)] and tyrosine kinase (TK) activity of the oncogenic proteins encoded by BCR/ABL transcripts, being characterized in the accelerated and acute phases by a recurrent disease course and unfavorable prognosis, with negative socio-economic impact [9-14].The biological significance of LDH and T315I mutation are under continuous research in order to develop a therapeutic strategy overcoming TKIs-resistance. The patients with advanced phases of CML experience marked disease burden in terms of symptoms and negative effects on quality of life, productivity, and daily living activities [6,12-14]. The commonly delayed diagnosis, increased degree of disability, morbidity and mortality rates in the age categories over 60 years [2,11] characterize CML as an actual subject of hemato-oncology and public health.

## Methods

This clinical-analytical, descriptive study enrolled 27 patients with different phases of CML, who were followed up and treated at the Institute of Oncology between 1995-2020. The following research methods were used: epidemiological, descriptive, comparative, clinical-analytical, and cohort statistics [12]. The diagnosis was nosologically identified according to the Revised 2017 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues [16,17]. CML cases were diagnosed by cytological, cytogenetic and molecular examinations of the bone marrow and peripheral blood [2-5,11]. The quantitative real-time PCR was used with the aim to detemine the expression of the BCR-ABL chimeric gene p210 and p190 transcripts while proceeding CML diagnosis. Five transcription products (b2a2, b3a2, b2a3, b3a3 si e1a2) were analyzed by the usage of the quantitative PCR test [8]. The venous blood samples were taken for molecular screening and detection of T315I mutation of the ABL gene in all registered patients in order to investigate the biological significance of T315I mutation and to develop a therapeutic strategy overcoming imatinib-resistance. LDH test was assessed in 22 cases at diagnosis and in 7 cases of relapse or progression to the acute phase. CML patients underwent conventional chemotherapy with alkylating agents, antimetabolites, 1st- and 2nd-line treatment with TKIs. The TKIs generation assessment and selection was performed according to the hematological and molecular response [1,4,10,15]. The accumulation of information for research was carried out by analyzing the data provided by the international scientific sources and official statistics related to the above mentioned nosological entities. Seventeen relevant primary sources were identified and selected with a scientific, reproducible and transparent approach to the subject under discussion, followed by the data extraction and analysis. When doing the qualitative research, a narrative synthesis of data has been performed.

## Results and Discussion

There were 17 males and 10 females (male:female ratio 1.7:1). The diagnosis of CML was established in the early chronic phase in 1 (3.7%) patient, late chronic phase in 25 (92.6%) patients and in the accelerated phase in 1 (3.7%) patient. The age range was 20-67 years (mean51.3±2,14), that proved the high involvement of the workable population. The ECOG-WHO score varied between 1-3. The quantitative real-time PCR revealed the p210 transcript of the BCR-ABL chimeric gene in all cases, with a range of 23.17-100% and median value of 74.73±3.21%. In 21 (77.8%) cases the rate of p210 transcript-positive peripheral blood cells exceeded 50%. The leukocyte count (LC) varied between 21.9-356×$10^9$/l (mean 141.4×$10^9$/l). The LC was ≤ 100×$10^9$/l in 10 (37.04%) cases, between 100-200×$10^9$/l in 7 (25.93%), between 200-300×$10^9$/l in 8 (29.63%), and exceeded 300×$10^9$/l in 2 (7.4%) cases. The expression of p210 transcript did not correlated confidentially with the LC.LDH at diagnosis ranged between 169-1609.4 U/L (mean 515,6 U/L). LDH was increased in 14 (63.6%) patients, especially in those with LC over 100×$10^9$/l and was found elevated in 6 of 7 cases with relapse or progression to the acute phase. The range of LDH in these patients was 401-1107 U/L. The single-agent therapy with imatinib was a first-line treatment in 4 (14.8%) patients, and followed the short-term cytoreduction with hydroxycarbamide in 15 (55.6%) patients. All these 19 patients (70.4%) obtained complete clinico-hematological response in 1-2 months. Conventional chemotherapy with busulfan, hydroxycarbamide and hydroxycarbamide combined with mercaptopurine was administered in 8 (29.6%) patients and led only to a partial clinico-hematological response. No patient achieved cytogenetic or molecular response. Five (62.5%) of these patients developed hematological relapse. All 8 cases required a switch of treatment to imatinib, as a second-line option, and obtained complete clinico-hematological response. Under the treatment with imatinib hematological relapse occurred in 4 of 6 cases with T315I mutation. These patients were switched to treatment with nilotinib and ponatinib, with achievement of complete clinico-hematological response. Five of 6 patients with T315I mutation failed toobtain complete cytogenetic and complete or major molecular responses under the treatment with imatinib.Complete cytogenetic and complete or major molecular responses were achieved after the treatment with nilotinib and ponatinib only in 2 of the last cases. Overall, complete cytogenetic and complete or major molecular responses were recorded under the

treatment with different generations of TKIs in 16 (59.3%) cases, including 3 cases with T315I mutation. Relapses occurred in 10 (71.4%) patients with initially increased LDH values and in 5 of 6 patients with T315I mutation. One (3.7%) patient with T315I mutation evolved into the acute phase, and achieved complete hematological response after the treatment with ponatinib. All patients are alive. The survival of patients from the disease onset till the last monitoring visit ranged between 21-234.8 months (median survival 93.97±4.52 months). Under treatment with TKIs the ECOG-WHO score was increased up to 0-1 in 100% of the patients, as compared to non-TKIs therapy. Regardless of age and gender of CML patients, the administration of TKIs as a first- or second-line therapy has considerably improved the patient short- and long-term results of treatment, contributing thus to the essential increase of life expectancy, their physical recovery, professional and social rehabilitation. The recent studies demonstrated the significant antileukemic activity of carnosic acid on CML KBM-7 cells with an $IC_{50}$ of 25 μM [18]. Carnosic acid is a polyphenol mainly isolated from the plant Rosmarinus officinalis. It was observed that carnosic acid inhibited the proliferation and invasion of CML KBM-7 cells due to downregulation of microRNA-780 expression as indicated by the quantitative RT-PCR analysis. This potential treatment compound deserves *in vivo* study aimed to overcome the relapses and resistance to TKIs in CML with T315I mutation and increased LDH values.

## Conclusions

The expression of BCR-ABL gene p210 transcript in the absolute majority of cases exceeded 50% and did not correlate comprehensively with the LC. The increased LDH values may indicate the activity at diagnosis and relapse of CML. In our study T315I mutation of the ABL gene and the increased values of LDH were associated with a higher rate of relapses and resistance to imatinib.The targeted treatment with TKIs remains the treatment option of choice for CML patients regardless of their age, and may be preceded by the short-term single-agent chemotherapy with hydroxycarbamide for cytoreduction. Notwithstanding the treatment line and in relapses, single-agent therapy with TKIs improves considerably the survival and ECOG-WHO score of CML patients. Carnosic acid may be considered as a potential treatment compound, which deserves *in vivo* study aimed to overcome the relapses and resistance to TKIs.

## Conflict of interests

The authors declare no conflict of interests.

## References


1. Hughes TP, Ross DM, Melo JV. Handbook of chronic myeloid leukemia. Springer International Publishing Switzerland, 2016:1-66.
2. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. Am J Hematol 2018; 93:442-59.
3. Dorfman LE, Floriani MA, Oliveira TM, Cunegatto B, Rosa RF, Zen PR. The role of cytogenetics and molecular biology in the diagnosis, treatment and monitoring of patients with chronic myeloid leukemia. J Bras Patol Med Lab 2018;54:83-91.
4. ESMO Guidelines Committee. Chronic myeloid leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:iv41-iv51.
5. Thompson PA, Kantarjian HM, Cortes JE. Diagnosis and Treatment of Chronic Myeloid Leukemia in 2015. Mayo Clinic Proceed 2015;90:1440-54.
6. Fitzmaurice C, Akinyemiju TF, Al Lami FH et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2016. A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2018; 4:1553-68.
7. Mehta J,Wang H, Iqbal SU, Mesaet R. Epidemiology of myeloproliferative neoplasm in the United States. Leuk Lymphoma 2014;55:595-600.
8. Bron D, Ades L, Fulop T, Goede V, Stauder R. Aging and blood disorders: new perspectives, new challenges. Haematologica 2015; 100: 415-7.
9. Geyer HL, Scherber RM, Dueck AC et al. Distinct clustering of symptomatic burden among myeloproliferative neoplasm patients: retrospective assessment in 1470 patients. Blood 2014;123:3803-10.
10. Hughes TP, Ross DM, Melo JV. Handbook of chronic myeloid leukemia. Springer International Publishing Switzerland, 2016:1-66.
11. Jaffe ES. The microscope as a tool for disease discovery-A personal voyage. Annu Rev PatholMech Dis2017;12:1-24.
12. O'Brien S, Radich JP, Deininger M et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Chronic myelogenous leukemia. Version 3.2014. National Comprehensive Cancer Network, Inc. 2014:1-96.
13. Yu J, Parasuraman SV, Paranagama DC et al. Impact of myeloproliferative neoplasms on patients' employment status and work productivity in the United States: re-

sults from the living with MPNs survey. BMC Cancer 2018; 18: 1-9.

14. Harrison CN, Koschmieder S, Foltz L et al. The impact of myeloproliferative neoplasms (MPNs) on patient quality of life and productivity: results from the international MPN Landmark survey. Ann Hematol 2017; 96:1653-65.
15. Li B, Rampal RK, Xiao Z. Targeted therapies for myeloproliferative neoplasms. Biomarker Res 2019;7:15: 1-8.
16. Carbone A. Classification of Tumors of the Hematopoietic and Lymphoid Tissues. Discovering Diseases - Defining Their Features. Blood2020;1:7-9.
17. Swerdlow SH, Campo E, Harris NL et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised 4th ed. IARC: Lyon, France, 2017.
18. Liu D, Wang B, Zhu Y et al. Carnosic acid regulates cell proliferation and invasion in chronic myeloid leukemia cancer cells via suppressing microRNA-708. JBUON 2018; 23:731-46.