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

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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 100×10⁹/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 3rd 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 into all cell lines [1-5]. CML morbidity increases with age, with a maximum between 55 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...
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 determine 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 TKIs-resistance. The patients with advanced phases of CML 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.

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 (mean 51.3±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 21.9-356×10⁹/l (mean 141.4×10⁹/l). The LC was ≤ 100×10⁹/l in 10 (37.04%) cases, between 100-200×10⁹/l in 7 (25.93%), between 200-500×10⁹/l in 8 (29.63%), and exceeded 500×10⁹/l in 2 (7.4%) cases. The expression of p210 transcript did not correlated confidentially with the LCL/DH 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 100×10⁹/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 hydroxyurea in 15 (55.6%) patients. All these 19 patients (70.4%) obtained complete clinico-hematological response in 1-2 months. Conventional chemotherapy with busulfan, hydroxyurea and hydroxyurea 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 21–254.8 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 hydroxy-carbamide 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

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