Case Report

T Lymphoblastic Transformation of Chronic Myeloid Leukemia with Isolated Maturing Precursors of Neutrophil Cell Line in the Cerebrospinal Fluid - δ

Natasa Colovic¹²*, Danijela Lekovic¹², Marko Jankovic³, Marija F. Dencic² and Mirjana Gotic¹²

¹²Medical Faculty, University of Belgrade, Dr Subotica 8, 11000 Belgrade, Serbia
³Clinic of Hematology, Clinical Center of Serbia, Koste Todorovica 2, 11000 Belgrade, Serbia

*Address for Correspondence: Natasa Colovic, Faculty of Medicine, University of Belgrade, Dr Subotica 8, 11010 Belgrade, Serbia, Tel: +381-11-361 55 69; E-mail: natasacolovic73@gmail.com

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ABSTRACT

Introduction: Imatinib mesylate, a potent inhibitor of BCR/ABL tyrosine kinase, is the first therapeutic choice in Chronic Myeloid Leukemia (CML). It poorly penetrates the brain-blood barrier so that therapeutic concentrations in the Cerebrospinal Fluid (CSF) can hardly be achieved. In effect, rare clonogenic stem cells that had anchored in the Central Nervous System (CNS) may eventually proceed towards the blastic transformation there.

Case Report: We report on a 25 - yr - old male treated with imatinib mesylate who developed T lymphoblastic blast crisis without the clinical signs of neuroleukemia. After treatment with chemotherapy and preventive intrathecal methotrexate, cytosine-arabinoside and hydrocortisone he achieved the remission. Six months later he contracted a general relapse in the bone marrow and peripheral blood. Remarkably, his CSF cytology demonstrated only the cells representative of chronic phase of disease. The subclone raising the extensive blasts crisis was resistant to chemotherapy.

Conclusion: The CML relapsing in the CSF with a chronic phase clone in parallel with a T-lymphoblastic crisis in the bone marrow and the peripheral blood has never been reported so far. We emphasize the importance of CNS surveillance strategy using PCR methods in patients with signs of CNS involvement in CML.

Keywords: Chronic myeloid leukemia; T lymphoblastic transformation; Imatinib mesylate; Neuroleukemia

INTRODUCTION

Central Nervous System (CNS) is rather infrequently affected in Chronic Myeloid Leukemia (CML) [1,2]. In the lymphoblastic transformation of CML the incidence of CNS involvement is comparable to that in Acute Lymphoblastic Leukemia (ALL) [1,2], To the best of our knowledge, the relapse of Chronic Myeloid Leukemia in cerebrospinal fluid with a chronic phase clone coinciding with T lymphoblastic crisis in bone marrow and peripheral blood has not been previously reported. Here we report the clinical course in such a unique case.

CASE REPORT

A 25 - yr - old male with a history of Philadelphia chromosome positive CML in chronic phase diagnosed on August 13th, 2013. At the time of diagnosis, he had a Sokal score of 1.08 and Hasford score of 207. The EUTOS score was 7, indicating low risk. He achieved a remission. Six months later he contracted a general relapse in the bone marrow and peripheral blood. Remarkably, his CSF cytology demonstrated only the cells representative of chronic phase of disease. The subclone raising the extensive blasts crisis was resistant to chemotherapy.

We report on a 25 - yr - old male treated with imatinib mesylate who developed T lymphoblastic blast crisis without the clinical signs of neuroleukemia. After treatment with chemotherapy and preventive intrathecal methotrexate, cytosine-arabinoside and hydrocortisone he achieved the remission. Six months later he contracted a general relapse in the bone marrow and peripheral blood. Remarkably, his CSF cytology demonstrated only the cells representative of chronic phase of disease. The subclone raising the extensive blasts crisis was resistant to chemotherapy.

Keywords: Chronic myeloid leukemia; T lymphoblastic transformation; Imatinib mesylate; Neuroleukemia
DISCUSSION

CML is a clonal myeloproliferative disease characterized by proliferation and accumulation of mature haemopoietic cells in the peripheral blood and bone marrow occasionally accompanied by extramedullary haemopoiesis. The genetic molecular basis of the disease is fusion of the \( bcr \) gene on chromosome 22 with the \( abl \) gene on chromosome 9, forming the Philadelphia chromosome. Imatinib mesylate is most efficacious in the treatment of chronic phase CML, its efficacy in cases of lymphoblastic infiltration of CNS in blast crisis has not been evaluated extensively due to rarity of this complication. Penetration of the drug into the central nervous system is poor so the drug level is inadequate for killing leukemic stem cells, if any. In consequence, CNS may turn into a refuge for leukemic stem cells that had settled there [7-10]. Anecdotal reports suggest that imatinib does not penetrate the blood-brain barrier and has limited effects against leukemic blasts in the CSF. Low levels of the drug in cerebrospinal fluid have been documented in experimental animals and in humans [7-11]. Bornhauser, et al. [8] reported a patient with CML on imatinib who developed an isolated CNS relapse, although he achieved a complete cytogenetic response, as the patient had significantly lower level of imatinib in CSF than in blood. Similar observation was reported by Takayama in patient with Ph positive ALL and concurrent CNS and marrow relapse [7]. Isobe, et al. [12] reported isolated lymphoid blast crisis in CNS in a patient with CML after viral meningitis while he was in complete cytogenetic remission on imatinib therapy. Park, et al. [13], found 15 published cases of the isolated CNS relapse in CML patients treated with imatinib, 10 of which had lymphoblastic immunophenotype, 1 mixed lineage and 3 myeloid, while in 2 patients the phenotype was not determined. Nine out of 15 had a full cytogenetic response. The median time from starting with imatinib ranged from 4 to 58 months and no predicting factors for CNS relapse were identified. So, the explanation for isolated CNS relapse could be the low level of the drug in CSF as a result of the poor CNS penetration mediated through P-glycoprotein efflux [14]. This emphasizes the problem of imatinib pharmacokinetics in the CNS, which might be worth to consider in patients taking the drug [13]. Even with a second generation of tyrosine-kinase inhibitor (dasatinib) that have an improved penetration into the CNS a single case of isolated CNS blast crises was reported [15].

Bornhauser, et al. [8] have suggested that the course of patients with CML on imatinib may be complicated by an unforeseen blast crisis in the CNS.

This quite unusual clinical course of CML, so far unreported, points at a need to define surveillance strategy with rare central and peripheral nervous system relapses associated with the blastic phase of CML. The analysis of BCR-ABL in cerebrospinal fluid and FISH analysis should be performed on the first sign of haematological relapse of CML, although regular CSF examination or prophylactic intrathecal chemotherapy due to rarity of CNS involvement is not still indicated. No treatment guidelines for documented CNS relapse in this kind of patients have yet been defined.
CONFLICTS OF INTEREST

The authors disclose no conflict of interests.

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REFERENCES


