

Promyelocytic blast crisis of chronic myeloid leukemia after one year of Imatinib treatment

Received: 19/4/2012

Accepted: 20/12/2012

Nawsherwan Sadiq *

Mohammed Dhahir Ali **

Abstract

A 60 year-old man in the chronic phase of chronic myeloid leukemia (CML-CP) was treated with imatinib mesylate for 1 year. After one year of the initial diagnosis of CML chronic phase, the patient progressed to a promyelocytic blast crisis, karyotyping showed 46,XY,t(9;22)(q34;q11.2), t(15;17)(q22;q21) in all cells examined. The patient was diagnosed with promyelocytic blast crisis of CML. With administration of all-trans retinoic acid (ATRA) and high-dose imatinib mesylate (800 mg/day), the patient has died of disseminated intravascular coagulation within 2 weeks. As karyotyping showed 46,XY,t(9;22)(q34;q11.2), t(15;17)(q22;q21) in all cells examined, this is suggesting that the clonal evolution of PML/RARa translocation occurred early in the CML-CP.

Keywords: acute promyelocytic leukemia, CML, BCR/ABL, PML/RARa, imatinib

Introduction

CML is a malignant clonal disorder of hematopoietic stem cells that results in increases in not only myeloid cells but also erythroid cells and platelets in peripheral blood and marked myeloid hyperplasia in the bone marrow¹. The marker of the disease is the reciprocal translocation between the long arms of chromosomes 9 and 22 – t(9; 22)(q34.1; q11.21) - named Philadelphia chromosome, and present in 95% of newly diagnosed patients². The presence of the Philadelphia chromosome in the cells of the patients diagnosed with CML was for many years the single specific cytogenetic anomaly associated with this neoplastic disease. The result of the translocation t(9; 22) is the hybrid gene BCR-ABL which codifies the p210 protein with high level increase of tyrosine kinase activity compared to the normal homologue p145, determining an uncontrolled cellular proliferation, inhibiting the adherence of cellular hematopoietic progenitors to the medullar stroma and blocking the apoptosis³. Imatinib mesylate selectively binds to the ATP-binding domain in the ABL protein, and is widely used as the drug of choice in treating chronic myeloid leukemia

(CML), producing high response rates (hematologic response 96.6%, cytogenetic response 85.4%), particularly in the chronic phase³. Since CML originates from stem cells, it can progress to any cell line of blast crisis⁴. Promyelocytic blast crisis of CML is extremely rare, accounting for fewer than 30 cases worldwide⁵⁻¹⁶. A case of promyelocytic blast crisis during imatinib treatment has been documented¹⁷. Here, we describe the occurrence of promyelocytic blast crisis in a CML patient after 1 year of treatment with imatinib.

Case Report

A 60 year-old man was referred to Azady Teaching Hospital in Duhok due to leukocytosis 23.3 ×10⁹/L (51% abnormal promyelocytes, 4% bands, 19% segmented neutrophils, 2% eosinophils, 0% basophils, 20% lymphocytes, 4% monocytes), anemia, and marked thrombocytosis. Splenomegaly was observed on physical examination. A bone marrow aspirate showed marked myeloid hyperplasia with 1.0% myeloblasts, 2.0% promyelocytes, 6.8% myelocytes, 18.6% metamyelocytes, 26.4% bands, 29.4% segmented neutrophils, 8.3% eosinophils, and 2.5% 1.

* Ministry of Health, Kurdistan Region, Erbil, Iraq

** Department of Pharmacology, College of Medicine, Hawler Medical University, Erbil, Iraq.

basophils. The myeloid/erythroid ratio was markedly increased to 22:1. The patient was diagnosed as CML chronic phase, and initially was treated with 400 mg of imatinib mesylate daily. After one year of the initial diagnosis of CML chronic phase, the patient admitted to Nanakaly hospital with aggravated anemia and thrombocytopenia, requiring several packed RBC transfusions. Peripheral blood analysis revealed a white blood cell count of $5.3 \times 10^9/L$ (36% abnormal promyelocytes, 6% bands, 22% segmented neutrophils, 5% eosinophils, 0% basophils, 23% lymphocytes, 8% monocytes), hemoglobin (8.9 g/dl), and platelets ($32 \times 10^9/L$). Prothrombin time was 17 sec (normal control, 13.0) and activated PTT was 54.0 sec (normal control, 34.0). The plasma concentrations of fibrinogen was 155 mg/dl (normal value, 200-400), while that of the D-dimer was 87.1 $\mu\text{g/ml}$ (normal value <0.4). Hypercellular marrow with a marked increase in abnormal promyelocytes (81% of marrow nucleated cells) was observed. The promyelocytes showed kidney-shaped nuclei and hypergranulated cytoplasm containing Auer rods. Cytochemical staining (Sudan Black B) for myeloperoxidase showed a granular-positive reaction on leukemic cells. Flow cytometry showed homogeneously positive reactions for CD13 and CD33, but negative reactions for CD34 and HLA DR on marrow leukemic cells. Karyotyping showed 46,XY,t(9;22)(q34;q11.2), t(15;17)(q22;q21) in all cells examined. The patient was diagnosed with promyelocytic blast crisis of CML. With administration of all-trans retinoic acid (ATRA) and high-dose imatinib mesylate (800 mg/day), the patient has died of disseminated intravascular coagulation within 2 weeks.

Discussion

Reports on promyelocytic blast crisis of CML are extremely rare, accounting for less than 30 cases worldwide 5-16. A report in 2007, and another one in 2008 dealt with promyelocytic blast crisis during imatinib mesylate therapy 17-18. Most patients with promyelocytic blast crisis have died of disseminated intravascular coagulation within 6 months. This patient had bleeding complications and evidence of disseminated intravascular coagulation. The duration from chronic phase to promyelocytic blast crisis has varied from 8 months to 9 years. In this patient blastic progression was evident within 1 year; there may be a small proportion of PML/RARa chimeric mRNA at the time of diagnosis of CML chronic phase, and then clonal evolution of the PML/RARa translocation had arisen in the chronic phase of CML. Although complete hematologic response was achieved with imatinib mesylate treatment, clonal dominance may have changed. The BCR/ABL chimeric clone fell into apoptosis upon tyrosine kinase targeted therapy, while the leukemic clone with both chimeric mRNAs expanded and was replaced rapidly 17. Imatinib mesylate does not appear to play a role, since the drug does not induce gene damage or secondary cancers, until now. Karyotypic analysis of BM aspirates at blast crisis showed Philadelphia chromosome t(9;22)(BCR/ABL), and t(15;17)(PML/RARA) in all cells examined. However, all previous studies focusing on promyelocytic blast crisis of CML revealed the simultaneous presence of PML/RARa and BCR/ABL chimeric genes, implying origin from the CML clone 18.

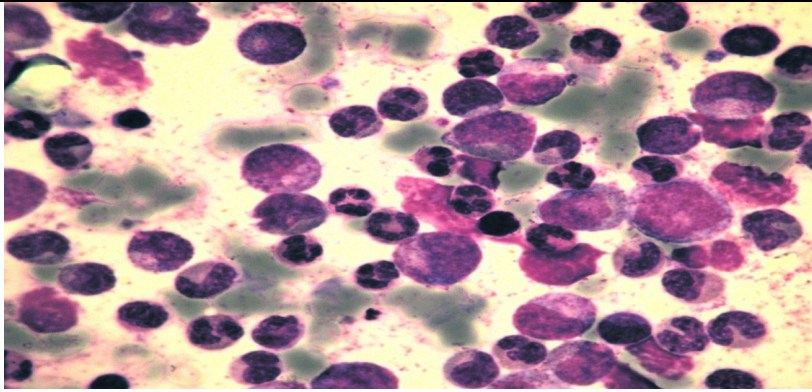


Figure 1: Patient's bone marrow slide, Chronic Phase of Chronic Myelogenous Leukemia.

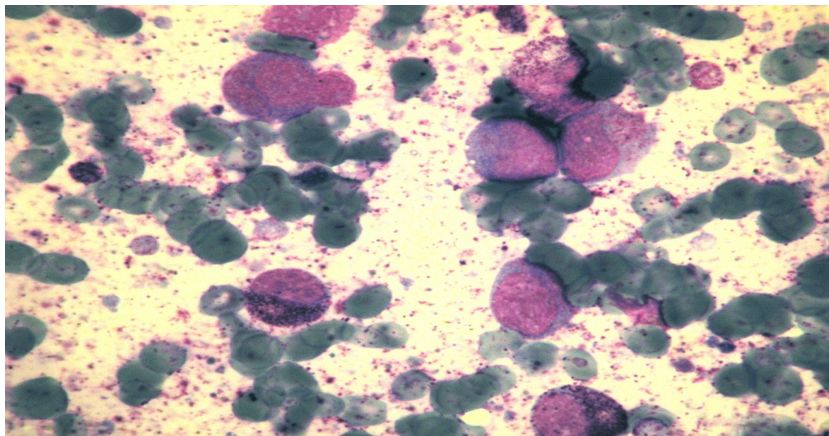


Figure 2: Patient's bone marrow slide, Promyelocytic blast crises.

References

1. Sawyers C. L. Chronic Myeloid Leukemia. Review Article. *New England Journal of Medicine* 1999; 340(17):1330-1340.
2. Martinelli, G.; Iacobucci, I. Imatinib resistance: the role of BCRABL dependent and independent mechanism in the loss of response to tyrosine kinase inhibitors. In: Education program of the 13th congress of the EHA, 2008, p. 8-12.
3. Calabretta B, Perrotti D. The biology of CML blast crisis. *Blood* 2004; 103:4010-4022.
4. Fuscaldo KE, Brodsky I, Kahn SB, Conroy JF, Marfurt K. Myeloproliferative disorders: III. CML. Further studies on the role of cytogenetics in diagnosis, prognosis and management. *Haematologica* 1981; 66: 461-488.
5. Abe R, Shichishima T, Kawaguchi M, Uchida T, Kariyone S. Promyelocytic crisis of chronic myelogenous leukemia without t(15;17). *Cancer Genet Cytogenet* 1986;21:175-179.
6. Emilia G, Sacchi S, Selleri L, Zucchini P, Artusi T, Torelli U. Promyelocytic crisis of chronic myeloid leukaemia. *Br J Haematol* 1987;66:276-277.
7. Hogge DE, Misawa S, Schiffer CA, Testa JR. Promyelocytic blast crisis in chronic granulocytic Leukemia with 15;17 translocation. *Leuk Res* 1984;8:1019-1023.
8. Louwagie AC, Mecucci C, Criel A, Van Hoof A, Van den Berghe H. Variant translocation t (15q;17q) accompanying a promyelocytic accelerated phase of Ph-positive chronic myeloid leukemia. *Cancer Genet Cyto-genet* 1987;28:349-352.
9. Matsue K, Yamada K, Takeuchi M, Tabayashi T. Rapid improvement of disseminated intravascular coagulation by donor leukocyte infusions in a patient with promyelo-cytic crisis of chronic myelogenous leukemia after reduced-intensity stem cell transplantation from an HLA 2-antigen-mismatched mother. *Int J Hematol* 2003;77:408-411.
10. Mijovic A, Rolovic Z, Novak A, Biljanovic-Paunovic L, Tomin D. Chronic myeloid leukemia associated with pure red cell aplasia and terminating in promyelocytic transformation. *Am J Hematol* 1989;31:128-130.
11. Misawa S, Lee E, Schiffer CA, Liu Z, Testa JR. Association of the translocation (15;17) with malignant proliferation of promyelocytes in acute

- leukemia and chronic myelogenous leukemia at blastic crisis. *Blood* 1986;67:270-274.
12. Oren H, Duzovali O, Yuksel E, Sakizli M, Irken G. Development of acute promyelocytic leukemia with isochromosome 17q after BCR/ABL positive chronic myeloid leukemia. *Cancer Genet Cytogenet* 1999;109: 141-143.
 13. Rosenthal NS, Knapp D, Farhi DC. Promyelocytic blast crisis of chronic myelogenous leukemia. A rare subtype associated with disseminated intravascular coagulation. *Am J Clin Pathol* 1995;103:185-188.
 14. Scolnik MP, Palacios MF, Acevedo SH, Castuma MV, Larripa IB, Palumbo A, et al. Promyelocytic blast crisis of chronic myelogenous leukaemia with translocations (9;22) and (15;17). *Leuk Lymphoma* 1998;31:231-236.
 15. van der Merwe T, Bernstein R, Derman D, Stanley A, Dukes I, Murray J, et al. Acute promyelocytic transformation of chronic myeloid leukaemia with an isochromosome 17q. *Br J Haematol* 1986;64:751-756.
 16. Wiernik PH, Dutcher JP, Paietta E, Hittelman WN, Vyas R, Strack M, et al. Treatment of promyelocytic blast crisis of chronic myelogenous leukemia with all trans-retinoic acid. *Leukemia* 1991;5:504-509.
 17. Gozzetti A, Bocchia M, Calabrese S, Pirrotta MT, Crupi R, Raspadori D, et al. Promyelocytic blast crisis of chronic myelogenous leukemia during imatinib treatment. *Acta Haematol* 2007;117:236-237.
 18. Chung, H. J, Chi, H. S, Cho, Y. U, Park, C. J, Seo, E. J, Kim, K. H et al. Case Report: Promyelocytic Blast Crisis of Chronic Myeloid Leukemia during Imatinib Treatment. *Annals of Clinical & Laboratory Science* 2008; 38: 283-286.