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Case Report Open Access

A Chronic Myeloid Leukemia Case Showing Spontaneous Ph-positive Clone Regression and Bone Marrow Hypoplasia after a Short Treatment with Dasatinib

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Abstract

Dasatinib is an orally bioavailable second generation TKI, more potent than imatinib. Bone marrow aplasia or hypoplasia secondary to TKI therapy is an uncommon adverse event. We report here the first case of chronic myeloid leukemia in chronic phase shortly treated with dasatinib that developed a prolonged bone marrow hypoplasia with concomitant response on the hematological disease with gradual improvement of the cytogenetic and molecular response after dasatinib discontinuation, without use of any other TKI therapy.

Keywords: Chronic Myeloid Leukemia; Dasatinib; Bone Marrow Hypoplasia

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm of the bone marrow stem cells and is associated with the BCR-ABL fusion gene (generated by the t(9;22)(q34;q11.2)), that results in a persistent tyrosine kinase activation and consequent uncontrolled cell proliferation and suppression of apoptosis in malignant cells [1].

Four tyrosine kinase inhibitors (TKI - imatinib, nilotinib, dasatinib and bosutinib), targeting the BCR-ABL1 fusion protein, are approved and currently used in clinical practice for fist-line treatment of chronic myeloid leukemia in chronic phase (CML-CP) [1,2].

Dasatinib is an orally bioavailable second generation TKI, more potent than imatinib and active against several imatinib-resistant BCR-ABL1 mutants [2,3].

Bone marrow toxicities associated with TKIs affect all cell lineages, but are usually dose-dependent and reversible with drug cessation or dose reduction [3]. Bone marrow aplasia or hypoplasia secondary to TKI therapy is an uncommon adverse event, and has rarely been reported in newly diagnosed patients [4-6]. However, to our knowledge, bone marrow hypoplasia secondary to dasatinib therapy with concomitant and gradual improvement of the cytogenetic and molecular response of CML after dasatinib discontinuation has never been reported before.

Case report

On July 2019 a 67-years-old woman was diagnosed a Chronic Myelogenous Leukemia in chronic phase with an important neutrophilic hyperleucocytosis (WBC 249.000/µl), monocytosis (4%), mild basophilia (0.5%) and eosinophilia (0.5%), severe anemia (Hb 7.7 g/dl), normal platelet count (355.000/µl) and a spleen palpable 5 cm below the costal margin. The diagnosis was confirmed by RT PCR for the detection of BCR-ABL1 fusion gene transcript on the peripheral blood (PB) and by the cytogenetic analysis on the bone marrow (BM), that did not show additional chromosomal abnormalities beside the t(9;22) translocation. Both Sokal and ELTS scores were intermediate. The patient was carrier of biologic valve prosthesis and of an implantable cardioverter defibrillator. Considering the cardiovascular risk and the risk of the disease, dasatinib at the standard dose of 100 mg daily was selected as starting TKI therapy. After only 20 days of therapy the patient developed a severe pancytopenia, leading to immediate discontinuation of the drug. The bone marrow aspirate showed severe hypoplasia without myelodysplasia, while an abdominal ultrasound showed splenomegaly regression. Infective causes were excluded and an immunological cause was suspected due also to a high-titer of antimitochondrial autoantibodies and presence of concomitant arthralgias, although in absence of other significant cholestatic signs and of primary biliary cirrhosis. No signs of thrombotic microangiopathy or presence of a paroxysmal nocturnal hemoglobinuria clone were found.

The patient remained pancytopenic with persistent erythrocyte and platelets transfusion-dependence for eight months after dasatinib discontinuation. A new bone marrow evaluation after 3 months from treatment start showed a persistent hypocellular bone marrow (cellularity 10-15% by trephine biopsy), with hypoplastic granulocyte and megacariocye series, without reticulin fibrosis or blasts increase, and with a cytogenetic disease assessment indicating a Major Cytogenetic Response (MCyR), while BCR-ABL1 transcript level in peripheral blood (PB) by RQ PCR was 10%^{IS}.

Because of the persistence of transfusion-dependence and considering the presence of autoimmunological markers, we decided to start immunosuppressive treatment with prednisone at the dose of 1 mg/kg daily for one month followed by a subsequent slow tapering of the drug, obtaining good benefit on arthralgias but no significant improvement of the cytopenias or decrease of the autoantibodies titers.

A subsequent cytogenetic and molecular response improvement was also observed after 6th month from dasatinib discontinuation, when the patient obtained a complete cytogenetic response (CCyR) and the BCR-ABL transcript level decreased to 1.6%IS, even in absence of any TKI therapy. At 9th month a worsening of the cytogenetic response (9% of Philadelphia-positive metaphases) and of the molecular response (quantitative BCR-ABL1 assessment= 5.7129%IS) was observed, but a subsequent cytogenetic and BCR-ABL1 quantitative assessment at 12th month showed again CCyR and a BCR-ABL1 transcript level of 1.2688%IS although still in absence of any TKI treatment (Figure 1).

However, as the hemoglobin and platelets values improved only slightly and the patient remained transfusion-dependent with bone marrow signs of acquired aplastic anemia, we decided to switch to a 2nd line immunosuppressive therapy with cyclosporine at the dose of 3 mg/kg daily.

This led to a partial improvement of the thrombocytopenia, but after 18 months from diagnosis, the patient still shows a persistent transfusion-dependent anemia. The last records at months 15 and 18, while the patient is still continuing cyclosporine but still without any TKI therapy show persistence of a BCR-ABL1 value of 1.0034%IS and 0.8696%IS, respectively (Figure 1).

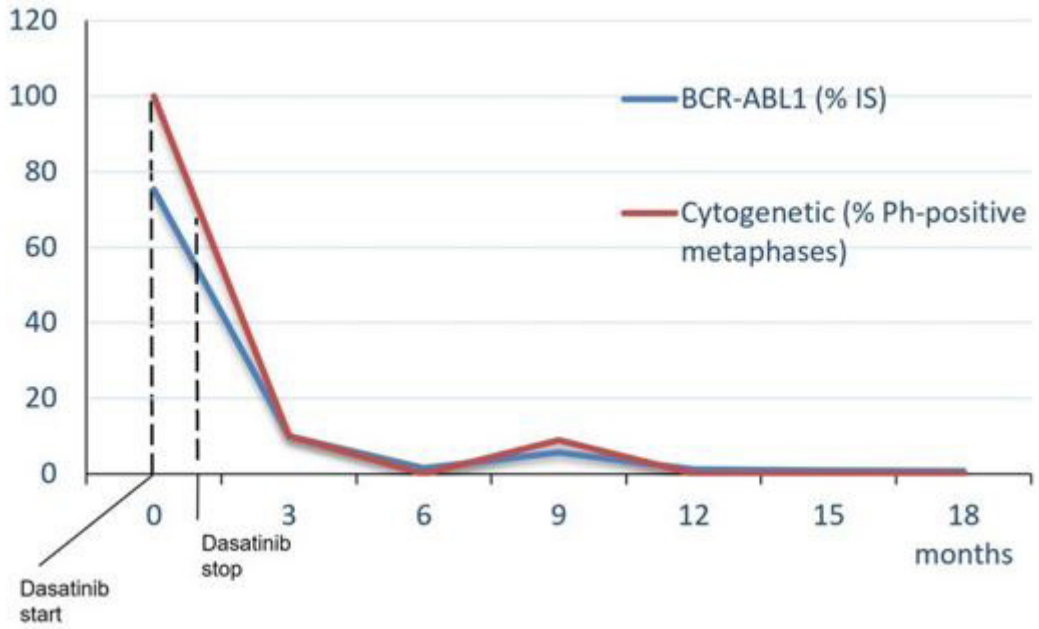

Figure 1: Molecular and cytogenetic response trend from dasatinib start and discontinuation. Molecular and cytogenetic response gradually improved during the months following dasatinib discontinuation. At 3 months: MCyR, BCR-ABL1 by RT PCR 10%IS. At 6 months: CCyR, BCR-ABL1 by RT PCR 1.6%IS. At 9months: MCyR (9% of Ph+ metaphases), BCR-ABL1 by RT PCR 5.7129%IS. At 12 months: CCyR, BCR-ABL1 by RT PCR 1.2688%IS. At 15 months: CCyR, BCR-ABL1 by RT PCR 1.0034%IS. At 18 months: CCyR, BCR-ABL1 by RT PCR 0.8696%IS

Discussion

This is a peculiar case of CML who developed severe, acute and prolonged pancytopenia with bone marrow hypoplasia after a short treatment with dasatinib. Cases showing similar myelosuppression with TKIs are reported in the literature, but the mechanisms underlying these manifestations are unclear [7,8]. One hypothesis could be that the presence of hypoplasia of the Philadelphia (Ph)-negative hematopoiesis may favour the onset and the growth of a Ph-positive clone endowed with a proliferative advantage. This hypothesis may be supported by the observation that the Hb level was abnormaly low for CML in chronic phase at diagnosis. Alternatively, we could speculate about an idiosyncratic hypersensitivity of the normal stem cell compartment to the TKI's action [7]. About the autoimmune manifestations observed in our patient, there is no clear relationship between autoimmune diseases and dasatinib treatment, and only few reports in the literature describe possible changes in the immune system due to dasatinib [9,10]. In

this case, no clear autoimmune disease was diagnosed and no clear relationship between autoimmune manifestations and cytopenias was demonstrated, except for partial thrombocytopenia improvement observed after cyclosporine treatment.

In our patient, because of the severe anemia observed at the beginning, we can hypothesize that the clonal hematopoiesis, highly sensitive to dasatinib, was largely prevalent, therefore leading to bone marrow hypoplasia after dasatinib short treatment. The peculiar trend of the molecular and cytogenetic response observed in this case was also never reported in the literature. Our patient showed a progressive improvement of the cytogenetic and molecular response during the months following TKI cessation, instead of other cases where a bone marrow aplasia with concomitant rapid disease response was described [6,11]. There's only one recent report where dasatinib was associated with bone marrow aplasia and pancytopenia in two patients but with only a transient response on the leukemic disease leading to successive need of other treatments. Of note, in this report the patients exposure to dasatinib was much more longer than in our case, and, unlike our patient, a bone marrow fibrosis of 2+ or higher was found [12]. In our case, despite the very brief drug exposure, the response was maintained for several months without further specific TKI therapy. Because it is well known that CML leukemic stem cells (CML-LSCs) may promote disease progression or relapse [13], in our patient it's conceivable that only few quiescent LSCs still persist in the bone marrow, not able to drive progression.

Conclusion

This case demonstrates that severe bone marrow hypoplasia may occur in CML during treatment with dasatinib although in this particular case the underlying mechanism remains elusive. Further studies are needed to understand if the concomitant and stable response of the Ph-positive clone obtained without the use of other TKI therapies is due to an abnormal sensitivity of the normal and CML stem cells to dasatinib therapy or to an immunological control similar to that responsible for the persisting hypoplasia.

Acknowledgements, Conflict of Interest and Ethics

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Ethics: This research was performed in accordance with the Declatation of Helsinki.

Contribution: Andrea Castelli followed clinically the patient, elaborated this research and wrote the manuscript. Maria Letizia Mosca Siez contributed to follow clinically the patient. Annarita Conconi contributed to the paper elaboration. Giuseppe Saglio contributed to the research elaboration and to write the paper. All authors reviewed the manuscript and approved the final version.

Conflict of interest: The authors declare that they have no relevant conflict of interest.

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