Recurrent gastrointestinal hemorrhage in treatment with dasatinib in a patient showing SMAD4 mutation with acute lymphoblastic leukemia Philadelphia positive and juvenile polyposis hereditary hemorrhagic telangiectasia syndrome

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Abstract

We report a case of a patient affected by juvenile polyposis and hereditary hemorrhagic telangiectasia linked to a SMAD4 mutation who developed acute lymphoblastic leukemia positive for the Philadelphia chromosome translocation and with a complex karyotype. During the treatment with the tyrosine kinase inhibitor dasatinib the patient presented recurrent severe gastrointestinal hemorrhages linked to the genetic background and aggravated by thrombocytopenia.

Introduction

Juvenile polyposis (JP) is a rare autosomal dominant disorder characterized by hamartomatous polyps in the gastrointestinal tract. The number of hamartomatous polyps varies from 5 to several hundreds. They can be ubiquitously distributed in the organism. Clinical manifestation can appear at any age but usually occur during the fourth decade. Epistaxis is usually the first symptom presented, while other diagnostic criteria include telangiectasia, appropriate family history and visceral lesions. Most mutations recur on ENO, coding for endoglucin, localized on chromosome 9, and ALK1, coding for activin receptor-like kinase 1 on chromosome 15. Both proteins modulate transforming growth factor (TGF)-β superfamily signaling in vascular endothelial cells, leading to abnormal vascular structure ranging from dilated microvessel to large arteriovenous malformations. Such vessels are more fragile and prone to hemorrhage than normal vessels. Rarely (2%) the mutations can be found on SMAD4 resulting in a combined syndrome JP-HHT. In particular, the two distinct diseases, JP and HHT overlap when SMAD4 mutations localize in the COOH-terminal MH2 domain of the protein. Therefore, patients with JP linked to SMAD4 mutations, which has a penetrance of 100%, should be screened for vascular lesions, especially those in visceral organs, to prevent serious medical consequences associated to HHT, that instead has variable onset and penetrance.

Case Report

In September 2011, a young 23-year old man presented to our institute with a diagnosis of acute lymphoblastic leukemia (ALL) positive for the chromosome Philadelphia, p190 (Ph+). The patient had a history of juvenile polyposis, which had led to a total colectomy at the age of 18 years. The molecular analysis of the genes responsible for JP, BMPRIA and SMAD4, had revealed a single nucleotide mutation IVS9 1139 +2 T>G on the SMAD4 gene. The mutation falls into the MH2 domain, the one most frequently involved in the development of the combined syndrome JP and HHT. Up to that date, he had not reported any symptoms or signs of hereditary hemorrhagic telangiectasia, which are presented in approximately 15-22% of SMAD4-related JPs. At the diagnosis of ALL, in January 2011, his peripheral blood count revealed severe anemia (hemoglobin 8.0 g/dL) and severe thrombocytopenia (platelets 12x10^9/L) with 9.46x10^9/L white blood cells of which 36% were peripheral blast cells. Flow cytometry on bone marrow aspirate demonstrated the presence of a broad population of blast cells (90%) positive for CD10, CD19, TdT, HLA-DR, CD79a, and negative for CyM, Sig and CD45. The cytogenetic analysis was positive for the presence of the Philadelphia chromosome translocation t(9;22), in a context of complex karyotype with the addition of the following abnormalities: t(1;2), +1, add(8)(p11), i(14)(q10).

He was first pre-treated with corticosteroids, but resulted resistant, with 3% of peripheral blasts at the end of the therapy. Then the patient received induction treatment according to GGRAF-2005 study: imatinib (half-dose 400 mg/die because of hepatotoxicity, Day 1-28), vincristine (2 mg Days 1, 8, 15, 22) and dexamethasone (40 mg Days 1-2, 8-9, 15-16, 22-23), obtaining a complete remission and the absence of Bcr-Abl transcript at fluorescence in situ hybridization (FISH) analysis. A lumbar puncture was performed for central nervous system localization prophylaxis that resulted negative for CNS localization.

The consolidation therapy in April with high-dose cytarabine and mithoxantrone was carried out without major complications; in June and July he received prophylactic cranial radiotherapy and remained on maintenance therapy with imatinib.

In September, the patient was admitted to hospital for the onset of thrombocytopenia and bone pain. Further investigation revealed the presence of bone marrow blastocytosis (54%) and disease relapse.

The patient was, therefore, brought to our attention to evaluate the progression of disease. The molecular analysis performed showed the presence of Bcr-Abl transcript,
evaluated as Bcr-Abl/AbI x100, of 65.34 and the absence of Bcr-Abl additional mutations, including the T315I, which notably relates to resistance to tyrosine-kinase inhibitors. On this basis, the patient was included in the CA 180-323 protocol: dasatinib 140 mg/die single dosing in association with SMO inhibitor, that he began 30th September. After 18 days of therapy with dasatinib alone the patient presented an important episode of gastrointestinal bleeding with melena, severe anemia (Hb 4.7 g/dL) and thrombocytopenia (platelets 17x10^9/L). An esophagogastroduodenoscopy was performed and showed a chronic petechial gastritis. The therapy with dasatinib was temporarily suspended for six days. Subsequently, SMO inhibitor BMS-833923 was added to dasatinib on 3rd November, but suspended after five days for a second important episode of melena, again due to gastrointestinal bleeding. In consideration of the persistent anemia and chronic gastritis, the association dasatinib-BMS-833923 was definitively interrupted. Dasatinib alone was continued at half-dosage 70 mg/die until December and then stopped as the hemoglobin level persisted at less than 6 g/dL with recurrent episodes of melena. The patient’s unresolved hemorrhagic complications led to the substitution of dasatinib with nilotinib but he died a few days later from gastrointestinal bleeding complications.

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