Imatinib-Induced Agranulocytosis in a Patient with Chronic Myelogenous Leukemia in Remission

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The pathogenesis of chronic myeloid leukemia is based on the appearance of the Philadelphia chromosome (Ph), which is the product of the translocation t(9;22). The gene resulting from this translocation, the Bcr-Abl oncogene, generates a constitutively activated tyrosine kinase protein. This protein is responsible for the progressive proliferation of the Ph chromosome-positive stem cell clone and the development of this malignancy [1].

Imatinib mesylate (Gleevec®, Glivec®, formerly STI571) is an oral anticancer agent that selectively inhibits the Bcr-Abl tyrosine kinase. There are other tyrosine kinase proteins that are potently inhibited by imatinib: the stem cell factor receptor (c-Kit), which is activated in all cases of gastrointestinal stromal tumors and the platelet-derived growth factor receptor which is associated with gliomas, melanomas, carcinomas and sarcomas [2]. Imatinib is approved by the U.S. Food and Drug Administration for use as first-line treatment in Ph chromosome-positive CML in all stages and in the chronic phase after failure of interferon-alpha treatment, and for use in c-Kit-positive malignant or unresectable malignant gastrointestinal stromal tumors.

Several trials have demonstrated the efficacy of imatinib in other hematological proliferative diseases like Ph chromosome-positive acute lymphoblastic leukemia, systemic mastocytosis, idiopathic hypereosinophilic syndrome, polycythemia vera, and in dermatological diseases. Thus, the indications for the drug are expanding and the number of treated patients is increasing.

Patient Description

A 40 year old woman presented to the emergency department with dyspnea and fever of one week. Her past medical history was significant for CML, hypertension, hypothyroidism and congenital agenesis of the right kidney. For the past 15 years she has been in the chronic phase of CML and was treated accordingly with IFNα, achieving complete cytogenetic remission (0% Ph+). However, this drug was stopped recently due to severe side effects including decreased appetite, severe fatigue and anemia (hemoglobin 10 mg/dl) and replaced by imatinib (400 mg/day) one month prior to the admission. Her physical examination was unremarkable except for fever and a previously documented mild systolic murmur.

Laboratory testing showed a white blood cell count of 2260/µl, with absolute neutrophil count of 140/µl, hemoglobin 9.64 g/dl and platelet count of 236,000/µl. A diagnosis of neutropenic fever was made. Further investigation including urine analysis and culture, chest X-ray and blood cultures failed to reveal the source of infection. Imatinib was stopped and broad-spectrum antibiotics and granulocyte colony stimulating factor (Neupogen®) were initiated. Under this treatment we witnessed a gradual resolution of fever and elevation in the white blood cell and neutrophil counts. The patient was discharged from hospital on the twelfth day afebrile and in good general condition.

Comment

The development of myelosuppression is particularly common in patients with CML treated with imatinib. Neutropenia (grade 3 and 4, neutrophils 500–1000/ml and neutrophils < 500/ml, respectively) is reported to occur in 35% of the patients, and thrombocytopenia (grade 3 and 4, platelets 10,000–50,000/ml and platelets < 10,000/ml, respectively) in 22% of them [3]. Myelosuppression can occur at any time during imatinib therapy, but it usually begins within the first 2 to 4 weeks of starting therapy for blast crisis, with a slightly later onset in patients in accelerated or chronic phases. Clinical features associated with a greater risk of myelosuppression include an increased percentage of bone marrow blasts, lower hemoglobin level, longer time from diagnosis, and a history of cytopenias induced by IFNα and previous busulfan therapy.

In patients with gastrointestinal stromal tumors treated with imatinib, 13% developed grade 3 neutropenia, while 5% treated with 800 and 1000 mg/day of imatinib had grade 4 neutropenia. In contrast, the incidence of grade 3 and 4 thrombocytopenia was less than 1% [4]. Thus, imatinib toxicity to normal hematopoiesis in patients with GIST is largely restricted to high doses and manifests primarily as neutropenia.

In patients with CML, the majority of hematopoiesis is derived from Ph-positive stem cells. Because imatinib effectively targets Bcr-Abl, myelosuppression is expected due to suppression of the malignant clone. However. the fact that myelosuppression developed also in GIST patients who were treated with imatinib and in our patient, who was in complete cytogenic remission, suggests

CML = chronic myeloid leukemia

IFNα = interferon-alpha

GIST = gastrointestinal stromal tumors

that imatinib induced myelosuppression also by other mechanisms. For instance, the stem cell factor receptor (c-Kit), which is another tyrosine kinase protein that is potently inhibited by imatinib, is postulated to be critical for the expansion of immature human hematopoietic stem cells, at least *in vitro* [5]. While it is not uncommon for CML patients to develop myelosuppression under imatinib, severe agranulocytosis in such a patient who has no risk factors for myelosuppression and who was treated successfully with interferon is an uncommon finding.

Since the indications for imatinib treatment are expanding, we may face more patients with myelosuppression, mainly neutropenia. Treating physicians should be aware of this severe life-threatening complication of imatinib and should take the necessary measures to diagnose and treat it.

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