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 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 count 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.

References:

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**Capsule**

**Growth and survival of tumor cells**

As tumors progress to a more aggressive state, they acquire multiple genetic alterations, some of which have little functional impact and others that are essential for the continued growth and survival of the tumor cells. Schlachab and co-authors (Science 2008;319:620) and Silva et al. (p. 617) have developed a functional genomics strategy that will allow, at a genome-wide level, systematic identification of genes required for cell growth and survival. Cell lines derived from human mammary and colorectal cancers and normal mammary tissue showed a similar pattern of so-called essential genes, with many residing within functional pathways known to be critical for fundamental cellular processes such as cell cycle and translational control. Importantly, however, additional genes were identified as being essential for the growth of specific cell lines. This functional genomics strategy complements the cancer genome sequencing approaches that have shown recent success and could set the stage for high-throughput discovery of cancer drugs.

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**Capsule**

**Cell phone cancer link**

An Israeli research group, led by physician and epidemiologist Siegal Sadetzki, studied heavy users of cell phones and their likelihood of getting a particular form of cancer. The study, whose results were published in the American Journal of Epidemiology, found that heavy cell phone users were at a 50% higher risk of benign and malignant tumors of the salivary gland (parotid) on the side where the phone is held compared to those who did not use cell phones. “Unlike people in other countries, Israelis were quick to adopt cell phone technology and have continued to be exceptionally heavy users. Therefore, the amount of exposure to radio frequency radiation found in this study has been higher than in previous cell phone studies. This unique population has given us an indication that cell phone use is associated with cancer,” says Sadetzki. The study subjects, 500 people diagnosed with benign and malignant tumors of the salivary gland, were asked to detail their cell phone use patterns in terms of frequency and length of calls, and were compared to 1300 healthy controls. The study also found an increased risk of cancer for heavy users living in rural areas. One explanation offered is that because there are fewer antennas in rural areas, cell phones need to emit more radiation to communicate effectively. Sadetzki predicted that the largest numbers of cancers would be found among heavy cell phone users and children.

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