Blood consult: high Sokal risk chronic myeloid leukemia and suboptimal response

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Case presentation

A 49-year-old man with no previous medical history was admitted to Poitiers University Hospital in March 2007 with a 1-week history of headache, dizziness, and nausea.

On examination, the patient described a moderate fatigue and a 3-kg weight loss over previous months. The neurologic, digestive, and respiratory examinations were normal. Abdominal palpation revealed a splenomegaly, 13 cm below the left costal margin.

Results of laboratory tests showed a hyperleukocytosis of 486.0 × 10⁹/L with an absolute neutrophil count of 37%, basophils 2%, eosinophils 2%, metamyelocytes 19%, myelocytes 28%, promyelocytes 4%, peripheral blasts 4%, anemia with a hemoglobin level of 9.4 g/dL, and a platelet count of 405.0 × 10⁹/L. Coagulation and kidney and liver function tests were normal. Lactic dehydrogenase was 4 × upper limit of normal. The chest x-ray showed minor interstitial infiltration compatible with hyperviscosity syndrome. Cerebral tomodensitometry was normal.

Bone marrow aspiration was consistent with the diagnosis of chronic myeloid leukemia in chronic phase (CP-CML), which was confirmed by the detection of a transcript BCR-ABL p210b3a2. Cytogenetic analysis revealed a t(9;22)(q34;q11) translocation without additional abnormality on 40 metaphases. Therefore, the Sokal score was high (calculator at http://www.roc.se/Sokal.asp).

Hydroxyurea was immediately administered in combination with leukapheresis (n = 3) because of hyperviscosity syndrome. Then, the patient was enrolled in the French Spirit trial and randomized to the standard imatinib arm.1 Imatinib was started at 400 mg daily. Because of the age and the high Sokal risk score, HLA determination was systematically performed.

Imatinib 400 mg was well tolerated. A rapid decrease of leukocytosis was observed within the first month, whereas a complete hematologic response was achieved at 2 months. A minor cytogenetic response (15 Philadelphia-positive [Ph⁺] metaphases/32) and a major cytogenetic response (7 Ph⁺/23) were achieved at 3 and 6 months respectively. No cytogenetic analysis was available at 12 months (dilated aspiration). Corresponding molecular analysis showed a progressive decrease of the Bcr-Abl/Abl ratio: 40%, 9%, 4%, and 2.4% according to the International Scale at 3, 6, 9, and 12 months respectively. Subsequently, repeat bone marrow evaluation was performed at 14 months: among 47 metaphases, 5 still harbored the Ph chromosome. At that time, there was no argument for an accelerated phase and no additional cytogenetic aberration had appeared. The Bcr-Abl/Abl ratio was stable at 2.5%, and no mutation of the Abl kinase domain (Abl KD) was detected. Residual plasma concentration of imatinib was systematically checked (1300 ng/mL).

Therefore, in June 2008, the patient switched to nilotinib 400 mg twice daily. Treatment was well tolerated despite a manageable cutaneous toxicity. An adequate response was observed with a complete cytogenetic response (CCyR) having being achieved at 6 months (30 metaphases Ph⁻). Simultaneously, the Bcr-Abl/Abl ratio was 0.45% and 0.34% (International Scale), at 3 and 6 months, respectively. However, the patient reported increasing chronic side effects, particularly a grade 2 fatigue that impaired his professional activity, a 10% weight loss, rash, pruritus (grade 1 or 2), and gynecomastia. In the absence of the Abl KD mutation, the treatment was switched to dasatinib 100 mg daily. Side effects resolved within 3 months, except for a mild remaining cutaneous eruption. After 1 year of dasatinib, the Bcr-Abl/Abl ratio that was initially slightly decreased at 0.18% remained stable at 0.15%. CCyR without additional cytogenetic abnormality and absence of mutation were confirmed each year (Figure 1).

Discussion

At presentation, the high tumor burden was in accordance with a high Sokal risk score, which accounts for ~ 25% of patients with CP-CML. During the last decade, the International Randomized Study of Interferon and STI571 study has taught us that the baseline relative risk determined by the Sokal score predicts the response to imatinib 400 mg. Indeed, the high-risk category had a decreased probability of CCyR (51% at 12 months vs 68% and 71% for the intermediate- and the low-risk score, respectively), and a poorer outcome in term of overall survival.2 According to the 2006 European LeukemiaNet (ELN) recommendations, careful monitoring of these patients is justified to make a rapid decision regarding alternative treatment options in case of an insufficient response to imatinib (ie, second-generation tyrosine kinase inhibitors [TKIs] or allogenic hematopoietic stem cell transplantation [alloHSCT]).3

Concerning the response to imatinib, the International Randomized Study of Interferon and STI571 study also demonstrated the CCyR as a prognosis surrogate maker in terms of event-free survival, progression-free survival, and overall survival. For this patient, the response to imatinib 400 mg appeared initially satisfactory regarding the ELN criteria because of the achievement of a complete hematologic response within 3 months and a partial cytogenetic response at 6 months. However, the cytogenetic response became suboptimal at 12 months after diagnosis, as the curve of molecular analysis drew a “plateau” at 2.5%, which was predictive of a failure at 18 months unless a change of the treatment could improve the response. Recommended tests failed to determine the mechanism of suboptimal response (chronic phase, absence of mutation, or genetic instability). Assessment of imatinib trough plasma levels at that time...
Figure 1. Molecular response during tyrosine kinase inhibitor treatment.

provided 2 advantages: (1) the high trough plasma level supported an adequate adherence to the treatment, which has been reported as a determining criterion of response; and (2) it raises the issue of the dose of treatment because retrospective analyses have determined the threshold of 1000 ng/mL of imatinib to be associated with an increased probability of achieving a major molecular response (MMR). However, prospective trials are needed to further validate this hypothesis.

Altogether, these elements supported the switch to a second-generation TKI rather than increasing the dose of imatinib for that patient. Moreover, a prospective randomized trial designed for high Sokal risk patients in front-line CP-CML failed to demonstrate the superiority of high-dose imatinib (600 or 800 mg) compared with standard-dose imatinib. In patients with CP-CML resistant to imatinib, studies using second-generation TKIs provided similar results as CCyR rates were 36% to 40% and 30% to 35% for dasatinib and nilotinib, respectively. Therefore, in the absence of mutation and any other medical history determining for a toxicity profile, any of these agents could be administered. In our case, nilotinib induced an optimal response (CCyR having being achieved within the first 6 months), but the patient developed side effects. Skin symptoms have been described with all TKIs, whereas rash and pruritus have been related to nilotinib for ~30% and 15% of patients, respectively. As in this case, they are usually improved with antihistaminic or local corticosteroids. Significant chronic constitutional symptoms and gynecomastia are less frequent and may help to manage the long-term tolerance of dasatinib, especially to prevent the secondary occurrence of pleural effusion.

In our case, this justifies the regular monitoring of the CML to check the adequate observance and to detect molecular progression, genetic instability, or mutation. Unless there were any warning signs, no alternative treatment needed to be proposed to the patient (for alloHSCT, Gratwohl risk score > 3).

In the most recent updated ELN recommendations of 2009, imatinib 400 mg was still considered the front-line therapy for all patients with CP-CML whatever the risk category. Since results of 2 randomized phase 3 trials using second-generation TKIs for newly diagnosed patients in CP-CML have been published, the Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients study randomized nilotinib either 400 mg or 300 mg twice daily and imatinib 400 mg. Of the patients with a high Sokal risk score (28% of the patients in each arm), rates of a CCyR by 12 months were 74%, 63%, and 49% among patients receiving nilotinib 300 mg twice a day, 400 mg twice a day, or imatinib 400 mg daily, respectively. MMR rates were analyzed at 12 months for the same subgroups and were 41%, 32%, and 17%, respectively. In the other study (DASISION), which randomized dasatinib 100 mg or imatinib 400 mg daily, patients have been categorized using the Hashford score (19% high risk in each arm). Rates of a CCyR by 12 months were 78% and 64% in the dasatinib and imatinib arms, respectively. The corresponding MMR rates by 12 months were 31% and 44%. Recent updates of these trials confirm these findings. In the 24-month updated Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients trial, the rate of MMR was superior for nilotinib at both doses compared with imatinib regardless of Sokal risk score, with rate of response of 71%, 67%, and 44%, respectively. In the 18-month updated DASISION trial, MMR rate was more frequent with dasatinib compared with imatinib in all risk groups (57% and 37%, respectively).
Despite a short follow-up, both studies indicate a significant benefit in terms of CCyR and MMR of the second-generation TKIs, which are now labeled in many countries for all new diagnosed CP-CML. This advantage is particularly pronounced for high Sokal risk score, which justifies their use as front-line therapy for that population. In addition, further studies are warranted to determine the significance of suboptimal response with second-generation TKIs. New alternative treatment strategies other than alloHSCT also need to be developed simultaneously for high-risk CP-CML patients to improve, even more, rates of responses in this category of patients.

References

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