Bone marrow fibrosis associated with long-term imatinib therapy: resolution after switching to a second-generation TKI

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Key Points
• Bone marrow fibrosis may be a late reversible toxicity of high-dose imatinib therapy in chronic myeloid leukemia.

Introduction

Imatinib therapy significantly improved overall disease and treatment-related morbidity and mortality of chronic myeloid leukemia (CML). However, the incidence of hematological toxicity is only slightly less compared with the historical standard of care.1 The incidence of anemia (any grade) varies between 45% and 84%;1-4 with grade 3-4 anemia being reported in 3% to 9%.1-5 Anemia occurs infrequently as a late complication of imatinib once the Ph1 clone falls in response to therapy.6 Furthermore, the development of hematological toxicity is not restricted to imatinib therapy alone, being well documented with all tyrosine kinase inhibitors (TKIs).5,7 The development of anemia complicates therapy and is considered an adverse predictor for achievement of cytogenetic responses, progression, and survival.8-10 Clinical data of 319 patients with chronic-phase CML (CP-CML) treated at our institution were reviewed; 204 treated with frontline imatinib were identified. High-dose imatinib (600-800 mg) was administered to 74 patients (36%). We identified 3 cases that developed late grade 3-4 anemia with concurrent bone marrow fibrosis while on imatinib therapy. Importantly, in all cases, anemia and bone marrow fibrosis reversed after imatinib cessation and the switch to second-generation TKI therapy.

Case description

Case 1

A 45-year-old white man was diagnosed with intermediate Sokal and Hasford–risk CP-CML in November 2008. Bone marrow karyotype confirmed that the Philadelphia chromosome and peripheral blood BCR-ABL1 was 58% international scale (IS) (e13a2 transcript). He was enrolled in a local clinical trial11 and was commenced on 600 mg of imatinib daily.

He achieved complete hematological response within 1 month and early molecular response (BCR-ABL1 ≤10% IS) by 3 months. Due to failure to achieve major molecular response (MMR; BCR-ABL1 ≤0.1% IS) by 12 months, the imatinib dose was increased to 800 mg daily. Despite the dose increase, there was no significant molecular improvement. However, there was a steady hemoglobin decline commencing in the third year of imatinib therapy requiring transfusion support (Figure 1G). Other hematological parameters were preserved with no evidence of splenomegaly. Alternate causes of anemia were excluded. Bone marrow biopsy at 37 months demonstrated hypocellularity with diffuse and dense increase in reticulin fibers with associated collagen bundles (myelofibrosis [MF] grade 3/3), substantially increased in comparison with the diagnostic sample (Figure 1). The corresponding blood film also demonstrated tear-drop poikilocytes that were not evident on earlier tests. JAK2 mutation testing was negative and there was no cytogenetic evolution nor kinase domain mutation identified. Given the moderate anemia and marked fibrosis, he was switched to 400 mg twice daily of nilotinib. The hemoglobin improved within 1 month and normalized after 6 months of TKI switch. Interestingly, the patient achieved MR4.5 (molecular response; BCR-ABL1 <0.0032% IS) and repeat bone marrow biopsy 13 months after starting nilotinib, demonstrated complete resolution in marrow fibrosis (Figure 1).
Case 2
A 36-year-old white man was diagnosed with intermediate Sokal and Hasford–risk CP-CML in November 2003. Bone marrow karyotype revealed a complex Philadelphia rearrangement between chromosomes 4, 9, and 22. BCR-ABL1 was 149% IS (e14a2 transcript). BCR-ABL1 values steadily decreased after commencing 400 mg daily of imatinib but plateaued at ~1% after 24 months of imatinib therapy with no detectable kinase domain mutations. Bone marrow biopsy at 24 months (Figure 2) revealed marked hypocellularity and no evidence of fibrosis. Imatinib was
increased to 600 mg daily, eventually increasing to 800 mg daily due to the lack of cytogenetic response and BCR-ABL1 >1% IS (Figure 2G). Almost 24 months later, he developed progressive anemia with tear-drop poikilocytes on blood film. Other causes of anemia were excluded and repeat bone marrow biopsy demonstrated grade 3/3 fibrosis (Figure 2), which was substantially increased compared with the diagnostic and previous bone marrow. JAK2 mutation analysis was negative with no palpable splenomegaly (confirmed with ultrasonography). In view of grade 3-4 anemia, the imatinib dosage was reduced to 600 mg daily, which reduced the transfusion frequency but failed to normalize his hemoglobin (Figure 2G).
Following ~12 months at the reduced dose of 600 mg daily of imatinib, he lost MMR and developed a BCR-ABL1 E275K mutation. He was switched to dasatinib, and MMR was rapidly regained within 3 months with hemoglobin normalization by 6 months. Repeat marrow biopsy 7 months following imatinib cessation demonstrated a significant reduction in the amount of marrow fibrosis (MF grade 1/3; Figure 2).

Case 3
A 45-year-old white woman was diagnosed with accelerated-phase CML in August 2007. Accelerated-phase CML was diagnosed on the basis of 18% bone marrow blasts (2% basophils) and there was no evidence of fibrosis in the diagnostic bone marrow sample. She was commenced on imatinib 600 mg daily with early increase to 800 mg daily. She tolerated imatinib with minimal toxicity and achieved target milestones including MMR by 12 months. However, after ~6 years of imatinib therapy, she developed progressive severe anemia requiring transfusion support (supplemental Figure 1G). Further investigations failed to demonstrate a cause of anemia, and bone marrow biopsy showed marked cellular streaming and increased fibrosis (MF grade 3/3; supplemental Figure 1).

Given her achievement of sustained MR4.5, imatinib was ceased for a treatment-free remission attempt that resulted in improvement in hemoglobin levels (supplemental Figure 1G). Unfortunately, the patient also had rapid molecular relapse necessitating TKI recommencement and was commenced on dasatinib 100 mg daily. Repeat bone marrow biopsy after almost 12 months of dasatinib therapy demonstrated resolution of the previously observed fibrosis (supplemental Figure 1).

Methods
This report was a retrospective review of CML patients treated at our institution, specifically focusing on those with identified bone marrow fibrosis. Ethics approval was provided by the institutional review board, and data were collected and prepared for publication per the Declaration of Helsinki.

Results and discussion
All 3 cases presented here developed late-onset progressive anemia, bone marrow fibrosis with resolution once imatinib was ceased. The mechanism of imatinib-induced anemia is poorly defined but may be attributed to the additional inhibitory action of imatinib on c-Kit–mediated pathways, resulting in suppression of hematopoiesis.12 Additionally, other off-target effects may also contribute. Rare patients have developed clonal cytogenetic changes in Ph– cells, eventually evolving to either acute myeloid leukemia or myelodysplasia, although this is more likely to be a reflection of genomic damage in addition to the initiating BCR-ABL1 event.13 Additional genetic testing by next-generation sequencing can provide insight into additional genetic abnormalities in these cases, which is a limitation of this study.

Bone marrow fibrogenesis has been linked to abnormal megakaryopoiesis and fibroblast stimulation, resulting in abnormal release of transforming growth factor-β (TGFβ) and platelet-derived growth factor receptor α and β (PDGFRα/β).14 In addition to inhibition of BCR-ABL1 tyrosine kinase, imatinib inhibits PDGFRα/β and TGFβ stimulation by ABL1 kinase activity, thereby reducing fibrogenesis.15 This is further supported by reversal of bone marrow fibrosis in CML and other myeloproliferative disorders16,17 with imatinib therapy, including normalization of bone marrow fiber content in 95% of imatinib-treated cases.15 Second-generation TKIs are also potent inhibitors of PDGFR and TGFβ in vitro and, in some instances, have lower 50% inhibitory concentration values compared with imatinib.18,19 Additionally, nilotinib and dasatinib are strong inhibitors of c-KIT20 and ABL1, a downstream mediator of TGFβ activity in fibroblasts.18,19

In contrast to the bulk of the published evidence and despite the known antifibrotic properties of imatinib, our 3 cases demonstrate instances in which imatinib has likely contributed to the development of late marrow fibrosis with resultant anemia. The fibrotic changes are unlikely to be CML related in cases 1 and 3 as both had achieved and maintained MMR and the changes resolved with imatinib cessation. Although case 2 had poorer disease control, potentially contributing to the evolution of fibrosis, the anemia improved with imatinib dose reduction and ultimate cessation while marrow biopsy demonstrated significant resolution of marrow fibrosis. Similar to our observation, bone marrow fibrosis increase has been reported in 14 of 59 imatinib-treated patients (24%).15 Notably, these patients were less likely to achieve complete cytogenetic remission and molecular responses.14 Furthermore, it is noteworthy that all 3 cases from our institution were receiving 600 to 800 mg per day of imatinib. Although the development of bone marrow fibrosis was not reported in the clinical trials investigating the safety and efficacy of high-dose imatinib therapy,2,21 there was a single case identified in the 10-year International Randomized Study of Interferon and STI571 (IRIS) follow-up.6

Although it is likely that most cases of grade 3-4 anemia are secondary to drug-induced myelosuppression, the possibility of late-onset myelofibrosis should be considered in long-term imatinib recipients with progressive anemia and investigated with a marrow biopsy. It is also noteworthy that this does not appear to be a class effect and that cessation of imatinib can lead to resolution of fibrosis despite switching to more potent TKIs.

Acknowledgments
N.S. received scholarship funding from the Royal Adelaide Hospital Research Foundation Dawes Scholarship. S.B. received support from the National Health and Medical Research Council of Australia (APP1104425). T.P.H. received support from the National Health and Medical Research Council of Australia (APP1135949). D.H. received research funding from the Royal Adelaide Hospital Research Foundation.

Authorship
Contribution: N.S. and D.H. conceptualized and analyzed the data and wrote the manuscript; and S.B. and T.P.H. reviewed the manuscript.

Conflict-of-interest disclosure: N.S. received honoraria from Novartis and Bristol-Myers Squibb, and travel and accommodation expenses from Novartis, Gilead, Amgen, and Janssen. S.B. is a member of the advisory boards of Qiagen, Novartis, and Bristol-Myers Squibb, and receives honoraria from Qiagen, Novartis, Bristol-Myers Squibb, and Cepheid. T.P.H. holds a consultancy role in, and has received research funding and honoraria from, Novartis, Bristol-Myers Squibb, and Ariad. D.H. received honoraria from Novartis.

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