ABSTRACT

Tyrosine-kinase inhibitors (TKIs) represent the only hopes for long-term survival for patients with chronic myeloid leukaemia (CML) and gastrointestinal stromal tumours. Thus, uninterrupted use of TKIs is of importance in such patients. Pure red cell aplasia (PRCA) is a rare disorder, not previously known to be associated with TKIs. We present, to the best of our knowledge, the first case of a patient with CML who developed PRCA secondary to both imatinib and nilotinib. Although PRCA was controlled on withdrawal of TKI, TKI continuation in the patient with CML is important. So we treated him with prednisone, but his haemoglobin started to drop on resumption of imatinib. He was changed to nilotinib but again developed PRCA, which did not improve with steroids. We treated him with cyclosporine and were able to reintroduce nilotinib at a reduced dose without further complications. This case report makes physicians aware of this rare complication of TKIs and also provides encouragement that PRCA could be controlled and TKI continued.

INTRODUCTION

Imatinib is a tyrosine-kinase inhibitor (TKI) that acts by selective inhibition of the BCR-ABL fusion protein through competitive binding at the adenosine triphosphate-binding site. Imatinib has revolutionised the treatment of chronic myeloid leukaemia (CML), effectively turning this otherwise lethal malignancy into a curable disease. Following success with imatinib, second and third generations of TKIs have emerged over the years as treatment options for CML and include nilotinib and dasatinib in the first line, and bosutinib and ponatinib in the second-line settings. These agents differ in their side effects and mutational selectivity, but evidence suggests that all these drugs can provide long-term remission. Imatinib, but not other TKIs, has also been proven to be highly effective with improved survival in the adjuvant and palliative settings of gastrointestinal stromal tumours.

Pure red cell aplasia (PRCA) is a rare disorder and its association with tyrosine-kinase inhibitors (TKIs) is not well known. Until now, there are only two case reports of PRCA secondary to TKIs, both with imatinib.

What is already known about this subject?

Pure red cell aplasia (PRCA) is a rare disorder and its association with tyrosine-kinase inhibitors (TKIs) is not well known. Until now, there are only two case reports of PRCA secondary to TKIs, both with imatinib.

What does this study add?

This case provides the first report of developing PRCA secondary to both imatinib and nilotinib. Although PRCA was controlled by withdrawing the TKI, we could continue TKI in the patient with steroid and cyclosporine support.

How might this impact on clinical practice?

Since TKIs provide a very realistic hope for long-term survival in patients with chronic myeloid leukaemia and gastrointestinal stromal tumours, it is of paramount importance to continue TKIs in such patients. Our case report provides an example of how it is possible to continue TKIs in patients who develop PRCA with steroid or cyclosporine support.

Key questions

- What is already known about this subject?
- What does this study add?
- How might this impact on clinical practice?
CASE PRESENTATION
A 35-year-old Nepalese male presented to his primary care physician with lethargy and abdominal discomfort in June 2013. Physical examination revealed pallor and mild hepatosplenomegaly. Laboratory investigation revealed a white cell count (WCC) of 320 000 µL (3% myeloid blast, 5% promyelocytes, 23% myelocytes, 15% metamyelocytes, 36% neutrophil, 3% basophil and 7% eosinophil), platelet count of 555 000 µL and haemoglobin (Hb) of 9.9 g%. Bone marrow aspiration and biopsy revealed a white cell count (WCC) of 320 000 µL (3% myeloid blast, 5% promyelocytes, 23% myelocytes, 15% metamyelocytes, 36% neutrophil, 3% basophil and 7% eosinophil), platelet count of 555 000 µL and haemoglobin (Hb) of 9.9 g%. Bone marrow aspiration and biopsy showed 3% myeloid blasts with no fibrosis. An empirical diagnosis of CML was made and bone marrow sample sent for fluorescence in situ hybridisation (FISH) analysis. He was started on hydroxyurea 500 mg four times a day pending molecular confirmation of the diagnosis. However, he was brought to emergency with fever and generalised weakness within a week. Blood counts in emergency showed an Hb of 7.6 g%, platelet count of 20 000 µL and WCC of 700 µL. He was transfused with four units of packed RBCs and two units of platelets. Growth factor support was given for 4 days after which his leucocyte count recovered (WCC 15 000 µL, platelet count 260 000 and Hb 9.6 g%). Results of FISH of the bone marrow sample was now available and revealed 100% BCR-ABL cells, which confirmed the diagnosis of CML. The bone marrow cytogenetic study was positive for Philadelphia chromosome in all 20 metaphases and other chromosomal abnormalities were not present. He was then started on imatinib 400 mg once a day and followed. Complete blood count and liver function tests were carried out regularly. He achieved complete haematological remission on imatinib. However, 4 months after starting imatinib, his Hb dropped to 6.3 g% with normal platelet and WCC. He was transfused with two units of packed RBCs which recovered his Hb. However, 15 days later, his Hb again dropped to 7 g% and he was then advised to stop imatinib. He was transfused with two more units of packed RBCs and was referred to our centre for further evaluation. The blood investigation in our hospital showed the following counts: WCC 6300 µL (neutrophil 74%, lymphocytes 20% and monocytes 6%), reticulocytes 0%, platelets 340 000 µL platelet count and Hb of 6.1 g%. The peripheral blood smear showed normochromic normocytic RBCs and normal morphology of neutrophil, lymphocyte and platelets. Blast cells were not present. Marrow examination revealed normocellular marrow with 3% erythroid precursor, normal maturation of myeloid series and megakaryocytes. PCR for BCR-ABL showed major molecular remission. Bone marrow cytogenetics revealed a normal male karyotype. The direct coombs test was negative. With these findings, we diagnosed that the patient had PRCA and sought to find out the cause. Contrast-enhanced CT scans of the neck, thorax and abdomen were normal. Autoimmune markers were negative and parvovirus antibodies were negative. We started the patient on oral prednisolone at 1 mg kg as a standard therapy for PRCA. This increased his Hb to 11 g% on day 21. He was rechallenged with imatinib 300 mg once daily and after 2 months of imatinib, while still on prednisolone 20 mg/day, his Hb dropped to 6 g%. A repeat bone marrow examination showed PRCA (figure 1). Imatinib was stopped and prednisolone was restarted on 1 mg kg but failed to show response. He was then changed to oral cyclosporine and in 2 weeks, his Hb improved to 10 g%. Imatinib was discontinued and he was switched to nilotinib 400 mg two times a day. However, after 40 days of nilotinib, while still on cyclosporine, his Hb dropped to 7 g%. The repeat bone marrow examination again showed PRCA (figure 2). Nilotinib was with-held and cyclosporine continued. His Hb improved to 11 g% in 3 weeks’ time. Nilotinib was restarted at 200 mg two time a day and cyclosporine was continued. In his last follow-up (January 2016), his Hb was 11 g%. All other blood counts stayed normal during all these Hb changes. The changes in Hb count parallel to the interventions are depicted graphically in figure 3.

DISCUSSION
To the best of our knowledge, we report the first case of developing acquired PRCA secondary to both imatinib and nilotinib. PRCA, which can be congenital or acquired, is characterised by severe normochromic normocytic anaemia, reticulocytopenia and absence of erythroblast from an otherwise normal marrow. Among the acquired causes of PRCA, parvovirus infection, collagen vascular disease, leukaemia, lymphoma, solid tumours, pregnancy and treatment with certain drugs are common,6 but TKIs are not known to cause PRCA. Until now, two case reports of PRCA secondary to imatinib have been reported.11 12 There has been no report of PRCA secondary to nilotinib. Imatinib and Nilotinib are both known to cause haematological toxicity. Cytopenia during TKI therapy is...
thought to reflect a reduced reserve of residual healthy Philadelphia chromosome negative marrow that is unable to reconstitute peripheral blood counts rather than toxicity towards a normal haematopoietic cell. Furthermore, imatinib and dasatinib have been associated with low rates of cytopenia in treatment of non-haematological malignancies, which argue against a direct toxic effect towards normal haematopoiesis. The pathogenesis of PRCA associated with TKIs is unknown as it is a very rare association.

In our patient, we ruled out other causes for PRCA such as collagen vascular disease, viral infections and other malignancies with appropriate radiological and laboratory tests. Relapse of CML was ruled out by bone marrow cytogenetics and quantitative PCR test. Furthermore, the maintenance of normal platelet and neutrophil counts throughout, the recovery of Hb on withdrawal of the TKI and decrease in Hb on the start of TKI helped reaffirm the causal relationship between the PRCA and TKI.

Immunosuppressive drugs have remained the backbone of treatment for PRCA. Cyclophosphamide, cyclosporine and corticosteroids are the most commonly used drugs in this setting. Our patient responded well to corticosteroids; however, the response was lost when imatinib was reintroduced. The patient was then treated with cyclosporine, which led to durable response. However, the exact role that the immunosuppressive drugs played in this patient is not known, as the patient developed PRCA while still on these drugs. Most probably, the recovery of Hb is a combined effect of TKI withdrawal or dose-reduction plus the administration of immunosuppressants.

This case report highlights the need for oncologists to be aware of PRCA as a possible side effect of TKI therapy. After careful ruling out of other possible causes for anaemia, TKI-induced PRCA can be diagnosed. Since TKI provides the only hope for long-term survival, administering TKI to patients with CML and gastrointestinal stromal tumours is of paramount importance. Although the patient’s Hb improved on withdrawal of TKI, we wanted to continue the patient on TKI for treating his leukaemia. Although not controlled with steroid alone, we were able to continue the patient on nilotinib with cyclosporine support for PRCA, thus maintaining the hopes for long-term remission.

Figure 2 Bone marrow examination showing the diagnosis of PRCA after nilotinib initiation.

Figure 3 Changes in haemoglobin over the course of the treatment in a patient with chronic myeloid leukaemia who developed pure red cell aplasia secondary to imatinib and nilotinib. The effect of each intervention in the haemoglobin count is depicted. Hb, haemoglobin.
In conclusion, we report for the first time a case of acquired PRCA secondary to both imatinib and nilotinib. Withdrawal of the TKI and introduction of steroids led to recovery of Hb. With cyclosporine therapy, the TKI could be continued, thus maintaining the possibility of achieving long-term remission.

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Contributors BSP and BG conceptualised the study and wrote the first draft. ST did the pathological studies. All authors contributed to the editing of the manuscript and consented for final submission.

Competing interests None declared.

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