Imatinib mesylate (STI-571) and porphyria cutanea tarda in a Chinese patient

Haematologica 2005; 90:(5)e54

A 76-year-old woman with chronic myeloid leukemia (CML) treated with hydroxyurea and interferon for 13 years suffered from gradual disease progression for one year (complete blood picture: CBP; hemoglobin (Hb) 8.6g/dL, white cell count (WCC) 152×10^9/L, platelet count (Plt): 1562×10^9/L). A bone marrow biopsy showed features of blastic transformation (BT) but cytogenetic study showed t(9;22)(q34;q11) only, with no additional abnormalities. She was started on imitanib mesylate (STI-571) 600mg daily. However, she suffered from nausea and pancytopenia and drug dosage was reduced to 200mg with good disease control (Hb 8.5g/dL, WCC $3.5x10^9$/l, Plt 352×10^9/l). Three months later, she complained of dark complexion, hirsuitism and facial skin coarsening with no dermal pain or eruption (Figure 1A and B). The non-exposed parts of body surface were spared (Figure 1C). Urine test showed raised uroporphyrins (11,218 nmol/day, normal <60), undetectable porphobilinogen and normal coproporyphyrin levels (194 nmol/day, normal 90-270), compatible with porphyria cutanea tarda (PCT). There was no history of alcohol or other drug exposure and liver ultrasound scan was normal. Her ferritin level was raised (33,000 pmol/l, normal 15-331) but liver biochemistry was normal, and tests for hepatitis virus B and C (HBV/ HCV) were negative. She was treated with iron chelation (desferoxamine 4g daily) and STI-571 was stopped for six weeks and then resumed, but there was no change in uroporphyrin clearance levels. A computerized tomogram scan showed multiple cervical and thoracic lymph node and biopsy confirmed nodal lymphoblastic transformation, despite STI-571 treatment. She died of blastic transformation of CML after two months. Acquired PCT is due to a relative deficiency of uroporphyrinogen decarboxylase (UPD) activity precipitated by HCV, alcohol, estrogen, aromatic halocarbons and malignancies. The commonest associated malignancy is liver cancer, but hemic and respiratory malignancies are also implicated.[1] Although HBV related liver cancer is common in Chinese, PCT is surprisingly rare, and may be related to lower genetic predisposition. The onset of PCT in Chinese is also more insidious and non-blistering. It is possible that pigmented skin in Chinese may result in lower photosensitivity.[2] Among 24 leukemia-related PCT reported in the English literature, 19 are associated with myeloid leukemia, including 12 cases of CML. Most cases occurred late in the disease course.[3,4] In our case, PCT may be related either to STI-571 drug treatment or CML blastic transformation per se. There were two Caucasian reports of STI-571 induced PCT in CML-BT cases. One case had previous interferon induced PCT, suggesting some inherent tendency.[5,6] However, PCT was not reported with the current worldwide trend of extensive upfront STI usage, and in our case the PCT apparently triggered by STI-571 did not appear to be reversible with drug omission. Retrospectively, the on-going occult extramedullary blastic transformation, the malignant clone per se may play a bigger role for PCT in our case. More interesting still, there were reports of PCT in CML cases after successful marrow transplantation, suggesting that even the presence of malignant CML clone was not necessary.[7,8] It may be possible that in late CML, iron overload and increased haemic iron turnover provide a favorable environment for PCT development.

Figure 1. A. B. Increased pigmentation and skin coarsening and facial hirsutism (arrow) after imatinib mesylate treatment. **C.** The skin changes are confined to the exposed parts, sparing the limbs.

References

1. Linet MS, Gridley G, Nyren O, Mellemkjaer L, Olsen JH, Keehn S, et al. Primary liver cancer, other malignancies, and mortality risks following porphyria: a cohort study in Denmark and Sweden. Am J Epidemiol 1999;149:1010-5.
2. Au WY, Tam SC, Ho KM, Lam CW, Kwong YL. Hypertrichosis due to porphyria cutanea tarda associated with blastic transformation of myelofibrosis. Br J Dermatol 1999;141:932.
3. Sacchi S, Kantarjian H, O'Brien S, Cohen PR, Pierce S, Talpaz M. Immune-mediated and unusual complications during interferon alfa therapy in chronic myelogenous leukemia. J Clin Oncol 1995;13:2401-7.
4. Kyle RA, Dameshek W. Porphyria Cutanea Tarda Associated with Chronic Granulocytic Leukemia Treated with Busulfan (Myleran). Blood 1964;23:776-85.
5. Breccia M, Latagliata R, Carmosino I, Mandelli F, Alimena G. Reactivation of porphyria cutanea tarda as a possible side effect of Imatinib at high dosage in chronic myeloid leukemia. Leukemia 2004;18:182.
6. Ho AY, Deacon A, Osborne G, Mufti GJ. Precipitation of porphyria cutanea tarda by imatinib mesylate? Br J Haematol 2003;121:375.
7. Dopfer R, Doss M, Ehninger G, Ostendorf P, Niethammer D. Appearance of an inherited porphyria cutanea tarda in a child after allogeneic bone marrow transplantation for chronic myelogenous leukaemia. Bone Marrow Transplant 1986;1:95-9.
8. Guyotat D, Nicolas JF, Augey F, Fiere D, Thivolet J. Porphyria cutanea tarda after allogeneic bone marrow transplantation for chronic myelogenous leukemia. Am J Hematol 1990;34:69-70.

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