Successful Pregnancies in a Nigerian Patient with Chronic Myeloid Leukaemia on Imatinib

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Abstract

Background: *Imatinib mesylate (IM) has become established as the first-line therapy for all patients with chronic myeloid leukaemia (CML) who have cytogenetic or molecular evidence of BCR/ABL mutation. However, animal studies have suggested some teratogenic potential. Additionally, it has been variously associated with reduced fertility due to hypospermia and oligomenorrhoea. In spite of the latter however, several conceptions have been reported among patients or their partners.*

Patient and Methods: *We report the first case of a CML patient conceiving twice in a 12-month period while on IM therapy. OE, a 34-year-old Nigerian lady with CML, who had been on IM since November 2006, became pregnant in March 2007, stopped IM as soon as pregnancy was confirmed, and was delivered vaginally at term of a healthy baby girl in November 2007. While lactating in February 2008, she became pregnant again, but she opted for elective termination due to a failure to attain complete cytogenetic remission from frequent therapy interruptions.*

Results and Conclusion: *Her baby continues to thrive normally after 16 months of follow-up. This suggests that the drug may not reduce the ability to conceive in some patients*.

Keywords: *Chronic myeloid leukaemia (CML), Pregnancy, Imatinib mesylate, Glivec, Nigeria*

Introduction

Chronic myeloid leukaemia (CML) is a clonal myeloproliferative disorder, characterized in over 95% of cases, by the Philadelphia chromosome [Ph, t(9;22)(q34;q11)], resulting in the BCR-ABL fusion gene that encodes a deregulated tyrosine kinase with increased activity. IM, the first molecularly-targeted drug, has radically changed CML management, significantly prolonging life-expectancy[1]. This oral drug specifically inhibits the mutant BCR-ABL tyrosine kinase; and demonstrates significant activity against platelet-derived growth factor receptor (PDGFR) and c-Kit, and these have been blamed for its side effects, including its teratogenic potential[2,3]. However, some patients, including the index case have experienced rather "positive" side effects; manifesting as apparently improved fertility[4, 5].

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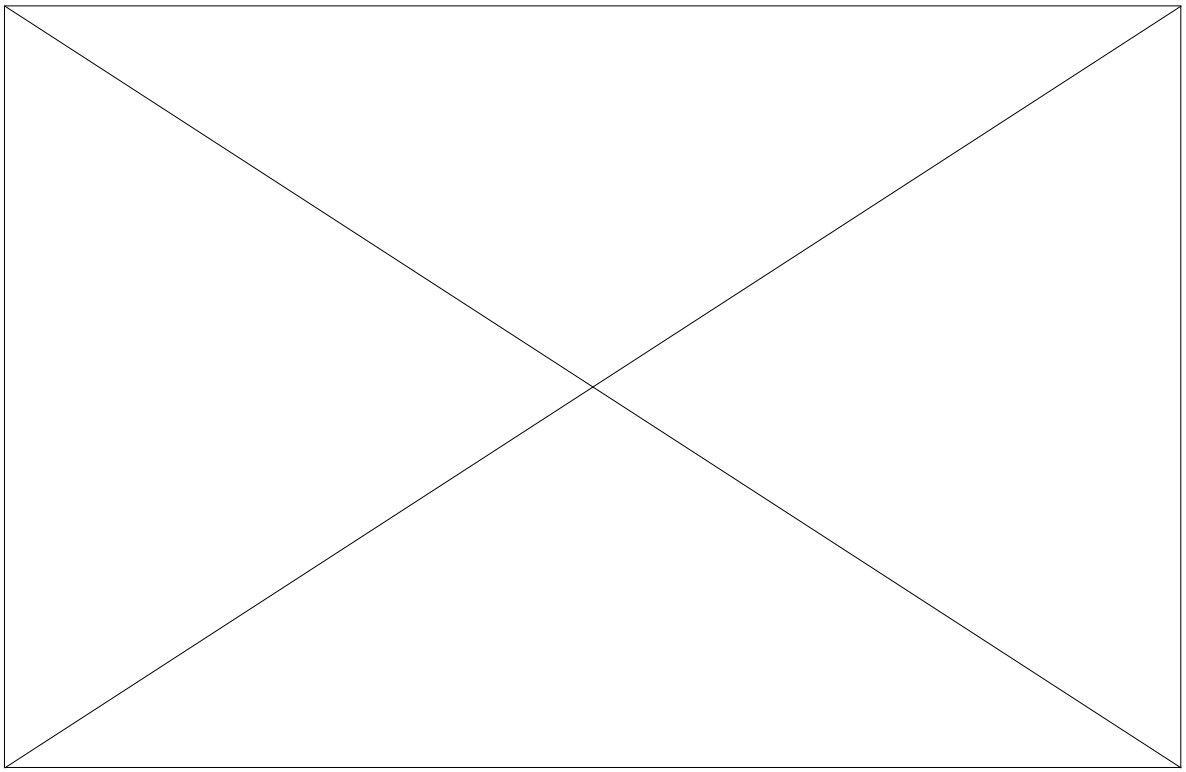
No conflicts of interest have been declared by the authors

Though IM is one of the best tolerated anti-cancer drugs, yet some concerns remain due to its demonstrated teratogenicity in rats[6]. Coupled with this is the paucity of data on its safety profile in pregnant humans. After the first report of pregnancies in CML patients receiving IM[7], several cases of successful pregnancies have been reported[4, 5, 8-11]. Conversely, IM has also been linked with ovarian insufficiency[12, 13]. Also, in spite of the reported link between IM and hypospermia in males, the work by Ault *et al*[7] and some recent works have reported pregnancies involving male CML patients[14, 15]. Though most of these reports are positive, some adverse reports have been published[3, 16.] The exact proportion of patients who may experience these side effects is yet unknown.



Case Report

Mrs OE, a 34-year-old civil servant was referred to us having been diagnosed with chronic myeloid leukaemia (CML) in accelerated phase (AP) at the National Hospital, Abuja, Nigeria in September 2006. On presentation, she had a 4-month history of weight loss and a 2-month history of recurrent, painful, hyper-pigmented skin nodules. There was associated occasional tiredness and headaches, and persistent upper back pain. She had been placed on hydroxyurea from the referral center. On examination, she was pale (haematocrit = 0.28), had three subcutaneous nodules measuring 3x5 cm, 3x3 cm, and 2x1 cm located at the lateral surface of the right mid-thigh, right popliteal region and left upper arm respectively. The abdominal organs were not palpably enlarged. The haemogram showed marked leucocytosis (120 x 10^9/l, 2% myeloblasts, and 9% promyelocytes) and thrombocytosis (750 x 10^9/l). Bone marrow fragments were hypercellular, with hyperplastic myelopoiesis and megakaryopoiesis.

The diagnosis of CML in AP was sustained. Fine needle aspirates of the nodules showed sheaths of immature myeloid cells, in keeping with granulocytic sarcoma. Her Sokal and Hasford scores were 0.74 and 158 respectively (both in the low-risk range). Qualitative reverse-transcriptase polymerase chain reaction (RT-PCR) done (at the Universitätsklinikum Hamburg-Eppendorf, Germany) in November 2006 showed BCR-ABL (b3a2) positivity, and she was started on IM 600 mg/day.

One month into therapy, there was resolution of the skin nodules but she had developed neutropenia and thrombocytopenia (Figure 1). IM was thus withheld till resolution of the cytopenias in January 2007, when it was recommenced at 300 mg/day. Two months later, her menstruation ceased, and an ultrasound confirmed cyesis. The potential teratogenic effects of IM were discussed with the couple, and it was stopped. Her haemogram was checked fortnightly, and leucocytes rose progressively to 40 x 10^9/l at the start of the second trimester. About this time some publications suggested that it may be safe to use the drug after the first trimester[17, 18]. This was discussed with the patient, and IM was re-started. Serial ultrasounds for anomalies were repeatedly normal. At term, she had an uneventful spontaneous vaginal delivery of a normal, live baby girl. There was evidence that IM is secreted significantly in breast milk[18] and it was thus withdrawn at birth, when breastfeeding was started. Two months into lactation, she progressed to AP, the baby had to be weaned and IM recommenced at 600 mg/day.

After another two months, she experienced a cessation of menstruation (she had resumed normal menstruation one month prior). An ultrasound on 27/03/2008 showed a bulky uterus containing both gestational and yolk sacs, with an MSD of 13mm (EGA = 6 weeks); liquor volume was adequate. Early cyesis was diagnosed, but she opted for termination. Pregnancy had occurred while she was on escalated dose of IM. Having considered her history of frequent reduction and stoppage of IM therapy, and the consequently increased risk of IM resistance, voluntary termination was done three days later. Our patient remains in haematologic but not cytogenetic remission, and has since been on 600mg/day while awaiting Nilotinib. A mutational study of the tyrosine kinase binding domain (Hammersmith Hospital, London) was negative. The baby girl has attained all relevant developmental milestones and remains normal after 16 months of follow-up.

Discussion

Pye *et al*[3] recently attempted to resolve the controversy surrounding the effect of imatinib on the foetus, when they examined retrospectively, the data of 180 female CML patients, who reported pregnancies while on IM. Their review showed that of the 125 patients in whom pregnancy outcomes were known, 50% had normal deliveries, 28% opted for elective termination (3 due to malformations), while 9.6% had live foetuses with malformations. Their work revealed that while IM may not be an abortifacient, it is associated with a significantly higher rate of malformations, especially some strikingly similar skeletal anomalies in 3 infants. There had been earlier reports of meningocoele and hypospadias[7, 16]. To date, 234 conceptions have been reported of CML patients on IM; of which the outcomes of 171 are known. Of these, there have been 26 (15.2%) spontaneous abortions and 15 (8.8%) fetal abnormalities – 10 live births, two stillbirths and three terminations (due to abnormalities)[3, 5, 8-10, 19]. Though this spontaneous abortion rate is not significantly different from that of the general population,(20) the congenital anomaly rate may be significant. It is therefore advisable that all female CML patients of reproductive age should have pregnancy tests every 3 months or definitely upon missing a menstruation; and if pregnancy is confirmed, should promptly stop the medication and report to their physician for subsequent monitoring.

In this case, the foetus was exposed to IM for the first four weeks of embryogenesis, before the patient was aware of the pregnancy. The drug was subsequently stopped and the baby developed normally. This is probably the first report of two conceptions occurring within a 12-month period in a CML patient on IM. This suggests that the drug may not reduce the ability to conceive in some patients. With the rapidly increasing number of CML patients on IM, there is going to be an increase in the number of reported cases of pregnancy and various complications. Clearly, the limiting factor for most of the reported studies was the lack of uniformly complete data, suggesting

that some patients and possibly some anomalies may have been missed. There is therefore an urgent need for an international clinical trial that will systematically collect data of all female CML patients of reproductive age, who are exposed to IM, either voluntarily or inadvertently. This effort would ultimately, result in the development of a valid protocol for the rational use of IM in pregnancy.

Acknowledgements
We thank the Novartis Pharma AG Glivec International assistance programme for donation of imatinib.

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