

Two successful pregnancies in a chronic myeloid leukemia patient treated with imatinib

The number of CML patients in child-bearing age and treated with imatinib is increasing. These women may want to be pregnant or are actually pregnant while on imatinib. Physicians do not know when to stop the treatment and what the risks are for the foetus and the mother. We report a case of a CML patient treated with imatinib who has two children, now 3 years and 10 months of age, in good health. The mother was in complete molecular remission, relapsed during pregnancy and reverted to remission in both cases after delivery.

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Imatinib mesylate is now standard therapy for patients with chronic myeloid leukemia (CML)¹. One area where there is limited information is the potential effect that imatinib may have on the developing fetus. Many young female patients are currently being treated with imatinib and they frequently face the dilemma of conception and pregnancy while receiving imatinib.

In a preclinical study, the drug was found to be teratogenic in mice but not in rabbits². Consequently, it was recommended that effective contraception be used during imatinib therapy to prevent pregnancy³. In practice, patients who receive imatinib at the time of conception may have normal pregnancies, but this is not always the case, and the data are still limited. Here, we report the first case describing the outcome of a patient with CML who became pregnant twice successfully while receiving imatinib at the time of conception.

A 21-year-old woman was diagnosed with Philadelphia positive CML in chronic phase in June 2001. Clinical examination was normal, without splenomegaly. Hematological values were: hemoglobin 13.6 g/dL, white blood cells: $109 \times 10^9/L$ (83% neutrophils), platelets: $335 \times 10^9/L$. Bone marrow examination was hypercellular without excess of blasts. Cytotype showed 46, XX, t(9;22) with no other abnormalities. She had no siblings. As initial treatment, hydroxyurea (800 mg/d) was begun. She entered a phase II trial testing cytosine arabinoside (20 mg/m^2) subcutaneously 14 days per month, plus imatinib 400 mg/d for eight cycles (CST1571AFR02 trial).

In February 2002, she was in complete hematological, cytogenetic and molecular remission. She was maintained on Imatinib 400 mg daily. 8 months later while still in remission and on imatinib therapy, she became pregnant (G1P1). Conception was estimated to have taken place 4 weeks earlier and imatinib was stopped immediately. She received no treatment at all throughout her pregnancy. Her WBC increased progressively, reaching a peak of $40 \times 10^9/L$ in the last month of pregnancy (Figure 1). At 5 months, amniocentesis revealed no abnormalities. Fetal growth remained satisfactory as well as amniotic fluid volume estimation. She delivered vaginally a healthy baby girl at 38 weeks of pregnancy (Apgar 10/10), weighing 3,18 kg. The total blood count of the newborn was normal. The mother did not breast-feed her baby and she resumed imatinib on 400 mg/day. She began a new near-complete molecular remission within a year.

2 years later, she became pregnant again while still on the same dose of 400 mg per day of imatinib that she had taken without interruption for the last 2 years. She was

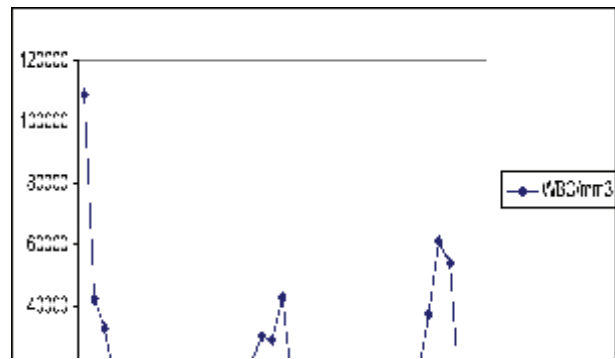


Figure 1. White blood count evolution during the two consecutive pregnancies.

still in complete remission and conception was thought to have occurred 3 weeks earlier. Imatinib was stopped and she received no treatment during pregnancy except for interferon (3 millions IU X 3 per week) in the last month because her WBC count rose above $50 \times 10^9/L$. Interferon was stopped after 3 weeks due to gastrointestinal intolerance. Amniocentesis was normal and she delivered vaginally a healthy baby girl (Apgar 9/10, 2.95 kg) after 39 weeks of gestation. After 3 months of breast feeding, she resumed imatinib at 400 mg/day. She is currently in complete hematological, cytogenetic (normal karyotype in April 2006) and molecular remission and her two children, now 3 years and 10 months old, are perfectly healthy.

This case can be added to the few case reports and the only series currently published in the English literature analyzing the outcome of pregnancy while on imatinib at one point.^{4,7} Most of them have been uneventful but sometimes it is not the case. Spontaneous abortions, small weight for gestational baby age and one case of pyloric stenosis have been described. More recently, a case of meningocele with fatal outcome was reported while on imatinib alone during the first one and a half months of pregnancy⁸.

The key period for embryogenesis occurs from week 3 to week 8 of post-conception life. Hence, many authors advise against the use of anti-neoplastic agents during the first trimester. In our patient, the fetus had been exposed to imatinib for approximately 4 weeks after conception in the case of the first pregnancy and 3 weeks for the second one. As for the babies, pregnancy and delivery were uneventful. There was no birth defect and apparently no late side-effect, the older girl being now 3 years old and the younger 10 months old. It is difficult to say whether imatinib had been stopped on time right before a potential teratogenic effect occurs. There has been one series and isolated case reports with a similar favorable outcome.

Another concern is the mother's hematological disease progression. Even though in both cases she began pregnancy in a state of complete molecular remission, she relapsed twice (Figure 1). This is now expected when imatinib is discontinued.⁹ WBC count went as high as $60 \times 10^9/L$ and returned to normal as soon as imatinib was resumed. After both pregnancies, she returned to complete molecular remission within 6 months (Figure 2). Therefore, patients who interrupt their therapy before, or during pregnancy should be advised of the risk of sub-optimal response or relapse, even if they have achieved

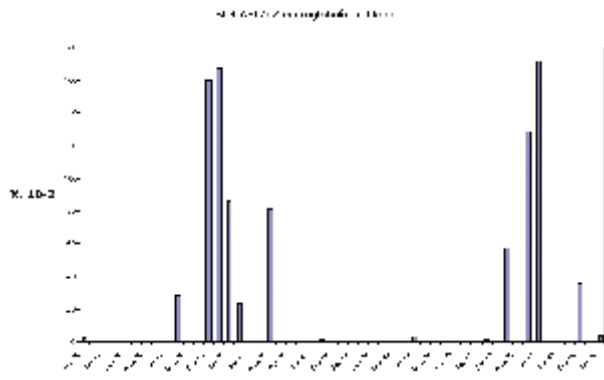


Figure 2. Kinetic of the ratio of Bcr-Abl transcripts (b2a2)/₂ microglobulin in blood.

a complete molecular remission. Leucostasis is a risk. Interferon alpha¹⁰ or leukapheresis¹¹ treatment could be used but it is still a debatable issue as to when to initiate it. Finally, blast crisis is the most potentially fearful event.

Concerning breast feeding, in animals, imatinib or its metabolites are extensively excreted in milk. It is not known whether imatinib is excreted in human milk; therefore, it is suggested that women taking imatinib should not breast feed.

Taking into consideration the risk for the fetus and the mother, and in view of the lack of sufficient information, it is currently recommended that patients use contraception while receiving imatinib and that therapy be discontinued immediately if the patient becomes pregnant. If pregnancy is to be continued, it is still unknown if it adversely affects the developing fetus.

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