Pregnancy on imatinib: fatal outcome with meningocele

We read with interest a recent letter by Prabhash et al. [1] showing a successful outcome of pregnancy in two patients on imatinib. There have also been a few other recent reports where no adverse effects have been reported [2–4]. However, we would suggest extreme caution, based on our experience in a patient who conceived while on imatinib with an adverse outcome.

A 25-year-old female was diagnosed as having chronic myeloid leukemia in chronic phase in July 2004. She had no significant past medical history and was nulliparous. Examination revealed spleen palpable 10 cm below costal margin. Hematological parameters (hemoglobin 7.8 g/dl, white blood cell count $23.4 \times 10^9/l$ and platelet count $383 \times 10^9/l$) and RT–PCR revealed positive BCR-ABL translocation. Her biochemical parameters, including liver, renal functions and uric acid, were within normal limits. Therapy was started with imatinib (Glivec; Novartis, Basel, Switzerland) 400 mg/day as part of a research project where the drug was provided free. She was counseled to avoid pregnancy. Complete hematological remission was achieved at the end of 1 month and molecular remission after 3 months. Imatinib was continued at the same dosage. The patient reported to the clinic with history of amenorrhea of one and half months’ duration in January 2005 and a pregnancy test was positive. After counseling, she declined termination of pregnancy, but imatinib was stopped.
No drug was administered until completion of the first trimester. As the patient could not afford interferon, hydroxyurea was administered to control the blood counts and symptoms. At 30 weeks, ultrasound abdomen revealed the presence of a meningocele. She delivered a dead fetus with the meningocele at the 34th week of pregnancy. She was restarted on imatinib with further advice for strict contraception and to stop the drug before any planned pregnancy.

The limited published literature suggests that imatinib is safe in pregnancy [1–4]. However, animal experiments suggest it is unsafe. Imatinib, an inhibitor of abl-tyrosine kinase, is teratogenic in mouse and rats when administered during organogenesis at doses of >100 mg/kg, causing exencephaly or encephalocele, and absent or reduced frontal and absent parietal bones [5]. The most critical period for teratogenicity is the first trimester as this period correlates with active organogenesis. Our patient had been exposed to imatinib during conception and for 6 weeks thereafter with development of a meningocele and a fatal outcome. The few reports of delivery of a normal fetus, even with intake of imatinib during pregnancy, should not suggest that the drug is safe. Our case clearly highlights that the drug is potentially teratogenic. To the best of our knowledge this is the first such complication reported in humans. We strongly recommend effective contraception for all patients who are on imatinib.

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doi:10.1093/annonc/mdj065
Published online 15 November 2005