Successful Pregnancy in a Patient with Chronic Myeloid Leukemia under Treatment with Imatinib

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Abstract

Contraception is recommended during imatinib therapy based on the teratogenicity data in rats. However, patients may become pregnant and here we describe a successful pregnancy and labor without any congenital anomaly in a patient with chronic myeloid leukemia (CML) under treatment with imatinib. The patient had received imatinib for 53 months before she became pregnant, with a complete cytogenetic response achieved after 6 months of therapy and a major molecular response (MMR) after 28 months. CML was in MMR at discovery of pregnancy and the fetus had been exposed to imatinib for 5 weeks. Treatment was discontinued, but MMR persisted during gestation.

Key words: chronic myeloid leukemia, pregnancy, imatinib

Introduction

The introduction of imatinib (Glivec; Novartis, Frimley, UK), an inhibitor of abl-tyrosine kinase, has made a considerable impact on the outcome and quality of life of patients with chronic myeloid leukemia (CML) (1). The drug is well tolerated by patients with few side effects. Imatinib is teratogenic in rats, but not in rabbits, whereas experience with this drug during pregnancy in humans and data for the human fetus are limited. Many young women with CML are currently being treated with imatinib, and they frequently face the dilemma of conception and pregnancy while receiving imatinib. In view of the lack of information, it is recommended that patients practice contraception while receiving imatinib and that therapy is discontinued if the patient becomes pregnant (2). Here, we describe a successful pregnancy and labor in a patient with CML who was receiving treatment with imatinib, and we comment on the outcome of discontinuation of imatinib therapy after achievement of molecular remission.

Case Report

A 23-year-old woman was diagnosed with leukocytosis in a company physical check-up in December 1995. The patient had no symptoms. On initial examination, her liver was palpable 1 cm below the right costal margin and her spleen was palpable 3 cm below the left costal margin. The bilateral neck lymph nodes varied in size from 0.5 to 1 cm. Peripheral blood (PB) findings were hemoglobin 10.9 g/dL; white blood count (WBC) 170.1×10^9/L with 1% myeloblasts, 1% promyelocytes, 4% myelocytes, 15% metamyelocytes, 17% bands, 1% promyelocytes, 4% myelocytes, 15% metamyelocytes, 17% bands, 51% neutrophils, 6% lymphocytes, 5% monocytes; and platelet count 265×10^9/L. Liver and renal parameters were in the normal range. The lactate dehydrogenase (LDH) level was 488 mU/mL (normal range 50-107 mU/mL) and the neutrophil alkaline phosphatase (NAP) score was 109 (control 255). A bone marrow (BM) examination revealed marked hypercellularity with 4.5% myeloblasts, 7.5% promyelocytes, 13.5% eosinophils, 1.5% basophils and 7% erythroblasts. Megakaryocytes were also increased in number. Chromosomal analysis of the BM cells revealed a Philadelphia (Ph) chromosome with 46,XX,t(9; 22)(q34;q11.2) in all 20 metaphase cells examined, leading...
to a diagnosis of CML in the chronic phase.

After reduction of the WBC with hydroxyurea, interferon-α (IFN-α) at a daily dose of 6×10⁶ U was started for treatment of CML in January 1996. IFN-α was reduced to a dose of 6×10⁶ U three times a week from February 1996 because of cytopenia. The patient achieved hematologic complete remission within 3 months, but a complete cytogenetic response was not achieved with IFN-α. Imatinib 400 mg daily was initiated in June 2002 and a complete cytogenetic response was achieved after 6 months of therapy. A major molecular response (MMR) occurred after 28 months of treatment, based on results from real time polymerase chain reaction (RT-PCR) analysis.

The patient got married in 2004. In the 53rd month of imatinib therapy, she did not menstruate and a urine pregnancy test was positive. An ultrasound scan confirmed the presence of a viable fetus of 5 weeks. Imatinib was stopped immediately because she wanted to have the baby. Detailed information about her disease and the possible complications of imatinib were provided to the patient, but she and her family requested continuity of the pregnancy and did not give permission for an invasive procedure or medical abortion. The patient remained off CML treatment during gestation, but MMR continued. Labor was induced at 36 weeks of gestation. A healthy boy of weight 2,560 g and length 50 cm with an Apgar score of 9 was delivered vaginally. The patient’s WBC at the time of labor was 5.3×10⁹/L, with hemoglobin 13.1 g/dL and a platelet count of 215×10⁹/L. The infant’s complete blood count was normal with no abnormalities. He was breast-fed for only 3 days because the patient restarted imatinib therapy. The baby is healthy and growing normally and the MMR status of the patient has continued for 20 months after delivery.

**Discussion**

Management of leukemia during gestation is a difficult problem because of the potential effects of the therapy on the mother and fetus. Therapeutic approaches to leukemia complicated with pregnancy may differ from those normally used to treat this disease. The differences are modified by several variables, including time of diagnosis, type of leukemia, clinical tolerance of the disease, toxic effects of the drugs on mother and child, and the wishes of the family. CML may not need to be treated immediately and pregnancy does not appear to affect the course of CML, but there are risks of leukostasis and placental insufficiency that may lead to a below-normal fetal birth weight, increased fetal prematurity and increased mortality if CML is left untreated for the duration of the pregnancy (3).

Imatinib, a bcr-abl tyrosine kinase inhibitor, is the first line therapy for CML. In preclinical studies, imatinib was teratogenic in rats. Based on the results in rats, women receiving imatinib should be made aware of the potential teratogenicity and effective contraception is recommended during imatinib therapy to prevent pregnancy. However, there is only limited information on the effects of imatinib therapy during pregnancy in humans, based mostly on case reports (4-6). Ault and colleagues published a series of 19 pregnancies during which either the male or female partner was undergoing treatment (7). Three of these pregnancies ended with spontaneous abortions and one with an elective termination, but 16 were identified as uneventful. Two of the 16 babies had minor abnormalities at or shortly after birth (hypospadias in one baby and rotation of small intestine in one baby) that were surgically repaired. Pye et al (8) reported a series of 180 women who were exposed to imatinib during pregnancy of the 125 (69%) with known outcomes, 50% delivered normal infants and 28% underwent elective terminations, including 3 following the identification of abnormalities, which emphasizes the risk of serious fetal malformation. There were a total of 12 infants (8 live births, 1 still birth and 3 terminations) in whom abnormalities were identified, 3 of which had strikingly similar complex malformations that are clearly a cause for concern. Out of 103 women exposed to imatinib in the first trimester, 40 had live births without a congenital anomaly. The present patient was under treatment with imatinib for about 53 months and the fetus had been exposed to imatinib for 5 weeks. The child was morphologically normal, and his growth and development has been normal without congenital anomalies. The child was breastfed for only 3 days because imatinib was restarted. Imatinib and its metabolite have been found to be excreted extensively in human milk (9-11). It is suggested that women taking imatinib should not breastfeed an infant (12).

What can we do if a patient with CML receiving imatinib wishes to become pregnant? It is unclear if imatinib therapy may be discontinued safely in patients who achieve complete remission, and this remains as an important question. Rousselot et al discontinued imatinib therapy in 12 cases of CML with undetectable disease for more than 2 years and found that 6 of the patients (50%) had a molecular relapse with a detectable bcr-abl transcript within 5 months (13). Therefore, discontinuation of therapy for patients who achieve molecular remission with imatinib is not currently recommended. IFN-α is an alternative therapy for CML. It was not teratogenic in rats and rabbits, but it has also been shown to have abortifacient effects in rhesus monkeys at dose of 90 and 180 times the recommended dose of 2×10⁷ IU/m². In view of this, it is recommended that IFN-α must be avoided during pregnancy (8). We conclude that women with childbearing potential should use adequate contraception while taking imatinib because of the risk of fetal toxicities and CML progression in the mother. In cases of accidental pregnancy, a risk and benefit evaluation must be carried out on an individual basis with careful counseling of both parents using the most recent data available. More experience and studies are necessary regarding the treatment of CML during pregnancy.

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