SUCCESSFUL CHILDBIRTH IN A PATIENT WITH CHRONIC MYELOGENOUS LEUKEMIA TREATED WITH IMATINIB MESYLATE DURING EARLY PREGNANCY

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Aims: To report a case of successful pregnancy in a patient with chronic myelogenous leukemia treated with imatinib mesylate for the first 4 months of pregnancy.

Results: Imatinib mesylate is potentially teratogenic and its use during pregnancy in humans can lead to abortion or development of fetal abnormalities in nearly 40% of fully reported cases. We report a case of a 28-year-old woman who delivered a healthy child of normal weight after having been treated with imatinib for Ph1-positive CML during the first four months of her pregnancy. She refused advocated interruption and for the rest of the pregnancy was treated with interferon. The treatment was associated with a rapid 2-log increase in the leukemia clone measured by the real-time polymerase chain reaction. Reintroduction of imatinib after delivery resulted in achievement of the complete cytogenetic response again.

Conclusions: We discuss possible strategies for successful management of pregnancy in CML patients treated with imatinib.

INTRODUCTION

Chronic myelogenous leukemia (CML) is a myeloproliferative disease characterized by the fusion gene BCR-ABL. Product of this gene, protein Bcr-Abl, has constitutive tyrosine kinase activity that plays a crucial role in the pathogenesis of the disease. Since its introduction in 1998, imatinib mesylate (IM), a competitive inhibitor of Bcr-Abl tyrosine kinase, has been used in CML and it became the drug of choice for first-line treatment of CML. In animal studies in rats but not rabbits, however, IM exerts potential teratogenicity and, consequently, contraception has been strongly recommended in all women with child-bearing potential during IM therapy¹. Occasional cases of conception or successful pregnancy during IM treatment have however been reported in the literature, mostly as case reports²⁻¹⁰. In two of the four reported cases treated with IM for the whole duration of pregnancy, delivery of low-weight children were found^{3,9}. We describe here a case of a 28-year-old woman with CML who was treated with IM during the first four months of pregnancy and who delivered a healthy child of normal weight.

CASE REPORT

A 20-year-old woman was diagnosed with chronic phase CML in December 1998. She had no complaints and her physical examination was normal. Hematologic values were as follows: hemoglobin 127 g/l, white blood

cell count $92.4 \times 10^9/l$ and platelets $574 \times 10^9/l$. On cytogenetic examination, all metaphases obtained from bone marrow cells contained Ph1 chromosome without any additional cytogenetic abnormalities. Her Sokal and Euro scores were within the low-risk ranges (0.555 and 123, respectively). Search for HLA compatible donors in her family was unsuccessful and she declined the option of hematopoietic stem cell transplantation from a voluntary unrelated donor. Therefore, after initial treatment with hydroxyurea, the patient was given the option of collecting her peripheral stem cells for the purpose of autologous peripheral stem cell transplantation later in the course of disease according to the results of conservative treatment. She gave her consent and five months later she was primed with mini-ICE (idarubicin 15 mg, etoposide 250 mg and cytarabine 1.4 g for 3 days) and G-CSF and has collected $7.817 \times 10^8/kg$ MNC and $1.97 \times 10^6/kg$ CD34+ cells in five aphereses. The graft was positive for Bcr-Abl by nested RT-PCR (reverse transcription polymerase chain reaction), while FISH (fluorescent in situ hybridization) examination gave variable results – the first apheresis was negative but all the following collections were positive in 5 % of cells. A major cytogenetic response (5 % out of 400 evaluated interphase cells were positive for BCR-ABL using FISH) was achieved one month after the harvest. The patient started treatment with interferon alpha at a dose of 9 MIU per day from June 1999 and achieved complete cytogenetic response that was maintained for nearly 2 years. Based on the finding of cytogenetic progression (43 % out of 316 evaluated interphase cells were

positive for BCR-ABL using FISH) she received IM in a dose of 400 mg daily in July 2001. She was informed about the potential teratogenicity of the drug and advised to use contraception. 2-log molecular response confirmed by quantitative RT-PCR was achieved after six months of treatment and was maintained thereafter (see Fig. 1). In February 2005, she informed her hematologist that she was 4 months pregnant. She continued IM treatment during this whole period. The risk of abnormal fetal development due to the teratogenicity of IM was discussed and an interruption was suggested. However, she decided to continue with her pregnancy. The IM treatment was withheld immediately and interferon alpha at a dose of 9 MIU was started. The routine outpatient obstetric controls started at 18th week of gestation, when pregnancy was confirmed for the first time. A detailed genetic examination including amniocentesis was performed. The placental fluid was normal. The newborn's karyotype was 46, XY and ultrasound examination showed no abnormalities. The course of pregnancy was uneventful with no obstetric complications. The patient maintained a complete hematologic response during the rest of her pregnancy. However, the level of Bcr-Abl expression in quantitative RT-PCR gradually increased over the following months (see Fig. 1). At the 39th week of pregnancy, labor was induced by infusion of oxytocin owing to signs of placental insufficiency and a healthy boy was delivered vaginally. He was 50 cm long, weighed 3160 g and was without postnatal complications. The Apgar score was 10-10-10. The clinical examination and blood count of the newborn were within the physiological ranges. The screening for congenital hypothyreosis and phenylketonuria was negative. Cytogenetic examination of fetal fibroblasts was normal; 46, XY. There were many infarctions in the placenta that weighed 650 g. The newborn boy was breastfed only during the first day of his life. Lactation was terminated two days after delivery and the patient resumed treatment with IM. An immediate improvement in molecular response was found (see Fig. 1) and a complete cytogenetic response was achieved 6 months later. The boys' growth and development have been normal to date.

DISCUSSION

Hematologic malignancies are among those most commonly diagnosed during pregnancy. However, their incidence seems to be pregnancy-independent¹¹. Data on human fetal development in pregnant women with CML are limited. CML constitutes 90 % of chronic leukemias and 10 % of leukemias in pregnancy with an estimated incidence of 1 in 750 000 pregnancies^{12, 13}. Treatment for CML in pregnancy is supportive and specific treatment is usually delayed in early pregnancy to avoid the potential risk to the developing fetus. Apheresis has been reported to decrease platelet and leukocyte counts¹². Leukapheresis can maintain acceptable blood count values and it can be used as a short-term and well-tolerated strategy. However, it does not interfere with the biological progress of the dis-

Fig. 1. Results of CML monitoring by quantitative RT-PCR (during the treatment with INFa patient was monitored by FISH and cytogenetics only) in the patient. Period of pregnancy in grey. Abbreviations: HU – hydroxyurea, INFa – interferon alpha, IM – imatinib mesylate.

ease and there may be the risk of significant CML progression. There are reports of successful use of hydroxyurea in patients with CML during the pregnancy despite the fact that the drug inhibits DNA synthesis and therefore has teratogenic potential⁴. Interferon alpha is another possibility for the treatment of CML during pregnancy. It crosses the placental barrier but it has no adverse effects on the human fetus and there are reports of normal infant deliveries¹⁴.

IM has dramatically changed the treatment strategies and results in CML. In animal studies in rats, IM has been shown to be teratogenic¹. The theoretical mechanisms responsible for the teratogenicity of the drug include inhibition of PDGFR-beta that is important for the development of the microvascular system and for myelination of the peripheral nervous system¹⁵. The data on human fetal development during IM treatment are lacking but based on rodent studies, contraception is strongly recommended. Overall, 48 conceptions during IM treatment have been reported in the literature to this date (2008). Twelve were terminated by elective abortion^{4, 8} and the report on 7 pregnancies was insufficient⁸. Thus, only the remaining 29 pregnancies were carried until delivery and have been fully reported. In these 29 pregnancies, the risk of reported spontaneous abortion (8 cases), fatal outcome (1 case with meningocele) or development of fetal abnormalities (2 cases of hypospadias) reached 38 %^{3-5, 8}. In two of the four patients treated with IM during the whole pregnancy, delivery of low-weight children was reported^{3, 9}. Many more pregnancies during IM therapy have been reported recently¹⁶. Importantly, 22 % risk of spontaneous abortion and 9.6% risk of fetal abnormalities of similar nature to those described in animals were noted¹⁶.

Recently, measurement of IM and its metabolite CGP74588 in umbilical cord blood, placenta homogenate and breast milk in two women during late pregnancy

was described¹⁰. In umbilical blood, IM was either not present or present at low concentrations with an umbilical blood/placenta concentration ratio of 0.064. The authors concluded that their observation was in accordance with the estimated properties of the drug (drugs highly bound to proteins and with a molecular weight of more than 500 have limited placental transfer)¹⁰. In contrast, high concentrations of IM and CGP74588 were detected in breast milk. Therefore, breast-feeding during IM treatment should be avoided despite the small amount of drug actually ingested¹⁰.

In our case, the fetus was exposed to IM for four months which is possibly one of the longest periods reported. Thereafter, the drug was stopped immediately and was substituted with interferon. During the interferon treatment, molecular progression of CML has been recorded, and might have been predicted here due to a history of previous interferon secondary resistance. Nevertheless, interferon maintained the complete hematologic response and the course of pregnancy was uneventful apart from terminal placental insufficiency. The baby was delivered without any problems, was normal on clinical examination and its weight was normal as in cases where IM was terminated immediately after confirmation of the pregnancy^{2, 4, 6}.

Our case, along with the others reported to date, provides evidence that the embryo/fetus may not be affected by IM in all cases. However, despite the recently reported low placental transfer of the drug, teratogenicity in humans is highly probable due to the high reported rate of spontaneous abortions and fetal abnormalities. Therefore, fertile women receiving IM should use adequate contraception. Importantly, after the recognition of conception, the treatment with IM should be interrupted immediately, in order to avoid prolonged exposure of the fetus, and alternative strategies like leukapheresis or interferon should be pursued for management of CML.

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