Successful Delivery after Planned Discontinuation of Imatinib in a Patient with Chronic Myeloid Leukemia

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Abstract

A 24-year-old woman with chronic myeloid leukemia (CML) chronic phase was started on imatinib in August 2004 and complete hematologic response (CHR) was achieved. In May 2006, controlled ovarian hyperstimulation was started after stopping imatinib. Her pregnancy test was positive in October 2006. At 32 weeks, she had 29% metaphases positive for the Ph chromosome; CHR was sustained. She had a normal delivery at 38 weeks without any complications. Five weeks after delivery, imatinib was resumed. Complete molecular response was sustained 5 months after re-administration of imatinib. A CML patient may give a birth after intentionally stopping imatinib before conception.

Key words: chronic phase, teratogenicity, female fertility

Introduction

Imatinib is standard medicine for chronic myeloid leukemia (CML). It improves the prognosis of CML-Chronic Phase (CP) patients dramatically (1). Now that CML patients are living longer, many face the dilemma of conception and pregnancy while receiving imatinib. Teratogenicity has been reported in rats exposed to imatinib (2) and imatinib during pregnancy may affect the fetal development in human, so it is recommended that effective contraception should be used during imatinib therapy to prevent pregnancy (3). There are some reports of successful pregnancies and deliveries without any congenital anomalies or complications for the mother or the child; one patient with CML stopped imatinib after becoming pregnant, and another patient continued imatinib treatment during pregnancy (4-7). However, some children born to mothers with CML who stopped imatinib after becoming pregnant developed pyloric stenosis, hypospadias, or meningocoele, but it was not clarified if imatinib was the cause (4, 7, 8). The effects of imatinib usage on the fetus are largely unknown.

Currently, no method has been established for CML patients receiving imatinib to safely conceive and deliver children. Here, we present the first reported case of a safe pregnancy and delivery achieved by a CML patient who deliberately stopped imatinib treatment and her CML was controlled during the pregnancy.

Case Report

A 24-year-old woman was found to have leukocytosis in August 2004. A clinical course of the patient is shown in Fig. 1. Complete blood count (CBC) showed white blood cell (WBC) at 27.6×10^9/L (neutrophil 77.1%, lymphocyte 12.8%, monocyte 3.8%, eosinocyte 2.8%, basocyte 1.7%), hemoglobin 10.4 g/dL, and platelet count of 363×10^9/L. Karyotype study was t(9;22)(q34;q11). She was diagnosed with CML-CP and was started on imatinib, 400 mg daily in September 2004. However, because of fever, pleural effusion, and interstitial shadow she was taken off imatinib 7 days later. After resolution of her symptoms she was re-
started on imatinib at a lower dose of 100 mg daily and the dose was increased to 400 mg; however, the imatinib dose, which was taken orally, ranged from 100 to 400 mg due to occasional nausea. Complete hematologic response (CHR) was achieved.

The patient was married in February 2005. Because suboptimal partial cytogenic response was not achieved 6 months after initiation of imatinib, the dose of imatinib was increased to 600 mg in May 2005. However, the dose ranged from 300 mg to 600 mg due to the occasional nausea although most of the other adverse effects had been relieved. Philadelphia (Ph) chromosome could be detected by fluorescence in situ hybridization (FISH) in February 2006. In April 2006, she told us that she wanted to become pregnant. Based on the report by Hensley and Ford (2), which was the largest study at that time, she was informed about the possibility of teratogenicity caused by imatinib and the risk of CML becoming worse after stopping imatinib; she gave consent and discontinued imatinib in May 2006. In spite of the risks for a baby and herself, she decided that she wanted to become pregnant at last. At that time, the optimal strategy of stopping imatinib remained uncertain and we stopped the imatinib administration due to her strong request. Interferon could be considered as an alternative treatment, however, it was not used due to the concern of its psychiatric adverse effects because she had attempted suicide during imatinib treatment. She had regular menses during the use of imatinib. To minimize the imatinib-free period, controlled ovarian hyperstimulation was started after stopping imatinib. Her pregnancy test was positive in October 2006. She had 4% positivity for the Ph chromosome by fluorescence in situ hybridization (FISH) and CHR was sustained. CBC showed WBC at 5.9×10^9/L (neutrophil 72.3%, lymphocyte 18.0%, monocyte 6.5%, eosinocyte 1.1%, basocyte 0.5%), hemoglobin 12.7 g/dL, and platelet count of 273×10^9/L. At 32 weeks, she had 12% positivity for the Ph chromosome; CHR was sustained. She had a normal delivery at 38 weeks without any complications. She delivered a healthy baby weighing 3,200 g. At birth, imatinib concentration in both the mother’s blood sample and the umbilical blood sample were below detection sensitivity. Five weeks after delivery, imatinib was resumed, again at a dose of 100 mg per day and was increased to a total of 400 mg per day. CMR was sustained 5 months after re-administration of imatinib. CBC showed white WBC at 5.1×10^9/L (neutrophil 66.5%, lymphocyte 26.1%, monocyte 2.7%, eosinocyte 4.3%, basocyte 0.2%), hemoglobin 11.0 g/dL, and platelet count of 179×10^9/L. One year later, the infant’s growth was normal.

**Discussion**

This case indicates a CML patient giving birth without complications for either mother or child after intentionally
stopping imatinib before conception. In all previous reports on pregnancy or childbirth and imatinib, the fetus has been exposed to imatinib. This report shows that planned pregnancy was successful after cessation of the drug for 5 months, which differs from previous reports.

There is little information about imatinib and female fertility. Christopoulos et al reported primary ovarian insufficiency associated with imatinib therapy for 2.5 years and suggested that prolonged administration of imatinib may have profound effects on female fertility (9). In the present case, the patient’s menstrual periods were normal while she was taking imatinib for about 20 months, and she became pregnant in her 4th menstrual cycle with controlled ovarian hyperstimulation after cessation of the drug.

There is a possibility that stopping imatinib for the long term may increase the patient’s risk of CML relapse. In this case, she had a cytogenetic relapse 5 months after imatinib was stopped but she maintained CHR without accelerated phase (AP) or blastic crisis (BC) during the 8-month stop period. Ault et al reported 10 cases of pregnancy in CML with CHR (7). In those reports, the duration of imatinib unexposure was a median of 7 months (1-21 months) and 4 of 10 patients developed hematological relapse during pregnancy. There were no cases of AP and/or BC during pregnancy (7). Theoretically CML may worsen due to immune tolerance in pregnancy, but there were no reports that patients developed AP and/or BC. There is little information about the effectiveness of resuming imatinib after delivery.

In the present case, molecular remission was achieved 5 months after restarting imatinib after delivery. Ault et al reported, however, 9 of 10 cases reached CHR but none of them reached molecular remission after restarting imatinib. This suggests that it remains uncertain that restarting imatinib after pregnancy can control CML. Although several studies on this topic have been reported (2, 3), it is still uncertain if stopping imatinib during pregnancy has any affect on the prognosis of CML. Further research is needed.

In conclusion, the present patient luckily had a normal delivery and a normal baby without adverse effects after stopping imatinib prior to conception to prevent fetal exposure to the drug. However, there is no evidence for the number of imatinib-free months prior to conception necessary to achieve a normal pregnancy and delivery. Although imatinib was stopped according to her strong desire to be pregnant in this case, this strategy is not necessarily recommended for patients with CML who want to be pregnant. Thus, future studies are warranted.

References