Successful maternal and fetal outcome in a patient with chronic myeloid leukemia on chemotherapy

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INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative-neoplasm accounting for 15% of adult leukemias.¹ Management of leukemia in pregnancy and effect of anti-neoplastic agents on pregnancy outcomes is not well investigated. Management of pregnancy in CML is complicated by the fact that drug used in its treatment i.e. imatinib can lead to teratogenicity in fetus, whereas withholding the drug may lead to relapse of disease. However, pregnancy itself does not alter the course of CML.

Keywords: Chronic myeloid leukemia, Imatinib, Pregnancy
We report a case of a nineteen-year-old pregnant female who was diagnosed with CML at the age of 15 years. Imatinib had been continued in this patient during the first trimester. No adverse fetal or maternal outcomes were noted in this case even though she was on a potentially teratogenic drug during the period of organogenesis.

CASE REPORT

A nineteen year old female had initially presented to our hospital four years ago with the complaints of fever, loss of appetite and weight loss for 2 months. On examination she had hepatomegaly of 5 cm below costal margin (BCM) and splenomegaly of 12 cm. On investigations her complete blood counts had revealed haemoglobin (Hb) of 9.1 g/dl, a total leucocyte count of (TLC) 171 × 103/cumm and a platelet count of 555 × 103/cumm. Her peripheral blood smear had shown marked leucocytosis with myeloblast cells comprising 5% of cells. A bone marrow examination had revealed marked myeloid preponderance with dysmyelopoiesis, eosinophilia and basophilia. She was diagnosed CML based on the above picture. The karyotype showed the presence of Philadelphia chromosome in all 10 metaphases examined [translocation (9; 22) (q34; q11.2)]. The Bcr/Abl transcript ratio by real time polymerase chain reaction (PCR) was 1.319%. The patient was started on Imatinib at the dose of 400 mg daily. The patient showed improvement with the above treatment and her TLC normalized after 4 weeks and the spleen became non-palpable. The patient was on imatinib and her monitoring based on the Bcr/Abl transcript levels were satisfactory throughout the course of the disease till date (Table 1).

Table 1: Bcr/Abl transcript by PCR and imatinib doses throughout the course of illness from diagnosis.

<table>
<thead>
<tr>
<th>Post diagnosis time elapsed (months)</th>
<th>At diagnosis</th>
<th>6</th>
<th>10</th>
<th>13</th>
<th>19</th>
<th>25</th>
<th>31</th>
<th>37</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCR/ABL transcript by PCR (%)</td>
<td>1.139</td>
<td>0.124</td>
<td>0.104</td>
<td>0.027</td>
<td>0.112</td>
<td>0.039</td>
<td>0.006</td>
<td>0.000</td>
</tr>
<tr>
<td>Dose of imatinib (mg/day)</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>

Table 2: Bcr/Abl transcript by PCR and imatinib doses during pregnancy.

<table>
<thead>
<tr>
<th>Post diagnosis time elapsed (months)</th>
<th>45</th>
<th>47</th>
<th>48</th>
<th>50</th>
<th>52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>8</td>
<td>16</td>
<td>20</td>
<td>28</td>
<td>36 (delivered a healthy baby boy)</td>
</tr>
<tr>
<td>Bcr/Abl transcript by PCR (%)</td>
<td>0.00</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>-</td>
</tr>
<tr>
<td>Dose of imatinib (mg/day)</td>
<td>Was on imatinib 500 mg/day. Imatinib stopped</td>
<td>Not on imatinib</td>
<td>Not on imatinib</td>
<td>Not on imatinib</td>
<td>Not on imatinib</td>
</tr>
</tbody>
</table>

The patient was doing well on imatinib. Three years after the diagnosis of her CML the patient was married and subsequently she became pregnant. The patient did not come for follow up after her marriage. Her next follow up was at 45 months post her diagnosis, with a history of amenorrhea for 8 weeks. She was being followed up by another obstetrician at her local city. Her ultrasound (USG) done at 5 weeks of gestational age (GA) had revealed a single live intrauterine embryo. She had been taking imatinib during this time period of organogenesis, so she was advised medical termination of pregnancy (MTP) by the treating oncologist. However, the patient consented against MTP at her risk, so her imatinib was stopped and pregnancy continued. She did not take any other drug for her CML during the entire course of pregnancy. The patient came to us at 27 weeks gestation and so far she had not undergone first or second trimester screening or level II USG for fetal malformations. She never consulted the genetic or fetal medicine specialist during the first and second trimester of pregnancy. Her blood pressure and metabolic profile during pregnancy were normal. The quantitative Bcr/Abl PCR at 16, 20 and 28 weeks of GA were not detectable (Table 2).

The patient did not develop any symptoms or signs suggestive of CML during pregnancy and the TLC of the patient remained normal throughout pregnancy. Her disease status was followed up with regularly Bcr/ Abl PCR transcript levels, and it was not detectable throughout pregnancy. The patient went into pre-term labor at 36 weeks of gestational age and subsequently delivered a healthy male baby weighing 3.1 kg. The baby was examined by the neonatologist and was not found to be dysmorphic and had a normal general and systemic examination. He passed meconium and urine normally. The USG of the abdomen of the baby was also normal.

DISCUSSION

CML is a myeloproliferative neoplasm which is characterized by the presence of Philadelphia chromosome translocation. The Philadelphia chromosome translocation (t 9; 22) (q34; q11) found in
CML is responsible for the genetic rearrangement that leads to the Bcr/Abl fusion protein. This protein is a tyrosine kinase that leads to hyperactivation of enzymes controlling the cell cycle. When CML is diagnosed during pregnancy various therapeutic options include interferon, tyrosine kinase inhibitor (TKI), hydroxyurea or leucapheresis. Imatinib mesylate which is a tyrosine kinase inhibitor is now standard therapy for patients with chronic myeloid leukemia (CML). In the chronic phase of CML a complete cytogenetic (CG) response has been achieved in 40% to 90% of patients treated with imatinib. Imatinib exposure in early pregnancy can lead to skeletal malformations (craniosynostosis, absent hemivertebrae, shoulder anomaly and scoliosis), renal agenesis, hypoplastic lungs and gastrointestinal i.e. omphalos or omphalocele. A patient of CML becoming pregnant is a rare event, so studies involving a large number of subjects are lacking in this area and data available are from case reports or case series. In cases of CML with pregnancy that have been reported in literature of which more than 50% have had successful pregnancy outcomes and in most cases the chemotherapy had been stopped or switched to an alternative one before conception.

The ratio of CML between male and female is 2:1 and few case reports also suggests a decreased testosterone production and gynaecomastia as an adverse effect of imatinib therapy. The effects of chemotherapy in the fetus include the abortive effects, teratogenic effects and late effects on development and growth. Imatinib has been found to be teratogenic in rats. Imatinib has not been found to affect the fertility in males in animal studies so it is not the practice to discontinue imatinib in males. In females imatinib intake has been associated with cluster of malformations especially if the intake is during the period of organogenesis. Pye et al, in a larger series of 180 women exposed to imatinib during pregnancy with outcome data available for 125 pregnancies found that 50% delivered normal infants. Of the pregnant women 28% underwent elective terminations, 3 following the identification of abnormalities. There was a total of 12 infants in whom abnormalities were identified. Spontaneous abortion occurred in 18 pregnancies and there was one still birth. Among the abnormalities identified three patients had a combination of exomphalos, bony abnormalities and renal abnormalities.

Our patient had a history of intake of imatinib throughout the period of organogenesis. Fortunately, she delivered a healthy new born male who had no apparent dysmorphism or malformations. Martin J et al, similarly reported a case of CML who had taken imatinib till her 10th week of gestation but delivered an apparently normal baby. Few studies also suggest use of leucapheresis during first trimester in pregnancy and later on switching over to TKI but leucapheresis is not available everywhere. Most patients with CML with pregnancy are advised to stop imatinib before conception. An alternative drug such as interferone or hydroxurea has been used in many cases. As imatinib crosses into the breast milk the drug should be kept discontinued till the time of lactation. Controversies regarding the restarting of imatinib exist. Some advocate restarting of imatinib only when the disease starts to relapse, whereas others prefer immediate restarting after lactation.

**CONCLUSION**

CML in pregnancy is rare and imatinib is the drug of choice with which a long-term survival is possible. Imatinib is large case series has been known to be associated with adverse fetal outcomes although evidence to the contrary also exists. Further studies and investigations are needed to draw a conclusion on this debatable issue.

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**REFERENCES**
