

## Outcome of 3 pregnancies in a patient with chronic myeloid leukemia who received 3 types of tyrosine kinase inhibitors each in different pregnancy: follow-up of the case with a review of published reports

Hussain Alizadeh,<sup>a,b</sup> Hassan Jaafar,<sup>b</sup> Béla Kajtár<sup>c</sup>

From the <sup>a</sup>Kaposi Mór Teaching Hospital, Kaposvár, Hungary; <sup>b</sup>Tawam Hospital, AlAin-United Arab Emirates; <sup>c</sup>Pécs University, Faculty of General Medicine, Department of Pathology, Pécs-Hungary

Correspondence: Hussain Alizadeh · Kaposi Mór Teaching Hospital, Tallián Gyula Street 20-32, 7400-Kaposvár, Hungary · T: (+36) 82-501341, F: (+36) 82-510076, M: (+36) 30-6436099 · alizadeh.hussain@gmail.com

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The management of patients with chronic myeloid leukemia (CML) during pregnancy remains a matter of continuous debate. Tyrosine kinase inhibitors (TKIs) have become the standard of care in managing patients with CML. These drugs have a good safety profile, but animal studies have shown that they are potentially teratogenic. Therefore, these drugs are not recommended for use during pregnancy or if a female patient plans to conceive. Despite the extensive clinical experience with TKIs, the available information about the effects of TKIs on fertility, pregnancy, and outcome of babies who were exposed to TKIs during pregnancy and lactation is limited. We reported on 1 female CML patient who conceived 3 times while being on different types of TKIs in each pregnancy. All 3 pregnancies were uneventful, and only 1 of the babies was diagnosed with a minor cardiac malformation at the age of 30 months, which was corrected surgically.

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm of a pluripotent stem cell first described by John Hughes Bennett in 1845 at the Royal Infirmary of Edinburgh.<sup>1</sup> In 1960, a unique chromosomal translocation was discovered in CML cells, which is known as Philadelphia (Ph) chromosome.<sup>2,3</sup> The causative molecular defect is Breakpoint cluster region-Abelson leukemia virus (BCR-ABL) protein that is encoded by the Ph chromosome, which is the result of translocation between chromosomes 9 and 22. This translocation results in the fusion of the BCR gene on chromosome 22 and the ABL gene on chromosome 9. The new (onco-)gene encodes a constitutively active protein kinase activating many proteins involved in the cell-cycle regulation that hasten cell proliferation.<sup>4-8</sup> In 1993, imatinib mesylate was tested in a preclinical setting as a targeted inhibitor of BCR-ABL tyrosine kinase, and in 2001 the US Food and Drug Administration approved it as the first-line

therapy for CML (Gleevec, Novartis Pharmaceuticals Corporation, NJ, USA). Imatinib has made a dramatic shift in managing CML patients, and it has become the standard of care for newly diagnosed CML patients. In recent years, new generations of BCR-ABL tyrosine kinase inhibitors (TKIs) have been developed and approved for treating either CML patients as first-line therapy or patients who are imatinib resistant or imatinib intolerant. TKIs are able to produce long-term remission in the majority of CML patients, and this has resulted in a significant improvement of overall survival. As a result, CML patients who are capable of adhering to effective TKI therapy on a chronic basis are expected to have excellent probability of achieving long-term survival and perhaps a normal life expectancy with an acceptable quality of life.<sup>8-10</sup> Despite the extensive clinical experience with TKIs, the available information about the effects of TKIs on fertility, pregnancy, and outcome of babies who were exposed to TKIs for a

variable length of time during pregnancy and lactation is limited.<sup>11,12</sup> Imatinib and other TKIs inhibit many proteins including BCR-ABL1, c-kit, PDGFR-A, and c-fms. Dasatinib inhibits c-Src as well.<sup>13</sup> Some of these proteins are involved in gonadal development, embryogenesis, and fetal maturation.<sup>13,14</sup> Although the median age of diagnosis for patients with CML is in the sixth decade, about 25% of patients are diagnosed before the age of 40 years. The advantages of TKI therapy in women of childbearing age are balanced by major concerns of TKIs increasing the risk of birth defects and malformations.<sup>15</sup> The TKIs have a very good safety profile, but animal studies have shown that they are potentially teratogenic. As such, currently these drugs are not recommended for use during pregnancy or if a patient plans to conceive. The available data about the use of second- and third-generation TKIs during pregnancy is even less compared with that of imatinib. The manufacturers of TKIs recommend that women of childbearing potential should avoid pregnancy while taking the drugs. In the case of planned or incidental pregnancy, other therapeutic options should be recommended.

This paper reported the outcome and the long-term follow-up of 3 pregnancies of a single patient while being on different TKIs during each pregnancy. Published reports and the current recommendations were also reviewed for the treatment of CML in patients who wish to conceive.

## CASE

In August 2001, a 33-year-old, 7 weeks' pregnant lady presented with vague abdominal discomfort, early satiety, and 2 weeks' history of blurred vision. Peripheral blood and bone marrow examination with cytogenetic analysis confirmed the diagnosis of CML in early chronic phase with Ph chromosome in all 22 analyzed metaphases. The leukocyte count was 520 g/L with 2% blasts, 6% eosinophils, 4% basophils, 8% metamyelocytes, 10% bands, 52% neutrophils, 4% monocytes, and 14% lymphocytes. Hemoglobin was 10.5 g/L, and the platelet count was 860 g/L. The spleen was palpable 12 cm below the left costal margin in the mid-clavicular line, and the liver was 4 cm palpable below the right costal margin. The Sokal score was 1.23 (high risk). Due to the extremely high leukocyte count, neurological symptoms, and pregnancy, the patient underwent 2 sessions of leukapheresis that resulted in good cytoreduction. Subsequently, the patient was commenced on alpha-interferon ( $\alpha$ -IFN) treatment, but she stopped taking the treatment after 1 week due to severe side effects. One week later, the patient presented to an outpatient clinic with an article in a local daily newspaper

about imatinib, and she insisted on getting this treatment. After explaining the available information on imatinib as a new class of targeted therapy, the potential teratogenic effects on developing fetus with a high risk of fetal malformations, and the paucity of clinical experience with imatinib, we strongly advised against the use of imatinib. Abortion was not an option in this case because of religious and cultural reasons. The patient and her husband insisted on imatinib treatment. The case was taken to the Ethical Committee of the hospital, which advised against the use of imatinib. Following a court order, the Ethical Committee agreed on the imatinib treatment after having taken written informed consent from both the patient and her husband. On gestational week 8, the patient was commenced on imatinib 400 mg/d under strict hematological and obstetrical monitoring. The patient had several ultrasonograms during pregnancy, which showed normal fetal development. She achieved complete hematological remission (CHR) after 3 weeks and a confirmed complete cytogenetic response (CCR) after 25 weeks of imatinib therapy. The patient continued on imatinib treatment till week 39 when she had uneventful vaginal delivery and gave birth to a healthy baby girl (Apgar score of 10). The patient continued taking imatinib during 8 months of breast feeding. At the age of 30 months, a diagnosis of a small ostium primum atrial septal defect was made that was successfully corrected by surgical intervention. She achieved major molecular response (MMR) 4.0 after 20 months of treatment. In December 2005, the patient lost her hematological response, and repeat investigations revealed Ph chromosome in all 20 metaphases analyzed with no additional chromosomal abnormalities and negative mutational analysis. The imatinib dose was escalated to 800 mg daily that she tolerated well, but only a partial cytogenetic response was achieved; therefore, the treatment was switched to nilotinib in July 2006 and this resulted in CHR in 4 weeks, CCR in 6 months, and MR4.5 in 18 months. The patient was repeatedly and strongly advised on adequate contraception and to avoid pregnancy while being on nilotinib treatment. In February 2008, after 20 months of nilotinib treatment, the patient became pregnant again and continued taking nilotinib during the entire pregnancy and 9 months of lactation. She had an uneventful delivery and gave birth to a healthy baby boy. The patient lost MMR in September 2009, and the treatment was switched to dasatinib 100 mg once daily. Mutational analysis revealed no kinase domain mutation, and conventional karyotyping did not show any additional chromosomal abnormality. Fourteen months after dasatinib treat-

ment, she achieved MMR 4.5 and at the 20th month of dasatinib treatment; the patient became pregnant in April 2001 for the third time while being on the third type of TKI treatment. On the 38th week of gestation, the patient had an uneventful delivery with a healthy baby girl. The patient was continued on 100 mg dasatinib treatment, and the latest quantitative real-time polymerase chain reaction (qRT-PCR) was consistent with BCR-ABL1/ABL1 ratio of 0.001%.

## DISCUSSION

The incidence of CML associated with pregnancy is estimated to be 1 in 100 000.<sup>6,7</sup> BCR-ABL TKIs have significantly improved the prognosis of CML patients. TKIs are very well tolerated, and their safety profile is excellent.<sup>8-10</sup> Although the median age of diagnosis for patients with CML is 64 to 65 years, about 20% to 25% patients are diagnosed between 20 and 44 years of age.<sup>11-15</sup> This means that a considerable number of young patients with CML are in the reproductive age at diagnosis. This younger subset of patients with CML faces difficulty in making decisions regarding conception and the continued control of their disease with TKI therapy, necessitating physicians to address issues related to fertility and pregnancy. Physicians are not infrequently being asked for advice regarding the need for and the appropriateness of stopping treatment to conceive.<sup>15</sup> The proper management of CML in pregnant patients presents a challenge to the treating physician, and it requires attention to important issues including medical, ethical, psychosocial, and cultural considerations. In countries where termination of pregnancy is unacceptable, managing a pregnant lady with CML is even more challenging. Currently, the recommended first-line treatment for CML outside of pregnancy is TKIs. However, in general, TKI treatment is not recommended during pregnancy because of concerns raised from animal experiments that have shown teratogenicity but not genotoxicity of these agents. Despite extensive clinical experience, available data on the outcome of pregnancy in patients exposed to imatinib are still limited. An increasing number of reports have demonstrated the use of imatinib following conception, and in the majority of these cases the conception was completed uneventfully with normal growth and development of newborns.<sup>16-18</sup> Cole and colleagues reported one of the most comprehensive data on the effect and outcome of TKIs on pregnancy.<sup>19</sup> They identified a total of 217 reported pregnancy events; of these, 171 carried their pregnancy to term and 24 had spontaneous abortions, but in 62 cases the outcome of pregnancy was unknown. Among the 109

pregnancies with reported and documented outcome, 36 had complications, including spontaneous abortion in 24 patients, stillbirth in 1 patient, malformations in 9 patients, and low birth weight in 2 patients. It appears that although most pregnancies exposed to TKIs are likely to have a successful outcome, there remains a risk that exposure may result in serious fetal malformations.<sup>20-22</sup> The number of CML patients in childbearing age is increasing and so is treatment with TKIs in this subgroup, particularly in countries where religious and cultural reasons are a determining factor. Alternative therapeutic options are available for CML in pregnancy: leukapheresis,<sup>23</sup> and alpha-interferon,<sup>24</sup> and hydroxycarbamide.<sup>25</sup> In recent years many reports and reviews have become available on the treatment of CML in pregnancy.<sup>26</sup> In addition, there are ongoing trials on discontinuation of TKIs in CML. A total of 9 trials have analyzed TKI discontinuation in CML. The review by Kendra and Vivian suggests that in patients with durable deep molecular response, stopping TKI therapy might be considered safe.<sup>27</sup> The current recommendation for CML patients who wish to conceive is to postpone the conception until they have achieved stable and deep molecular remission for at least 18 to 24 months. TKI can then be discontinued for a short period before ovulation or at least during the critical period of organogenesis with very close monitoring of the remission status, especially monitoring of BCR-ABL transcripts by qRT-PCR analyses. Based on available data from published reports, it is recommended that all female patients should be advised to use effective contraception during TKI therapy. If conception does take place, balancing the risk of interrupting the mother's treatment versus the risk of continued treatment to the developing fetus remains a difficult task. Patients who interrupt TKI therapy during pregnancy should be advised on the risk of CML relapse, even if they have achieved a complete molecular response. In animal studies, imatinib or its metabolites are extensively excreted in milk; therefore, it is recommended that women taking imatinib should not breastfeed. Accumulating evidence suggest that conceptions in which the male partner takes imatinib do not have an increased risk for congenital malformations.

To date, the patient in this manuscript is the first reported case of a female patient who became pregnant on 3 occasions while on treatment with 3 different types of TKIs, and she continued the treatment during the breastfeeding period. Regarding the rare type of cardiac defect diagnosed in first baby, it was believed that this defect was not related to TKI use because the imatinib treatment was started on the eighth week of gestation when the heart had already developed.

In conclusion, conception in CML patients who are on TKI therapy may result in normal pregnancy. The possible effects of TKI on pregnancy outcome and fetal abnormalities cannot be ruled out. Therefore, it is recommended that female patients in childbearing age should be discouraged of becoming pregnant while on TKI therapy, and they should be advised to practice adequate contraception. In the case of planned pregnancy, the patient should be advised to discontinue treatment at least 7 to 10 days before ovulation. In patients who become pregnant while on TKI therapy, the TKI treatment should be stopped immediately, especially during the organogenesis, but risks and benefits should be evaluated on an individual basis considering the wish of patient, biology and status of disease, reassurance of patient about the adequate response with restarting the TKI therapy, and the availability of safe and effective alternative therapies.

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