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Case Report Open Access

Successful Management of Three Pregnancies Under Imatinib Treatment in a Chronic Myeloid Leukemia Patient: A Case Report and Review of the Literature

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Abstract

Background:

Imatinib Mesylate (IM), the first tyrosine kinase inhibitor recommended for the treatment of Chronic Myeloid Leukemia (CML) patients with presence of Philadelphia chromosome (Ph), led to marked improvement in the survival of patients in all phases of disease. The incidence of CML associated with pregnancy is not that rare, however, patients normally avoid exposure to IM treatment during the pregnancy due to potential teratogenic effects possibly leading to malformation in the fetus and also secondarily providing a risk for the patient's life.

Case report:

We report three successful pregnancies with deliveries of healthy offspring in one female diagnosed with CML. She was treated with IM (400 mg/day) as a first-line therapy and lost complete hematologic response twenty-two months after IM treatment started. At this point she planned a pregnancy, despite her doctor's concerns. Due to non–-availability of drugs and the political situation in her home country the patient could not take IM regularly, leading to a Ph-positiveness since 2009. Still, during this period the patient successfully delivered three normal babies without any regular medical control for IM treatment. Thus, the patient and her fetuses were exposed to various doses of IM (400, 600 and 800 mg per day), in parts throughout first trimester and during lactating.

Results:

The use of IM did not have any adverse effects on any of the three fetuses, except for potential positive influence on birth weight in the first child she delivered.

Conclusion:

Pregnancy is an important part of life in young cancer patients. If possible, it is paramount to counsel pregnant patients to switch to drugs without adverse effects on the developing fetus. However, as highlighted by the present case, pregnancies exposed to tyrosine kinase inhibitors such as IM do not necessarily lead to adverse outcomes.

Keywords: Chronic myeloid leukemia; Imatinib mesylate; Pregnancy; Outcomes; Tyrosine kinase inhibitors

Introduction

Chronic Myeloid Leukemia (CML) is a hematological myeloproliferative disorder defined by the presence of Philadelphia chromosome (Ph), which is due to a reciprocal translocation t(9;22)(q34.1;q11.2); Ph can be observed as a sole chromosomal anomaly in more than 90% of the CML cases. At the molecular level, this rearrangement involves the breakpoint cluster region gene (BCR) (22q11.2) and the c-Abelson (ABL1) gene (9q34), resulting in the BCR-ABL1 fusion gene, and encoding a constitutively active tyrosine kinase protein. The effects of ABL kinase activity have been found to be successfully reversed by a first-generation of tyrosine kinase inhibitor (TKIs) knows as STI571 or Mmatinib Mesylate (IM=Gleevec, Novartis Pharmaceuticals Corporation, East Hanover, NJ) which specifically binds to the ATP binding site of the BCR-ABL kinase and inhibits it [1,2].

Prognosis of CML has improved dramatically over the recent years, for the most part due to earlier diagnosis, superior outcome by the introduction of targeted TKIs, more sensitive and standardized assays for molecular monitoring, better supportive care and ongoing research including clinical trials. The majority of CML patients can now achieve longstanding cytogenetic and molecular response on first-line TKI therapy. The current consensus recommendation is that IM or one of the second-generation TKIs has to be continued life-long, with regular

molecular monitoring [3,4]. Despite some 15 years of experience with IM in the treatment of CML, there is still quite sparse of data on the effects of IM on fertility, pregnancy and embryonal/fetal development because the median age of CML patient at the time of the diagnosis is approximately 60 years [5].

In this paper, we report a new and unique example of three successful planned pregnancies and deliveries in one female CML patient under IM treatment, leading to no adverse effects on the developing fetuses.

Case Report

In January 2007, a 33-year-old female patient without significant personal or familial medical background presented with hepatosplenomegaly but without skin nodules. Her peripheral blood test results were as follows: White Blood Cell (WBC) 81.5 × 10^9/l, hemoglobin level 7.8 g/dl and platelet count 498 × 10^9/l. The diagnosis of CML in chronic phase according to World Health Organization recommendations was made i.e., a chromosome analysis on bone marrow (BM) sample using GTG-banding according to standard procedures [6] was performed before the treatment started revealed a karyotype of 46,XX,t(9;22)[20] (karyotype according to the International System for Human Cytogenetic Nomenclature-ISCN 2013) [7]. Fluorescence in situ hybridization a BCR/ABL probe confirmed the presence of the BCR-ABL1 fusion. Karyotypes prior and post treatment are summarized in Table 1.

The patient was treated initially using Hydroxyurea (HU) (1,000 mg/day) for two weeks; then she started taking IM (400 mg/day) as a first-line treatment with good tolerance and adherence to the medication. After twenty-two months, she showed signals of IM treatment failure after; she lost Complete Hematologic Response (CHR), had an increase in WBC, and was Ph-positive in 30% of all cells examined. Two months later she achieved CHR but she lost it again after one month.

The patient had already four healthy children and one spontaneous abortion in November 2016. The Muslim patient planned for further pregnancies (the traditions in her society prohibit termination of pregnancy for any reason, and encourage multi-birth), despite her MD's concerns with respect to malformation in the fetus and risk of maternal life. Accordingly, the patient did not inform her MDs about her further family planning. Besides, due to non-availability of drugs in addition to the political situation in her home country recently, the patient could not take IM on a regular base and as prescribed since 2009. Thus, she experienced also different phases with levels of Ph-positiveness (Table 1). Nonetheless, since 2009 the patient successfully delivered three normal births without any coordinated medical control for IM levels and treatment. Thus, the patient and her fetuses were exposed to various doses of IM (400, 600 and 800 mg per day), in parts during first trimester. In addition, during the lactating, all her babies were exposed to various doses of IM. Her children's birth weight was on average 4-5 kg, but she delivered the first baby under IM treatment with a birth weight of 7 kg.

Since 2007 the patient achieved a Complete Cytogenetic Response (CCgR) once, when she treated with a Nilotinib (800 mg per day) for 6 months. Recently, the patient restarted treatment with IM (400 mg/day) for three months; she achieved CHR and now is still under IM treatment. She agreed with scientific evaluation of her case and the study was approved by the ethical committee of the Atomic Energy Commission, Damascus, Syria.

Discussion

According to the literature, IM produces CCgR in 82% of patients receiving IM as first-line treatment [8]. Still, the incidence of CML associated with pregnancy is estimated to be only 1 in 100,000 [9] as most CML patients are diagnosed late in life (the median age at diagnosis 60 years in most Western registries) and only around 25% of them are younger than 40 years at diagnosis [5,10-13]. The latter patients are in the reproductive age group and are likely to be concerned about the effects on fertility and pregnancy of both, the disease itself, and the drugs administered for its management. In the absence of clear guidelines regarding the management of CML prior to or during pregnancy, clinical decisions are often made on a case by case basis. However, with increasing understanding about the physiology of the disease and its response to TKIs, there may remain little reason to suggest that a normal pregnancy could not be carried to term in this group of patients-under careful monitoring by a multidisciplinary team.

No therapy offered to a pregnant women suffering from CML is completely safe and effective; thus, clinicians are faced with the challenge of balancing the safety of the mother while treating with IM against the safety of the unborn baby, which may be affected by potential teratogenic effects of the drugs [11,14-17]. Currently the recommended 1st line treatment of CML is TKI, but this option is not recommended for patients who are pregnant or planning to conceive. Alternative therapeutic options for CML in pregnancy are: leukapheresis [18], alpha-interferon [19], and HU [20]. The safety and feasibility of leukapheresis and interferon in pregnancies have been published in previous reports. HU inhibits RNA synthesis and is known to cause embryo toxicity in animals, however, the potential effects of HU on developing human fetus is not well-established [20]. Available data on the outcome of pregnancies in patients exposed to IM and other TKIs are still limited [21] and the most information regarding the reproductive effect of IM is derived from pre-clinical animal studies. In a rat model, high doses of IM increased embryonic loss and malformations (exencephaly, encephalocele and chemical bone hypoplasia) [22].

A patient willing to conceive who has achieved and maintained an optimal response by European Leukemia Net (ELN) criteria 2013 [23] is a good candidate for pregnancy planning and therapy interruption. Although ELN suggest that therapy with TKIs should never be stopped, multiple studies have been conducted so far enrolling patients planned to pregnancy should be only after the milestone of a stable major molecular response (MMR) or better reached more than 18-24 months strictly followed after interruption of TKIs treatment especially during the organogenesis (post menstrual days 31-71, weeks 5-13), and reverse transcription quantitative polymerase chain reaction must be monitored monthly or every 2 months [24,25]. Almost all cases with good control of CML at conception and a good response to a specific TKI stopped taking it during pregnancy and resumed after delivery, have re-reached MMR within 3-6 months, confirming the possibility of a safe therapy manipulation during pregnancy [9,26,27]. However, in case of planned pregnancy, female should stop taking TKI before implantation (7-10 days after ovulation), absolutely no TKI during organogenesis period and or breast-feeding (all patients can breast feeding the first 2-5 days post-delivery to give the baby the colostrum) [24,26].

In the present case presented here, the patient planned pregnancies because of the traditions in her society prohibit termination of pregnancy for any reason, and encourage multi-birth; she avoided to

inform her MDs about her planned pregnancy because the MDs here in our country said "no pregnancy all time during TKI treatment"; and due to non-availability of drugs in addition to the political situation in her home country recently the patient could not take IM on a regular bases. For this reason, our patient remained without full medical managed, and she successful delivered three healthy pregnancies and all children delivered during the disease were exposed to different types of TKIs for various doses after conception and during breast-feeding. Our observations outcomes were agreed with Alizadeh et al. [25].

Pregnancy per se does not affect CML, but there are the risks of leukostasis and placental insuffiency with consequent low birth weight, premature delivery and increased mortality [28]. However, low birth weight outcome is not uncommon in CML patient planned pregnancy [29-31]. Surprising, in our case presented here, the first baby was born with enhanced birth weight (approximately 7 kg).

In conclusion, the presented data comprises the first report of subsequent pregnancies in a CML patient on IM treatment from Syria. It is noteworthy that all three pregnancies had a good outcome, even though IM treatment was continued during conception.

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Consent for Publication

Written informed consent was obtained from the patient's father for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Appointments in	Types of pregnancy	Prior conception			1st trimester exposure	IM	Post termination of pregnancy			Pregnancy	Notes
		Treatment	CHR	GTG or FISH results			Treatment	CHR	GTG or FISH results	outcome	
2009	Planned	IM (400 mg/day) for 5 months at begin of pregnancy and later 600 mg/day for 2 months	Yes	Ph+ in 30%	9th week	IM continued during conception	IM (400 mg/day)	Yes	Ph+ in 100%.	Healthy male child with birth weight ~7 kg	During pregnancy she lost CHR and increasef her WBC by 5 times
2011	Planned	IM (400 mg/day) for 7 months	Yes	Ph+ in 50%	10th week	IM continued during conception	IM (400 mg/day)	No	Ph+ in 30%.	Healthy female child	During pregnancy she lost CHR and increased her WBC by 2 times
2013	n.a.	Nilotinib (800 mg/day for 6 months)	No	Ph+ in 100%.	n.a.	n.a.	Nilotinib continued (800 mg/day)	Yes	Ph-	n.a.	She achieved CHR and CCgR
2014	Planned	IM (400 mg/day) for 3 months and later HU (1000 mg/day) for 2 months	No	Ph+ in 90%	5th week	IM continued during conception	None	No	Ph+ in 100%.	Healthy female child	During pregnancy she lost CHR and increased her WBC

Table 1: Clinical data of the patient together with prior and post pregnancy outcomes with the corresponding cytogenetic findings. Abbreviations: CCgR: Complete Cytogenetic Response; CHR: Complete Hematological Response; FISH: Fluorescence in situ hybridization; GTG, G-banding; HU: Hydroxyurea, IM: Imatinib Mesylate Treatment; Ph: Philadelphia Chromosome.

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