Pediatric Research and Child Health

CASE REPORT

Neonatal Outcome of Pregnant Mother with Chronic Myeloid Leukemia on Anticancer Medication (Imatinib)

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Abstract

Pregnancy in chronic myeloid leukemia (CML) is uncommon. Management of leukemia during pregnancy and the effect of anticancer medication on pregnancy outcome is not well investigated. Imatinib, the target therapy for CML during pregnancy has been known to be associated with fetal teratogenicity, whereas withholding the treatment may leads to relapse of the disease. Here we successfully managed a mother with CML on imatinib, detected her pregnancy status incidentally in 2nd trimester, immediately stopped the medication. Subsequently a healthy baby was delivered with no apparent malformation.

Key words: CML, pregnancy, imatinib, neonatal outcome.

Introduction:

Chronic myeloid leukemia(CML) is a neoplasm of the white blood cells characterized by increased and unregulated growth of myeloid cells accounting for 15% of all leukemias [1]. CML develops due to reciprocal translocation between chromosome 9 and 22. This translocation creates a fusion gene - the breakpoint cluster region (bcr) and the abelson leukemia(abl) proto-oncogene. This rearrangement is known as the Philadelphia chromosome, the hallmark of CML [2, 3]. The proto-oncogene encodes an oncoprotein that has active tyrosin kinase (TK) activity.

Imatinib mesylate(IM) is a tyrosin kinase inhibitor (TKI), molecularly targeted anticancer drug that demonstrates remarkable clinical activity in patients with CML. Imatinib potentially inhibits bcr-abl and blocks proliferation of tumor cell and induces apoptosis. Imatinib, one of the first cancer therapies showing the potential for such targeted action. Imatinib was called as "magical bullet"when it revolutionized the treatment of CML in 2001 (FDA approval of the drug). It was recommended that women of child bearing age should be avoided becoming pregnant while on imatinib [4]. Simultaneous presentation of pregnancy and CML is an uncommon event, because CML presents mostly in elderly patients. The incidence of pregnancy in a patient with CML is about 1 in one million [5], whereas the prevalence of leukemia during pregnancy is approximately 1 in 10000 pregnancies. The management of CML during pregnancy poses a therapeutic dilemma because of the potential adverse effect of chemotherapy on the mother and teratogenicity in the fetus. Spontaneous abortions and congenital anomalies have been reported by women taking imatinib during pregnancy. The congenital defects identified following maternal exposure to imatinib are cleft palate, polydactyly , meningocoele, scoliosis, hydrocephalus, cerebellar hypoplasia, atrial septal defect, overriding aorta, ascites, pericardial effusion , hypospadias, pyloric stenosis, left duplex kidney, right absent kidney, hemivertebrae, and exomphalos etc [6,7]. However, pregnancy itself does not alter the course of CML. On the other hand, withholding medication in pregnant CML mother may lead to a relapse of the disease seriously. Because of this difficult choice between taking teratogenic medication versus cancer progression, there is no strong medical recommendation regarding a potential wash-out period for cancer survivors taking imatinib and seeking pregnancy [8, 9]. If pregnancy is planned in case of CML patient on treatment, physician need to achieve a molecular response for 18-24 months, after which treatment should discontinue, ideally 3 months before conception and throughout the pregnancy and thereafter therapy should resume following birth of new-born [10]. A more complicated issue is raised for unplanned pregnancy or incidental diagnosis of CML during pregnancy. Targeted

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Imaging for fetal anomaly (TIFFA) scan is being done as part of the routine prenatal care in the 2nd trimester to rule out developmental anomaly as well as anatomical defects of growing fetus.

There are very limited data available on the outcome of pregnancies exposed to imatinib [11]. We report a case of a pregnant CML patient treated with imatinib during the period of organogenesis, subsequently delivered a healthy newborn baby with no adverse fetal or maternal outcome.

Case report:

An inborn male baby was delivered by LUCS at 36+ weeks of gestation due to prolong rupture of membrane for 18 hours. Mother, 33 yers old, primi gravida, had history of recurrent vulvovaginitis and was treated by her obstetric physician. Mother was a known case of chronic myeloid leukemia (CML), treated by cytotoxic drugs since last eight years. Initially she was treated by dasatinib, followed by imatinib, the dose gradually reduced to 400 mg daily (maintenance dose). As her menstrual period was irregular, she did not realized her pregnancy status and noticed incidentally by her routine ultrasound checkup at 25 weeks of gestation. She had no history of hypertension, diabetes or bronchial asthma.There was no perinatal complication. After delivery, APGAR score was 7/10 at 1st minutes and 8/10 at 5th minutes. The baby was Low birth weight (LBW) 2450gm, head circumference 32.5 cm, supine length 48 cm. The heart rate of baby was 146 /min, respiratory rate 48/min, 1st & 2nd Heart sounds were audible, air entry was good on both lungs, Abdomen: soft, not distended. Hearing screening revealed normal (bilaterally passed).

After 24 hours of age, baby presented with fever, excessive cry and poor sucking for which septic workup was done and treated for suspected sepsis. Echocardiography showed small atrial septal defect(ASD) with persistent pulmonary hypertension of newborn(PPHN). PPHN was treated by high flow oxygen and other supportive care. USG of brain revealed right sided lenticulostriate vasculopathy, kept in special consideration for future follow up. The baby was thoroughly evaluated for all the features of imatinib overdose/toxicity including teratogenicity. Surprisingly the baby escapes most of the serious effect of maternal imatinib as she was treated for her CML and finally went home with normal physical status and exclusive breast feeding.

Narrative review:

Management of CML in case of pregnant woman is a real challenge. Over the last few decades CML treatment consisted of conservative management of leukapharesis, hydroxyureas, interferon and lastly imatinib [12-14]. Each of which is potentially unsafe during pregnancy; although interferon may be a safer option though less effacious than imatinib [15]. In our reported case, a diagnosed CML mother was on imatinib for last eight years and incidentally found pregnant at her 25 wks of gestation. Subsequently, she stopped the medicine, were fretful for fetal malformation throughout the pregnancy. According to Pye et al. it is important that woman be made aware of the potential complications of imatinib therapy during pregnancy, close monitoring may facilitate control of disease and delivery of a normal neonate [6]. Although most pregnancies exposed to imatinib are likely to have a normal outcome, there remains an increased risk of congenital fetal abnormalities or spontaneous abortion or still birth [6]. Treating patients with CML, who wish to become pregnant is another challenge for a number of reason. There is no single anticancer therapy that can be offered to a pregnant woman that is both completely safe and effective, and clinicians are therefore faced with the challenge of balancing the safety of the mother and treating her malignancy against the safety of the fetus [11]. Pregnancy per se does not affect CML but there are risk of leukostasis, placental insufficiency of mother with consequent low birth weight, premature delivery and increased mortality of newborn. Our reported case was borderline premature and LBW but clinically well. Similar finding of LBW was found by Cole et al., they also found maternal complications of spontaneous abortion, stillbirth, congenital malformations in their study [16]. Ault and colleagues were the first to publish 19 pregnancies in which 3 pregnancies ended with spontaneous abortions and 16 pregnancies were identified to be uneventful [17]. Weiwei Sheng reported a successful pregnancy diagnosed with CML treated with imatinib (400 mg/day) as a first-line therapy. Imatinib treatment was stopped after 5 months of gestation then treated with interferon-alpha for the remainder of her pregnancy. She successfully gave birth to a male infant at 39 weeks of gestation without adverse sequelae or malformation [18].

Data on pregnancy outcome in patients treated with imatinib are limited. One of the largest collections of data on the effect of imatinib on pregnancy outcome was compiled by Pye et al. They reported 50% delivered normal infants (out of 125 cases) , 18 pregnancies ended in spontaneous abortion & there were a total of 12 infants in whom abnormalities like meningocoele, premature closure of skull sutures, scoliosis, hemivertebrae, small exomphalos, pyloric stenosis, hydrocephalus, cerebellar hypoplasia, atrial septal defect, overriding aorta, ascites, pericardial effusion, hypospadias, left duplex kidney, right absent kidney were identified [6]. Webb and Jafta reported 2 cases in which one infant was born with clinodactyly, short fifth fingers and slightly downward slanting palpebral fissures, whereas another infant had clinodactyly and low-set ears [11]. Jain et al. also reported a case of low-birth-weight (2.25 kg), late preterm (35 weeks) male baby born with microtia of the right ear, left preauricular tag, absent right depressor angular oris muscle and imperforate anus. The newborn was operated for imperforate anus and subsequently went home [19].

Tyrosine kinase inhibitors, which are used in the treatment of CML, selectively inhibit the activity of the constitutively active protein kinase and regulate the cell cycle. IM is a

tyrosine kinase inhibitor which is effective in producing long-term suppression of CML in the majority of patients [4]. Some questions have not been answered yet in the literature such as the time to wait between discontinuation of the drug and conception, whereas some authors suggest it may be reasonable to consider a wash-out period of a few days before conception [20]. Goldman reported that once achieving complete cytogenetic response (CcyR) and major molecular response (MMR), it might be possible to stop imatinib for a period of time to allow the patient to conceive and carry the child without exposure to the drug but being aware of the risk of progression [21]. Effective contraception should be used during IM therapy to prevent pregnancy [7] because IM crosses the placenta easily and very high concentrations have been found in the placenta [22].

Data from the Stop Imatinib (STIM) Trial indicate that imatinib can be discontinued in a selective subgroup of patients those who can achieve complete molecular response and maintain it for 2 years [20]. This may be the ideal method to manage a pregnancy in some cases but may not be applicable to others. Patients with the CML cases that is not optimally controlled, as per the European Leukemia Net (ELN) guidelines, may be even more difficult to manage [23]. In such cases continuation of therapy with close monitoring of the pregnancy may facilitate effective therapy but poses the risk of adverse fetal outcome. As imatinib cannot be considered totally safe for treatment of CML in pregnancy, its use might be safer in the later period of pregnancy and after delivery leading to better maternal and fetal outcome [24]. It is essential to consider the parents' wishes, mother's disease status, current molecular and haematological response to imatinib before taking any dicision regarding continuation or discontinuation of the medication. With counseling and a considered approach to disease monitoring, CML mother can still become pregnant with minimum effects to fetus or their disease status.

Conclusion:

Pregnant mothers who are on Imatinib may have a teratogenic outcome or a normal outcome. Therefore women should avoid being pregnant while on imatinib. We recommend the mother to undergo regular scans for detecting an associated anomaly in the fetus.

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