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Outcome of imatinib mesylate in women with child-bearing age diagnosed with chronic myeloid leukemia

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Abstract:

BACKGROUND: Imatinib Mesylate (IM) is an oral tyrosine kinase inhibitor, which demonstrates great effect in the treatment of both chronic myeloid leukemia (CML) and gastrointestinal stromal tumors. The effects of this chemotherapeutic drug on women with child bearing age, fertility, and reproductive system have been reported in some studies as case series; therefore, this study was designed to demonstrate the outcome of imatinib on females with child-bearing age.

PATIENTS AND METHODS: This is a prospective cross-sectional study conducted in the National Center of Hematology/Mustansiriyah University in Baghdad. The study started on February 2018 and was ended in July 2020. It included 55 female patients. A questionnaire was designed to elicit the effects of imatinib mesylate on fertility and outcome of pregnancies.

RESULTS: Out of 55 women diagnosed with CML in chronic phase, 13 patients were able to conceive during the study. All of them were treated with imatinib mesylate 400 mg per day before pregnancy. All of them were at least in complete cytogenetic response. Four (30.7%) pregnant patients continued treatment throughout pregnancy with uneventful pregnancy and delivery, without any congenital anomalies. other 4 (30.7%) pregnant patients received IM during 1st and 2nd trimester only and then discontinued treatment with IM. Five (38.4%) pregnant patients who received IM during 1st trimester ended with abortion (either elective or missed abortion).

CONCLUSION: Treatment of CML with IM during the pregnancy has different perspectives and the data are still limited. Hence, each case decision should be individualized balancing the risk to the fetus of continuing IM versus the risk to the mother of interrupting treatment.

Keywords:

Child-bearing women, chronic myeloid leukemia, imatinib mesylate

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Introduction

Imatinib mesylate (IM) has an inhibitory effect on tyrosine kinase receptor with precise activity against BCR-ABL fusion protein and was approved by the Federal Drug Administration (FDA) for patients with chronic myeloid leukemia (CML) in 1998.[1-3] The use of tyrosine kinase inhibitors (TKIs) in CML radically changed the prognosis of the disease. Based on long-term follow-up, 10-year overall survival (OS) in the chronic phase (CP) of CML with imatinib therapy was 83% and 12-year OS was 79%. The main aim of therapy was to achieve deep remission diseases with a good quality of life of patients and finally for treatment free remission.[4,5] As a result, the wish of female patients to have children increases and the hematologists are more often asked for advice regarding the management

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of treatment to conceive. This problem appears in a particular epidemiological context, because, if the incidence of CML remains constant, its prevalence increases with the prognostic improvement.[6]

Effects of TKI in pregnancy have been related to teratogenicity and TKIs are considered category D in pregnancy by FDA; there is evidence of human fetal risk.[7] Congenital malformations have been observed in newborns of women who received TKI in pregnancy, so its use is prohibited particularly in the period of organogenesis. These congenital malformations may include premature closure of the cranial sutures, craniosynostosis, and hemivertebrae; abnormalities of the shoulder; heart chamber defects; renal agenesis; pulmonary hypoplasia; hydrocephalus; meningocele; omphalocele; and exomphalos. The incidence of the latter was 100 times higher than usual.[8]

Congenital anomalies formed by TKI could be related to its mechanism of action.[9] It is important to remember that the BCR-ABL is not the only target of TKI, but also it has effective inhibition of ABL1, ABL2, c-kit, (PDGFR α/β), and c-FMS. In the cases of dasatinib therapy and Bosutinib therapy, TKI can inhibit Src and related proteins while some of its functions(i.e tyrosine kinase) could be important in development gonadal, fetal, and implantation.[8,10,11]

There are currently no established guidelines for treatment of CML in pregnancy but expert recommendations have been published and recently updated;[12] which was based on some studies and several case reports of conception or successful pregnancy during IM treatment that have been reported in the literatures.[9] The aim of the current study is to evaluate the outcome of IM in female patients with child-bearing age diagnosed with CP CML.

Patients and Methods

This is a retrospective, cross-sectional study conducted in two centers: the National Center of Hematology/ Mustansiriyah University in Baghdad. The study was started on February 2019 and was ended in July 2020. It included 55 female patients. All patients were in CP CML, in child-bearing age (18–45 years); there was no comorbidities and no gynecological or obstetric disorders before starting treatment with IM. A questionnaire was designed to elicit the effect of IM on fertility and outcome of pregnancy. The study was approved by the Review Ethical Committee of the National Center of Hematology, and all patients had given their written inform consent.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS)/IBM/Chicago, Illinois, USA/version 23.

Table 1: Distribution of outcome of pregnant CML patients on IM

CML Pregnant outcome	No.(%)
Total no. of enrolled child bearing age patients with CML in study	55 (100)
Total no. of CML patients able to conceive	13 (23.6)
Elective abortion	3 (23)
Miss abortion	2 (15.3)
Normal delivery (received treatment in early(1st and 2nd trimester) or throughout pregnancy) with normal babies	8 (61.5)

Results

Out of 55 female patients in child-bearing age, 13 were able to be pregnant; all of them were treated for CML with 400 mg per day of imatinib mesylate at first trimester. Four (30.7%) out of 13 pregnant patients had continued treatment throughout pregnancy with uneventful pregnancy and delivery, without any congenital anomalies in delivered babies. Other 4 (30.7%) out of 13 pregnant patients who received IM during the 1st and 2nd trimester discontinued treatment with IM, and were either given interferon-alfa or remained without therapy till end of pregnancy. Five (38.4%) out of 13 pregnant patients treated with IM during the 1st trimester ended with abortion (either elective or missed abortion); elective abortion was done based on patients request to avoid stopping IM and to maintain their molecular response based. Among pregnant patients who interrupted therapy with IM, they maintained complete hematological and cytogenetic response after delivery.

So in total eight (61.5%) pregnant lady with CML who received IM in the early and throughout pregnancy had uneventful pregnancy and delivered by either normal vaginal delivery or caesarian section with healthy male or female babies see Tables 1 and 2 for details.

Discussion

The current study showed that 13 (23.6%) were able to conceive during the period of study. significant proportion 8 (61.5%) from 13 pregnancies have been exposed to imatinib during the 1st and 2nd trimester (4 pregnancies) while another 4 pregnancies received IM throughout pregnancy and the course of pregnancy was uneventful with normal vaginal delivery of healthy babies. All patients who stopped IM during pregnancy were maintained complete hematological and cytogenetic response after delivery. Ali *et al*. and Skoumalova *et al*. described the clinical presentation, course, and outcome of pregnant patients with CML who was treated with imatinib in 1st and 2nd trimesters of gestation and the tow patient tolerated the drug well and achieved complete

Table 2: Outcome and characteristics details of 13 Patients with CML who were able to conceived while on IM therapy

Patient no.	Age (years)	Duration of IM therapy before conceive (years)	Response status before pregnancy (ELN criteria)	Dose of IM therapy during pregnancy (mg)	Exposure of IM during pregnancy (months)	Type of delivery and outcome of pregnancy
1	29	3	MMR	400	1st , 2nd , 3rd trimester	NVD Healthy male baby
2	23	2	MMR	400	1st , 2nd , 3rd trimester	NVD Healthy male baby
3	20	5	CMR	400	1st , 2nd , 3rd trimester	NVDHealthy male baby
4	27	7	CMR	400	1st , 2nd , 3rd trimester	NVD Healthy female baby
5	21	8	CMR	400	1st , 2nd trimester	NVD Healthy female baby
6	29	6	CMR	400	1st , 2nd trimester	C/S Healthy male baby
7	35	5	MMR	400	1st , trimester	NVD Healthy male baby
8	34	3	CCyR	400	1st trimester	NVD Healthy female baby
9	33	4	MMR	400	1st trimester	Missed abortion, No congenital malformation in fetus
10	28	3	CCyR	400	1st trimester	Missed abortion, No congenital malformation in fetus
11	36	7	CMR	400	1st trimester	Elective abortion, no congenital malformation in fetus
12	27	5	MMR	400	1st trimester	Elective abortion, no congenital malformation in fetus
13	24	2	CCyR	400	1st trimester	Elective abortion, no congenital malformation in fetus

Abbreviations: CMR = complete molecular response, MMR = Major Molecular Response, CCyR = complete cytogenetic response. NVD = normal vaginal delivery, C/S = caesarian section

hematological and cytogenetic remission, there was no imatinib related maternal complications during the pregnancy, fetal growth remained normal as well as amniotic fluid volume estimation, and labor was induced at the 39th gestational week, resulting in the uneventful vaginal delivery of a healthy male infant without any congenital anomaly.[13,14]

Five pregnant patients included in this study had abortion which was either elective or missed abortion, three pregnant patients requested to have elective abortion as measure so that they can continue their therapy to keep their molecular response during pregnancy.

Russell *et al*. reported that imatinib can poorly cross mature placenta, which might suggest that IM is unlikely to play a significant role in fetal abnormalities, in contrast to that IM and CGP74588 are found in breast milk, and therefore avoidance of breastfeeding is advisable.[15] The uteroplacental and fetoplacental circulation and active transport mechanism are established after 10 weeks.[16] In umbilical blood, imatinib was either not present or present at low concentrations due to properties of the drug (drugs highly bound to proteins and with a molecular weight of more than 500 have limited placental transfer).[6] In contrast, high concentrations of IM and CGP74588 were detected in breast milk. Therefore, breastfeeding during IM treatment may be avoided despite the small amount of drug actually.[15] In contrast to that, another study showed that women who restarted or who restart TKI, imatinib, and nilotinib are demonstrated not to reach therapeutic concentrations in an infant's blood during breastfeeding by a mother on these agents.[17] However, lack of clinical evidence of IM use in children with CML under 1 year of age and existence of bottle feeding as alternative to breast feeding supports this strategy for breast feeding patient receiving any TKI.[18]

Although the results of this study showed that spontaneous or missed abortion rate was 15% in comparison with expected percent in general population (spontaneous abortion rates of 10%–15%),[8] spontaneous abortion may be due to effect of Imatinib despite it is reported that Imatinib may not cause chromosomal damage.[9] There were no congenital anomalies detected

in those pregnant females who spontaneously and electively aborted.

Ault *et al*. reported the experience on 19 pregnancies with CML who conceived while receiving imatinib. All pregnant patients discontinued IM therapy immediately on recognition of pregnancy while four pregnancies ended with abortion and all other pregnancies were uneventful. Two of the 16 babies had minor abnormalities at or shortly after birth (hypospadias in one baby and rotation of small intestine in one baby); all babies have continued normal growth and development. Among female patients who interrupted therapy, five of nine in CHR at the time of treatment interruption eventually lost CHR, and six experienced an increase in Philadelphia chromosome-positive metaphases.[19]

Conclusion

Considering reported cases and our experience, treatment of CML during the second and third trimesters of gestation seems to be safe, but the data are still limited. Hence, each case decision should be individualized balancing the risk to the fetus of continuing imatinib versus the risk to the mother of interrupting treatment.

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Conflicts of interest
There are no conflicts of interest.

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