original reports abstract

Pregnancy Outcomes in Chronic Myeloid Leukemia: A Single Center Experience

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PURPOSE The aim of the current work was to report the effect of imatinib on pregnancy in patients with chronic myeloid leukemia (CML).

METHODS Data were collected between January 1998 and December 2014. One hundred four patients met inclusion criteria, and we report the results of 104 pregnancies—conceived by the participant or partner—while being on imatinib therapy for CML.

RESULTS Fifty-eight patients were male and 46 were female. Eighty-three patients, 20 patients, and one patient were had CML in the chronic phase, accelerated phase, or blast phase, respectively. Of 46 female patients, 21 underwent abortion (spontaneous, n = 36.9; elective termination, n = 8.6%). In the case of full-term pregnancy in the female partners of male patients with CML, all outcomes were uneventful. Of 46 female patients, 25 had full-term pregnancy outcomes. During the pre–imatinib era (total n = 6), patients were treated with hydroxyurea, interferon-alpha, and therapeutic leukapheresis. A total 10 of 19 pregnant patients continued on imatinib until their delivery and experienced the following outcomes: normal full-term deliveries (n = 7), preterm delivery (n = 1), omphalocele (n = 1), and craniosynostosis (n = 1). Of those who discontinued imatinib after counseling (n = 9), eight patients had full-term normal delivery, of which two patients required leukapheresis and one patient expired. All patients who continued on imatinib while pregnant were in complete cytogenetic response and major molecular response (MMR) before pregnancy, during pregnancy, and postpregnancy. Of nine patients who discontinued imatinib, two lost MMR during the third trimester and all of these patients were in complete cytogenetic response and MMR before pregnancy.

CONCLUSION It is clear that there is no standard of care for the best treatment of CML in the case of pregnancy. Interferon and/or leukapheresis will be included as treatment options. Patients can have normal pregnancies even with the administration of imatinib at the risk of congenital anomalies, intervention for which can be done after birth.

INTRODUCTION

It has been observed that, during pregnancy, the prevalence of leukemia is less than one in 10,000 pregnancies.[1] Today, for patients with chronic myeloid leukemia (CML), imatinib mesylate has become the standard therapy. If a patient wants to get pregnant, it is advisable to plan the pregnancy and to aim for a response as deep as possible, at least a major molecular response (MMR). Therapy should then be interrupted, with a preference for a 3-month washout before conception and for the duration of the pregnancy. Therapy should be resumed immediately after birth; however, if there is an unplanned pregnancy or if the patient is diagnosed while pregnant, the issue is more complicated. Although there have been some instances reported in which patients continued therapy throughout pregnancy with no problems for the baby, it is not recommend to use a tyrosine kinase inhibitor (TKI) at all during pregnancy.[2] In the current study, we report the outcomes of imatinib therapy in pregnant patients or their female partners—for male patients with CML—conceived while receiving imatinib for CML.

METHODS

In this retrospective analysis from a single center in India from January 1998 to December 2014, a total of 2,008 patients with CML were treated at our center. Of 2,008 patients, 5.1% met the inclusion criteria for this study. This study was permitted by our institution review board and written informed consent was obtained from all eligible patients. Data on age, sex,

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symptoms, signs, and laboratory parameters were extracted from the medical record department of our center and entered into Excel (Microsoft, Redmond, WA). From January 1998 to February 2002, patients were treated with non–TKI-based treatments, including hydroxyurea, interferon-alpha, and/or leukapheresis. After US Food and Drug Administration (FDA) approval of imatinib, most patients were treated with this TKI.

Inclusion Criteria

We included pregnant patients and male patients with female partners who conceived while taking imatinib who were diagnosed with Ph chromosome–positive CML (CP or AP or BC) by conventional cytogenetics, fluorescence in situ hybridization (FISH) for BCR-ABL or by reverse transcript quantitative polymerase chain reaction (RT-qPCR) for BCR-ABL.

Exclusion Criteria

No pregnant patients were excluded.

Assessment

At our tertiary care center, any patients with suspected CML underwent assessment, including CBC, renal function test, liver function test, lactate dehyrogenase, serum uric acid, serum electrolytes, abdominal sonography, bone marrow aspiration, and conventional cytogenetics. If marrow cytogenetic assessment failed, then FISH or RT-qPCR was performed from peripheral blood. Immunophenotyping was performed if blast crisis was present.

Treatment

All pregnant patients who were taking imatinib at the time of diagnosis during the first, second, or third trimester of the conception were counseled regarding teratogenicity, toxicity, and safety data of imatinib and advised to stop imatinib and undergo therapeutic abortion if possible and, if at near term, were advised to undergo preterm delivery after consulting with an expert gynecologist. If the patient wanted to continue the pregnancy at her own risk and was not willing to undergo leukapheresis and interferon-alpha therapy, she was allowed to take imatinib at a dose of 400 mg per day. All male patients with CML were allowed to take imatinib at a dose of 400 mg per day.

Leukapheresis is offered in all three trimesters and interferon alpha is advised in second and third trimester. Hydroxyurea 25 mg/kg was continued in pre–imatinib era.

Diagnostic Criteria for Different Phases of CML

Peripheral blood can be used to diagnose CML. Typical indications of CML are an elevated WBC count with left shift, frequently with basophilia, and an enlarged spleen. For proper workup, a bone marrow aspiration along with cytogenic analysis is mandatory, although FISH or polymerase chain reaction for BCR-ABL can be used to confirm the presence of BCR-ABL.

Response Evaluation

We used European LeukemiaNet guidelines to assess the response of imatinib and for additional monitoring of patients. Response was assessed with standardized RT-qPCR and/or cytogenetics at 3, 6, and 12 months. BCR-ABL1 transcript levels of 10% or less at 3 months, less than 1% at 6 months, and 0.1% or less from 12 months onward define optimal response, whereas levels of more than 10% at 6 months and more than 1% from 12 months onward define failure, requiring a deviation from current path of treatment. Similarly, partial cytogenetic response at 3 months and complete cytogenetic response (CCyR) from 6 months onward define optimal response, whereas no cytogenic response (Ph positive $>$ 95%) at 3 months, less than partial cytogenetic response at 6 months, and less than CCyR from 12 months onward define failure.

RESULTS

Clinical characteristics of patients at presentation are as follows: Median age at presentation for males was 36 years (range, 25 to 45 years) and for females was 27 years (range, 21 to 36 years); 55.7% of patients (n = 58) were male and 44.3% (n = 46) were female. We noted common initial clinical symptoms in patients, such as generalized weakness (67.3%), heaviness of the left hypochondriac region (65.3%), abdominal pain (62.5%), fever (54.8%), and bleeding (1%). The hematologic profile of the study population is as follows: Average hemoglobin was 8.4 g/dL (range, 6 to 14 g/dL), WBC per cubic millimeter was 32,000 (range, 4,500 to 120,000/cubic mm), and platelet count per cubic millimeter was 290,000 (range, 19,000 to 940,000/cubic mm). The disease profile at presentation was CML-CP in 79.8% (n = 83), CML-AP in 19.2% (n = 20), and CML-BC in 1% (n = 1) of patients. Distribution of pregnant female patients (n = 46) according to the trimester of the pregnancy are as follows: first trimester, 45% to 6% (n = 21); second trimester, 32.6% (n = 15); and third trimester, 21.7% (n = 10). Of 46 female patients, 21 patients underwent therapeutic abortion (Table 1).

Outcomes in Male Patients

Outcomes of full-term pregnancy in female partners of male patients with CML were uneventful and without any congenital malformations to infants.

Outcomes in Female Patients

Of 46 female patients, 25 had full-term pregnancy outcomes. During the pre–imatinib era, of six patients, three were treated with hydroxyurea, interferon alpha (n = 1), and/or therapeutic leukapheresis (n = 2), and all patients had normal full-term deliveries without any complications. Nineteen pregnant patients were receiving imatinib at the time of enrollment and were counseled regarding the safety of the drug and advised to discontinue. Even after proper counseling, 10 of 19 patients continued imatinib until the time of delivery. Of 10 patients, seven had normal full-term

TABLE 1. Landmark Studies of Imatinib in Pregnant Patients With CML

First Author	Year	No.	Conclusion
Ault et al[14]	2005	19 (female, n = 10; male, n = 8)	There is no evidence that a short exposure to imatinib during conception and pregnancy negatively affects the developing fetus
			Most patients lose their response after interruption of imatinib
			Patients receiving imatinib should take efficient contraception
Pye et al[32]	2008	180	Outcomes were accessible for 125 patients (69%), of which 50% delivered normal infants and 28% underwent optional terminations, three of which followed the identification of abnormalities, and 14% had a miscarriage
			There were a total of 12 infants in whom abnormalities were identified, three of which had strikingly comparable complex malformations that are obviously a cause for worry
			Although most pregnancies exposed to imatinib are likely to have a successful result, there remains a risk that exposure may result in grave fetal malformations
Nomura et al[33]	2011	9	Of nine patients, four were treated with imatinib when they became pregnant, with treatment being interrupted in the first trimester in three patients and in the second trimester in one
			During pregnancy, three patients (33.3%) required no chemotherapy after discontinuation of imatinib, and six (66.7%) were treated with interferon (n = 5) and/or hydroxyurea (n = 3).
			The mean gestational age at delivery was 37.6 weeks and the mean birth weight was 2,870 g in CML-associated pregnancies
Alizadeh et al[34]	2014	22 (female, n = 9; male, n = 5)	Despite exposure of either partner to imatinib, parents can most likely expect an uneventful outcome to a pregnancy
Zhou et al[22]	2013	25 (female, n = 18; male, n = 7)	All seven male patients had normal pregnancies
			In female patients, eight had elective abortion, three had spontaneous abortion, and seven passed to term, resulting in the birth of eight healthy babies
			The authors concluded that female patients should use contraceptives with no such requirements in male patients
Iqbal et al[35]	2014	90 (female, n = 21; male, n = 40)	Twenty-eight pregnancies occurred in female patients, whereas 62 were from male patients
			Among female patients, 19 (67.9%) pregnancies were uneventful, whereas six (21.4%) resulted in adverse events
			There is a need for better communication and counseling regarding contraception in female patients

Abbreviation: CML, chronic myeloid leukemia.

delivery, there was one preterm delivery, one with omphalocele, and another infant had craniosynostosis. Of those who discontinued imatinib (n = 9), eight patients had full-term normal delivery, of which two patients required leukapheresis. One patient expired from multiorgan failure as a result of septic shock during the perinatal period because of postpartum sepsis, which was determined to be unrelated to CML because her hematologic profile and RT-qPCR were normal except neutrophilia with left shift. All patients who continued imatinib even after counseling while pregnant were in CCyR and MMR prepregnancy, during pregnancy, and postpregnancy (Table 2).

Observation of Newborns

- Newborns of male patients with CML who are receiving imatinib: All newborns (age range, newborn to 11 years old), toddlers, and children were doing well with normal development of all milestones (gross motor, fine motor, language, cognitive, social skills, vision, and hearing).
- Newborns of female patients with CML in the pre–imatinib era: All six newborns (age range, 13 to 22 years old), toddlers, and children were doing well with normal development of all milestones.
- Newborns of female patients with CML in the post–imatinib era:
  - Newborns of female CML patients who discontinued imatinib after proper counseling: All nine newborns (age range, 4 to 8 years old), toddlers, and children were doing well with normal development of all milestones.
  - Newborns of female patients with CML who continued imatinib after proper counseling: All eight newborns

TABLE 2. Outcome of Pregnancy in All Patients

Treatment	No.	Response	Outcome of Pregnancy
Female partners of the male patients with CML on imatinib or hydroxy urea	58	Not applicable	All female partners of the patients with CML had normal full-term deliveries without any congenital malformations
Abortions:	21	Not applicable	Not applicable
Spontaneous	17		
Elective termination	4		
Full-term pregnancy:	25		
Pre–imatinib era:	6		
Patient required hydroxy urea (n = 3)/ interferon alpha (n = 1)/therapeutic leukapheresis (n = 2)		Records are not available for RT-PCR and FISH	All six patients had normal full-term delivery without any congenital malformations
Imatinib era:	19	All patients were in CCyR and MMR prepregnancy, during pregnancy, and postpregnancy	
Patients continued imatinib even after counseling	10	All patients were in CCyR and MMR before pregnancy	Seven normal full term delivery, 1 preterm delivery, and 2 congenital malformations (omphalocele, n = 1; craniosynostosis, n = 1)
Patients discontinued imatinib after counseling	9	Two patients lost MMR during the third trimester	Eight patients had full-term normal delivery, of which 2 patients required leukapheresis, and 1 patient expired during perinatal period because of sepsis

Abbreviations: CCyR, complete cytogenic response; CML, chronic myeloid leukemia; FISH, fluorescence in situ hybridization; MMR, major molecular response; RT-PCR, reverse-transcription polymerase chain reaction.

(age range, 4 to 8 years old), toddlers, and children were doing well with normal development of all milestones.

- Newborn with omphalocele: Primary surgical repair was performed on the second day of the neonatal period. The child had manageable feeding problems and was doing well. He is now 6 years old studying at the first standard.
- Newborn with craniosynostosis: The newborn was having scaphocephaly, and total cranial vault remodeling intervention was performed at the fifth month of infancy. The child is now 2.5 years old with normal milestone development to date.

Recommendations for Female Patients With CML Receiving Imatinib and Planning Pregnancy or Diagnosed With CML During Pregnancy

Figures 1 and 2 show suggested algorithms for the management of pregnancy in patients with CML who are on treatment with imatinib with unplanned pregnancy or diagnosis of CML in pregnancy (Fig 1), and who are on treatment with imatinib and planning an elective pregnancy or planned pregnancy (Fig 2). Generally, RT-qPCR increases if the patient is taken off treatment, but this increase does not necessitate the treatment to be intervened. When the patient is taken off treatment, the first measurement should be performed after 2 to 3 three months. However, the frequency of additional monitoring will be decided by the rate at which the full blood count of the patient increases initially and RT-qPCR. Another treatment approach that considers leukemic burden and pregnancy terms may be helpful for avoiding interventions in treatment in the case of favorable situations and takes into account the interests of both the child and mother when treatment initiation becomes necessary. For female patients with CML, this treatment approach can significantly increase the chances of having children. Even so, both the patient and physician should understand the possible risks. Managing CML at pregnancy with huge leukemic mass is still a complicated task; pregnancy with CML should be

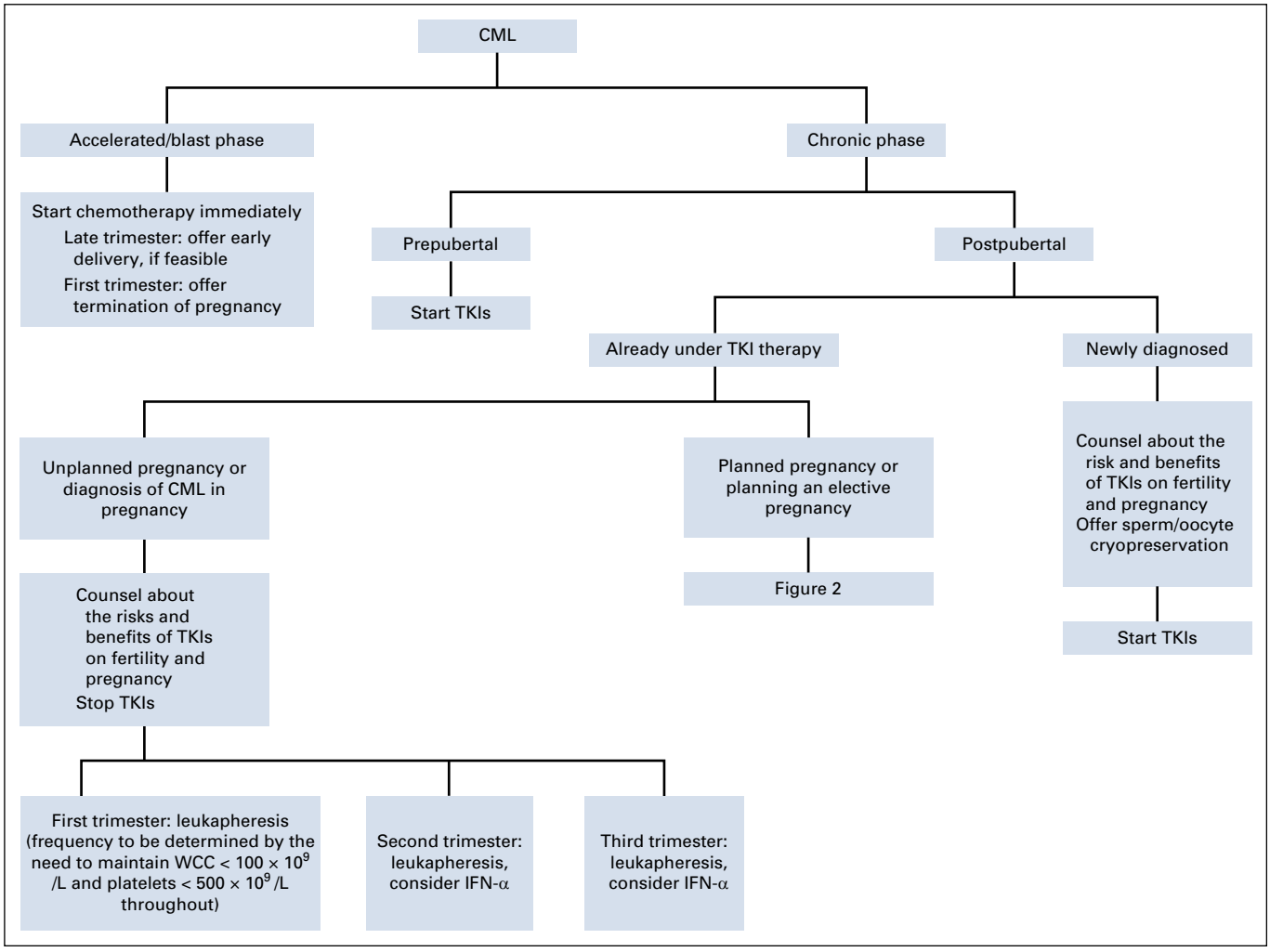

FIG 1. Suggested algorithm for management of pregnancy in patients with chronic myeloid leukemia (CML) who are on treatment with imatinib with unplanned pregnancy or diagnosis of CML in pregnancy. IFN-α, interferon alpha; TKI, tyrosine kinase inhibitor; WCC, white cell count.

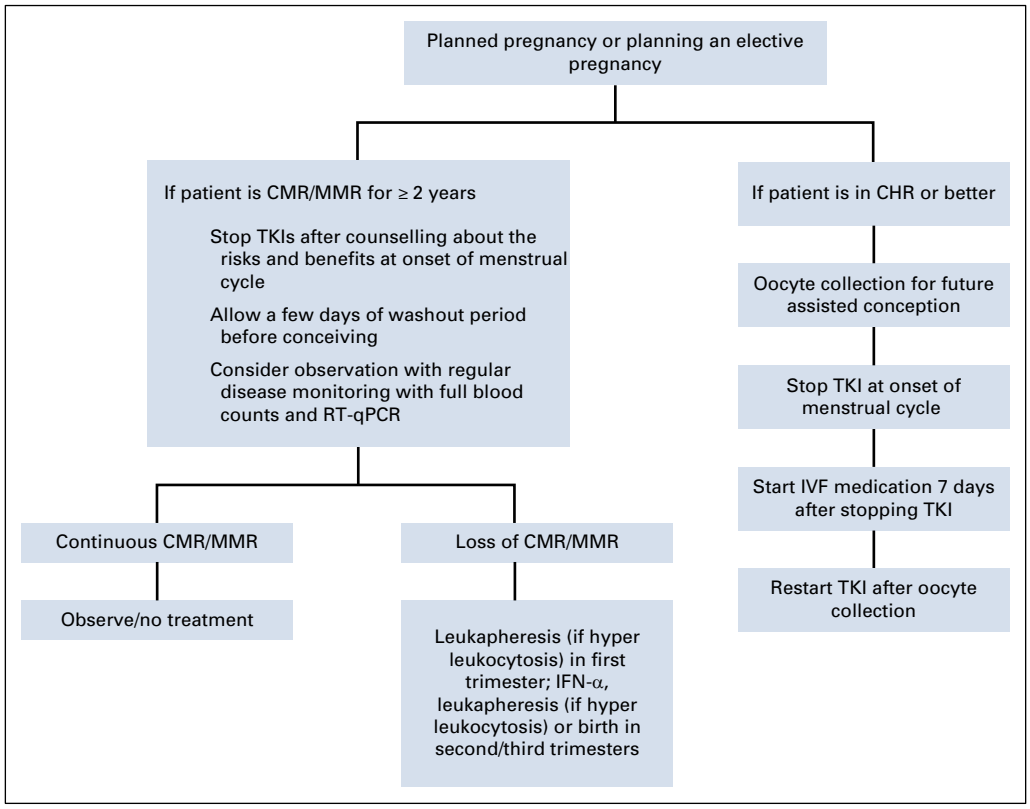

FIG 2. Suggested algorithm for management of pregnancy in patients with chronic myeloid leukemia (CML) who are on treatment with imatinib and planning an elective pregnancy or planned pregnancy. CHR, complete hematological response; CMR, complete molecular response; IFN-α, interferon alpha; IVF, in vitro fertilization; MMR, major molecular response; TKI, tyrosine kinase inhibitor.

thoroughly planned at deep remission. In patients with less than 15 weeks of gestation, TKIs should be stopped and patients should be observed without treatment. After 15 weeks of gestation, if BCR-ABL is less than 1% we can observe without any treatment, and if BCR-ABL is more than 1% we can restart therapy with imatinib, nilotinib, and no dasatinib.

DISCUSSION

The most common malignancies associated with pregnancy are cervical cancer, breast cancer, melanoma, lymphomas, and acute leukemia.[3] CML presents as approximately 10% cases of pregnancy-associated leukemia. CML in pregnancy is not associated with an increase in premature infants, low birth weight, or abortion rates, which were concerns previously. The disease course is akin to that in nonpregnant females.[4]

Management options for CML diagnosed in pregnancy are imatinib, hydroxyurea, interferon alfa, and leukapheresis.[5] During the pre–imatinib era, literature has revealed reasonably varied facts regarding hydroxyurea, but not enough to be endorsed by the FDA.[6] Hydroxyurea was used as a cytotoxic agent before the discovery of TKI and has been documented to cause fetal growth restriction, intrauterine death, and craniofacial and spinal defects.[7,8] Cytotoxic chemotherapy, such as busulphan, is significantly associated with fetal malformations.[9] Interferon alpha works slowly but the FDA has approved interferon alpha as category C during pregnancy. There are several case series that have demonstrated that leukapheresis may be considered a safe procedure in situations when protection of the fetus is preferred, mainly during hyperleukocytosis.[10,11] As compelling data do not exist at present, use of TKIs and other cytotoxic agents could not be suggested for regular use. Interferon alpha has a higher molecular weight—unable to cross the placenta—and does not inhibit DNA synthesis. Hence, it is considered safe in pregnancy.[7,12]

Imatinib has changed a mortal disease with a median survival of 6 to 7 years into a chronic condition for a large number of patients. Apart from inhibiting the BCR-ABL1 protein, TKIs also reduce stem-cell factor (c-kit), platelet-derived growth factor receptors, arg, c-fms, and src—especially by dasatinib—proteins, which are pertinent to implantation, fetal maturation, and gonadal development, at least revealed by animal studies.[5,13]

Imatinib in Men

There is no increased jeopardy of congenital malformations or increased abortion with usual and higher doses of

imatinib.[9,14-16] Previous studies have shown that imatinib can potentially hamper postnatal testicular development and sperm capacitation in animal studies.[13,17] Newer studies have shown that imatinib exposure leads to a significant decline in testosterone levels in adult patients with CML[18,19]; however, outcomes of pregnancy in more than 150 patients were uneventful, excluding the malrotation of the intestine and single stillbirth with malformations.[20] An imatinib-treated patient with hyper eosinophilic syndrome developed oligospermia.[21] No special safety measures are relevant for male patients receiving TKIs.[22]

Imatinib in Women

Imatinib use in pregnancy comes under category D according to FDA. Women should be well informed about the impending danger to the fetus if used during pregnancy or if the patient becomes pregnant while taking this drug. It is recommended that female patients follow adequate contraception. With imatinib, the majority of patients achieve deep, long-lasting responses, which is associated with normal life expectancy. Mammalian ovaries express c-kit, c-abl, and platelet-derived growth factor, which are inhibited by TKI, that are imperative in the growth and maturity of oocytes and follicles.[23-25] When CML is diagnosed in the first trimester, termination of pregnancy is considered harmless for the mother; however, TKIs are associated with fetal malformations if used in the second trimester. Platelet-derived growth factor A inhibition of imatinib resulted in teratogenicity in mice.[26]

Distinguishing congenital abnormalities have occurred after the administration of imatinib in early pregnancy. These include exomphalos, omphaloceles, pulmonary hypoplasia, duplex kidneys, renal agenesis, skeletal malformations (craniosynostosis, shoulder anomaly, and scoliosis), and spontaneous abortion.[22] The incidence of exomphalos is approximately 100-fold greater than predictable. Once pregnancy has been documented, if the patient is receiving imatinib it should be stopped. Close monitoring of fetal growth, especially a nuchal scan, should be performed for fetal anomalies. No trial has demonstrated cumulative toxicity of imatinib and fetal malformations.[3] Cole et al[27] studied the cases of 215 women who became pregnant while taking imatinib until 2009. Of 215 women, 171 sustained their pregnancy to term—62 of them had unknown outcomes, whereas 109 pregnancies had known outcomes: 33% (n = 36) had complications, such as spontaneous abortion (n = 24), stillbirth (n = 1), malformations (n = 9), and low birth weight (n = 2).[27] Imatinib does not have any effect on folliculogenesis or spermatogenesis.[28] Until now, the number of cases of pregnant women with CML reported in the literature is more than 200; however, with the exception of imatinib, there are no data available on the use of targeted agents nor various landmark studies of imatinib in pregnant patients with CML (Table 1).

Second-Generation TKI During Pregnancy[20,29] (Table 3)

Nilotinib for men: Little has been reported regarding conception during nilotinib treatment.[30]

Nilotinib for women: As for men, little has been reported for women who become pregnant while being treated with nilotinib. One patient at the 3-month ultrasound showed a large omphalocele, which resulted in the pregnancy interruption, and another patient's fetus was exposed to nilotinib for 5 weeks before stopping therapy and pregnancy was unremarkable, with the delivery of a healthy girl.

Dasatinib for men: Cortes et al[30a] studied the effects of dasatinib on pregnant partners of nine male patients who conceived children while receiving dasatinib. Of these patients, one mother experienced preeclampsia but eventually delivered a healthy baby at 37 weeks, free of any birth defects or neonatal complications.[30,31]

Dasatinib for women: To study the effect of dasatinib on pregnant women, 13 pregnant patients were observed. Of these patients, only one normal newborn was delivered; one patient gave birth to a premature newborn, four women had to undergo induced abortions, another two had spontaneous abortions, and five women were pregnant at last reported follow-up. In conclusion, temporarily discontinuing TKIs nilotinib and dasatinib, then observing or intervening with interferon alpha and/or leukapheresis, can be considered to be the safest and thus the best potential therapeutic options for the management of CML in pregnancy.[31]

Other TKIs: No conceptions/pregnancies have been reported while receiving ponatinib.

Breast Feeding

Imatinib and its active metabolite are excreted into human milk.

Future Perspectives

Some stopping imatinib studies (TWISTER [A phase II study to determine relapse-free interval after withdrawal of imatinib therapy in adult patients with chronic phase chronic myeloid leukaemia in stable complete molecular remission] and STIM [Stop Imatinib] trials) have demonstrated that even after discontinuing imatinib and attaining complete molecular response for 2 years, nearly 40% of patients maintain a deep response with undetectable BCR-ABL1 transcripts.[30,31] On the basis of existing data, female patients with CML who have a desire become pregnant should be advised to wait until persistent MMR is achieved for a minimum of 2 years with monitoring of CBC and RT-qPCR. For future assisted conception in patients who at least achieve complete hematologic response and who plan for future pregnancy, it is advised to collect oocytes. Start in vitro fertilization drugs 7 days after stopping TKI and resume TKI after the oocytes collection (Table 4).

Impact of Imatinib and Other 2G-TKIs on Pregnancy in Patients With CML

Physiologic changes, which also include changes in hematologic parameters accompanying pregnancy, may

TABLE 3. CML in Pregnancy Outcomes After 2G-Tyrosine Kinase Inhibitor Therapy

CML	First Trimester	Outcome
Dasatinib (n = 4)	n = 1[38]	Fetal hydrops and cytopenias
	n = 1 (5/40 weeks)[39]	Normal pregnancy, induction of labor
	n = 1 (4/40 weeks)[40]	Normal pregnancy, LSCS at 33 weeks
	n = 1 (6/40 weeks)[41]	Normal pregnancy, SVD at 37/40 weeks
Dasatinib[36] (n = 8)		TOP, n = 3; SA, n = 2 (8/40 and 9/40)
		Deliveries, n = 3; normal infant, n = 1 LSCS at 7 months, small for dates
		Normal pregnancy at 21 weeks
		Outcome unknown
Dasatinib[20] (n = 13 of 17)		n = 1 normal newborn
		n = 1 premature newborn
		n = 4 induced abortion
		n = 2 spontaneous abortion
Dasatinib[45] (n = 2)	5-8/38 weeks	Normal pregnancy and both delivered at 38 weeks
Dasatinib[48] (n = 46)		n = 15 healthy live births
		n = 5 abnormal infants
		n = 18 elective abortion
		n = 8 spontaneous abortion
		n = 7 fetal and infantile complications
Dasatinib in men[49] (n = 9)		n = 7 normal newborns
		n = 1 one mother experienced preeclampsia
		n = 2 Outcomes unknown
Nilotinib[37]	8/40 weeks	Normal pregnancy LSCS at 33 weeks
Nilotinib[43]	5-9/38 weeks	Normal pregnancy and delivered female twins at 38 weeks
Nilotinib[44]	11/37 weeks	Normal pregnancy LSCS at 37th week
Nilotinib[45]	7.4/38 weeks	Normal pregnancy, delivery at 38 weeks
Nilotinib[46]	9/10.2 weeks	Miscarriage at 10.2 weeks
Nilotinib[20] (n = 2; 1 patient twice conceived)	16/38 weeks	Normal baby by LSCS
	7.4/33 weeks	Normal baby by LSCS
	5 weeks	Big omphalocele, pregnancy interrupted
Nilotinib[20] (n = 1)	5/38 weeks	Healthy female baby
Nilotinib[20] (n = 45)		n = 1 fetal abnormality
		n = 1 twins, one baby died because of congenital transposition of great vessels, and another one with nonserious heart murmur
		n = 43 healthy babies
Nilotinib in men[20] (n = 1)		Healthy baby
Nilotinib in men[20] (n = 36)		n = 35 healthy babies
		n = 1 therapeutic abortion because of fetal abnormality
Bosutinib[47] (n = 33)		
Father exposure (n = 17)		n = 8 vaginal deliveries of healthy babies
		n = 1 LSCS healthy baby
		n = 4 induced abortion
		n = 1 spontaneous abortion
		n = 3 unknown outcomes

(Continued on following page)

TABLE 3. CML in Pregnancy Outcomes After 2G-Tyrosine Kinase Inhibitor Therapy (Continued)

CML	First Trimester	Outcome
Maternal exposure (n = 16)		n = 5 vaginal deliveries of healthy babies
		n = 1 partial molar pregnancy
		n = 1 baby delivered, data not known
		n = 2 induced abortion
		n = 1 spontaneous abortion
		n = 6 unknown outcomes

Abbreviations: CML, chronic myeloid leukemia; LSCS, lower-segment cesarean section; SA, spontaneous abortion; SVD, single vaginal delivery; TOP, termination of pregnancy.

complicate the diagnosis of CML during pregnancy as they may mask the symptoms.

As the prothrombotic proteins and hemostatic factors increase physiologically, and the venous blood flow is obstructed physically, the prothrombotic potential of a normal pregnancy is recognized. Hence, it is clear that thrombosis can be considered to be the most common cause of maternal morbidity. In the case of myeloproliferative diseases, this may be compounded where there is an associated increase in blood platelet count.[5,13]

All TKIs have similar class effects as they inhibit BCR-ABL1. TKIs also have a lot of off-target effects as a result of the inhibition of c-kit, platelet-derived growth factor receptors, arg, and c-fms. Furthermore, it should be noted that one of the 2G-TKIs, dasatinib, also inhibits src and related proteins, which are relevant to gonadal development, embryonic implantation, and fetal maturation.[5,13]

Less experience has been reported with 2G-TKIs[36-42] (Table 3; bosutinib, dasatinib, nilotinib, and ponatinib) in pregnancy. Dual BCR-ABL/src kinase inhibitor dasatinib crosses the placenta and results in considerable levels of fetal plasma. It has been reported that, in the first trimester, dasatinib causes fetal hydrops and severe fetal bicytopenia; however, there have been reports of some pregnancies as well.

In conclusion, the management of CML during pregnancy poses a therapeutic dilemma because of the potential teratogenic effect of therapy and requires the contemplation of both maternal and fetal life. Imatinib use during pregnancy is a double-edged sword, because discontinuation of the drug is associated with a loss of cytogenetic and molecular response, as well as consequences of the disease and, if

TABLE 4. Management of a Female Patient With CML Planning a Pregnancy[20]

Preconception	> 18-24 months stable > MMR
	Counseling with an ob/gyn to check on:
	Fertility
	Routine preconception tests
	Monitor ovulation
TKI interruption	Interruption of TKI can be done 7-10 days after ovulation (before implant)
	Absolutely no TKI therapy between 5 and 13 weeks or 31 and 71 days after the last menstrual cycle (organogenesis)
	If available, get in touch with the team that will follow the pregnancy-delivery (hematologist, ob/gyn, neonatologist)
Disease monitoring	Blood counts according to pregnancy follow-up
	Q-PCR every month if no 4.5 CMR*
	Q-PCR every 2 months if CMR
	In the case of loss response, always consider the risk to the mother and baby; consider treatment if loss of MMR/CCR
	Restart treatment if there is a loss of hematologic response
Post delivery	Breast feed the first 2-5 days to give the child colostrum; if in MMR/CCR consider continuing breast feeding depending on PCR results
	Restart treatment with the same TKI used before

Abbreviations: CCR, complete cytogenetic response; CML, chronic myeloid leukemia; CMR, complete molecular response; MMR, major molecular response; Q-PCR, quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor.

*4.5 CMR corresponds to a BCR-ABL transcript of ≤ 0.0032% copies.

continued, results in fetal jeopardy. Several treatment approaches have been used for CML with pregnancy, including hydroxyurea, leukapheresis, and interferon alpha. There are various adverse pregnancy outcomes with TKIs, such as spontaneous abortion, miscarriage, stillbirth, preterm delivery, and malformed child. The various malformations of TKIs are omphalocele, craniosynostosis, clinodactyly, short fifth fingers, slightly downward slanting palpebral fissures, renal and vertebral anomalies, as in our case (right renal agenesis and hemivertebrae), and low birth weight.

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Collection and assembly of data: Irappa Madabhavi, Nagaveni Kadakol
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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