Abstract. Discovery of tyrosine kinase inhibitors has led to improvement in survival of chronic myelogenous leukemia (CML) patients. Many young CML patients encounter pregnancy during their lifetime. Tyrosine kinase inhibitors inhibit several proteins that are known to have important functions in gonadal development, implantation and fetal development, thus increasing the risk of embryo toxicities. Studies have shown imatinib to be embryotoxic in animals with varying effects in fertility. Since pregnancy is rare in CML, there are no randomized controlled trials to address the optimal management of this condition. However, there are several case reports and case series on CML in pregnancy. At the present time, there is no consensus on how to manage different pregnancy situations in CML. In this article, we review current literature on CML in pregnancy, discuss the effects of several tyrosine kinase inhibitors on fertility and pregnancy and suggest an evidence-based treatment of CML in pregnancy.

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder characterized by the BCR-ABL oncogene, which results from a reciprocal t(9; 22) chromosomal translocation (1, 2). CML constitutes 15% of adult leukemia (3). Incidence rates vary from 0.6 to 2.0 cases per 100,000 persons, increase with age and are higher in men than in women (4). The median age at diagnosis is 64 years old (4); however, CML can affect any age group. In fact, approximately 17% of cases occur in the age group of 20-44 years (5). With the discovery of the pathogenetic BCR-ABL oncogene and the advent of tyrosine kinase inhibitors (TKI) in the treatment of CML, there has been a significant change in the natural course of the disease, changing the once fatal disease into a truly chronic condition (6, 7).

Leukemia in pregnancy is a rare condition, with an annual incidence of 1-2/100,000 pregnancies (8). Since the first administration of imatinib (the first of the TKIs) to patients with CML in June 1998, it is estimated that there have now been 250,000 patient years of exposure to the drug (mostly in patients with CML) (9). TKIs not only target BCR-ABL tyrosine kinase but also c-kit, platelet derived growth factors receptors α and β (PDGFR-α/β), ARG and c-FMS (10). Several of these proteins are known to have functions that may be important in gonadal development, implantation and fetal development (11-15). Despite this fact, there is still only limited information on the effects of imatinib on fertility and/or pregnancy. Young CML patients are likely to encounter pregnancy during their lifetime. We discuss the effects of several TKIs on fertility and pregnancy and suggest a treatment strategy for CML in pregnancy based on the latest literature.

Effects of Tyrosine Kinase Inhibitors on Fertility: Review of Animal Studies

Male fertility issues. Animal studies on the effects of imatinib on gonadal functions have yielded inconsistent reports. In a pre-clinical study, male rats were given imatinib at doses of 60 mg/kg/day and 20 mg/kg/day for 70 days prior to mating and female rats were also dosed similarly to male rats 14 days prior to mating and through to gestational day 6. Testicular and epididymal weights, as well as percent motile sperm were decreased at 60 mg/kg (approximately three-fourths the maximum clinical dose of 800 mg/day based on body surface area). There were no significant decreases in testicular and epididymal weights or sperm motility at doses ≤20 mg/kg (one-fourth the maximum human dose of 800 mg). The fertility of male and female rats was not affected at any dose (16).

In another study by Nurmi et al. (17), a three-day treatment of immature male rats with imatinib (150 mg/kg) on postnatal days 5-7 delayed the formation of the germ-line stem cell pool, reduced proliferation of type A spermatogonia and induced germ cell apoptosis. Similarly, there was a decrease in PDGFR-mediated proliferation of...
mesenchymal myoid precursors and reduction in the length of the seminiferous cord. However, at the age of 11 weeks, the exposed animals had normal epididymal sperm counts, whereas plasma levels of luteinizing hormone and follicle stimulating hormone were significantly higher. The Authors emphasized the need for further studies with primates and human models, as development of the human testis is controlled by the same mechanisms, and to explore whether imatinib affects the testsis in children as well. These findings were correlated with the study by Basciani et al. who observed a profound reduction of spermatogonia with intra-peritoneal imatinib administered to newborn mice at 50 mg/kg for 5 days. However, the counts returned to normal later as the mice aged (18). These investigators attributed the effects of imatinib to inhibition of PDGFR-ß, which is known to be required for proliferation and migration of gonocytes in the early postnatal period. Similarly, another study by Nurmio et al. (19) showed that imatinib significantly reduced the litter size sired by the treated animals and led to permanently slightly elevated serum levels of the gonadotropins in the treated animals. Testicular morphology and mRNA levels of ligands and receptors involved in stem cell factor/c-kit and PDGF signaling returned to control levels and the offspring were born healthy. Reassuringly, no differences were seen in the fertility index, live birth index, sex ratio or frequency of survival to the time of weaning. A report by Prasad et al. (20) found significant reduction in intratesticular testosterone level in imatinib-treated male albino mice groups. The effect was profound in week 4 and 5 post-treatment. The intratesticular level of lactate dehydrogenase (LDH) was increased significantly indicating extensive damage to germ cells. These changes were reversible upon discontinuation of the drug.

Fertility was not affected in the preclinical fertility and early embryonic development study although lower testes and epididymal weights, as well as a reduced number of motile sperm were observed in male rats treated with high doses of imatinib (16). In a preclinical per- and postnatal study in rats, fertility in the first generation offspring was not affected by imatinib (16). Contrary to the above reports, Junia Melo et al. found no difference in spermatogenesis between imatinib-treated and untreated adult mice when they were exposed to imatinib; 150 mg/kg/day continuously for 2 months (21).

Female’s fertility issues. Only limited data on the effects of TKIs on ovarian function is available. During the development of imatinib for clinical use, female rats were given imatinib 14 days before mating and through day 6 of gestation (16). Fertility was not affected. Rats treated with imatinib doses of 45 mg/kg or more experienced post-implantation loss, evidenced through early fetal resorption or stillbirths, nonviable pups and early pup mortality between postpartum days 0 and 4. When imatinib was administered during organogenesis at doses of 100 mg/kg or more, it induced teratogenic effects, including exencephaly or encephalocele, absent or reduced frontal bones and absent parietal bones. At doses higher than 100 mg/kg, fetal loss was noted in all animals. Fetal loss was not seen at doses of 30 mg/kg/day or less (approximately equivalent to 300 mg) (16).

In the first-generation offspring at this dose level, mean body weights were reduced from birth until terminal sacrifice. First-generation offspring fertility was not affected (16).

Like in the studies in male mice, Melo et al. found no difference in the numbers or morphology of ovarian follicles at any stages of development between the female mice treated with equal dose to male mice (150 mg/kg/day orally for 2 months) and control mice. In addition, there was no evidence of increased follicular atresia in the animals exposed to TKI, suggesting that there may be no effect on fertility (21).

Effects of Imatinib on Human Fertility

Men. Although animal studies have shown that imatinib can potentially inhibit postnatal testicular development and sperm capacitation (17, 22), there are few published reports on the effects of imatinib in human fertility. Most of them are in the form of case reports. There are two reported cases of impaired spermatogenesis potentially related to imatinib use (23, 24). In one report, an 18-year-old patient diagnosed with hypereosinophilic syndrome was started on imatinib at 400 mg per day for one month, then, owing to lack of response, escalated to 600 mg per day for five months and continued at 800 mg per day. A semen analysis performed after 14 months of imatinib therapy showed marked oligospermia (volume, 2.5 ml; sperm count, <1 million per milliliter, with 25 percent showing low motility and 75 percent complete immotility). The testosterone levels were normal (23). Similarly, semen analysis in an 18-year-old man showed severe oligozoospermia after long-term administration of imatinib started before puberty for CML. The inhibin-B/ follicle-stimulating hormone (FSH) ratio was reduced along with reduced bone mineral density for chronologic age (24).

A recent study by Ghalaut et al. revealed significant decrease in serum testosterone and significant increase in luteinizing hormone (LH) and FSH levels at 6 months of imatinib therapy in comparison to baseline levels in 34 newly diagnosed male BCR-ABL-positive CML patients. The findings documented that imatinib exposure caused a decrease in testosterone levels in adult CML patients much earlier compared to a previous report (25). A recent longitudinal study of men with CML also showed a significant, but largely transient, decrease in sex hormone-binding globulin (SHBG) levels in response to imatinib therapy. No marked therapy-
Figure 1. Management of CML in pregnancy. CML: Chronic myelogenous leukemia. TKI: Tyrosine kinase inhibitor. CMR: Complete molecular remission. MMR: Major molecular response. PCR: Polymerase chain reaction. IFN-α: Interferon alpha.
induced changes were observed for other reproductive hormones. There was no impairment in the androgen status from imatinib. In general, however, testosterone levels tended to be low in the patients under study both before and during imatinib therapy (26). However, there have been multiple reports of men on imatinib conceiving with no significantly higher risk for anomalies in the offspring (10). Martee L. Hensley and John M. Ford described 13 pregnancies in the partners of partners men who were taking imatinib at conception. Out of the 8 known outcomes, 3 ended in abortion (2 therapeutic but with normal fetus and 1 spontaneous), 1 in-utero death occurred at 13 weeks and 4 normal pregnancies resulted in 4 normal infants (27).

A later report from M.D. Anderson was more encouraging with 7 normal pregnancies and 1 spontaneous abortion in the partners of 8 men treated with imatinib for a median of 20 months. One infant was born with a malrotation of the gastrointestinal tract, which required surgical correction (28). After these initial publications, another 10 uneventful pregnancies were reported in the partners of 9 men on both standard and high doses of imatinib (29, 30).

Women. Imatinib and its active metabolite CGP74588 cross mature placenta poorly and are in low concentrations in umbilical cord (31).

The data on the impact of imatinib on fertility in female patients are limited to a few case reports. A recent publication described the occurrence of primary ovarian failure in a 30-year-old woman within 2 years of starting imatinib for CML (32) and another case report describes severely compromised response to gonadotropin stimulation while on imatinib, with a normal ovarian response after stopping the medication in a 17-year-old Asian woman desiring fertility preservation prior to using chemotherapy for CML (33).

There are several reports on pregnancy outcome in women who conceived while taking imatinib but ceased treatment either in the first trimester or remained on the drug throughout their pregnancy. Most publications report favorable outcomes (34-36). Ault and colleagues were the first to publish outcomes of 19 pregnancies in which either the male or female partner was undergoing treatment. Although 3 pregnancies ended with spontaneous abortions and 1 with an elective termination, 16 pregnancies were uneventful (28). A recent report from Zhou et al. (37) describes their experience in CML patients who conceived children and/or became pregnant while receiving a TKI.

Among 7 male patients, 7 pregnancies resulted in the birth of 7 healthy babies. Among 18 female patients, 8 pregnancies ended in elective abortion; 3 had spontaneous abortion and 7 carried to term, resulting in the birth of 8 healthy babies. All children had normal growth and development. The authors suggested special precautions for female patients with adequate contraception with no such suggestions for male patients. A recent study showed that six out of 28 pregnancies among female patients with CML on imatinib resulted in adverse events (38).

One of the most comprehensive data sets on the effect of imatinib on pregnancy was reported by Pye et al. (39). In this study, the effects of imatinib were evaluated in 180 women who were exposed to treatment during pregnancy; outcomes were available for 125 patients. In total, 50% delivered a healthy baby, 28% elected to have a termination, 3 of which followed the identification of abnormalities and 14% had a miscarriage. There were a total of 12 infants in whom abnormalities were identified, 3 of which had strikingly similar complex malformations, a cause for concern. Those with bony abnormalities are especially pertinent as similar bony defects, including exencephaly, encephalocele and deformities of the skull bones, were observed in the rodent studies. The expected incidence of exomphalos in the general population is approximately 1 in 3,000 to 4,000 births (40) and the finding of 3 infants out of 180 is higher than would be predicted. It is of note that the infants with exomphalos had a combination of very similar, quite complex defects that are likely imatinib-induced. Among the total 12 pregnancies with identified abnormalities, the dose but not the exact duration of imatinib taken by the mother was known for 10 of these cases. The data was, therefore, insufficient to assess any potential relationship between cumulative dosage and the occurrence of fetal abnormalities. No maternal exposure to alcohol, tobacco or drugs, including chemotherapeutic agents, was reported in any of these cases. This finding raises considerable safety concern for the use of imatinib in pregnancy.

A review of literature by Cole et al. identified a total of 215 women who became pregnant while taking imatinib. Of these, 171 continued their pregnancy to term. Sixty-two of these had unknown outcomes. Among the 109 pregnancies with the known outcome, 36 (33%) had complications, including spontaneous abortion in 24 patients, stillbirth in 1 patient, malformations in 9 patients and low birth weight in 2 patients (41). Although this study reports mostly the favorable outcome, the risk of teratogenicity of imatinib still cannot be discounted.

Effects of Imatinib Postpartum

Most of the available literature suggests that imatinib and its active metabolite are secreted in human milk to variable extent. However in female rats exposed to imatinib at a dose of 100 mg/kg, the concentrations of both imatinib and its active metabolites were 3-times higher in milk than in plasma. Estimates suggested that approximately 1.5% of a maternal dose would be excreted into milk (10). Imatinib levels have been measured in the milk of women taking imatinib postpartum. Of the 3 case reports, 2 had substantial excretion of imatinib into breast milk. One patient had active metabolite N-DesM-IM accumulation approximately
therapy, including therapy with imatinib, and suppress the resistance or intolerance to prior therapy, including imatinib. Dasatinib and nilotinib are FDA approved as first-line therapy for CML.

Role of Newer Tyrosine Kinase Inhibitors

Dasatinib and nilotinib are FDA approved as first-line therapy for CML.

Dasatinib, an oral multi-targeted kinase inhibitor of BCR-ABL and Src kinases, was initially approved for the treatment of adults with chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy, including imatinib. Dasatinib has been shown to overcome intolerance to prior therapy, including therapy with imatinib, and suppress the activity of imatinib resistant BCR-ABL mutants (46). The drug is structurally unrelated to imatinib and is able to bind and inhibit both the active and inactive conformations of ABL, resulting in 100- to 300-fold higher activity than imatinib (46, 47). Although dasatinib has an excellent efficacy profile, there has been very limited experience with this agent in women with CML who become pregnant while on therapy. To date, only a few recent studies of the use of dasatinib during early pregnancy have been reported (48, 49). Cortes et al. described the outcomes of pregnancies of 16 patients (8 females and 8 males) who received dasatinib therapy. Of the eight females who conceived while receiving dasatinib, three had therapeutic abortions (two due to patient decision, one for unknown reasons), two had spontaneous abortions (one at eight weeks in a 38-year-old patient (G1P1), one at nine weeks gestation in a 33-year-old (G3P3) and three delivered viable infants (one by normal vaginal delivery, one by cesarean and one unknown) (48).

Conchon et al. (50) described a case of an 18-year-old female who became pregnant while in hematologic remission on dasatinib therapy for CML. The pregnancy was discovered during the first trimester of gestation (after 4 weeks of amenorrhea). Dasatinib treatment was discontinued. The patient relapsed during pregnancy and was treated with interferon (IFN)-α without complete hematologic response. She delivered a healthy infant without any abnormalities detected through 8 months of age. This patient was exposed to the drug 8 weeks post conception, during the critical period of embryogenesis. Similarly Oweini et al. reported a case of 38-year-old male, whose partner conceived successfully while under dasatinib treatment for CML (51).

nilotinib. There is one published report on the outcome of pregnancies in women taking nilotinib for CML. Conchon et al. described two cases of pregnancy while on nilotinib, both in the same woman. The woman was exposed to nilotinib during the first trimester of both pregnancies, with no obstetric complications or structural anomalies in the neonates noted in either pregnancy. Both babies’ growth and development were reported normal (50).

Bosutinib. Bosutinib is a dual kinase inhibitor of ABL and Src kinase autophosphorylation. This mechanism results in the inhibition of abnormal cell growth and promotes apoptosis. Bosutinib also demonstrates significant cytogenetic and molecular remissions with minimal adverse effects (52).

Despite the availability of several alternative TKIs in the treatment of CML and multiple reports of their favorable outcomes in treatment of pregnant patients with CML, it would still be premature to rule out any adverse outcomes. The safety of these newer TKIs in pregnancy cannot be validated, simply due to insufficient studies.
Treatment of CML in pregnancy. Two distinct scenarios exist with CML and pregnancy. 1. Pregnancy antedates the diagnosis of CML or CML is an incidental finding during routine blood investigations done during the pregnancy. 2. The diagnosis of CML antedates pregnancy. This scenario would include planned or unplanned pregnancy in CML patient.

CML Diagnosed During Pregnancy

The disease diagnosis is occasionally an incidental finding during the routine blood investigations done during pregnancy (10). Literatures suggest the use of several different options in such scenarios, including TKI with varying pregnancy outcomes. However, there is no definitive consensus.

(a) Interferon-alpha (IFN-α). IFN-α was the non-transplant treatment of choice for most patients with CML before the advent of TKI (imatinib) (53). Due to its high molecular weight (19 kDa), IFN-α does not cross the placental barrier to a great extent (54). Treatment with IFN-α adequately controls the leukemic cell mass in the majority of newly diagnosed patients with CML. However, the degree of response ranges from no ‘hematologic’ response to complete suppression of the leukemic clone. The mechanism(s) by which IFN-α elicits these responses is unknown but in vitro studies have indicated that IFN-α might function by (i) selective toxicity against the leukemic clone, (ii) enhancement of ‘immune’ regulation and (iii) modulation of bone marrow micro-environmental regulation of hematopoiesis (55).

Animal studies (37) have revealed the non-teratogenic effects of IFN-α in rats and rabbits resulting in normal offspring but it has also been shown to have abortifacient effects in rhesus monkeys at higher doses (37). In view of this, the official recommendation is that IFN-α be avoided during pregnancy unless “the potential benefit justifies the potential risk to the fetus” (37).

A systematic review of fetal safety of IFN-α by Brojeni et al. (56) was able to locate only case reports of IFN-α exposure in pregnancy. IFN was given for several indications, the most common of which was essential thrombocytosis (ET). Among the 63 cases of IFN-α exposure in pregnancy, no cases of major malformations or stillbirths were reported. There was one case of spontaneous abortion and 13 preterm deliveries (20% of all exposed cases) suggesting that IFN-α does not significantly increase the risk of major malformation, miscarriage, stillbirth or preterm delivery above general population rates. Several case reports of pregnant patients with CML treated with interferon have been documented (57-63). None were associated with congenital malformation and all pregnancies resulted in healthy babies, as well as normal maternal outcome. Unfortunately, IFN therapy is associated with significant toxicities, mostly constitutional, neuropsychiatric, hematologic and hepatic effects. These toxicities have a major impact on the patient’s quality of life.

Four out of 5 different case reports of women with CML treated with hydroxyurea at conception reported delivery of normal infants. One patient developed eclampsia at 26 weeks gestation and a morphologically normal male infant was subsequently delivered stillborn (65, 68, 69, 71). Overall, the risk for teratogenicity does not seem as high as suggested by animal models. Hydroxyurea is known to be excreted in breast milk and, therefore, should not be given to lactating women (73).

(b) Hydroxyuria. Hydroxyuria is a cytotoxic drug that inhibits DNA synthesis by decreasing the production of deoxyribonucleotides by inhibition of the enzyme ribonucleotide reductase (53). It was commonly used in the treatment of CML prior to the introduction of imatinib-mesylate. Although up to 90 percent of CML patients treated with hydroxyurea may experience clinical and hematological remission, this treatment is not curative, does not prolong overall survival and only rarely results in attaining cytogenetic response (53). Several cases of hydroxyurea administration during pregnancy have been reported (65–72). Thauvin et al. described a single center experience of 31 patients and reviewed 19 published reports of women treated with hydroxyurea due to diverse hematological disorders (essential thrombocytosis, chronic myelogenous leukemia, sickle cell disease) during various terms of pregnancy (72). Of the total 50 cases, there were 2 cases of intra-uterine fetal death (IUFD), which occurred in patients treated with hydroxyurea during the 1st trimester, 3 had minor malformations (hip dysplasia, unilateral renal dilatation, pilonidal sinus) and 9 cases of premature delivery. Second and third trimester exposure to hydroxyurea was associated with an increased risk of pre-eclampsia. 4 out of 5 different case reports of women with CML treated with hydroxyurea at conception reported delivery of normal infants. One patient developed eclampsia at 26 weeks gestation and a morphologically normal male infant was subsequently delivered stillborn (65, 68, 71). Overall, the risk for teratogenicity does not seem as high as suggested by animal models. Hydroxyurea is known to be excreted in breast milk and, therefore, should not be given to lactating women (73).

(c) Leukapheresis. Several cases of successful use of leukapheresis in treatment of a pregnant patient with chronic myelogenous leukemia in chronic phase have been reported (74-80). Srobl et al. described a case of CML in a pregnant woman who was treated with leukapheresis procedure initiated during the 13th week of gestation and performed...
over approximately 7 weeks. The patient’s white blood cell count (WBC) dropped from 242,000/μl to 19,300/μl after 20 leukapheresis procedures. The WBC remained stable over the ensuing 17 weeks until the time of delivery. The patient gave birth by cesarean section to a healthy 2,640 g boy at 37.5 weeks of gestation (74). Similarly Broccia et al. (75) and Ali et al. (79) also reported the use of leukapheresis as the sole treatment for CML in pregnancy without any adverse effects on the patient and fetus.

Regular leukapheresis may avoid drug therapy and be particularly useful during the first trimester of pregnancy (75-79). Occasionally, the platelet count may not be adequately controlled using leukapheresis alone and aspirin or low molecular weight heparin (LMWH) may be required (10). The safety profile of these agents in pregnancy has been investigated at some length and has reassuring results (81). These findings suggest that where leukapheresis is available, it may provide an alternative treatment to chemotherapy, especially in light of the potential teratogenic and leukemogenic side-effects of chemotherapy. It may be a possible short-term alternative to chemotherapy for pregnant patients near the end of the 1st trimester.

(d) Busulphan. Busulphan is an alkylating agent that does not alter the natural course of the disease and is inferior to both hydroxyurea and IFN-α in terms of overall and progression-free survival. It is now rarely used in the management of CML in chronic phase and should certainly be avoided in pregnancy (82, 83).

(e) Stem cell transplantation. Allogeneic stem cell transplantation remains an important treatment option for patients with CML, particularly younger individuals who failed treatment with imatinib and have an HLA-identical donor. Given that there are no reports regarding stem cell transplantation in pregnancy and the aggressiveness of this treatment, it should be contra-indicated during pregnancy.

Pregnancy After Diagnosis and Treatment of CML

Unplanned pregnancy while on CML treatment (imatinib). Balancing the potential teratogenic risk to the fetus from TKI therapy (imatinib) against the risk to the mother, if she discontinues treatment, is difficult. One option is to continue imatinib and have the pregnancy closely monitored, with termination considered if significant abnormalities in the fetus are identified. Another option would be to discontinue imatinib and have the mother closely monitored for hematological and cytological relapse. While it is difficult to predict if the patient with CML would maintain a hematologic and cytogenetic remission after a variable period of discontinuing imatinib, several examples in the literature suggest favorable outcome (84).

The French STIM study (85) showed that imatinib can be safely discontinued in those patients who achieved complete molecular remission (CMR) (>5 log reduction in BCR-ABL levels and undetectable transcripts on quantitative PCR) for at least 2 years. In another study by Merante et al. (86), 2 out of 4 patients in CMR relapsed after discontinuation of imatinib. The 2 patients who had relapsed promptly responded after restarting therapy again. The other 2 patients remained in CMR even after 1 year of discontinuation of imatinib (86).

A study by Gog et al. showed that although imatinib cannot be discontinued completely, intermittent therapy can be considered for the treatment of patients with CML in particular situations (87). Their study involved 26 Philadelphia chromosome positive (Ph+) patients with CML. Imatinib was discontinued when they achieved complete cytogenetic response (CCyR) or CMR and they were retreated with imatinib in case of hematologic, cytogenetic or molecular relapse. Except for one patient who progressed and two patients who were in persistent molecular remission without imatinib resumption, all other patients regained their best response after imatinib resumption.

A study by Rousselot et al. (88) involved 12 CML patients with undetectable residual disease for more than 2 years. Prior to interrupting imatinib therapy, the median duration of real-time quantitative-polymerase chain reaction (RTQ-PCR) negativity was 32 months (range, 24-46 months) and the median duration of imatinib therapy was 45 months (range, 32-56 months) before imatinib interruption. Six patients displayed a molecular relapse with a detectable BCR-ABL transcript at 1, 1, 2, 3, 4 and 5 months. Imatinib was then reintroduced and led to a molecular response in most patients. The other six patients (50%) remained in CMR after a median follow-up of 18 months (range, 9-24 months) without resuming imatinib therapy (88).

It is essential to consider the parents’ wishes, mother’s disease status, current response to imatinib, availability of other alternative therapies and ability to re-induce responses to imatinib after a prolonged period without treatment before any decision regarding continuation or discontinuation of imatinib. It is crucial that the patient is educated about the potential risks, particularly regarding first trimester exposure of the use of imatinib and the risk of relapse if imatinib is discontinued.

Planned pregnancy. A. Patient not on Imatinib. It is important to discuss the issues of fertility and pregnancy before starting treatment with TKI with patients in fertile age groups. Patients may be offered the option of sperm or oocyte cryopreservation in light of the reported adverse outcomes in fertility and pregnancy in animals/humans studies.

B. Patient already on Imatinib. Management of pregnant CML patients on imatinib or other tyrosine kinase inhibitors depends upon the disease status, the response to
the imatinib therapy and the age of gestation. Due to the teratogenic effects of imatinib, it is reasonable to discontinue the drug before planned conception. However, the literature suggests that this is reasonable only for those women who have achieved optimal molecular responses. Based on the findings of the STEMI study, achievement of CMR for at least 2 years is a relatively safe time point for discontinuation of imatinib (89). Goldman reported that for patients in CCyR and major molecular response (MMR), it might be possible to stop imatinib for a period of time to allow them to conceive and carry the child without exposure to the drug (90). Although it is unlikely for patients in persistent MMR/CMR to require treatment, if molecular progression is observed, treatment must be reinstituted immediately. Regular monitoring for molecular relapse should be instigated. If the patient is not in durable CCyR/CMR, then cessation may lead to cytogenetic or hematologic relapse (87). Given that patients will not take imatinib for the duration of the pregnancy, physicians may consider suggesting that the period between stopping imatinib and becoming pregnant should not exceed 6 months (10).

However, some questions still remain unanswered, such as the wait time between discontinuation of the drug and conception. Some authors suggest it may be reasonable to consider a wash-out period of a few days before conception (85), with one author suggesting that this period should not last more than 7 days (10). Non-teratogenic treatments during pregnancy are not well-defined but leukapheresis (78), hydroxyurea or IFN-α (58) in the second or the third trimester could be a safe option (10).

Evidence-based Management of CML in Pregnancy

Based on the available literature, we propose the following treatment of CML in pregnancy. A patient with accelerated or blast phase CML should be started on chemotherapy immediately. If the patient is in late trimester, early delivery should be offered, if feasible, while termination should be considered during the first trimester. For a chronic phase CML, pre-pubertal patients should be counseled about the risks and benefits of TKIs, including effects in fertility, and started on TKIs. All newly diagnosed post-pubertal patients should be counseled about the effects of TKIs on fertility and pregnancy and also offered sperm/oocyte cryopreservation before starting on TKIs. If a patient is already under TKI therapy and is pregnant, patients should be counseled on the risks and benefits of stopping TKIs. TKIs can be stopped if the patient is in CMR for at least 2 years. If relapse occurs, leukapheresis can be considered until the end of the first trimester and leukapheresis/IFN-α or combination of both can be considered in the second and third trimester of pregnancy. For a woman who has been in CMR for at least 2 years, TKIs may be discontinued before planned conception. The patient should also be educated on the risks and benefits of stopping TKIs and a few days of washout period should be allowed before conceiving. The patient should be followed-up regularly with blood counts and real time PCR. If the patient continues to be in CMR/CCyR, she could be followed-up until after delivery and started on TKIs. If there is loss of CMR then leukapheresis in the first trimester and IFN-α, leukapheresis or both in the second and third trimesters can be considered (Figure 1).

Conclusion

With the development of imatinib and various other TKIs, today the concepts in the management of CML in pregnancy are evolving. While partners of most male CML patients on imatinib treatment can conceive normally with little or no adverse outcome in pregnancy, the same is not true for female patients. Therefore, the treatment for every female patient should be individualized based on the patient’s wishes, her molecular or hematological response to imatinib, duration of remission she has achieved and the availability of other alternative therapies. With counseling and a considered approach to disease monitoring, many women wishing to conceive can still become pregnant with minimal effects to fetus or their disease status.

References


Bhandari et al.: CML in Pregnancy (Review)


