

Review

Management of Chronic Myelogenous Leukemia in Pregnancy

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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).

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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 Nurmio *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 testis in children as well. These findings were correlated with the study by Basciani *et al.* who observed a profound reduction of spermatogonia with intraperitoneal 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- β , 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 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 pre- and postnatal study in rats, fertility in the first generation offspring was also 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-

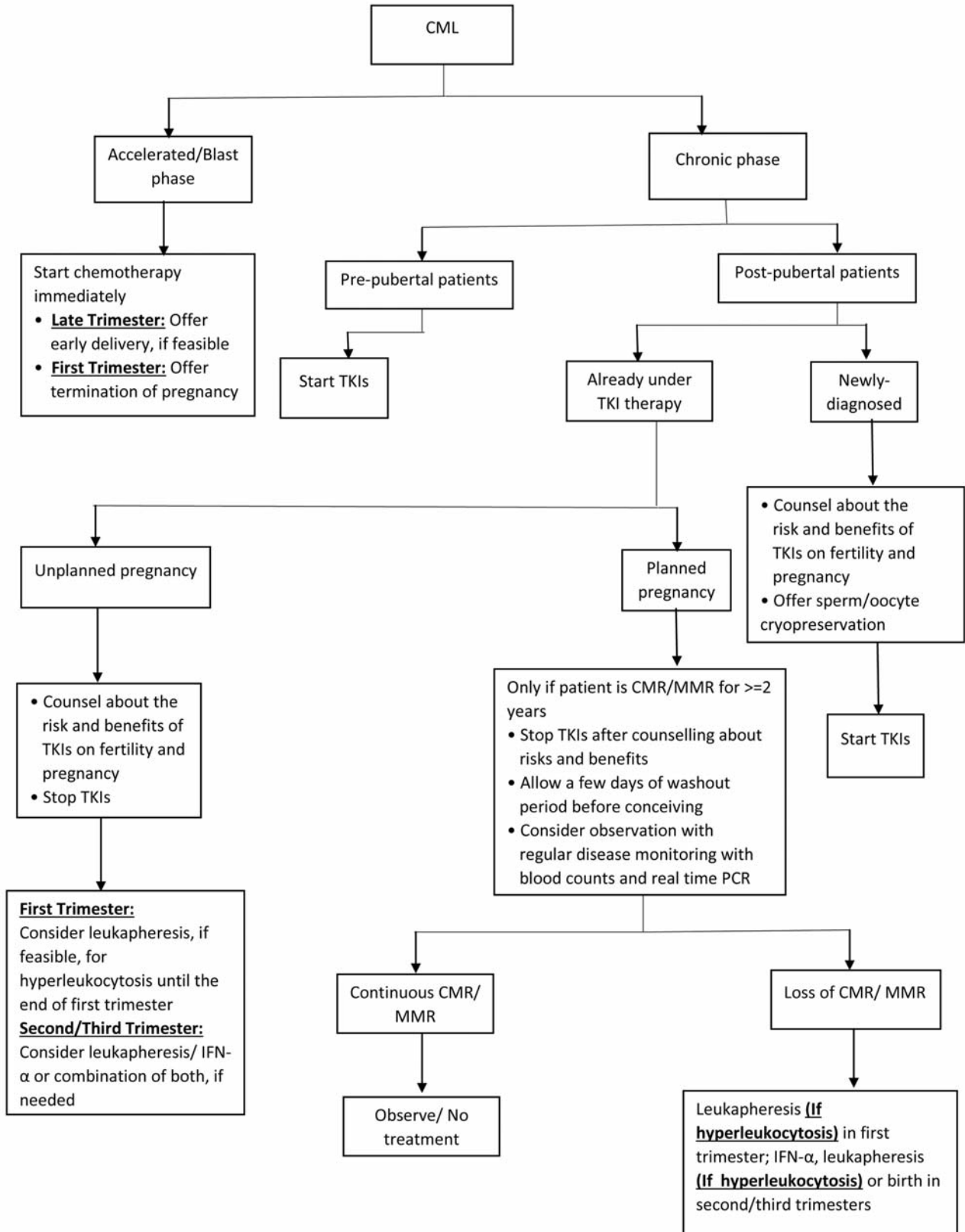


Figure 1. Management of CML in pregnancy. CML: Chronic myelogenous leukemia. TKI: Tyrosine kinase inhibitor. CMR: Complete molecular remission. MMR: Major molecular response. PCR: Polymerase chain reaction. IFN-α: Interferon alpha.

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

three times higher in breast milk compared with plasma levels (38, 42, 43). In another study, serum and milk levels of imatinib and its active metabolite (CGP 74588) were measured 4 weeks postpartum in a woman receiving oral imatinib 400 mg daily for CML. The levels of imatinib and CGP74588 were measured before the dose and several times during the 9 hour period after the dose. The highest concentrations of imatinib and its metabolite were at 2 and 4 hours after the dose with peak concentration ranging between 1.1 and 1.4 mg/l for imatinib and 0.8 mg/l for the metabolite. The concentrations of both were 25 to 50% lower 9 hours after the dose. Milk and serum levels of the two compounds were also measured during the second month of breastfeeding with similar results. Based on these data, the authors estimated that the maximum dosage of the drug and metabolite that an exclusively breastfed infant would receive is 0.3 mg/kg daily or 4.5% of the maternal weight-adjusted dosage (44).

Authors from another study estimated that an exclusively breastfed infant would receive between 1.2 and 2 mg of the drug and metabolite daily with 400 mg/day maternal dose (38). In another woman who was begun on imatinib 400 mg daily, immediately after delivery, 5 breast milk samples were obtained over a 7-day period after the first dose, on days 1, 2, 3 and 7 postpartum, approximately 3 hours after the daily doses. Imatinib milk levels were about half of maternal plasma levels and ranged from 151 to 1,153 µg/m. Milk levels of the metabolite, N-desmethylimatinib were about 3 times those in maternal plasma and ranged from 409 to 1,052 µg/l (43).

Effects of Imatinib in Breastfed Infants

In a woman receiving oral imatinib 400 mg daily for chronic myeloid leukemia who breastfed her infant, no adverse effects were noted in the infant during the first 2 months of nursing (44). In another woman with CML who received imatinib 400 mg daily throughout pregnancy and during breastfeeding (extent not stated) for nearly 6 months postpartum, no adverse outcome to infant was noted and her infant reportedly grew and developed normally (45). Because of the potential for serious adverse reactions in nursing infants and due to lack of sufficient studies, breast feeding should be discouraged for women taking imatinib.

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.

Due to the lack of evidence regarding any teratogenic effect of interferon, it is considered a safe drug to be administered throughout pregnancy. No data is available regarding the safety of IFN during breastfeeding and it is unknown if any component of the drug is excreted in breast milk. Careful attention to all aspects of patient care can result in improved tolerability of this difficult but promising therapy (64).

(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.

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).

(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/ μ l to 19,300/ μ l 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 reinstated 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

- 1 Sawyers CL: Chronic myeloid leukemia. *N Engl J Med* 340(17): 1330-1340, 1999.
- 2 Faderl S, Talpaz M, Estrov Z, O'Brien S, Kurzrock R and Kantarjian HM: The biology of chronic myeloid leukemia. *N Engl J Med* 341: 164-172, 1999.
- 3 Weisberg E, Manley P, Mestan J, Cowan-Jacob S, Ray A and Griffin JD: AMN107 (nilotinib): a novel and selective inhibitor of BCR-ABL. *Br J Cancer* 94(12): 1765-9, 2006.
- 4 Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ and Cronin KA: SEER Cancer Statistics Review, 1975-2010, National Cancer Institute, 2012 http://seer.cancer.gov/csr/1975_2010/
- 5 Kantarjian HM and Talpaz M: Definition of the accelerated phase of chronic myelogenous leukaemia. *J Clin Oncol* 6: 180-182, 1988.
- 6 Hasford J, Pfirrmann M and Hochhaus A: How long will chronic myeloid leukemia patients treated with imatinib mesylate live? *Leukemia* 19(4): 497-499, 2005.
- 7 O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen JL, Rousselot P, Reiffers J, Saglio G, Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Kantarjian H, Taylor K, Verhoef G, Bolton AE, Capdeville R, and Druker BJ. *N Engl J Med* 348(11): 994-1004, 2003.

- 8 Liesveld JL and Lichtman MA: Chapter 89. Acute myelogenous leukemia. In: Prechal JT, Kaushansky K, Lichtman MA, Kipps TJ and Seligsohn U, eds. Williams Hematology. 8th ed. New York: McGraw-Hill; 2010. <http://www.accessmedicine.com.proxy.healthwa.org/content.aspx?aID=6140629>. Accessed August 5, 2014.
- 9 Pye SM, Cortes J, Ault P, Hatfield A, Kantarjian H, Pilot R, Rosti G and Apperley JF: The effects of imatinib on pregnancy outcome. *Blood* *111*(12): 5505-5508, 2008.
- 10 Apperley J: Issues of imatinib and pregnancy outcome. *J Natl Compr Canc Netw* *7*(10): 1050-1058, 2009.
- 11 Soriano P: Abnormal kidney development and hematological disorders in PDGF beta-receptor mutant mice. *Genes Dev* *8*(16): 1888-1896, 1994.
- 12 Soriano P: The PDGF alpha receptor is required for neural crest cell development and for normal patterning of the somites. *Development* *124*(14): 2691-2700, 1997.
- 13 Hoch RV and Soriano P: Roles of PDGF in animal development. *Development* *130*(20): 4769-4784, 2003.
- 14 Tybulewicz VL, Crawford CE, Jackson PK, Bronson RT and Mulligan RC: Neonatal lethality and lymphopenia in mice with a homozygous disruption of the c-abl proto-oncogene. *Cell* *65*: 1153-1163, 1991.
- 15 Mauduit C, Hamamah S and Benahmed M: Stem cell factor/c-kit system in spermatogenesis. *Hum Reprod Update* *5*(5): 535-545, 1999.
- 16 http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf (Accessed in 08/05/2014)
- 17 Nurmio M, Toppari J, Zaman F, Andersson AM, Paranko J, Jahnukainen K and Söder O: Inhibition of tyrosine kinases PDGFR and C-Kit by imatinib mesylate interferes with postnatal testicular development in the rat. *Int J Androl* *30*(4): 366-376, 2007.
- 18 Basciani S, De Luca G, Dolci S, Brama M, Arizzi M, Mariani S, Rosano G, Spera G and Gnessi L: Platelet-derived growth factor receptor beta-subtype regulates proliferation and migration of gonocytes. *Endocrinology* *149*(12): 6226-6235, 2008.
- 19 Nurmio M, Kallio J, Toppari J and Jahnukainen K: Adult reproductive functions after early postnatal inhibition by imatinib of the two receptor tyrosine kinases, c-kit and PDGFR, in the rat testis. *Reprod Toxicol* *25*(4): 442-446, 2008.
- 20 Prasad AM, Ramnarayan K, Nalini K and Bairy KL: Effect of imatinib on the biochemical parameters of the reproductive function in male Swiss albino mice. *Indian J Pharmacol* *43*(4): 389-392, 2011.
- 21 Schultheis B, Nijmeijer BA, Yin H, Gosden RG and Melo JV: Imatinib mesylate at therapeutic doses has no impact on folliculogenesis or spermatogenesis in a leukaemic mouse model. *Leuk Res* *36*(3): 271-274, 2012.
- 22 Baker MA, Hetherington L, Curry B and Aitken RJ: Phosphorylation and consequent stimulation of the tyrosine kinase c-Abl by PKA in mouse spermatozoa; its implications during capacitation. *Dev Biol* *333*(1): 57-66, 2009.
- 23 Seshadri T, Seymour JF and McArthur GA: Oligospermia in a patient receiving imatinib therapy for the hypereosinophilic syndrome. *N Engl J Med* *351*(20): 2134-2135, 2004.
- 24 Mariani S, Basciani S, Fabbri A, Agati L, Ulisse S, Lubrano C, Spera G and Gnessi L: Severe oligozoospermia in a young man with chronic myeloid leukemia on long-term treatment with imatinib started before puberty. *Fertil Steril* *95*(3): 1120.e15-e17, 2011.
- 25 Ghalaut VS, Prakash G, Bansal P, Dahiya K, Dokwal S and Ghalaut PS, Bala M and Dhankhar R: Effect of imatinib on male reproductive hormones in BCR-ABL positive CML patients: A preliminary report. *J Oncol Pharm Pract*. 2013 doi: 10.1177/1078155213500686.
- 26 Bay K, Bjerrum OW, Olsson-Strömberg U, Porkka K, Dufva IH and Andersson AM: Reproductive hormone profiles during imatinib therapy in men with chronic myeloid leukemia. *Andrology* *2*(105): 2167-0250, 2013.
- 27 Hensley ML and Ford JM: Imatinib treatment: specific issues related to safety, fertility, and pregnancy. *Semin Hematol* *40*(2 Suppl 3): 21-25, 2003.
- 28 Ault P, Kantarjian H, O'Brien S, Faderl S, Beran M and Rios MB, Koller C, Giles F, Keating M, Talpaz M and Cortes G: Pregnancy among patients with chronic myeloid leukemia treated with imatinib. *J Clin Oncol* *24*(7): 1204-1208, 2006.
- 29 Ramasamy K, Hayden J, Lim Z, Mufti GJ and Ho AY: Successful pregnancies involving men with chronic myeloid leukaemia on imatinib therapy. *Br J Haematol* *137*(4): 374-375, 2007.
- 30 Breccia M, Cannella L, Montefusco E, Frustaci A, Pacilli M and Alimena G: Male patients with chronic myeloid leukemia treated with imatinib involved in healthy pregnancies: report of five cases. *Leuk Res* *32*(3): 519-520, 2008.
- 31 Russell MA, Carpenter MW, Akhtar MS, Lagattuta TF and Egorin MJ: Imatinib mesylate and metabolite concentrations in maternal blood, umbilical cord blood, placenta and breast milk. *J Perinatol* *27*(4): 241-243, 2007.
- 32 Christopoulos C, Dimakopoulou V and Rotas E: Primary ovarian insufficiency associated with imatinib therapy. *N Engl J Med* *358*(10): 1079-1080, 2008.
- 33 Zama AM, Mauro MJ, Druker BJ, Oktay k, Egorin MJ, Cedars MI and Rosen MP: Will imatinib compromise reproductive capacity? *Oncologist* *16*(10): 1422-1427, 2011.
- 34 Ali R, Ozkalemkaş F, Özçelik T, Ozkocaman V, Ozan U and Kimya Y, Köksal N, Gülten T, Yakut T and Tunalı A: Pregnancy under treatment of imatinib and successful labor in a patient with chronic myelogenous leukemia (CML): Outcome of discontinuation of imatinib therapy after achieving a molecular remission. *Leuk Res* *29*(8): 971-973, 2005.
- 35 AlKindi S, Dennison D and Pathare A: Imatinib in pregnancy. *Eur J Haematol* *74*(6): 535-537, 2005.
- 36 Heartin E, Walkinshaw S and Clark RE: Successful outcome of pregnancy in chronic myeloid leukemia treated with imatinib. *Leuk Lymphoma* *45*(6): 1307-1308, 2004.
- 37 Zhou L, You JH, Wu W, Li JM, Shen ZX and Wang AH: Pregnancies in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitor. *Leukemia research* *37*(10): 1216-1221, 2013.
- 38 Iabal J, Ali Z, Khan AU and Aziz Z: Pregnancy outcomes in patients with chronic myeloid leukemia treated with imatinib mesylate: short report from a developing country. *Leuk Lymphoma* 2014. doi:10.3109/10428194.2013.866662
- 39 Pye SM, Cortes J, Ault P, Hatfield A, Kantarjian H, Pilot R, Rosti G and Apperley JF: The effects of imatinib on pregnancy outcome. *Blood* *111*(12): 5505-5508, 2008.
- 40 Calzolari E, Bianchi F, Dolk H and Milan M: Omphalocele and gastroschisis in Europe: a survey of 3 million births 1980-1990. EUROCAT Working Group. *Am J Med Genet* *58*(2): 187-194, 1995.

- 41 Cole S, Kantarjian H, Ault P and Cortés JE: Successful completion of pregnancy in a patient with chronic myeloid leukemia without active intervention: a case report and review of the literature. *Clin Lymphoma Myeloma* 9(4): 324-327, 2009.
- 42 Ali R, Ozkalemkas F, Kimya Y, Koksall N, Ozkocaman V, Gulten T, Yorulmaz H and Tunali A: Imatinib use during pregnancy and breast feeding: a case report and review of the literature. *Arch Gynecol Obstet* 280(2): 169-175, 2009.
- 43 Kronenberger R, Schleyer E, Bornhauser M, Ehninger G, Gattermann N and Blum S: Imatinib in breast milk. *Ann Hematol* 88(12): 1265-1266, 2009.
- 44 Gambacorti-Passerini CB, Tomaghi L, Marangon E, Franceschino A, Pogliani EM, D'Incalci M and Zucchetti M: Imatinib concentrations in human milk. *Blood* 109(4): 1790, 2007.
- 45 Jiang Q, Jiang B, Chen SS, Jiang H, Qin YZ, Lai YY and Shi HX, Huang XJ: Pregnancy outcome among patients with chronic myelogenous leukemia treated with tyrosine kinase inhibitors. *Zhonghua Xue Ye Xue Za Zhi* 33(1): 6-9, 2012.
- 46 Shah NP, Tran C, Lee FY, Chen P, Norris D and Sawyers CL: Overriding imatinib resistance with a novel ABL kinase inhibitor. *Science* 305(5682): 399-401, 2004.
- 47 Tokarski JS, Newitt JA, Chang CY, Cheng JD, Wittekind M, Kiefer SE, Kish K, Lee FY, Borzillieri R, Lombardo LJ, Xie D, Zhang Y and Klei HE: The structure of dasatinib (BMS-354825) bound to activated ABL kinase domain elucidates its inhibitory activity against imatinib resistant ABL mutants. *Cancer Res* 66(11): 5790-5797, 2006.
- 48 Cortes J, O'Brien S, Ault P, Borthakur G, Jabbour E, Bradley-Garelik B, Debreczeni K, Yang D, Liu D and Kantarjian H: Pregnancy outcomes among patients with chronic myeloid leukemia treated with dasatinib. *Blood* 112: abstract 3230, 2008.
- 49 Conchon M, Sanabani SS, Serpa M, Novaes MM, Nardinelli L, Ferreira PB, Dorliac-Llacer PE and Bendit I: Al. Successful pregnancy and delivery in a patient with chronic myeloid leukemia while on dasatinib therapy. *Adv Hematol*, 2010 doi: 10.1155/2010/136252.
- 50 Conchon M, Sanabani SS, Bendit I, Santos FM, Serpa M and Dorliac-Llacer PE: Two successful pregnancies in a woman with chronic myeloid leukemia exposed to nilotinib during the first trimester of her second pregnancy: case study. *J Hematol Oncol* 2: 42, 2009.
- 51 Oweini H, Otrrock ZK, Mahfouz RA and Bazarbachi A: Successful pregnancy involving a man with chronic myeloid leukemia on dasatinib. *Arch Gynecol Obstet* 283(1): 133-134, 2011.
- 52 Quintas-Cardama A, Kantarjian H and Cortes J: Imatinib and beyond-exploring the full potential of targeted therapy for CML. *Nat Rev Clin Oncol* 6(9): 535-543, 2009.
- 53 Shapira T, Pereg D and Lishner M: How I treat acute and chronic leukemia in pregnancy? *Blood Rev* 22(5): 247-259, 2008.
- 54 Roth MS and Foon KA: Alpha interferon in the treatment of hematologic malignancies. *Am J Med* 81(5): 871-882, 1986.
- 55 Dowding C, Gordon M, Guo AP, Maison D, Osterholz J, Siczkowski M, and Goldman J: Potential mechanisms of action of interferon- α in CML. *Leuk Lymphoma* 11(Suppl 1): 185-191, 1993.
- 56 Brojeni PY, Matok I, Bournissen FG and Koren G: A systematic review of the fetal safety of interferon alpha. *Reprod Toxicol* 33(3): 265-268, 2012.
- 57 Mesquita MM, Pestana A and Mota A: Successful pregnancy occurring with interferon-alpha therapy in chronic myeloid leukemia. *Acta Obstet Gynecol Scand* 84(3): 300-301, 2005.
- 58 Mubarak AAS, Kakil IR, Awidi A, Al-Homsi U, Fawzi Z, Kelta M and Al-Hassan A: Normal outcome of pregnancy in chronic myeloid leukemia treated with interferon- α in 1st trimester: report of 3 cases and review of the literature. *Am J Hematol* 69(2): 115-118, 2002.
- 59 Regierer AC, Schulz CO, Kuehnhardt D, Flath B and Possinger K: Interferon alpha – therapy for chronic myeloid leukemia during pregnancy. *Am J Hematol* 81(2): 149-156, 2006.
- 60 Al Bahar S, Pandita R and Nath SV: Pregnancy in chronic myeloid leukemia patients treated with alpha interferon. *Int J Gynecol Obstet* 85(3): 281-282, 2004.
- 61 Kuroiwa M, Gondo H, Ashida K, Kamimura T, Miyamoto T, Niho Y, Tsukimori K, Nakano H and Ohga S: Interferon alpha therapy for chronic myeloid leukemia during pregnancy. *Am J Hematol* 59(1): 101-102, 1998.
- 62 Haggstrom J, Adrinsson M, Hybbinette T, Harnby E and Thornbert G: Two cases of CML treated with alpha- interferon during second and third trimester of pregnancy with analysis of the drug in the newborn immediately postpartum. *Eur J Haematol* 57(1): 101-102, 1996.
- 63 Hiratsuka M, Minakami H, Koshizuka S and Sato I: Administration of interferon- α during pregnancy: effects on fetus. *J Perinat Med* 28(5): 372-376, 2000.
- 64 Jonasch E and Haluska FG: Interferon in Oncological Practice: Review of Interferon Biology, Clinical Applications, and Toxicities. *The Oncologist* 6(1): 34-55, 2001.
- 65 Tertian G, Tchernia G, Papiernik E and Elefant E: Hydroxyurea and pregnancy. *Am J Obstet Gynecol* 166(6 Pt 1): 1868, 1992.
- 66 Fadila SAW, Ahmad-Zaliani H, Soon-Keng C and Norlaila M: Successful treatment of chronic myeloid leukemia during pregnancy with hydroxyurea. *Leukemia* 16(6): 1202-1203, 2002.
- 67 Celiloglu M, Altunyurt S and Undar B: Hydroxyurea treatment for CML during pregnancy. *Acta Obstet Gynecol Scand* 79(9): 803-804, 2000.
- 68 Jackson N, Shukri A and Ali K: Hydroxyurea treatment for CML during pregnancy. *Br J Haematol* 85(1): 203-204, 1993.
- 69 Delmer A, Rio B, Bauduer F, Ajehenbaum F, Marie JP and Zittoun R: Pregnancy during myelosuppressive treatment for CML. *Br J Haematol* 82(4): 783-784, 1992.
- 70 Baykal C, Zengin N, Coşkun F, Güler N and Ayhan A: Use of hydroxyurea and alpha-interferon in chronic myeloid leukemia during pregnancy: a case report. *Eur J Gynaecol Oncol* 21(1): 89-90, 2000.
- 71 Patel M, Dukes IAF and Hull JC: Use of hydroxyurea in CML during pregnancy: a case report. *Am J Obstet Gynecol* 165(3): 565-566, 1991.
- 72 Thauvin-Robinet C, Maingueneau C, Robert E, Elefant E, Guy H, Caillot D, Casasnovas RO, Douvier S and Nivelon-Chevallier A: Exposure to hydroxyurea during pregnancy: a case series. *Leukemia* 15(8): 1309-1311, 2001.
- 73 Sylvester RK, Lobell M, Teresi ME, Brundage D and Dubowy R: Excretion of hydroxyurea into milk. *Cancer* 60(9): 2177-2178, 1987.
- 74 Strobl FJ, Voelkerding KV and Smith EP: Management of chronic myeloid leukemia during pregnancy with leukapheresis. *J Clin Apheresis* 14(1): 42-44, 1999.
- 75 Broccia G, Casula P and Andria M: Chronic myelocytic leukemia in pregnancy: report of a case treated with leukapheresis. *Tumori* 70(4): 371-374, 1984.

- 76 Caplan SN, Coco FV and Berkman EM: Management of chronic myelocytic leukemia in pregnancy by cell pheresis. *Transfusion* 18(1): 120-124, 1978.
- 77 Fitzgerald D, Rowe JM and Heal J: Leukapheresis for control of chronic myelogenous leukemia during pregnancy. *Am J Hematol* 22(2): 213-218, 1986.
- 78 Bazarbashi MS, Smith MR, Karanes C, Zielinski I and Bishop CR: Successful management of Ph chromosome chronic myelogenous leukemia with leukapheresis during pregnancy. *Am J Hematol* 38(3): 235-237, 1991.
- 79 Ali R, Ozkalemkaş F, Ozkocaman V, Ozçelik T, Ozan U and Kimya Y and Tunali A: Successful pregnancy and delivery in a patient with chronic myelogenous leukemia (CML), and management of CML with leukapheresis during pregnancy: a case report and review of the literature. *Jpn J Clin Oncol* 34(4): 215-217, 2004.
- 80 Mehander Y and Medlin S. CML in pregnancy: a case report using leukapheresis and literature review. *Blood* 122(21): 5177, 2013.
- 81 Girling JC and de Swiet M: Thromboembolism in pregnancy: an overview. *Curr Opin Obstet Gynecol* 8(6): 458-463, 1996.
- 82 Doll DC, Ringenberg QS and Yarbrow JW: Antineoplastic agents and pregnancy. *Semin Oncol* 16(5): 337-346, 1989.
- 83 Rahman ME, Ishikawa H, Watanabe Y and Endo A: Carpal and tarsal bone development is highly sensitive to three antiproliferative teratogens in mice. *Reprod Toxicol* 10(6): 485-489, 1996.
- 84 Guastafierro S, Falcone U, Celentano M, Coppola M, Ferrara MG and Sica A: Is it possible to discontinue imatinib mesylate therapy in Chronic Myeloid Leukemia patients with undetectable BCR/ABL? A case report and a review of the literature. *Leuk Res* 33(8): 1079-1081, 2009.
- 85 Mahon FX, Réa D, Guilhot J, Guilhot F, Huguet F, Nicolini F, Legros L, Charbonnier A, Guerci A, Varet B, Etienne G, Reiffers J and Rousset P: Discontinuation of imatinib in patients with chronic myeloid leukemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre stop imatinib (STIM) trial. *The Lancet Oncol* 11(11): 1029-1035, 2010.
- 86 Merante S, Orlandi E, Bernasconi P, Calatroni S, Boni M and Lazzarino M: Outcome of four patients with chronic myeloid leukemia after imatinib mesylate discontinuation. *Haematologica* 90(7): 979-81, 2005.
- 87 Goh HG, Kim YJ, Kim DW, Kim HJ, Kim SH, Jang SE, Lee J, Kim D, Kim WS, Park SH and Kweon IY: Previous best responses can be re-achieved by resumption after imatinib discontinuation in patients with chronic myeloid leukemia: implication for intermittent imatinib therapy. *Leuk Lymphoma* 50(6): 944-51, 2009.
- 88 Rousset P, Huguet F, Rea D, Legros L, Cayuela JM, Maarek O, Blanchet O, Marit G, Gluckman E, Reiffers J, Gardembas M and Mahon FX: Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years. *Blood* 109(1): 58-60, 2007.
- 89 Pavlovsky C, Giere I and Van Thillo G: Planned pregnancy in a chronic myeloid leukemia patient in molecular remission: A Case Report. *Case Rep Hematol* 624590, 2012.
- 90 Goldman JM: Initial treatment for patients with CML. *Hematology Am Soc Hematol Educ Program*, 2009 doi:10.1182/asheducation-2009.1.453.

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