

Planned Pregnancy for a Patient with Chronic Myeloid Leukemia

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Abstract

Management of chronic myeloid leukemia (CML) during pregnancy can be difficult for patients, their families and care providers. Treatment of CML and pregnancy remains a clinical challenge. Current recommendations, for women of childbearing potential, are to use adequate contraception and avoid pregnancy while taking kinase inhibitors. Consequences of exposure to kinase inhibitors to a fetus during pregnancy are unknown. Treatment may result in an increased risk of serious fetal abnormalities or spontaneous abortion. Lack of treatment for CML, during a pregnancy, may result in disease progression. In the absence of detailed information, difficulty arises to guide this patient through a decision making process. Patients who wish to interrupt therapy and become pregnant should receive intense counseling for both parents, using the most recent data available. Decisions concerning patients with CML and pregnancies must be based on individual cases. This report describes a 25 year old woman with newly diagnosed CML who purposefully arranged harvesting and storage of her unfertilized ova, prior to commencing bosutinib chemotherapy for CML.

INTRODUCTION

Major discoveries in diagnosis and treatment of chronic myeloid leukemia (CML) were achieved in the 1990's when CML became the targeted therapy success in oncology. First generation tyrosine kinase inhibitor, imatinib, revolutionized the treatment of CML, and is now frontline therapy. Imatinib provides substantial cytogenetic and molecular remissions, with minimal normal hematopoiesis suppression or side effects.¹ Currently, a new therapy, bosutinib, is under clinical trial investigations for CML. 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.² Chronic myeloid leukemia may occur within any age group including women of child-bearing age. Leukemia occurs during the course of pregnancy in approximately 1 in 75,000 to 100,000 pregnancies. Among those pregnancies approximately 10% comprise CML.^{3,4} New targeted therapies are given as lifetime treatment, and pregnancies are increasingly becoming an issue in young women with CML. In view of the lack of sufficient information, it is recommended that patients practice contraception while receiving kinase inhibitors and that therapy is discontinued if the patient

becomes pregnant. Decision to continue or start a pregnancy requires careful counseling, consideration and discussion. Foremost important considerations are, a need to treat mothers as intensively as possible with anti-neoplastic agents, and to avoid harmful fetal exposure to teratogenic drugs.

Management of CML during pregnancy poses challenges to both hematologists and obstetricians. Currently, consensus is lacking in management of CML in pregnancy; therefore, clinical observations have become important. Most of these observations are derived from small case series or case reports. Reports not found in the literature, of patients with CML on bosutinib therapy with associated pregnancies; therefore, information from multiple case series of case reports of patients with CML receiving imatinib and associated pregnancies will be extrapolated for this report.

Hensley and Ford (2003), reported pregnancies on clinical trials with imatinib, detected at 5-22 weeks gestation.⁵ Results are: 9 elective therapeutic abortions, 1 spontaneous abortion and 2 normal infants. Additionally, 11 non-clinical trial pregnancies, on imatinib therapy, detected at 5-23 weeks of gestation were similar to the clinical trial results. A literature review by Cole, Kantarjian, Ault and Cortes' summarized many case series of women with CML who had

received imatinib treatment during pregnancy.⁶ In most cases the treatment was discontinued unless the women elected to have a therapeutic abortion. Many pregnancies were allowed to come to term, and most infants were healthy. Additionally, one report included a patient with CML who experienced a successful pregnancy to delivery of a healthy infant, without interventions, through observation only. Pye et al reported outcome data for 125 patients with a diagnosis of CML exposed to imatinib during pregnancy. Of those with known outcomes, 62 delivered normal infants, and 38 underwent elective terminations.⁷ Twelve infants had mild abnormalities, and 3 of those 12 had complex malformations which significantly is a cause for concern. It appears that although most pregnancies exposed to imatinib are likely to have successful outcomes, a risk remains, exposure may result in serious fetal malformation.^{5,6,7}

Historical evidence shows a median survival of patients with untreated CML is approximately 30 months, and does not evolve very rapidly at the clinical levels.⁸ Based on this knowledge, resistance or disease progression is unlikely to occur during the relatively short time of pregnancy. However, CML cells become resistant or disease progression, and patients may require anti-neoplastic therapy during pregnancy. Sparse reports of alternative approaches for blood count control include use of : 1) leukapheresis, 2) hydroxyurea, and 3) interferon. Lack of long term data of potential teratogenicity effects are of concern. Therefore, leukapheresis may be an intermittent short-term alternative option for pregnant patients, and prevents fetal exposure to teratogenic drugs. However, leukapheresis is cumbersome, costly, and a time consuming procedure, with risk of infection, thrombosis and hypotensive events that may affect the fetus and patient.⁹ Koh and Kanalingams' (2006) literature review included oral hydroxyurea and interferon for patient with CML and pregnancy.¹⁰ Hydroxyurea inhibits DNA synthesis and has a potential to cause abortion, intrauterine growth retardation, congenital malformations, and teratogenic consequences to the fetus. Additionally, evidence suggests that interferon crosses the barrier and increases the incidence of spontaneous abortion. Reports are sparse concerning adverse effects in pregnancy and developing fetus following treatment with interferon. Another option is dose interruption during pregnancy. Rousselot et al. (2007) investigated dose interrupting of kinase therapy, and reported no evidence of disease progress in about 60% of patients that stop therapy for a period of time. However, duration of this interruption is unclear, and implications of an interruption of therapy have not been fully

explored.¹¹

Given the rarity of CML in pregnancy, and the ethical concerns involved, prospective or randomized clinical trials are unlikely to surface. Pregnancy safeties of targeted drugs have not been established, and management of patients with CML during pregnancy continues to be a dilemma. Many questions remain unanswered such as: 1) Is there a viable option for women with a diagnosis of CML wishing to continue a natural birth life cycle? 2) Can targeted therapy be administered safely in second trimester pregnancy? and 3) Is careful monitoring of clinical course an option until a term pregnancy reaches delivery phase? In the absence of detailed information, difficult decisions have to be considered, to help guide patients through a safe decision making process. Thus, patients who wish to interrupt therapy to become pregnant should be advised of risks of relapse, and possible progression of disease. Decisions for pregnancies in patients with CML must be based on individual cases, and included careful counseling of both parents, using the most recent data available.

CASE REPORT

A 25 year old Caucasian female presented to primary care physician for abdominal pain. A complete blood test revealed leukocytosis, and subsequently underwent a bone marrow biopsy that confirmed a diagnosis of CML. Prior to beginning treatment for CML a purposefully arranged harvesting and storage of unfertilized ova was performed. Thereafter, preceded with enrollment in a trial comparing bosutinib to imatinib as front-line therapy for CML. Results were randomization to bosutinib, and continues therapy with bosutinib 500 mg daily for approximately 1 year. She is a recent college graduate, now relocated, who comes to this clinic for continuing therapy of her CML. The patient and her husband were extensively counseled, about natural history of the disease, and treatment options for CML were explained. The patient expresses a desire to plan a pregnancy in the near future. Scarcity of information about pregnancies with CML precluded advisement against therapy interruption at this time. However, future plans will include revisiting this decision after achieving a durable molecular remission for one or two years. Currently, the patient is in complete hematologic and molecular remission. Molecular studies show BCR-ABL to ABL transcript levels at 0.01 by quantitative real-time PCR analysis.

DISCUSSION

Cytogenetic and molecular alterations in transformed

leukemic stem cells provide initiating and development of clonal expansion. Molecular pathology of leukemia is an acquired chromosomal abnormality occurring in hematopoietic stem cells. Chronic myeloid leukemia is a myeloproliferative disorder caused by a chromosome abnormality reciprocal translocation. Chronic myeloid cells a chromosomal t (9:22) translocation, identified as Philadelphia chromosome (Ph). Protein product of this gene rearrangement, BCR-ABL, leads to an active proliferation of tyrosine kinase, which is implicated in pathogenesis. Additional, deregulation causes proliferation of CML cells.⁸

¹² Tyrosine kinase inhibitor blocks actions of BCR-ABL pathways, and affects additional signaling pathways. Kinase inhibitors are successfully used in malignancies in which these kinases are over expressed. Side effect, safety, and clinical response of imatinib are excellent for CML treatment. Imatinib inhibits inactive configuration of BCR-ABL protein by blocking adenosine triphosphate (ATP) binding site. This process inhibits cellular proliferation and produces a decrease in CML growth without inhibiting normal colony growth. Imatinib is the first targeted drug that inhibits abnormal tyrosine kinase protein, c-kit and platelet-derived growth factor receptor (PDGFR), and is used in treatment of CML. Kinase inhibitors, bosutinib, have similar properties of imatinib, and inhibits both BCR-ABL and Src kinase.¹³ Teratogenicity of any drug depends on timing of exposure affecting placental transfer. Occurrences of teratogenicity associated with chemotherapeutic agents observed in first trimesters are reported to be 10-20%. Evidence shows a critical period for teratogenicity is during first trimester. This is a period of active organogenesis that is usually completed by 13 weeks gestations. Preclinical safety results showed tyrosine kinase inhibitors are teratogenic in rats when administered during organogenesis, causing exencephaly and encephalocele, resulting in absent or reduced frontal and absent parietal bones.¹⁴

Imatinib is 95% bound to plasma proteins and has a molecular weight of 590. Drugs that are highly bound to plasma proteins or have molecular weights higher than 500 have limited placental transfer. In contrast, high concentrations of imatinib are detected in breast milk.¹⁵ Additional information of effects of first generation imatinib in placentas is sparse, with no reports in literature concerning effects of bosutinib on placentas of patients with CML and pregnancies. Therefore, imatinib information extrapolation is important for patients receiving third generation kinase inhibitor, bosutinib. Abellar et al (2009) describes placentas of a patient with CML who was exposed

to a kinase inhibitor.¹⁶ This investigations of the placentas included standard pathologic analysis, computer assisted morphometry, and fluorescence in situ hybridization (FISH) analysis. This patient was treated with a targeted tyrosine inhibitor during first trimester of a first pregnancy and during the third trimester of a second pregnancy. Major findings were: 1) the placenta of the first pregnancy displayed nonspecific histopathology findings of acute chorioamnionitis, vacuities funistis, and thrombus, and 2) the second placenta showed uneven villous maturation, villous hypermaturity and distal villous hypoplasia. Both placentas weights were appropriate for gestational age (AGA). Both pregnancies resulted in term delivery of healthy infants. Additionally, Russell et al (2007) analyzed the maternal blood, placenta, and umbilical cord blood and breast milk of two women with a diagnosis of CML during pregnancy. The umbilical cord blood and breast milk findings were: 1) low imatinib and metabolite concentration levels found in the umbilical blood suggest limited placental transfer in late pregnancy, and 2) high concentration levels of imatinib and metabolites were found in breast milk.¹³

Embryonic development is under complex control by the cytokine receptor, c-kit and PDGFRa (platelet derived growth factor receptor) as a major role in placental development and angiogenesis, suggesting that the congenital abnormalities result from inhibition of member of this extensive kinase family. Studies of mice with PDGFR mutations show birth defects including facial clefting, spina bifida, vertebral and rib fusion abnormalities, cardiac defects, omphalocele, renal, lung development, and urogenital anomalies.¹⁷ Both c-Kit and PDGFR are known target of imatinib, and the anti-angiogenic effect of imatinib is mediated by PDGFR that binds with high affinity. However, the human umbilical vein endothelial cells are not affected, as they do not express PDGFR. Salomon et al (2009) provided evidence to support the view that the vertically transmitted cancer transmission of CML to a fetus is improbable even if the mother's treatment during pregnancy is suboptimal.¹⁸ Prior to 10 weeks of gestation no maternal arterial connections with the intervillous space exist, and the embryo obtains nutrients by simple diffusion from blood pooled in the trophoblastic lacunae. The uterus and fetus placental circulations and active transport are established after the tenth week of gestation; therefore, more risk of cell transfer is at the beginning of a pregnancy.

Rousselot et al (2007) reported imatinib may be discontinued in patients who achieved a complete molecular

remission for a period of at least 2 years without evidence of disease progression. Evidence is lacking about numbers of tyrosine kinase free months prior to conception necessary to achieve a normal pregnancy and delivery.¹¹ Gambacorti-Passerini et al (2009) reported the imatinib concentration in breast milk reaches a steady-state level at 0.8 ug/ml. The milk intake in infants is known to average 728 to 777 ml/d, (range of 450 to 1165 ml/d); considering this milk intake and the infants are unlikely to receive more than 3 mg/d imatinib daily.¹⁹ This amount is far from therapeutic range, therefore, concluding that mothers with CML could safely breast-feed the infant. However, the effects of low-dose chronic exposure of infants to imatinib are not known, and have not undergone long-term investigation; therefore, breast feeding should not be recommended after resuming therapy.

CONCLUSION

Clinical questions in regard to risk to both fetus and patient remain unresolved. Future discussions need to include detailed description of possible risks to the patient and fetus to include: possible birth abnormalities, birth defect, deformities and/or termination of pregnancy. Discussions must also include a detailed plan if disease progression occurs, and treatments need to be initiated. Treatment options will include hydroxyurea, interferon and/or leukapheresis. Additionally, increased monitoring frequency of the BCR-ABL transcript level and hematological examination will be required to evaluate disease status. A successful pregnancy, delivery, birth and CML management requires a close cooperation between team members and patient.

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