



Caring for Two: Pregnancy and Chronic Myeloid Leukemia

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A 27-year-old Australian-born woman named Mrs. B presented to her general practitioner in December 2010 with a three-month history of excessive tiredness. She has a supportive husband, and they have four children aged four months to five years old. Mrs. B was breastfeeding her youngest child and had initially attributed her fatigue to her busy home life. A blood test revealed an elevated white blood cell count (WBC) of $43.7 \times 10^9/L$ (reference range: $4\text{--}11 \times 10^9/L$); hemoglobin and platelets were within normal range. Mrs. B was subsequently referred to a specialist hematology service.

Mrs. B had no significant past medical history. She denied a history of fevers, infections, night sweats, or unintentional weight loss. Her vital observations on examination were unremarkable. No palpable lymphadenopathy or hepatosplenomegaly were noted. A repeat complete blood count (CBC) and film assessment confirmed high WBC of $55.3 \times 10^9/L$ with a marked left shift in the myeloid series in addition to basophilia and eosinophilia, raising suspicion of chronic myeloid leukemia (CML). Mrs. B was told to wean her child from breastfeeding in preparation for treatment. A bone marrow biopsy confirmed a diagnosis of chronic phase CML with 100% cytogenetic evidence of the Philadelphia chromosome. She was prescribed imatinib 400 mg daily and was educated on the management of potential side effects and importance of adherence. During this time, Mrs. B discussed her desire to have more children. She was counseled about the potential teratogenic risk associated with treatment, the need to use adequate contraception, and the risk of blast phase transformation in poorly managed CML. Mrs. B was advised to attain at least a major molecular response (MMR) (BCR-

ABL transcript $\leq 0.1\%$) for two years before considering pregnancy.

Mrs. B attained hematologic remission (HR) with normalization of CBC within four weeks of starting imatinib. She initially experienced issues with fatigue and nausea. At three and six months after starting imatinib, Mrs. B was achieving an ideal molecular response with BCR-ABL transcripts of 2.9% and 0.12%, respectively.

In August 2011, Mrs. B admitted during clinic review that she had stopped imatinib therapy six weeks earlier with the goal of becoming pregnant. Her hematologist and nurse reiterated the potential loss of disease response with this course of action. Mrs. B demonstrated understanding of the potential risk but was undeterred. Two months later, Mrs. B was approximately four weeks pregnant. Her BCR-ABL transcript was rising (39%), and she had lost HR. She was started on aspirin 100 mg daily for anticoagulation prophylaxis, given the rise in her platelet count ($440 \times 10^9/L$) (reference range: $150\text{--}400 \times 10^9/L$), and was referred to a specialist obstetric service. At eight-weeks gestation, treatment with interferon- α (IFN- α) 3 million IU, three days per week, was started in response to rising WBC ($16.8 \times 10^9/L$). Mrs. B experienced the expected side effects of IFN- α , including fevers, myalgia, headache, and fatigue. By December, she regained HR and maintained this until early May 2012 when, at 37-weeks gestation, her WBC had risen to $20 \times 10^9/L$. Two weeks later, Mrs. B delivered a healthy baby girl weighing 3.3 kg.

Following the birth, Mrs. B was advised to resume imatinib; however, she elected to breastfeed and remained off treatment. By September 2012, her WBC was $80 \times 10^9/L$. Mrs. B weaned breastfeeding, resumed imatinib 400 mg daily, and HR was achieved within four

weeks. Despite attaining HR, Mrs. B was experiencing side effects to imatinib, which limited her adherence. A repeat bone marrow biopsy confirmed a minor cytogenetic response of 50%, and BCR-ABL transcripts of 11%. She was switched to second-line treatment with dasatinib 100 mg daily in December 2012 with the anticipation of better adherence and tolerance to therapy. Surprisingly, her BCR-ABL transcript rose to 22% in February 2013, raising questions of non-adherence, which Mrs. B denied.

One month later, Mrs. B contacted her specialist nurse and reported delayed menses. Blood work subsequently revealed an unexpected pregnancy with fetal exposure to dasatinib during the first two to four weeks of gestation. She was advised that limited information was available to inform on fetal risks. Mrs. B and her husband chose to continue the pregnancy, and her dasatinib was stopped. She was started on IFN- α three days per week once again. Reassuringly, fetal development appeared normal. Again, IFN- α was poorly tolerated and, at 17-weeks gestation, with a rising WBC, her IFN- α dose was increased to five days per week. This did not halt the rising of WBC ($52 \times 10^9/L$) and BCR-ABL transcript (110%). After careful deliberation, Mrs. B was advised to switch to imatinib therapy in the third trimester. This was significantly better tolerated than IFN- α . She again achieved HR and reduction in BCR-ABL transcripts by 32-weeks gestation. In October 2013, at 36-weeks gestation, a healthy 3 kg boy was born.

Again, Mrs. B declined her imatinib to breastfeed, against medical advice. Four weeks later, she remained in HR

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but had developed a right calf venous thrombus requiring anticoagulation treatment, which was contraindicated in breastfeeding women. Given this development, Mrs. B resumed imatinib therapy. Mrs. B also experienced postnatal depression, which negatively affected her adherence to imatinib and anticoagulation therapy. With psychological support and antidepressant medication, her emotional well-being improved. Three months later, Mrs. B was adhering to treatment, experiencing minimal side effects, and had almost attained a MMR. She has no intention of having additional children. Follow-up of both children reveals ongoing healthy development.

Background

CML is a rare malignancy with an incidence of 1–1.3 cases per 100,000 people and a median age at diagnosis in the sixth decade (Huang, Cortes, & Kantarjian, 2012; Milojkovic & Apperley, 2014). It occurs in the presence of the Philadelphia chromosome, a reciprocal translocation of the *ABL* gene on chromosome 9 and the *BCR* gene on chromosome 22 in the hematopoietic stem cell (National Comprehensive Cancer Network [NCCN], 2014). The translocation creates an active tyrosine kinase protein BCR-ABL that inhibits apoptosis, increases proliferation, and causes genomic instability (Baccarani et al., 2012; NCCN, 2014). CML occurs in three phases—chronic, accelerated, and blast phase—with most cases diagnosed in the chronic phase (NCCN, 2014). Untreated chronic phase CML progresses to the accelerated and blast phase within three to five years and has a poor prognosis (NCCN, 2014).

Tyrosine kinase inhibitor (TKI) therapy has transformed outcomes for people with CML; previously only allogeneic transplantation allowed for long-term survival (Baccarini et al., 2013; Sawyers, 1999). Imatinib was the prototype; second-generation TKIs dasatinib and nilotinib are now available for front-line treatment. Patients diagnosed with CML presently require long-term daily treatment with a TKI and regular monitoring to assess treatment responses (Baccarini et al., 2012; NCCN, 2014). Prior to TKI therapy, median survival was six years; the current survival rate is estimated at 85%–95% at five years with a genuine plateau trend (Baccarani et al., 2012;

Huang et al., 2012). Accordingly, survival improvements are resulting in a rising prevalence of CML (Baccarani et al., 2012).

With the excellent long-term outlook, survivorship issues, such as fertility and the ability to conceive a child are emerging (Pye et al., 2008; Zhou et al., 2013). While CML is generally diagnosed in an older population, patients may present during their childbearing years. The chronic nature of CML, coupled with the need for indefinite therapy to sustain a state of remission, creates a challenging and somewhat unique management issue for clinicians.

Pregnancy in Women With Chronic Myeloid Leukemia

Pregnancy in women with CML is a clinical dilemma, and each situation requires counseling, support, and an individualized approach to optimize outcomes for mother and infant. Literature regarding this issue is limited but growing as more clinicians gain experience with patient management and more treatment-related information becomes available.

Planned pregnancy: Mrs. B was initially advised to attain a deep remission with TKI therapy—at minimum a MMR—but, ideally, undetectable minimal residual disease (UMRD) for at least two years before discontinuing treatment and attempting conception. Experts agree with this recommendation in planned situations (Baccarani et al., 2013; Cortes & Kantarjian, 2012). Reassurance providing such advice comes from results of the STIM and TWISTER clinical trials, which prospectively explored the outcomes of people with CML who discontinued imatinib after having achieved UMRD for at least two years (Mahon et al., 2010; Ross et al., 2013). Both studies found that about 40% of people maintained UMRD for at least 12 months following imatinib cessation, and, encouragingly, all people who had lost UMRD were responsive to imatinib when retreated. Opinions differ regarding the length of time between cessation of TKI and attempting conception. Cortes and Kantarjian (2012) suggested a three-month washout before attempting conception, whereas Milojkovic and Apperley (2014) proposed discontinuing treatment just before ovulation to minimize time off treatment. Milojkovic and Apperley (2014) suggested limiting attempts to conceive to six months unless

close molecular monitoring continued to demonstrate low disease burden. In addition, they suggested using in vitro fertilization techniques in situations where rapid conception or embryo storage is preferred, particularly for women who may have a less deep or durable remission.

Unplanned pregnancy: The first trimester of pregnancy is a significant period of organogenesis and is also the time of greatest risk in fetal development (Ali et al., 2009). Although planning for pregnancy is ideal, several cases of conception occurring during TKI treatment have been reported. Most available literature on TKI exposure during pregnancy refers to imatinib. In preclinical studies, imatinib was found to be teratogenic in rats; consequently, effective contraception is advised (Hensley & Ford, 2003). Ault et al. (2006) were the first to report a case series of 10 women who had conceived while on imatinib, with average fetal exposure of four to nine weeks. Imatinib was discontinued in all women once pregnancy was confirmed. Two pregnancies resulted in miscarriage, another was electively aborted, and seven pregnancies were carried to term with eight births, including one set of twins. One baby had hypospadias; the remaining were healthy. They concluded that, while normal pregnancies can be achieved, most women lost disease control during pregnancy (Ault et al., 2006). Pye et al. (2008) published a comprehensive case series of 180 women with imatinib exposure during pregnancy, with known outcomes for 125 women; 63 healthy births and 18 miscarriages occurred, in addition to 32 elective abortions. Twelve pregnancies resulted in infants with varying congenital abnormalities, including bone malformations, hydrospadias, and three cases of exomphalos; eight were live births (one was premature and died following birth), one was stillbirth, and three were electively aborted. Ten of the 12 infants were exposed to imatinib in the first trimester, with information unavailable for the remaining two. The incidence of exomphalos was significantly higher than in the general population, making imatinib a probable causative factor. This report established that imatinib exposure increases the risk of serious congenital abnormalities, particularly during early pregnancy. Zhou et al. (2013) reported on a small series of eight women who conceived while on

imatinib, which resulted in one miscarriage, three elective abortions, and four healthy births.

Literature regarding fetal exposure to second-generation TKIs is limited. Dasatinib and nilotinib have caused embryo toxicities in animal models (NCCN, 2014). Twelve cases of dasatinib exposure at conception have been described. One pregnancy was ongoing and appeared to be progressing normally, whereas two miscarriages and three elective abortions took place (Cortes et al., 2008). Five healthy births were documented with dasatinib exposure at seven-weeks gestation (Bayraktar, Morency, & Escalon, 2010; Conchon et al., 2010; Cortes et al., 2008; Kroll, Ames, Pruett, & Fenske, 2010). Berveiller et al. (2012) reported a case of first trimester dasatinib exposure causing fetal hydrops and severe cytopenias, leading to a termination at 16-weeks gestation.

One published case of nilotinib exposure during the first trimester was identified, resulting in the birth of a healthy baby (Conchon et al., 2009).

Management of chronic myeloid leukemia during pregnancy: When caring for women with CML who are pregnant, nurses must focus on the mother, who requires optimal CML management, and ensure that fetal health is not compromised (Ault et al., 2006). In women with stable, low-molecular burden or UMRD, withholding treatment may be acceptable provided close monitoring takes place (Apperley, 2009; Cole, Kantarjian, Ault, & Cortes, 2009; Cortes & Kantarjian, 2012; Pavlovsky, Giere, & Thillo, 2012; Sora, Bajer, D'alo, Leone, & Sica, 2009).

The decision to commence treatment during pregnancy is done following careful deliberation of risks and benefits and parental counseling (Pye et

al., 2008). In Mrs. B's pregnancies, the decision to administer IFN- α was made because regaining disease control was imperative. IFN- α was an essential CML treatment prior to TKIs (Sawyers, 1999). IFN- α is demonstrated to be nonteratogenic in animal studies and, given its high molecular weight, should not cross the placenta (Milojkovic & Apperley, 2014). Numerous successful births are reported following IFN- α use during pregnancy in CML and other conditions (Apperley, 2009). In their review of fetal safety of IFN- α , Yazdani-Brojeni, Matok, Garcia Bourissen, and Koren (2012) found that no cases of major malformations or still births were seen in 63 pregnancies.

Mrs. B restarted imatinib during the third trimester of her second pregnancy. Despite previous intolerance, imatinib was selected because some researchers have reported imatinib use in second

Clinical Highlights

Chronic Myeloid Leukemia in Women of Childbearing Age

- Pregnancy in women with chronic myeloid leukemia (CML) requires an individualized approach, balancing risks and benefits to optimize outcomes for mother and infant.
- Planned pregnancy is preferred in patients with a CML diagnosis; experts recommend first achieving at least a major molecular response (MMR) but, ideally, undetectable minimal residual disease (UMRD) sustained for at least two years prior to discontinuing tyrosine kinase inhibitor (TKI) to attempt pregnancy (Baccarani et al., 2012; Milojkovic & Apperley, 2014).
- Imatinib exposure at the time of conception and during the first trimester has known risks of congenital abnormalities (Pye et al., 2008).
- Should CML-directed treatment be required during pregnancy, leukapheresis may be used during the first trimester to reduce very high white blood cell counts (Cortes & Kantarjian, 2012; Eskander, Tarsa, Herbst, & Kelly, 2011; Milojkovic & Apperley, 2014). A number of healthy births have been documented following interferon-alpha (IFN- α) use during pregnancy in CML and in other conditions (Yazdani-Brojeni, Matok, Garcia Bourissen, & Koren, 2012).
- Experts are divided regarding the use of imatinib later in pregnancy. The decision to use imatinib must be carefully considered following counseling with both the implications to the mother and fetus in mind.
- Breastfeeding is not recommended in women receiving treatment with imatinib or IFN- α as both medications are excreted in breast milk (Ali et al., 2009; Kronenberger et al., 2009; Milojkovic & Apperley, 2014; Russell et al., 2007).
- Evidence suggests that no increased risk of fetal abnormalities has been noted in children born to men taking imatinib (Apperley, 2009; Ault et al., 2006; Zhou et al., 2013).

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and third trimester resulting in successful gestational outcomes (Ali et al., 2009; Eskander, Tarsa, Herbst, & Kelly, 2011; Zhou et al., 2013). In addition, several cases have been reported of successful pregnancy where imatinib treatment has been continued throughout pregnancy, with evidence suggesting that imatinib poorly crosses the mature placenta (Pye et al., 2008; Russell, Carpenter, Akhtar, Lagattuta, & Egorin, 2007). Regardless, Cortes and Kantarjian (2012) do not recommend using TKIs for any circumstance during pregnancy. Eskander et al. (2011) cautioned that insufficient knowledge exists regarding potential late-developing toxicity following fetal exposure to imatinib; however, use “beyond the first trimester treatment should not be withheld if its use is medically necessary” (p. 1732).

Treatment with leukapheresis is safe for the developing fetus and may be beneficial in women requiring reduction of very high WBC, particularly during the first trimester (Cortes & Kantarjian, 2012; Eskander et al., 2011; Milojkovic & Apperley, 2014). Whereas Cortes and Kantarjian (2012) supported the intermittent use of the cytotoxic agent hydroxyurea in managing high WBCs, Milojkovic and Apperley (2014) suggested it be avoided.

Breastfeeding

Breastfeeding is not recommended in women taking imatinib because the drug is excreted in breast milk, and concerns exist regarding the consequences of chronic infant exposure (Ali et al., 2009; Kronenberger et al., 2009; Russell et al., 2007). Animal studies suggest similarly for second-generation TKIs (Apperley, 2009). Milojkovic and Apperley (2014) caution against breastfeeding in women taking IFN- α because of probable breast milk excretion. Formula feeding is recommended in this scenario. When women have remained off all treatment during pregnancy and continue to experience UMRD or low disease burden following birth, breastfeeding has been considered in the short term (Cole et al., 2009; Pavlovsky et al., 2012; Sora et al., 2009).

Fatherhood

Mounting evidence suggests that infants conceived by men managed on imatinib at conception have no increased

risk of developing fetal abnormalities (Apperley, 2009; Ault et al., 2006; Zhou et al., 2013). Limited cases of oligospermia following imatinib exposure have been described; therefore, some authors advocate for sperm cryopreservation prior to TKI initiation (Shash et al., 2011; Zhou et al., 2013). Information is available from nine cases regarding infant outcomes of men who conceived while taking dasatinib, and, although the data are limited, all have resulted in the birth of healthy babies (Cortes et al., 2008; Gentile et al., 2014; Oweini, Otrrock, Mahfouz, & Bazarbachi, 2011). One man was identified as taking nilotinib during conception and the resulting birth was a healthy outcome (Zhou et al., 2013).

Nursing Implications

A diagnosis of CML during a woman's reproductive years may significantly alter her family planning expectations. Initiating the conversation with patients early allows them to communicate their wishes and optimize management. Nurses have a role in providing current evidence-based information to facilitate informed decision making. For women contemplating pregnancy, sustaining a deep molecular response (MMR or UMRD) for at least two years prior to discontinuing treatment to attempt pregnancy is ideal. Nurses should educate patients about contraceptive precautions to minimize unplanned pregnancies while on treatment because of the teratogenic risks of TKIs, as well as potential risk of suboptimal therapeutic response for the mother. Referral to a specialty fertility clinic may be required in situations where rapid conception or embryo storage is recommended.

Nurses may act as a liaison point among hematologist, general practitioner, obstetrician, and midwife in providing multidisciplinary collaborative care to women with CML who are pregnant. For patients who discontinue treatment during pregnancy, nurses are in a position to assess and monitor for disease progression. If CML therapy is recommended during pregnancy, nurses must ensure that women and their partners fully understand the potential risks and benefits of treatment. Experience using imatinib in the second and third trimester is limited. IFN- α and imatinib may cause unpleasant side effects in addition to similar pregnancy-related symptoms. Toxicity management and

careful monitoring will contribute to optimal outcomes for both mother and fetus.

The nurse in this case developed a trusting, nonjudgmental relationship with Mrs. B, as continued engagement with the hematology service was imperative. This relationship proved to be beneficial when Mrs. B developed symptoms of postpartum depression, which she had never previously experienced. The rapid recognition of these symptoms allowed for prompt assessment and initiation of psychological supports, further enhancing Mrs. B's outcome.

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