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Case Report
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Successful Management of Twin Pregnancy via *In Vitro* Fertilization in a Patient with Chronic Myeloid Leukemia

AlSaffar WA[1], Abdulbaqi M[2], Jatham A[2] and Al-Anazi KA[2]*

[1]*King Abdulaziz University, Saudi Arabia*

[2]*Department of Hematology and Hematopoietic Stem Cell Transplantation, King Fahad Specialist Hospital, Saudi Arabia*

Abstract

The diagnosis of leukemia during pregnancy is a rather uncommon event. Also, the diagnosis of chronic myeloid leukemia (CML) in females during the child bearing age is rare. In certain parts of the world, CML may be diagnosed at a much younger age than in the western countries. After the introduction of tyrosine kinase inhibitors (TKIs), patients with CML are enjoying long-term survival with an excellent quality of life comparable to that of healthy individuals, so younger female patients can become pregnant while receiving their CML treatment.

We report a young female patient with CML and primary infertility who underwent *in vitro* fertilization (IVF) that lead to twin pregnancy. The patient received successful management for her pregnancy then optimal control of her CML at King Fahad Specialist Hospital (KFSH) in Dammam, Saudi Arabia.

Keywords: Chronic myeloid leukemia; Pregnancy; Tyrosine kinase inhibitors; Interferon; *In-vitro*-fertilization

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Correspondence:
Khalid Ahmed Al-Anazi, Department of Hematology and Hematopoietic Stem Cell Transplantation, Oncology Center, King Fahad Specialist Hospital, P.O. Box: 15215, Dammam 31444, Saudi Arabia, Tel: 966 - 03- 8431111; Fax: 966 -13- 8427420;
E-mail: kaa_alanazi@yahoo.com

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Introduction

CML is a clonal myeloproliferative disease characterized by neoplastic proliferation of pluripotent myeloid stem cells and the Philadelphia chromosome which arises from the reciprocal chromosomal translocation t 9,22 (q34,q11) [1-4]. CML is the third most common type of leukemia as it represents 15-20% of all adult leukemias [4,5]. The disease course consists of three phases: a chronic phase, an accelerated phase and a blast cell crisis [5].

The advent of TKIs has revolutionized the management of patients with CML to the extent that the vast majority of patients can enjoy long-lasting clinical, hematological remissions and a substantial proportion of them achieve molecular remissions of their previously fatal disease [6,7]. However, hematopoietic stem cell transplantation (HSCT) remains the only known curative therapeutic option [5,6].

Case Presentation

A 24 year old Saudi lady was diagnosed to have CML at KFSH in Dammam on 03/05/2011. At presentation, she was found to have splenomegaly of 2 centimeters below costal margin, but she had no palpable liver or external lymphadenopathy. Her complete blood count (CBC) showed white blood count (WBC): 117.2×10^9/liter (L), hemoglobin (Hb): 12.7 gram/ deciliter (g/dL), platelets (PLT): 172×10^9 /L. Differential cell count showed 84.3% neutrophils. Peripheral blood film (PBF) revealed neutrophilia with band forms, myelocytes and metamyelocytes but no blast cells. Bone marrow (BM) aspirate showed a dry tap, while trephine biopsy showed a hypercellular marrow consistent with chronic myeloproliferative neoplasm without significant fibrosis and less than 1% blast cells. Cytogenetic analysis revealed the presence of Philadelphia chromosome and molecular testing for BCR-ABL, p210 transcript by real time quantitative polymerase chain reaction (RQ-PCR) was 71% on the international scale (IS) (Table 1). Ultrasound of abdomen and pelvis showed mild hepatosplenomegaly with features of fatty liver infiltration, but no evidence of internal lymphadenopathy. Prior to the diagnosis of her CML, she was married for 5 years, but without offspring as she had primary infertility. After confirming the diagnosis of CML, the patient received cytoreductive therapy with hydroxyurea then she was commenced on imatinib 400 mg per day. Thereafter, the patient had regular follow up at the outpatient clinic and her disease was showing good response to imatinib as reflected by her clinical and laboratory profiles. For her infertility,

Table 1: BCR-ABL values during the course of the illness.

Date	BCR-ABL p210 on international scale
May 2011	71 %
February 2012	7 %
June 2012	60 %
August 2012	100 %
April 2013	42.6 %
July 2013	5.2 %
June 2014	0.39 %
June 2015	0.089 %
February 2016	0.023 %
August 2016	0.003 %

the patient was having follow up at a private institution and she was undergoing ovarian stimulation. One year after the diagnosis of her CML, she underwent *in vitro* fertilization (IVF) at the private institution. After confirming pregnancy at KFSH in Dammam, imatinib treatment was discontinued and the patient was commenced on pegylated recombinant interferon alpha therapy. The initial dose of interferon was 60 microgram (mcg) per day subcutaneously and it was doubled two weeks later, but due to encountering side effects, the original dose was resumed. After finishing 3 months of interferon therapy and entering the second trimester of her pregnancy, the patient was shifted back to imatinib on 28/08/2012. Meanwhile, there was an increase in BCR-ABL transcript to 100% on the IS, so a new BM biopsy was taken and it showed evidence of continued first chronic phase (Figure 1). In December 2012 and during week 32 of gestation, the patient underwent lower segment Cesarean section (LSCS) and the delivered male babies were 267 and 276 grams in weight so they were kept in the neonatology unit for 4 weeks before their discharge. The mother was advised not to breast feed her newly born babies whilst receiving imatinib therapy.

Despite the continuation of imatinib therapy after delivery, the BCR-ABL transcript started to rise again from 42.6% to 60%. Clinically, there was no hepatosplenomegaly or external palpable lymphadenopathy. The blood indices remained normal and PBF did not show any blast cells. A new BM biopsy was performed and it showed that the disease was still in chronic phase. After encountering imatinib failure that was most likely caused by treatment interruptions, it was decided to shift the patient to dasatinib at 100mg/day in August 2012. Thereafter, the patient continued to have her regular follow up and she remained clinically stable. Her blood counts remained within normal limits and the BCR-ABL decreased to 42.6% in April 2013 and 5.2% in July 2013 (Table 1).

In June 2014, despite the further decrease in the BCR-ABL transcript to 0.39% on the IS, the patient became intolerant to dasatinib so she was shifted to nilotinib 400 mg twice daily. Thereafter, the patient was continued on nilotinib and she remained stable from clinically and laboratory points of view and her BCR-ABL continued to decrease further as shown in Table 1. The patient was last seen at the outpatient clinic on 04/08/2016. She was totally asymptomatic and her physical examination showed no abnormality. Her CBC showed WBC of 7.82×10^9/L, Hb of 11.8 g/dL and PLTs of 215×10^9/L with neutrophils of 4.7×10^9/L. She was continued on nilotinib and she was given new follow up appointment in 3 months.

Discussion

For adult patients who present with CML in chronic phase, the initial therapy should be in the form of TKIs, such as imatinib, which have recently become the treatment of choice for CML [6,8]. The best method of monitoring the response of patients with CML to TKI therapy is by performing RQ-PCR for the BCR-ABL transcript at three monthly intervals [8]. In case failure of imatinib therapy is encountered, initiation of treatment with second generation TKIs such as dasatinib and nilotinib is usually recommended [8].

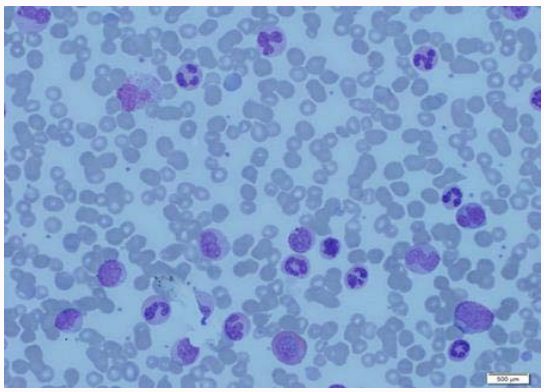

Figure 1: Bone marrow aspiration 15 months after the diagnosis of CML. It shows granulocytes at various stages of development, without excess of blast cells.

A small proportion of female patients with CML are diagnosed during the childbearing age as the median age at the diagnosis of CML is in the sixth decade of life [9,10]. CML occurs in 10% of pregnancy-associated leukemias [9,10]. The management of CML during pregnancy is a difficult task because of the potential adverse effects of the treatment on both the mother and the fetus [11]. The therapeutic approaches to CML diagnosed during pregnancy include supportive care including leukapheresis, cytotoxic chemotherapy such as hydroxyurea, interferon-α and TKIs such as imatinib [9,10].

There are very few reports of successful outcome of pregnancy in mothers having CML and receiving imatinib throughout pregnancy [11]. Exposure to imatinib in early pregnancy has been associated with spontaneous abortion and a number of congenital abnormalities such as skeletal malformations in addition to renal, respiratory as well as gastrointestinal defects [9,10,12]. There is no evidence that a brief exposure to imatinib therapy during pregnancy can adversely affect the developing fetus [10,13]. However, female patients with CML who wish to become pregnant should be advised to wait till they have achieved sustained major molecular responses (MMRs) or better responses for at least two years [9,10,14]. Decisions on the interruption of TKI treatment and starting alternative therapies and planning delivery should all be made after making thorough discussions with the patient, her family as well as obstetricians and neonatologists [10].

Dasatinib is an orally administered inhibitor of multiple kinases including BCR-ABL and SRC family kinases [15,16]. It is indicated for the treatment of: newly diagnosed CML in chronic phase, CML in accelerated or blastic phase in addition to resistance or intolerance to imatinib [15,16]. It has approximately 325 fold potency than imatinib [15-17]. It was approved for the treatment of CML in the year 2006 [18]. It has the following adverse effects: neutropenia, thrombocytopenia, diarrhea, headache, fatigue, dyspnea and pleural effusions [16].

Nilotinib is a selective inhibitor of BCR-ABL and is more potent

than imatinib as it has been shown to achieve deeper and earlier molecular responses [14,19-21]. It is indicated for the treatment of: newly diagnosed CML in chronic phase and for the treatment of CML after failure of imatinib or in case of intolerance to imatinib [4,20-22]. However, it has the following side effects: nausea, vomiting, diarrhea, constipation, pruritus, skin rash, BM suppression, increased lipases, hyperglycemia, prolongation of QT interval and sudden death [22].

Interferon-α inhibits cell proliferation by its effects on protein synthesis, RNA degradation and possibly by modulation of the immune system [12]. It does not inhibit DNA synthesis and due to its high molecular weight it does not cross the placental barrier to a significant degree [9,12]. Its use in pregnancy is generally safe and is not usually associated with congenital malformations or any other fetal adverse effects [9,12]. Hence, CML diagnosed during gestation can preferably be treated with interferon-α throughout pregnancy without any apparent increase in adverse fetal outcome or congenital malformations [12]. However, due to the high rate of encountering side effects, many pregnant ladies cannot tolerate interferon therapy [12].

Ideally female patients with CML belonging to the child bearing age who like to become pregnant should wait till they achieve at least MMR of their disease. Our patient was seeking gestation, as she had been suffering from infertility, before achievement of optimal control of her CML. Dealing with pregnancy in an uncontrolled CML patient was a real challenge to the treating team. The initial step was stopping imatinib and shifting her to interferon till the end of the first trimester of pregnancy so as to avoid the possible adverse effects of imatinib on the developing embryos. After passing the stage of organogenesis, she was resumed on imatinib then she was continued to have follow up on almost weekly basis during her pregnancy. After passing the second trimester of her pregnancy and after prior arrangements with the obstetricians, she had LSCS at week 32 of gestation. The healthy, but underweight baby boys, were kept under close supervision in the neonatology unit for almost four weeks. Their physical and laboratory evaluations showed that they were healthy without congenital or other abnormalities.

After delivery, the focus shifted to controlling the mother's CML. Initially, she was shifted to dasatinib after encountering imatinib failure. Thereafter, dasatinib made significant change in her management, but unfortunately she become intolerant to the drug, so the treating team to start her on nilotinib. The third TKI brought her disease under more optimal control.

Conclusion

Young females with CML should wait till their disease is optimally controlled before becoming pregnant. Interferon is the safest medication that can be administered during the first trimester of pregnancy in CML patients. Coordination between hematologists, obstetricians and neonatologists is of vital importance to guarantee safety of both the mother and her infant(s).

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