Successful pregnancy in two chronic myeloid leukaemia patients

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Abstract

The management of cancer during pregnancy is a complex situation for patients, as well as their physicians; although it is an uncommon event.

We describe the successful management of two pregnant women with chronic myeloid leukaemia (CML). The first was a 23 years old patient, who was newly diagnosed with Philadelphia-positive CML in chronic phase during the first trimester of her pregnancy. This patient was treated successfully with alpha interferon until her delivery at 36 weeks of gestation without significant adverse effects on the patient or fetus. The patient gave birth by cesarean section to a healthy male weight 3 kg. The second was a 25-years-old woman who is a known case of Philadelphia-positive CML in chronic phase since 2003; she was receiving imatinib for four years, and she was in haematological remission. In 2008 the patient got pregnant; she stopped imatinib two months prior to her pregnancy. This patient received no medical treatment for CML; she was managed by close follow up with full blood count (FBC) until her delivery at 36 weeks of gestation, because she was in haematological remission, The patient gave birth by cesarean section to a healthy female twin weight 2.2 & 2.4 kg.

Introduction

Chronic myelogenous leukemia (CML**)** is a myeloproliferative disorder with clonal expansion of transformed primitive hematopoietic progenitor cells. It is characterized by a biphasic or triphasic clinical course in which a terminal blastic phase follows a chronic phase of variable duration. It affects predominantly older individuals, although all age groups may be affected[1].

The coincidence of (CML) and pregnancy is an uncommon event. Leukaemia occurs in approximately one in 75,000 to 100,000 pregnancies, CML accounts for less than 10% of these cases, in part because it occurs mostly in older age groups[2]. The management of CML during pregnancy is a difficult problem because of the potential effects of the therapy on the mother and fetus. While CML may not need to be treated immediately, and pregnancy does not appear to affect the course of CML, there is still a risk of leukostasis, as well as the risk of placental insufficiency with consequent below-normal fetal birth weight, increased fetal prematurity, and increased mortality if CML is left untreated for the duration of the pregnancy[3].

Case Report

CASE (1)

A 23 years old patient, referred to the Oncology department, National Cancer Institute, central Sudan, at 8 weeks pregnancy, complaining of low grade fever and headache. On initial examination she was well, not pale, spleen was 8 cm below the left costal margin, no lymphadenopathy or hepatomegaly. FBC showed features of CML with white blood cell (WBC) count 165.5 x 10^3 ,neutrophils 31%, lymphocytes 1% ,eosinophils 2%, basophils 7% ,stab 14% metamyelocytes 6% ,myelocytes 33% ,promyelocytes 2% ,blast 2% ,NRBC 2%. Haemoglobin 10.3g/dl , platelets 512.000.Bone marrow examination showed features of CML in chronic phase with hyperactive myelopoiesis dominanated by promyelocytes ,myelocytes ,metamyelocytes ,neutrophils and basophils .Philadelphia chromosome was positive.

RFT and LFT were normal .Abdominal ultrasound scan showed moderately enlarged spleen with normal texture, slightly enlarged liver with normal texture. Intrauterine eight weeks viable pregnancy.

The options of treatment were discussed with the patients either to have an elective abortion or to be given alpha Interferon with close monitoring of the FBC and pregnancy.

Patient chose to start alpha Interferon. She started on 3 mega unit subcutaneously every other day; the dose was gradually increased to 9 mega unit every other day which was continued till her delivery.

She was followed closely in the combined gynaecology /oncology clinic. There was a good clinical and haematological response, FBC showed reduction in WBC count to 26x10^3 at term, as shown in the diagram.

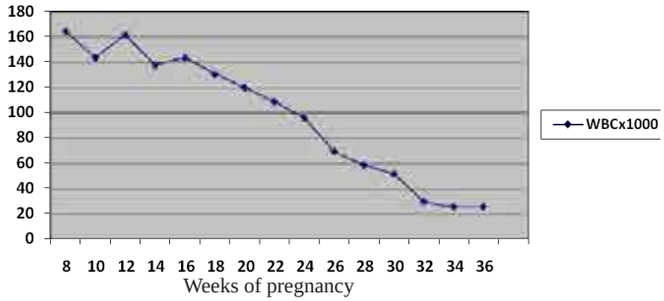

Fig. 1: White blood count evolution during pregnancy.

Serial pregnancy ultrasound scans were normal with no gross congenital malformations. Cesarean section was performed at 36 weeks of gestation which was uneventful; the outcome was a male weight 3 kg.

The patient started on Imatinib after delivery, she was advised not to breast feed her baby due to the potential for serious adverse reactions in nursing infants.

CASE (2)

A 25 years old woman was diagnosed with Philadelphia positive CML in chronic phase in March 2004. She successfully achieved remission with imatinib which she had been used for four years . The patient then got married; she was educated about the risk of receiving Imatinib during pregnancy, so she stopped taking Imatinib two months before conception.

She presented in the follow up clinic at 8 weeks of gestation .She was asymptomatic. On initial examination she was well, not pale, no lymphadenopathy or hepatosplenomegaly. Haematological values were :WBC count was $10.3x10^3$. haemoglobin 11.8 g/dl, platelets 328.000. The patient was followed closely in the combined gynaecology/oncology clinic She was managed by a close follow up with FBC and ultrasound scan of pregnancy. WBC count didn't exceed $12x10^3$ during the whole period of pregnancy. Ultrasound scan showed twin, viable and active fetuses with no gross congenital malformations .She delivered at 36 weeks of gestation by cesarean section, the outcome were a healthy female twin weighing 2.2 and 2.4 kg.

They were exclusively breast fed for 4 months according to their mother decision, and then the patient resumed Imatinib after she weaned her babies.

Discussion

The management of CML in pregnancy involves prevention of placental insufficiency and other complications of hyperleukocytosis by control of maternal WBC, while avoiding harmful fetal exposure to cytotoxic drugs.[3]

Conventional therapeutic options of chronic phase CML include hydroxyurea, busulfan, interferon-based regimens and stem cell transplantation, with stem cell transplantation being the only curative therapy [4]. The standard therapy for patients with chronic myeloid leukemia (CML) is imatinib mesylate which is a bcr-abl tyrosine kinase inhibitor .It entered clinical trials in 1998 and has since been shown to induce dramatic hematologic and cytogenetic responses ,it offers a new hope for patients with CML[5].

Alpha-interferon has been used for the treatment of CML during pregnancy with variable success .Alpha-interferon appeared to be a safe drug as it has no known effects on DNA and, being a large molecule, is assumed not to cross the placental barrier to any great

extent. Very low levels of alpha-interferon in newborns compared with maternal levels confirmed this hypothesis[6].

There are no reports about its adverse effects on pregnancy and the developing fetus in humans, but there are reports of normal infants delivered following treatment with alpha-interferon during pregnancy[7].

The therapeutic management of CML in pregnant women with targeted therapies often presents divisive dilemmas and poses substantial challenges to both patients and their physicians[6].

The number of CML patients in child-bearing age and treated with imatinib is increasing. These women may want to be pregnant or are actually pregnant while on imatinib[8]

However, despite its remarkable efficacy and toxicity profile, little is known about imatinib potential for long-term toxicity. In preclinical studies imatinib was teratogenic in rats, but not rabbits[4].Because of the teratogenicity data in rats, it is recommended that women treated with imatinib should be aware of the potential teratogenicity of imatinib and effective contraception should be used during imatinib therapy[4].

Although most of the existing data on the effects of imatinib on pregnancy have shown satisfactory outcomes, they do not indicate that it can be safely recommended during the first trimester of gestation[6]. The key period for embryogenesis occurs from week 3 to week 8 of post-conception life ,hence, many authors advise against the use of anti-neoplasic agents during the first trimester[8].

Both imatinib and its active metabolite can be distributed into human milk. Considering the combined concentration of imatinib and of the metabolite and the maximum daily milk intake by infants, the total exposure would be expected to be low (~10% of a therapeutic dose). However, since the effects of low-dose exposure of the infant to imatinib are unknown, women taking Glivec should not breast feed.[9].

Conclusion

In view of the successfully treated patients reported in the literature, and our own experience, we would suggest that Alpha-interferon can be considered for the treatment of an active CML safely during pregnancy. While a close follow up of a pregnant CML patient who is in haematological remission could represent a satisfactory management option.

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