HYDROXYUREA IN CHRONIC MYELOID LEUKEMIA DURING PREGNANCY

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INTRODUCTION

The concomitant occurrence of pregnancy and chronic myeloid leukemia (CML) is uncommon.[1] Various modalities of treatment have been used in these patient which include Splenic irradiation (with shielding of the uterus), leukapheresis, cytotoxic drugs and more recently interferon.[1,2,3]

Hydroxyurea a cytotoxic agent that inhibits DNA synthesis, is useful in both the chronic and accelerated phase in the course of CML.[1] There are about five reports of the use of hydroxyurea in pregnancy with CML in the literature.[4] We report our observation of a woman with CML who was administered hydroxyurea through out pregnancy with successful outcome for both mother and fetus.

CASE REPORT

A 27 year old woman was diagnosed as having Ph–positive CML, at a clinic visit in August 1995. Her response to Busulphan was poor. She was therefore, commenced on hydroxyurea. Her total leucocyte count was controlled with a dose of 1.5 gm/day. She had five previous pregnancies all of which had resulted in a normal vaginal delivery at term. At a routine follow-up for her malignant disease, she was found to be 12–14 weeks pregnant. On examination she was pale and had hepato–splenomegaly. Her total leukocyte count was 90 x 10 /L with 80% neutrophilis, 2% promyelocyte, 6% myelocyte, 6% metamyelocyte and 6% lymphocytes. The haemoglobin level was 11.5 gm/dl and the platelet count was 250 x 10 /L. As she was already taking hydroxyurea, this drug was continued with the dose ranging between 1 to 2 gm/day during the pregnancy. At 36 weeks gestation she was admitted in the Obstetric unit at the Hayatabad Medical Complex.

She had two episodes of antepartum haemorrhage while in hospital and was transfused whole blood to correct her anaemia. At 38 weeks she went into spontaneous labour and had a vaginal delivery of a normal, physically healthy, male infant weighing 3.2 kg. The baby's blood count was within normal limits at birth. Both the mother and baby are well to date. The baby is seven months old and is physically and developmentally normal. He has a haemoglobin level of 12.5 gm/dl, white cell count of 8.5 x 10 /L, and a platelet count of 359 x 10 /L.

DISCUSSION

The association of CML and pregnancy is infrequent. The successful management of CML during pregnancy revolves around the

need to treat the mother appropriately to ensure and maintain maternal well being and the desire to avoid fetal compromise especially in the first trimester of pregnancy.

To this end, accepted treatment modalities in pregnant women with CML generally involves the use of ionizing radiation, leukapheresis, interferon and cytotoxic drugs.

Women of child bearing age who develop CML may be treated with bone marrow transplant (BMT). The Radiotherapy and cytotoxic drugs induce ovarian failure which is almost always irreversible. However, spontaneous recovery of gonadal function and subsequent pregnancy has been reported. Successful pregnancy, after BMT for CML can be achieved, if the oocytes are collected and fertilized and the embryo cryopreserved before the transplant procedure. There is a greater incidence of fulminating pre–eclampsia in these patients. The patients also run the risk of a relapse of the malignant disease during pregnancy.[5]

Interferon alpha is a glycoprotein of biological origin with antiviral and anti–proliferative properties. It acts at cell membrane level and does not inhibit DNA synthesis.[6] It is therefore a very safe drug when used in pregnant patients with CML. The infants born to mothers while on treatment with interferon alpha are normal with appropriate growth and development. Nevertheless, recommendations regarding the use of this drug to treat CML during pregnancy must await further experience and long term studies which are as yet unavailable. Other constraints to its use are that it is a very expensive drug which is available in injection from only and a significant number of patients experience problems with conception (short luteal phase that need clomiphene therapy).[2,7,8]

Splenic irradiation with shielding of the uterus has been used with out obvious teratogenic effect. However, there are potential leukemogenic effects of in utero exposure to radiation.[1] Leukapheresis has been used successful and may be considered the treatment of choice in selected patients because of its lack of teratogenic effects, it also has the added advantage of not adversely influencing the course of CML and can result in improvement in symptoms. However, it is costly, time consuming and may be inconvenient for some patients. In certain center it may not be readily available.[9,10]

Interestingly, a review of the literature shows that children born to mothers with haematological malignancies (Hodgkins disease, non–Hodgkins lymphoma, acute and chronic leukemia) who received chemotherapy during some portion of their pregnancy, including the first trimester, did not suffer from the teratogenic effects of the drugs when followed from three to nineteen years. In all these studies, the children's physical, neurological, psychological haematological, immunofunction and cytogenetics were normal.[11]

Of the cytotoxic drugs, Buslfan has been the most widely used agent with a favorable outcome in the vast majority of patients. However, gonadal failure, invariably occurs with in a year of starting treatment and is irreversible.[1,12]

In recent years hydroxyurea has been increasingly used in the management of pregnant patients with CML. Its advantages are ease of administration, short duration of action and absence of cross sensitivity with and resistance to alkylating agents. When compared with those of other cytotoxic drugs, side effect are uncommon. It is well tolerated and serves as a useful alternative to leukapheresis.[1]

In our case report and in all the other patients reported, continue administration of hydroxyurea before and through out pregnancy did not show any teratogenic or haemotologic effects in the fetus. Teratogenic effects of hydroxyurea have been

demonstrated in mammals when given at the onset of gestation and at doses at least five times the commonly use dose in humans. Clinical reports in humans have shown that the risk of teratogenicity was often overestimated. In none of the published cases was any untoward effect observed on either the course of the pregnancy or in the fetus.[13]

As the chance of mutagenicity is greatest at the onset of gestation and in the first trimester of pregnancy, it will probably be safer to try leukaphersis (if available) or inteferon alpha during this period and later in the 2nd and 3rd trimester to replace it with oral hydroxyurea.[1,9] Further trials on the use of combination therapy in pregnancy complicated by CML need to be conducted before it can be generally recommended.

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