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Chronic Myeloid Leukemia and Pregnancy – A Case Report

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ABSTRACT

The occurrence of pregnancy and chronic myeloid leukemia is uncommon. We describe a case report of 38-year-old G3 P2 woman who was diagnosed to have chronic myelogenous leukemia before pregnancy and received imatinib orally. After 2 months of therapy she was diagnosed to be 8 weeks pregnancy and counselled for termination of pregnancy. She lost to follow up and again reported in her third trimester of her pregnancy. Labour was induced and she delivered a healthy male child with no obvious congenital malformation. Tab imatinib was restarted on 2nd day of delivery. Although our case was not imatinib after 8 weeks of pregnancy, literature shows that the use of imatinib did not have any adverse effects on the foetus, except for low birth weight and low APGAR at birth. We can conclude that imatinib can be continued even at the third trimester in a pregnant lady with CML, if necessary but careful monitoring should be done for haematological response to imatinib and its side effects.

Keywords: Chronic myeloid leukemia, Pregnancy, congenital malformation, imatinib

INTRODUCTION

Management of pregnancy with neoplasm of any organ is a challenging situation for an obstetrician as majority of the drugs used for chemotherapy are cytotoxic and have teratogenic potential. Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterised by reciprocal translocation between BCR-ABL genes located on chromosome 9 and 22. CML is characterised by a biphasic or triphasic clinical course in which a terminal blastic phase follows a chronic phase of variable duration. It affects predominantly older indivisuals, although all age group may be affected.[1,2]

Incidence of CML in pregnancy is 1 in 100,000.[3] Incidence of CML in general population varies from 0.6-2 cases per 100,000 persons.[1] Incidence of CML is higher in men as compared to women. After the successful use of Imatinib BCR-ABL tyrosine kinase inhibitor in patients with CML the course of the disease has changed from fatal to chronic disease. Here we are presenting a case report of 38 year old female with CML with successful pregnancy and delivery.

CASE REPORT- A 38 year old female G3P2 came to ANC for routine check up in her third trimester at 36 weeks as she was referred from medicine department for termination of pregnancy as her TLC were 111.71 x10^9 /L with blast cell 1%, promyelocyte 5%, myelocyte 42%, metamyelocyte 7 %, band form +, neutrophils 92.5 %, lymphocyte 1.8 %. Haemoglobin concentration was 5.6 % and platelet counts were 3.76 lacs/cu mm. LFT and KFT were within normal limits.

History date back to 1 year when she visited to medicine OPD for weakness and breathlessness during household works. On clinical examination, She was morbidly obese with BMI 45.5 kg/m2, pallor was present. Routine blood investigations were done. CBC with PBF was suggestive of myeloproliferative disorder. TLC counts were 410 .71 x10^9 / L with blast cell 3 %, promyelocyte 1 %, myelocyte 53 %, metamyelocyte 18 %, band form +, neutrophils 36% , lymphocyte 4%. Haemoglobin concentration was 11.7 % and platelet count was 4.38 laks/cumm . BCR-ABL mutation was positive. She was admitted and 2 units of blood transfusion were given and started on TAB imatinib 400 mg /day. After 2 months of therapy, she missed her period and UPT was positive. She was referred to ANC for evaluation. On examination she was 8 weeks pregnant. Routine investigations and USG was advised and she was counselled for termination of pregnancy. She refused for termination so Imatinib was stopped and folic acid was given. She lost to follow up and then reported at 36 weeks for termination of pregnancy. No treatment was taken by her for CML throughout the pregnancy. She had 2 ultrasound reports with her which was normal with no gross congenital anomaly in the foetus.

She was admitted in labour room for Induction of labour. On General physical examination BMI was 47.5 kg/m2. BP was 120/80 mm of mercury. Pulse 80/min. Anemia was present.

On obstetrical examination: P/A – Uterus was 36 weeks, longitudinal lie, cephalic presentation, head fixed, FHS 146/min regular.

On per vaginal examination external cervical os was closed, cervix 2.5 cm in length 30% effaced. Vertex was at -3 station and pelvis was adequate.

Induction of labour was done by intracervical instillation of dinoprost gel. She delivered a

healthy male child of 3.5 kg with APGAR score 9/10. There was no gross congenital anomaly in the baby. Breast feeding was started within a hour of delivery. Two units of blood were transfused. Physician was consulted and on 2nd day of delivery breast feeding was stopped and tab Imatinib 400 mg/day started. She was discharged from the hospital with advise to have regular follow up.

DISCUSSION

Pregnancy with CML is rare as the mean age of diagnosis of CML is 65 years. Introduction of tyrosine kinase inhibitors (TKI) into clinical practice has significantly improved the outcome of pregnancy and life expectancy. When women conceive with ongoing treatment with TKI there are chances of embryonic toxicity in developing foetus.

Pregnancy does not affect the course of CML. There are risks of leukostatsis, uteroplacental insufficiency, low birth weight, prematurity and increased fetal mortality if CML is left untreated for the duration of pregnancy.[4]

Treatment with cytotoxic drugs on foetus may be studied from two perspectives: immediate effects in terms of abortion and teratogenic effects and late effects which are gonadal toxicity, endocrinal disorder, growth and developmental problems which involves CNS, immunosuppression, genetic and teratogenic disorders. [5,6]

There are multiples chemotherapeutic agents that can be used to treat CML. These are hydroxyurea, busalphan , Tyrosine kinase inhibitors, interferons based regimens and stem cell therapy.

Hydroxyuria: Hydroxyuria inhibits DNA synthesis by decreasing the production of deoxyribonucleotides by inhibition of the enzyme ribonucleotide reductase.[7] It was commonly used in the treatment of CML prior to the introduction of imatinib. Thauvin et al. described various outcomes of pregnancy when hydroxuria was used in first trimester. They observed that out of 50 cases, 2 had intrauterine foetal death, 3 had major malformations (hip dysplasia, unilateral renal dilatation, pilonidal sinus) and 9 cases of premature delivery. Hydroyuria used in second and third trimester caused increased risk of pre-eclampsia.[8] Hydroxyurea is excreted in breast milk therefore should be avoided in lactating women.

Busulphan: Busulphan is an alkylating agent that does not alter the natural course of the disease. It is now rarely used in the management of CML in chronic phase and should be avoided in pregnancy. [9]

Interferon-alpha(IFN-α): IFN-α was the non-transplant treatment of choice for most patients with CML before the advent of TKI (imatinib).[7] IFN-α does not cross the placental barrier due to its high molecular weight (19kDa).[10] The mechanism(s) by

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which IFN-α acts is unknown but it might function by (i) selective toxicity against the leukemic clone, (ii) enhancement of 'immune' regulation and (iii) modulation of bone marrow micro- environmental regulation of hematopoiesis.[11] Brojeni et al. in their study observed that IFN-α does not significantly increase the risk of major malformation, miscarriage, stillbirth or preterm delivery above general population rates. [12] IFN therapy is associated with significant toxicities, mostly constitutional, neuropsychiatric, hematologic and hepatic effects.

Leukapheresis: Several cases of successful use of leukapheresis in treatment of a pregnant patient with chronic myelogenous leukemia in chronic phase have been reported.[13,14]. Ali et al. [13] also reported the use of leukapheresis as the sole treatment for CML in pregnancy without any adverse effects on the patient and foetus. It causes a rapid lowering of high total leucocyte counts but it is inconvenient, costly and time-consuming.

Imitinib: Imitinib is a bcr-abl tyrosine kinase inhibitor (TKI). Tyrosine kinases are proteins and act as chemical messengers or critical signaling molecules for the cellular regulation of proliferation, differentiation, survival, function and motility. Imatinib is currently the best medical treatment available for patients with CML. Pye et al. [15] in their study stated that out of 180 women who were exposed to imitinib treatment during pregnancy; outcomes were available for 125 women only. Out of 125 women, 50% delivered a healthy baby, 28% elected to have a termination and 14% had a miscarriage. No adverse effects were noted in the infant of the mother who was on oral imitinib 400 mg per day for CML.[16]

Newer Tyrosine Kinase Inhibitors:

Dasatinib and nilotinib are FDA approved as first-line therapy for CML.

Dasatinib, an oral multi-targeted kinase inhibitor of BCRABL and Src kinases, was initially approved for the treatment of adults with chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy, including imatinib.[17]

Bosutinib. 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 [18].

Stem cell transplantation. Allogeneic stem cell transplantation is an important treatment option for patients with CML, particularly younger individuals who failed treatment with imatinib and have an HLA-identical donor. It should be contra-indicated during pregnancy.

A patient with accelerated or blast phase CML should be started on chemotherapy immediately. If the patient is in late trimester, early delivery should be offered, if feasible, while termination should be considered during the first trimester. If a patient is already under TKI therapy and is pregnant, patients should be counseled on the risks and benefits of stopping TKIs. TKIs can be stopped if the patient is in CMR for at least 2 years. If relapse occurs, leukapheresis can be considered until the end of the first trimester and leukapheresis/IFN-α or combination of both can be considered in the second and third trimester of pregnancy. The patient should be followed-up regularly with blood counts and real time PCR. If the patient continues to be in CMR/CCyR, she could be followed-up until after delivery and started on TKIs. If there is loss of CMR then leukapheresis in the first trimester and IFN-α, leukapheresis or both in the second and third trimesters can be considered.

Conclusion

With the use of imatinib and other TKIs during pregnancy with CML and regular follow-ups normal outcome of pregnancy is observed. Treatment should be individualized depending on the haematological response to imatinib, duration of remission and other available alternative therapies. However women should be counselled about the possible adverse effects on foetus.

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