

Tretinoin in Pregnancy Complicated With Acute Promyelocytic Leukaemia

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Summary

Acute promyelocytic leukemia (APL) in pregnancy poses serious danger to both the mother and fetus. Cytotoxic chemotherapy may cause teratogenicity to the fetus. APL is unique because it is usually associated with a coagulopathy that markedly increases the risk for the mother and fetus. A 21 year old lady with APL in her third trimester of pregnancy was treated with oral tretinoin. Tretinoin reversed the coagulopathy and normalised her blood counts without causing cytotoxic damage associated with cancer chemotherapy. Fetal distress occurred at 37 weeks of gestation and an emergency caesarean section was performed without complications and no blood transfusion support was needed as her coagulopathy and thrombocytopenia had resolved. A remission was achieved with only tretinoin induction. She subsequently had consolidation and maintenance chemotherapy. The mother and baby remain well at 4 years from completion of chemotherapy. A total of 10 pregnancies associated with APL have been reported in the current literature. Premature delivery and a fetal arrhythmia were the only complications. Although tretinoin is considered teratogenic, its use so far in second and third trimester has been safe.

Introduction

Acute promyelocytic leukemia (APL) represents 15% of acute myeloid leukaemia. Prior to tretinoin usage, the treatment of APL was difficult and remission rates were low especially in developing countries due to mortality resulting primarily from bleeding¹. APL is associated with a coagulopathy which may be due to a combination of disseminated intravascular coagulation and primary fibrinolysis. Tretinoin usage is able to limit this complication and is now the standard induction for APL. Experience with tretinoin (all trans retinoic acid, ATRA) has been limited because of the relative rarity of APL in pregnancy. We report its use in pregnancy and review the current literature.

Case Report

A 21 year old Malay lady G1P0 at 33 weeks pregnancy was admitted for gum bleeding and spontaneous

bruising of 2 weeks duration. Physical examination revealed multiple bruises mainly on her limbs. She was pale, afebrile and not jaundiced. Lymph nodes, liver and spleen were not palpable. The uterine fundal height was consistent with 33 weeks gestation. Fetal heart sounds were heard. Investigations showed a haemoglobin of 6.4gm/l, WBC $3.4 \times 10^9/l$, platelet count $20 \times 10^9/l$. Her renal and liver profiles were normal. Coagulation tests demonstrated a compensated coagulopathy with normal PT and APTT and positive for fibrin degradation products. Ultrasound revealed a normal fetus consistent with gestation. Bone marrow examination confirmed a diagnosis of acute promyelocytic leukemia.

She was transfused with fresh frozen plasma and platelet concentrates. Her platelet count was maintained above $20 \times 10^9/l$. After informed consent, she was prescribed oral tretinoin (all trans retinoic acid, ATRA) at $45\text{mg}/\text{m}^2$ in 3 divided doses.

CASE REPORT

She did not have any further spontaneous bruising after a week of therapy. Her blood counts gradually improved and she did not require further transfusion support after 16 days of treatment. A total of 10 units of packed cells, 31 units of platelets, 2 units of FFP and 13 units of cryoprecipitate were used. Prednisolone was started on day 14 of therapy when the white cell count rose above $10 \times 10^9/l$ to prevent leucostasis. She experienced headaches, dry mouth and skin with tretinoin. No other complications were observed.

At 37 weeks gestation, 30 days after admission, she noticed decreased fetal movements and a CTG showed little variability in heart rate. An emergency lower section caesarean section was performed under general anaesthesia. She did not require any transfusion support then as her blood counts were haemoglobin 11.0gm/L, platelet count $97 \times 10^9/l$ and white blood count $5.3 \times 10^9/l$. The coagulation studies were also normal. No surgical complications were encountered. A baby boy was delivered weighing 2450gm. Apgar score was 6 at birth and 10 at 5 minutes. On examination of the placenta, an area of infarction was identified.

She was discharged on the 10th postoperative day. A bone marrow examination done after 6 weeks of therapy confirmed remission and tretinoin was discontinued. Her blood counts then were haemoglobin 11.1 gm/L, platelet $462 \times 10^9/l$ and white blood cells $6.1 \times 10^9/l$.

She received consolidation and maintenance chemotherapy as previously reported¹. She remains in remission 4 years after treatment. Her child is now 4 years old and has normal development with no physical abnormalities detected.

Discussion

Acute promyelocytic leukemia in the past signifies a high risk leukemia which is prone to severe bleeding resulting from the associated coagulopathy. We only had a remission rate of 23% prior to ATRA. Currently remission rate in our centre is 93% ($n = 27$) with ATRA induction.

In general, pregnancy in the setting of acute myeloid leukemia poses significant risks to the mother and baby. The chemotherapy agents used are teratogenic and the

treatment of the leukemia cannot be delayed. Tretinoin is not a cytotoxic drug and was first used by Chinese investigators in 1986. It is a retinoic acid derivative and causes maturation of the leukaemic cells. These cells then differentiate into neutrophils which naturally have a lifespan of 7 hours. Thus leukaemic cells can be eliminated. With ATRA, the white cell count would initially increase as abnormal leukaemic cells mature and differentiate. Subsequently, as leukaemic cells are eliminated, normal haemopoiesis is restored and the white cell count fall to normal. Platelet count and haemoglobin return to normal. There is no cytotoxic damage to tissues. The most serious adverse effect of tretinoin is retinoic acid syndrome which is life-threatening, causing acute respiratory distress and a capillary leakage syndrome. This is thought to result from the leucostasis of abnormal leukemic cells in the lungs and microcirculation. Another serious complication that has been reported is thrombosis occurring while on tretinoin. Interestingly, her placenta had an area of infarction. There is a possibility that this may have contributed to the fetal distress. The thrombosis² may occur resulting from low grade disseminated intravascular coagulation (DIC) that continues while the primary fibrinolysis resolve thus resulting in a net increase tendency to thrombose, or from a rebound increase in coagulation factors including fibrinogen as DIC resolves.

A review of the literature found no reports of serious adverse events to the fetus. A total of 10 pregnancies in which tretinoin was prescribed have been reported with 11 livebirths. All have resulted in a favourable outcome. Tretinoin has been demonstrated to be teratogenic in animals especially if administered in the first trimester. However the studies utilised much larger equivalent doses than that used in humans. Our patient was already in the third trimester when she presented.

The associated complications reported in the literature were premature delivery and fetal arrhythmia. No teratogenicity has been reported. Prior to ATRA, 12 patients reported in the literature with APL were treated with cytotoxic chemotherapy in pregnancy. Only 8 resulted in a livebirth³.

We can therefore conclude that the use of tretinoin in pregnancy is relatively safe and is certainly safer than

conventional chemotherapy during pregnancy. Trying to induce labour and delivery first and then prescribing chemotherapy as may be practiced in other oncological conditions, including acute leukemias, is not feasible in APL because of the coagulopathy and thrombocytopenia. We believe that a caesarean section would be hazardous to the patient unless the coagulopathy is corrected first. Tretinoin corrects

coagulopathy and thus she underwent surgery without any increase in bleeding. Her child is now 4 years old and has no signs of any physical disabilities. We can conclude that in this case, no teratogenicity was evident.

Tretinoin induction for acute promyelocytic leukemia has made treatment of APL in pregnancy safe and is probably safe for the fetus.

References

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