Fetal Loss in a Patient with Acute Myeloblastic Leukemia Associated with FLAG-IDA Regime

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ABSTRACT

Acute leukemia in pregnancy offers a unique management dilemma in the absence of clear guidelines. There is some transporters localized into the placental trophoblasts plays an important role in limiting the passage of substrate drug. Herein, we reported a case of fetal loss in a pregnant patient in 34 gestational weeks, with acute myeloblastic leukemia who treated with high dose cytarabine plus fludarabine chemotherapy, to discuss the effects of cytotoxic agent on fetus. There were many reports about pregnancies complicated with AML treated with standart dose cytosine arabinoside and antracyclin combination. We suggest that high dose chemotherapy, mainly FLAG-IDA regime may cause fetal death, although in nearby term periods. Understanding the role of drug transporters in moderating transplacental passage of substrates has important clinical implications for choosing specific drugs to achieve therapeutic objectives.

Key Words: Pregnancy, Leukemia, Fludarabine, High-dose chemotherapy

ÖZET

Akut Myeloblastik Lösemili Bir Hastada FLAG-IDA Rejimi ile İlişkili Fetal Ölüm

Gebelikte ve lösemi tedavisi, açık kılavuzların olmaması nedeni ile oldukça büyük bir çıkmazdır. Plasental trofoblastlarda lokalize bazı transporterler ilaç ve ürünleri için önemli bariyerlerdir. Biz bu yazımızda 34 haftalık gebeliği olan akut myeloblastik lösemi hastasında, yüksek doz sitozin arabinozid ve fludarabin kemoterapisi sonrası oluşan bir gebelik kaybı vakasını sunmayı ve sitotoksik ilaçların fetüs üzerine etkilerini tartışmayı amaçladık. Akut lösemi tanısı almış birçok gebede standart doz sitozin-arabinozid ve antrasiklinin kullanımına dair çok sayıda vaka tarif edilmiştir. Yüksek doz kemoterapinin, özellikle de FLAG-IDA rejiminin terme yaklaşmış gebelikte bile ölüme neden olabildiğini gördük. İlaç transporterlerinin rollerini araştırmaya yönelik çalışmalar pratikte ilaç seçimi ve gebe hastayı bekleyen riskleri daha iyi öngörmeyi sağlayabilir.

Anahtar Kelimeler: Gebelik, Lösemi, Fludarabin, Yüksek doz kemoterapi

INTRODUCTION

Acute leukemia in pregnancy offers a unique management dilemma in the absence of clear guidelines. There is an increased risk of infection, hemorrhage and abortion consequent to neutropenia, anemia, thrombocytopenia or the cytotoxic treatment. The most critical period for teratogenicity is between 3rd and 10th weeks because this period correlates with the stage of active organogenesis. Hence many authors advise against the use of cytostatic agents during the first trimester. However, chemotherapy after the second trimester is associated with fetal malformations at a rate no higher than normal. When leukemia is diagnosed in the second or third trimester, induction chemotherapy should be undertaken, as in the nonpregnant patient, in an attempt to achieve complete remission before delivery.[1] Many chemotherapeutic agents cross the placental barrier and have been implicated of congenital malformations. The human placenta is a protective barrier, and a site for nutrient and waste exchange between mother and fetus.[2] Herein, we reported a case of fetal loss in a pregnant patient in 34 gestational weeks, with acute myeloblastic leukemia who treated with high dose cytarabine plus fludarabine chemotherapy, to discuss the effects of cytotoxic agent on fetus.

CASE REPORT

A 32-year-old woman, gravida 4, parity 2, abortus 1 was admitted to the Dicle University Hospital, Department of Hematology in the 16th week of her pregnancy with gradually inreasing weakness, fatigue, fever, oronasal and gingival bleeding for 10 days. On examination marked pallor was noted with pulse 110/min, respiration 19/min, blood pressure 100/60 mmHg, and fever 39.1^{0}C. Scattered petechiae, small hemorrhages in the right fundus, gingival bleeding, 16-week-size uterus and normal fetal heart tones was also noted. Hemarocrit was 26%, hemoglobin level was 8.6 g/dL, platelet count was 7000/dL, and WBC 12.000/mm^3 with 35% myeloblasts. Bone marrow aspirate confirmed the diagnose of acute myeloblastic leukemia with 70% myeloblasts. Antileukemic therapy was initiated immediately after admission. The patient received idarubicin 12 mg/m^2 in 30 minutes, day 1-3, cytosine arabinoside 100 mg/m^2 continious infusion, day 1-7. The patient was substituted with packed RBC and HLA cross matched platelets when Hb decreased below 9 g/dL or platelet count was less 20.000/dL. Aplasia developed 11 days after initiation of therapy. Three weeks after the initial course of therapy, her bone marrow demonstrated normal myeloid serie and erythropoiesis, with 2% myeloblasts. Her pregnancy was followed up regulary and this treatment regime was completed without any serious maternal or fetal complication. Patient did not come to her regular controls for postremission therapies untill the eight month of her pregnancy, and the patient returned with relapsed myeloblastic leukemia presented with weaknes, pallor, fever and purpuric skin lesions. Her hemoglobin level was 5.9 g/dL and platelet count was reduced to 11.000/dL. Bone marrow aspirate demonstrated a 60% myeloblastic infiltration. After maternal and fetal initial evaluation FLAG-IDA regime was started as salvage therapy (fludarabine 30 mg/m^2, day 1-5, cytosine arabinoside 2 g/m^2, day 1-5, and idarubicin 12 mg/m^2, day 1-3). Although, the patient well tolerate the treatment and achieved a remission at the end of this regime, fetal death occured 7 days after the initiating of the treatment.

DISCUSSION

Treatment decisions for pregant patients with acute leukemia must be based on several factors, including the stage of gestation and the maternal and fetal health at the time of diagnosis, the mother's prognosis and her likelihood of future pregnancies after treatment, and the known carcinogenic potential of the drugs in question. When leukemia was diagnosed in the first or second trimester, there was a high incidence of abortion and premature delivery. However, the incidence of fetal malformations or complications of pregnancy is similar with non-leukemic pregnants.[1]

Our patient well tolerate the first induction regime of acute myeloblastic leukemia that developed in the second trimestr of her pregnancy. However, the second fludarabine containing regime caused to fetal death at the 7th day of initiating the FLAG-IDA regime, 4 days after the last day of fludarabine administration. The main difference between first and second regimes is consisting of fludarabine and the dose of cytarabine. Besides the progress of the

pregnancy, high dose cytosine arabinoside plus fludarabine caused to fetal loss. The fetal-placental circulation is established by 21 days' gestation, and is fully formed by the end of the fourth month of gestation.[3] Therefore, the immaturity of fetal-placental barrier is not seems to be as a cause of fetal loss developed in the last trimestr of her pregnancy.

Placenta facilitates the transfer of nutrients and other physiological substances at the maternal-fetal interface via specific transporters. Assisting in this function are several ATP binding cassette (ABC) family proteins (that include P-glycoprotein (P-gp), multidrug resistance proteins 1-3, breast cancer resistance protein), organic anion transporter, serotonin transporter, norepinephrine transporter, and several organic cation transporters. These transporters localize to the placental trophoblasts and play an important role in limiting the passage of substrate drug through the placenta to reach the fetal circulation. We suggest that these transpoters and their capacity on limiting the passage of their substrates may influence on fetal loss. P-gp has a quite broad substrate specificity including anticancer drugs (e.g., vincristine, vinblastine, anthracyclines, etoposide, taxol, and mithramycin), cytotoxic agents (e.g., colchicine and emetine), HIV protease inhibitors (e.g., sequinavir, indinavir, and ritonavir), and abusable drugs (e.g., morphine). Two different equilibrative nucleoside transporters (ENT1 and ENT2) have been cloned from placenta. Both of them mediate the transport of purine and pyrimidine nucleosides such as adenosine and uridine. A number of anticancer nucleoside analogs (e.g., cladribine, cytarabine, gemcitrabine, and fludarabine) are transportable substrates for ENT1 and ENT2. Most of chemoterapeutics are transport via these proteins in placental barrier. Their drug transport limiting capacity is not well established. We suggest that the cause of this fetal loss may be related with dose intensity or fludarabine addition.[2,3]

There were many reports about pregnancies complicated with AML treated with standart dose cytosine arabinoside and antracyclin combination. Ara-C has been used safely in about 30 cases of pregnancy and leukemia especially in later trimestrs. However, there is no reported case of pregnancy and leukemia treated with fludarabine.[4,5]

In conclusion, we suggest that high dose chemotherapy, mainly FLAG-IDA regime may cause fetal death, although in nearby term periods. These result may be related with limited capacity of placental drug transporters or the primary effect of fludarabine. The determining the main causes of fetal losses in patient with leukemia and pregnancy are not easy because of performed therapeutic abortions in most cases before or during antileukemic treatments. Understanding the role of drug transporters in moderating transplacental passage of substrates has important clinical implications for choosing specific drugs to achieve therapeutic objectives in the expectant mother while minimizing fetal drug exposure.

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