

Idarubicine Treatment of Acute Myeloblastic Leukemia During Pregnancy: Case Report

Gebelikte Akut Myeloblastik Löseminin İdarubisin Tedavisi

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ABSTRACT The occurrence of acute myeloid leukemia is a rare event during pregnancy. We report a case of acute myeloblastic leukemia (AML; FAB M1) diagnosed in 20 year-old female at the 16th week of gestation. Fluorescence in situ hybridization (FISH) examination showed no gene fusions of t (8;21), t (15;17) and t (16;16). According to the result of immunologic typing, she was diagnosed as having acute myeloblastic leukemia, subtype (M1). The patient elected to maintain the pregnancy and underwent induction therapy with idarubicine and cytarabine. Then a high dose of cytarabine was used as a consolidation therapy at 23rd week of gestation. In the 29th of pregnancy, she had spontaneous uterine contractions and gave birth to a 950 gram (g) male infant. The newborn had no structural congenital abnormalities and cardiotoxicity. Pancytopenia was developed in the newborn 5 days later. The newborn died due to respiratory distress syndrome and sepsis in neonatal intensive care unit. Using of idarubicine as an anthracycline during pregnancy has been reported in a few cases to date. In this report, maternal and newborn outcomes of using of idarubicine have been reported in a pregnant woman with AML..

Key Words Leukemia, myelocytic, acute; idarubicine; pregnancy

ÖZET Gebelik süresince akut myeloid lösemi gelişmesi nadir bir durumdur. Biz 20 yaşında 16. gebelik haftasında akut myeloblastik lösemi (AML; FAB M1) tanısı konmuş bir olgu sunuyoruz. Flüoresan in situ hibridizasyon (FISH) muayenesinde t (8;21), t (15;17) ve t (16;16) gen füzyonu saptanmadı. Hasta gebeliğini sürdürme kararı verdi. İdarubisin ve sitarabin ile indüksiyon tedavisi almayı kabul etti. Yirmi üçüncü gebelik haftasında konsolidasyon tedavisi olarak yüksek doz sitarabin verildi. Yirmi dokuzuncu gebelik haftasında spontan uterin kasılmalar gelişti ve 950 gram ağırlığında bir erkek çocuk doğurdu. Yenidoğanda yapısal konjenital anomaliler ve kardiyotoksisite yoktu. Beşinci günde yenidoğanda pansitopeni gelişti. Takiben respiratuar distres sendromu ve sepsise bağlı olarak yenidoğan yoğun bakımda öldü. Gebelikte antrasiklinlerden idarubisin kullanımı günümüzde çok az vakada bildirilmiştir. Burada AML'li bir gebe kadında idarubisin kullanımının maternal ve yenidoğan sonuçları bildirilmiştir.

Anahtar Kelimeler Akut myeloid lösemi, idarubisin, gebelik

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The occurrence of acute myeloblastic leukemia (AML) during pregnancy is rare. The presence of leukemia during pregnancy brings several concerns about the effect of pregnancy on the prognosis of leukemia, the effect of the disease on pregnancy and teratogenic effect of chemotherapeutic agents on the fetus. Careful consideration of the risks and benefits of treatment for both fetus and mother should be considered.

Fetal harm appears less in the second and third trimester of pregnancy.¹ Anthracyclines, mainly idarubicine, represented common chemotherapeutic agent administered to the mother in acute myeloblastic leukemia.^{2,3} Idarubicine has relatively lower cardiotoxicity on fetus than other anthracyclines. For this reason, many clinicians have begun to use idarubicine in the treatment of leukemia during pregnancy.^{4,5}

CASE REPORT

In December 2006, a 20-year-old woman at the 16th week of gestation of pregnancy presented with AML. Her complaints began firstly as cough, phlegm, swelling and gingival bleeding. Within one week, malaise, palpitations and dyspnea were added to the clinical picture. An antimicrobial agent was started empirically with suspicion of upper respiratory tract infection. She referred to our hematology clinic for further investigation when blood count revealed severe anemia (hemoglobin; 3.6 g/dL; hematocrit; 8.9 %) and thrombocytopenia (platelets 53,000 /mm³). Peripheral blood was with increased ratio of monocytes (65.6%). Bone marrow was hypercellular with 94% blasts, 5% lymphocytes and 1% segmented cells. FISH on peripheral blood revealed negative results for gene fusions of t (8;21), t (15;17) and t (16;16). According to the FAB classification she was diagnosed as having acute myeloid leukemia, subtype M1. After consultation with the high-risk maternal-fetal medicine team and hematology team, the patient elected to maintain the pregnancy and decided to take chemotherapy. A baseline maternal and fetal echocardiography did not show any abnormalities. Induction therapy was begun with cytarabine 150 mg/m² given as continuous intravenous infusion over 24 hours on days 1-7, and idarubicine 12 mg/m² given daily over 30 minutes on days 1-3.

Two weeks later, she developed febrile neutropenia. Imipenem (2 g/day) and teicoplanin (400 mg/day) were started. Hematopoetic recovery was with resolution of fever. Bone marrow biopsy performed on 25th day of chemotherapy showed remission. The transfusion need during

chemotherapy was as 11 units' red blood cell and three aphaeresis units of platelets.

At 4 weeks after the remission induction, 23rd week of pregnancy, high-dose cytarabine (3 gr /m² every 12 hours on days 1, 3, and 5) was started as consolidation.⁶ She developed bronchopneumonia as complication which resolved after imipenem (2 g/ day) and teicoplanin (400 mg/ day). In the 29th week of pregnancy, she had spontaneous uterine contractions and gave birth to a 950 g male infant. Except for intrauterine growth retardation, the newborn had not any dysmorphic features and cardiac abnormality. Complete blood count (leukocyte: 8500/ml³, platelet: 260 000/ml³, heamoglobin: 12.6 g/dl) showed normal range but pancytopenia (leukocyte: 600/mm³, platelet:18 000/mm³, heamoglobin: 8.2 g/dl) developed in five days and he died due to respiratory distress syndrome and sepsis caused by pancytopenia and severe prematurity, in neonatal intensive care unit. Patients' blood count was still normal after delivery and a second consolidation was planned.

DISCUSSION

Chemotherapeutic agents administered during pregnancy may have some teratogenic effects. These teratogenic effects include intrauterine growth retardation, fetal malformations, cardiac and hematologic abnormalities, as well as fetal death. There are also other delayed effects of these agents such as secondary malignancies, mental retardation, sterility and long term growth retardation in the child.^{7,14} In pregnant woman who require chemotherapy, antitumour efficacy should be balanced against lowest possible toxic effects to the fetus. In patients with AML, a meta-analysis found that induction regimens including idarubicine resulted in improved remission rates and survival rates compared with other anthracyclines.¹¹

To our knowledge, in the literature, there are only two cases with AML, in which high doses of idarubicine and cytarabine were used together like our case.^{7,8} In the first report, AML was diagnosed 21st gestational week with subtype M5. Complete remission was achieved in patient. Except for in-

trauterine growth retardation, the baby in the first report had no dysmorphic features or major congenital anomalies. In addition to the fetal outcomes, normal echocardiogram findings were detected in this baby. In the second report, minimally differentiated AML was detected in a pregnant woman. Gestational week at diagnosed was 21. Initial complete remission was achieved but patient relapsed and died 10.5 months after diagnosis. In fetal outcomes, intrauterine growth retardation, ventricular septal defect and dysmorphic features such as short digits and limbs, and prominent frontal skull with mild macrognathia were detected.

We did not detect any dysmorphic features and cardiac abnormalities in our fetal outcomes. Intrauterine growth retardation and pancytopenia were detected as adverse effects. Because premature labour occurred, our neonate had some complications related to prematurity and intrauterine growth retardation. Respiratory distress syndrome and necrotizing enterocolitis developed in the 7 days of postpartum period and the neonate was required ventilator support and antibiotherapy for sepsis in the neonatal intensive care unit. The newborn died because of respiratory distress syndrome and sepsis. Nosocomial causes such as stay on ventilator support for a long time, surfactant treatment, and some invasive applications may lead to sepsis. It is well known that RDS incidence is very high at these weeks due to severe prematurity. Absence of dysmorphic features and cardiac abnormalities in our fetal outcomes may relate to prematurity. Due to time of exposure of the chemotherapeutics in prematurity is shorter than normal term, these abnormalities may not occur.

AML is a rapidly dividing hematologic tumor that results in death if not treated promptly. Idarubicin has high lipophilicity and DNA-binding ability and has a greater anti-leukemic effect with relatively lower cardiotoxicity than other anthracyclines.^{9,10} In patients with AML, results of a meta-analysis found that induction regimens including idarubicin resulted in improved remission rates and survival compared with other anthracyclines.¹¹ In a recent review of anthracycline use during pregnancy, the authors reported only two cases of cardiac toxicity in the 110 fetuses exposed to an anthracycline during the second trimester.¹² In the literature, many cases with AML during the pregnancy were treated with daunorubicin or doxorubicin.⁸ However there are a few pregnancies with AML treated with idarubicin as an anthracyclines. For this reason, large series of pregnancies with AML is needed to introduce the effects of idarubicin on maternal and fetal outcomes.

Administration of idarubicin during second trimester of pregnancy is not safe due to its possible cardiotoxic effects. Management of acute myeloblastic leukemia during pregnancy should be evaluated carefully. Besides teratogenic effects on the fetus, administration of chemotherapeutic agents may cause other complications of pregnancy such as premature rupture of membrane and premature delivery.^{13,14} In addition these effects, premature newborn have several medical problems and this newborn generally dies due to these medical problems, as in our newborn. For these reasons, if acute myeloblastic leukemia has been determined in early period of pregnancy, termination of pregnancy should be discussed well with patient and her family.

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