

Case Report

Management of acute myeloid leukemia during pregnancy and after birth: a report of two cases

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Abstract: The present study was to report the management of two cases of successful mother and fetal outcome of acute myeloid leukemia (AML) during pregnancy and after birth. Both patients were diagnosed with AML in their third trimesters of pregnancy. They have normal karyotype. The fusion gene of *AML/ETO* for case 1 was negative and of *CBFB/MYH11* for case 2. Then they received combination chemotherapy (daunorubicin plus cytarabine) during pregnancy and both of them were in remission. They successfully delivered a normal infant at 35 weeks and 37 weeks of gestation and prepared for allogeneic hematopoietic stem cell transplantation (Allo-HSCT). The peripheral blood stem cells for case 1 were provided by Chinese bone marrow bank with an HLA-match of 5.5/6 and for case 2 were by her brother with an identical HLA-match. Then they received conditioning regimen of busulfan and cyclophosphamide, and Graft-versus-Host Disease prophylaxis of cyclosporine A in combination with short-course methotrexate before Allo-HSCT. Both of them received successful bone marrow transplantation and achieved hematopoietic recovery after Allo-HSCT. No serious manifestations of acute graft-versus-host disease were found in them. They were both survived and resumed to a normal life and work, with respective survival time of 81 months and 62 months at recent follow-up. The two male infants were survived and grew up with normal development. Rapid diagnosis and immediate treatment for pregnant patients with AML in the third trimesters can provide more successful opportunities for Allo-HSCT, and also may be beneficial for the survival of both mothers and fetuses.

Keywords: Acute myeloid leukemia, pregnancy, allogeneic hematopoietic stem cell transplantation, combination chemotherapy

Introduction

Acute myeloid leukemia (AML) is the most common form of acute leukemia among adults and the first leading cause of leukemia-related deaths in United States, characterized by a clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues [1, 2]. AML is also a heterogeneous group of leukemia and several factors such as patients age, mutational status and karyotype can influence clinical outcomes [3]. AML occurs mostly in older patients, while it also may happen to women of childbearing age [4]. Not surprisingly, the management of patients with AML during pregnancy will be difficult. However, pregnancy complicated by AML is not common, with an estimated incidence of 1 per 100,000 pregnancies [5, 6]. Treatment for AML coexisting with pregnancy easily falls into an ethical dilemma due to the concern that the optimal

therapy for the mother may have varying risks to the fetus [7, 8]. In the present study, we reported the outcome of two cases diagnosed with AML in their third trimesters of pregnancy and managed with chemotherapy without delay. Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is a potentially curative treatment for many patients with AML, with already 20 years of history up to now [9]. Although Allo-HSCT is not used in the management of all AML, particularly those with core binding factor mutations (*RUNX1-RUNX1T1* and *CBFB-MYH11* fusion genes), it has been demonstrated to be more effective on achievement of complete disease remission and improved prognosis in patient with leukemia and suitable for Allo-HSCT than standard chemotherapy or autologous transplantation [10-12], especially for younger patients. In this study, we also evaluated the outcome of Allo-HSCT in these two cases after chemotherapy. We hoped our report would pro-

vide additional information on the management of AML during pregnancy in their third trimesters and after birth.

Case report

This study was approved by the ethical committee of Zhejiang provincial people's hospital and both patients provided written informed consent.

Case 1

A 25-year-old G1P0 woman in her 28+ weeks of pregnancy presented to our hospital with a one-month history of breathlessness and a three-day history of fever, sore throat and cough. She was noted to be severely anemic and with sternal tenderness. Coarse breath sounds were heard in both lungs. In addition, she had a swollen belly of seven-month pregnancy and the fetal heart rate was 160 beats/min. After admission, she was diagnosed with AML [French-American-British (FAB) class M2] and pulmonary infection. RHG banding analysis revealed a 46, XX karyotype and the fusion gene of *AML/ETO* detected by Real-time PCR was negative.

After consultation, she was treated with standard chemical therapy (DA regimen: daunorubicin, 40 mg/m² per day, days 1-3; cytarabine, 150 mg/m² per day, days 1-7) (Table S1). The dose of chemotherapy was used based on the pre-pregnancy weight of this patient. After chemotherapy, she experienced myelosuppression and aggravated lung infection. Then she was treated with several antibiotics or anti-fungal drugs including imipenem, vancomycin and fluconazole, and given symptomatic supportive treatment like nutrient-supporting treatment. She got much better after these treatments and her leukemia went into remission with 2% myeloblasts.

During chemotherapy, fetal anomalies were assessed by ultrasound and fetal heart rate was monitored by fetal electrocardiogram. The average fetal heart beat was 140 beats/min before delivery. The biparietal diameter and femur length were 86 mm and 65 mm, respectively. Fetal spine trimly arranged, and fetal movement could be detected. The placenta was located on the anterior wall of the uterus, with irregular shaped chorionic plates. Ultrasound revealed an uneven echo and micro calci-

fication. The pregnant uterus is divided into four quadrants and the depth of amniotic fluid in each quadrant is 37 mm, 26 mm, 26 mm and 9 mm, respectively. Moreover, the amniotic fluid was limpid, with an amniotic fluid index of 9.8. The fetal face was not visible due to the fetal position. For umbilical arteries blood flow, the systolic and diastolic peak velocity (S/D) ratio was 2.44. Based on these clinical indicators, the fetus was healthy before delivery.

At 35 weeks of gestation, she delivered a normal male infant by cesarean section. During cesarean section, she had achieved complete remission. She had a normal blood routine tests and the platelet count was within the normal range. The baby weighed 2240 g and the APGAR score were 10 at 5 minutes. The infant was also monitored for cardiac problems by a pediatrician. He was not found with heart murmurs, overt cyanosis and tachypnea. Since the mother continued to receive chemotherapy, the neonate did not received breastfeeding to avoid the anti-leukemia drugs affecting the growth and development of neonates via breast milk. Since she was in financial difficulty, bone marrow transplantation has not been implemented after remission induction chemotherapy. After delivery, this patient was re-admitted to our hospital for another standard chemical therapy as consolidation. Before chemotherapy, CT examination revealed infection in her right lung and *Klebsiella pneumoniae subsp. pneumoniae* was isolated from her sputum specimen. Then she was given cefoperazone-sulbactam sodium for seven weeks until pulmonary lesions basically disappeared assessed by CT examination. Afterwards, she was given two courses of chemotherapy with DA regimen: a course of high-dose cytosine arabinoside (HD Ara-C) treatment (4.5 g/d, days 1, 3, 5) and a courses of chemotherapy with MA regimen (mitoxantrone, 10 mg/m² per day, days 1-3; cytarabine, 150 mg/m² per day, days 1-7) (Table S1). Before each course of chemotherapy, methotrexate (10 mg), Ara-C (50 mg), and dexamethasone (5 mg) were administered to her via an intrathecal injection to prevent central nervous system leukemia (CNSL). Cerebrospinal fluid (CSF) examination was normal during the period of chemotherapy.

After two courses of chemotherapy, she accepted donations from society and found an appropriate donor with an HLA-match of 5.5/6 after

Table 1. Patient's data and hematopoietic stem cell information in two cases with acute myeloid leukemia

Cases	Age at diagnosis	Diagnosis of leukemia	Type for Allo-HSCT	Donor source	HLA-match
Case 1	25	AML-M2, AML/ETO-	Unrelated Allo-HSCT	Chinese bone marrow bank	HLA-match of 5.5/6
Case 2	29	AML-M4, CBFB/MYH11-	HLA-identical sibling Allo-HSCT	Brother	HLA-match of 10/10

Note: Allo-HSCT, allogeneic hematopoietic stem cell transplantation.

HLA-matching in Chinese bone marrow bank and cytomegalovirus (CMV) screening negativity. Patient data and hematopoietic stem cell information were shown in **Table 1**. Before Allo-HSCT, she received the conditioning regimen of busulfan at a dose of 3.2 mg/kg/day divided every 6 hours from day -7 to day -4 and cyclophosphamide at a dose of 60 mg/kg/day on days -3 and -2. Then she was given T cell-depleted peripheral blood stem cells (PBSCs) from this unrelated donor: mononuclear cell amount (MNC) of 6.05×10^8 /kg and CD34 cell number of 4.86×10^6 /kg. The Graft-versus-Host Disease (GVHD) prophylaxis consisted of cyclosporine in combination with short-course methotrexate (MTX): intravenous injection of CsA (2.5 mg/kg/day) daily, starting on day -7; oral administration of mycophenolate mofetil, 0.5 g/day on day +1 twice daily and continuing with decreased dose until day +28; intravenous infusion of MTX (10 mg/d) on day +1, day +3, and day +6. Except for these drugs against GVHD, she was administered with antithymocyte globulin (ATG) at a dose of 2.5 mg/kg/day from day -4 to day -1.

She achieved hematopoietic recovery after transplantation. The main results were shown in **Table 2**. The time to neutrophils engraftment ($> 0.5 \times 10^9$ /L) was 13 days, to platelets engraftment ($> 20 \times 10^9$ /L) was 16 days. ABO blood group polymorphism detection and short tandem repeat-PCR (STR-PCR) revealed 100% donor chimerism after engraftment, indicating success of allogeneic bone marrow transplantation. She was found with grade II skin acute GVHD, which was controlled by several anti-rejection drugs such as methylprednisolone and MMF. Moreover, she had not been infected by CMV and CMV-related pneumonia was not found in her.

She was followed up every three months after Allo-HSCT. She was survived free of disease, and the survival time was 81 months at recent follow-up. Moreover, blood routine examination and bone marrow smear were both normal. The male infant was survived and he was six

years old. He grew up with normal development and had equivalent intellectual performance compared with age-matched children.

Case 2

For case 2, she was a 29-year-old G3P2 woman in her 32th weeks of pregnancy. She presented to our hospital with skin ecchymosis for one month, and dizziness and fatigue for three days. She was diagnosed with AML (FAB M4) after admission. RHG banding analysis revealed a karyotype of 46, XX and the fusion gene of *CBFB/MYH11* detected by real-time PCR was negative.

After consultation, standard chemical therapy with DA regimen was recommended to her. The dose of chemotherapy used was based on her pre-pregnancy weight. Partial detumescence with 15% primitive and immature leukemia cells had been achieved when reviewing her bone marrow after chemotherapy.

During chemotherapy, fetal monitoring was performed by ultrasound above mother's symphysis. The average fetal heart rate was 134 beats/min monitored by fetal electrocardiogram. The biparietal diameter and femur length were 89 mm and 63 mm, respectively. Fetal spine trimly arranged, and fetal movement could be detected. The placenta is located on the left posterior wall of the uterus, with irregular shaped chorionic plates. Ultrasound revealed an uneven echo and micro calcification. The pregnant uterus is divided into four quadrants and the depth of amniotic fluid in each quadrant is 41 mm, 22 mm, 25 mm and 20 mm, respectively. The amniotic fluid was limpid. The fetal face was also not visible due to the fetal position. For umbilical arteries blood flow, the S/D ratio was 2.5. She also had a grade 2 placenta and an amniotic fluid index of 10.8. All these indicators showed a normal baby before delivery.

At 38+ weeks of gestation, she delivered via cesarean section a healthy male baby weighing

Table 2. Main outcome of hematological parameters and complication after Allo-HSCT

Cases	Mononuclear cells ($\times 10^8/\text{kg}$)	CD34+ cells ($10^6/\text{kg}$)	Days for neutrophils amount $> 0.5 \times 10^9/\text{L}$	Days for platelets amount $> 20 \times 10^9/\text{L}$	Complications
Case 1	6.05	4.86	13	16	Skin rash, associated with acute graft-versus-host disease
Case 2	4.99	3.47	11	13	No obvious manifestation

Note: Allo-HSCT, allogeneic hematopoietic stem cell transplantation.

3080 g with an APGAR score of 10 at 5 minutes. Then the baby was monitored for cardiac problems by a pediatrician. No fetal murmurs, overt cyanosis and tachypnea were found by postnatal echocardiography. The neonate did not receive breastfeeding to avoid the anti-leukemia drugs affecting the growth and development of neonates via breast milk. During cesarean section, she had achieved partial remission, and the hemoglobin level, the counts of erythrocyte, leukocyte and blood platelets returned to normal. Subsequently, she was given three courses of chemotherapy with IA regimen (idarubicin, 8 mg/m² per day, days 1-3; cytarabine, 150 mg/m² per day, days 1-7) (Table S1) for consolidation therapy. Also, before each course of chemotherapy, she was given an intrathecal injection of 10 mg methotrexate, 50 mg Ara-C, and 5 mg dexamethasone to prevent CNSL. CSF examination was normal during the period of chemotherapy.

After chemotherapy, she received PBSCs from her brother who was HLA identical with her (10/10) and CMV screening negativity. Patient data and hematopoietic stem cell information for her were shown in Table 1. The conditioning regimen was performed on her as same as on case 1. Prophylaxis against GVHD consisted of cyclosporine A and MTX and the detailed information were described for case 1. She was given PBSCs collected from her brother without T-cell depletion: MNC of $4.99 \times 10^8/\text{kg}$ and CD34 cell number of $3.47 \times 10^6/\text{kg}$.

She also achieved hematopoietic recovery after transplantation and the results were shown in Table 2. The time to neutrophils recovery was 11 days, and to platelets recovery was 13 days. Detection of ABO blood group polymorphism and STR-PCR revealed 100% donor chimerism after engraftment. She was free of acute GVHD and CMV infection.

She was also followed up every three months after Allo-HSCT. At recent follow-up, the dis-

ease-free survival time for her was 62 months. She had normal blood routine test and bone marrow smear. Her male infant was also survived and he was 5 years old at recent follow-up. He grew up with normal development and had equivalent intellectual performance compared with age-matched children.

Discussion

The first description of leukemia occurring during pregnancy was traced back to 1845 [13], and a rising number of similar cases have been reported successively. More than two-thirds pregnant patients with leukemia are diagnosed with AML [14, 15], moreover the diagnosis generally occurs during the second and third trimesters [14]. In our study, two patients with AML during pregnancy were at their third trimesters of gestation. Additionally, both of them have normal karyotypes.

Leukemia occurring during pregnancy is not common. Sometimes, reaction of pregnancy may conceal the symptoms and signs of leukemia, leading to a delayed diagnosis of this disease. Leukemia in a pregnant woman is supposed to have greatly harmful influence on the pregnant women as well as the fetus [14]. Leukemia in a pregnant woman carries an increased risk of miscarriage, fetal growth restriction and perinatal mortality [16]. Pregnancy in a patient with AML requires cytostatic treatment, but it also poses a difficult therapeutic dilemma since this treatment would compromise the fetus [17]. As recommended by the recent guidelines for the diagnosis and management of AML in pregnancy [18], pregnant woman with AML should be managed by a multidisciplinary team consisting of hematologists, obstetricians, neonatologists and anesthetists and they should be fully informed about the diagnosis, the treatment and possible complications during pregnancy. A successful pregnancy outcome is unlikely for

patient diagnosis in the first trimesters of pregnancy and spontaneous abortion would bring considerable risks for the mothers. When diagnosis was made during second and third trimesters, patients were advised to continue with pregnancy and start chemotherapy. Additionally, for gestations beyond 28 weeks, the risk of fetal prematurity should be weighed against the risk of fetal chemotherapy exposure. In our study, case 1 was diagnosed with AML in her 28+ weeks pregnancy, fetal maturity has not been achieved. Early delivery would result in the birth of premature infants and low birth weight infants. For case 2, she was found with AML in her 32th weeks of pregnancy. She presented with an abnormal blood test and her estimated date of birth was uncertain. After consultation, our doctors believed that there is a high risk for both mothers experiencing early delivery. Based on their situation, early delivery without chemotherapy may aggravate hemorrhage and increase the risk of delivery, which also carry a risk to their babies. Compared to the fetal risk related to prematurity, chemotherapy appears to carry a low risk to fetus. So early delivery at their diagnosis has not been advised and chemotherapy treatment has been performed for both patients.

The adverse effects of chemotherapy may be ascribed to two aspects, one is the immediate effects in terms of abortion and teratogenicity, the other is the late effects which may influence the normal development of gonad, central nervous system and genetic and teratogenic disorders affecting future generations [19-21]. Since the period between 3rd and 10th weeks which correlates with the stage of active organogenesis is considered to be the most critical period for teratogenicity, chemotherapy drugs are not recommended for patients during their first trimester [22]. There is a lower incidence of fetal malformations associated with chemotherapy after the second trimester than the normal [17, 22, 23]. Some anthracyclines, such as daunorubicin and doxorubicin are considered relatively safe when administered to patients during the second and third trimesters of pregnancy [24]. Daunorubicin in combination with cytarabine is a well-studied AML treatment [25]. This combination treatment has a category 1 recommendation from the National Comprehensive Cancer Network (NCCN) guidelines for first-line treatment of AML in adult patients younger than 60 years [25]. In our

study, both patients received “3 + 7 regimen” (Daunorubicin, 40 mg/m² per day, days 1-3; Cytarabine, 150 mg/m² per day, days 1-7) as induction, which has been also recommended by the “Guidelines for the diagnosis and management of AML in pregnancy” [18]. Additionally, a close monitoring of fetal anomalies was performed in both patients by ultrasound and fetal electrocardiogram and both fetuses were normal during the chemotherapy.

After induction chemotherapy, both cases achieved complete or partial remission and the counts of erythrocyte, leukocyte and blood platelets of both patients returned to normal. Additionally, case 1 was a 25-year-old G1P0 woman and case 2 was a 29-year-old G3P2 woman. For both cases, the estimated date of birth was uncertain. Moreover, case 2 had a scarred uterus and indications for cesarean section. Since cesarean section could be performed designedly and the patient could receive prompt anti-leukemia treatment after surgery, cesarean section was advised to both of them to ensure the health of fetus. Then both cases delivered normal and healthy infant at 36 weeks and 38+ weeks of pregnancy, respectively. After prompt chemotherapy treatment, leukemia in both patients has been eased and they delivered normal and healthy infants. Our results confirmed that delay in appropriate treatment may exacerbate the disease, affect the maternal prognosis and increase the mortality [26, 27] and successful maternal or fetal outcomes can be achieved when leukemia is treated during pregnancy [8, 28, 29]. The chemotherapy provided a favorable condition for continued gestation and the normal growth and development of fetuses. In addition, early execution of appropriate treatment for pregnant patients would provide more opportunities for subsequent Allo-HSCT and increase the survival rate of both mothers and fetus. Therefore, we supposed that it is beneficial for both mothers and infants to make a choice of chemotherapy before delivery.

After delivery, both cases had indications for Allo-HSCT. However, case 1 had a financial difficulty, so bone marrow transplantation has not been implemented after remission induction chemotherapy. This patient received high-dose cytosine arabinoside as consolidation after delivery. Afterwards, several media coverage has reported her experience and many kind-

hearted people donated money to her. She accepted donations from society and found an appropriate donor with a HLA-match of 5.5/6 after HLA-matching in Chinese bone marrow bank. Case 2 received PBSCs from her brother with a HLA-match of 10/10. We also evaluated the outcome of both patients after Allo-HSCT. Allo-HSCT is the most effective option for maintaining remission and preventing relapse, which is a priority in AML treatment [30, 31]. Previous study indicated that the benefit of Allo-HSCT is limited to patients under 35 to 40 years of age, since non-relapse mortality negates it in older patients [32, 33]. In our study, both patients were under 35 years when Allo-HSCT was performed on them. They were both survived after allogeneic HSCT and resumed to a normal life and work.

There are some limitations in our study. We only reported two cases of AML during pregnancy and the follow-up period was relatively short. The effects of chemotherapy during the pregnant period on offspring and the long-period outcome of patients after Allo-HSCT remain still undetermined. However, our results added some useful information for the treatment of AML during pregnancy and after birth.

In conclusion, our report indicated that rapid and prompt diagnosis as well as immediate treatment for pregnant patients with AML in the third trimesters (between 28 and 32 weeks) could provide more successful opportunities for Allo-HSCT, and may be beneficial for the survival of both mothers and fetuses.

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Disclosure of conflict of interest

None.

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Combination of chemotherapy with Allo-HSCT for treating AML

Table S1. The chemotherapeutic agents used in both cases

Therapeutic regimen	Agent	Dose	Manufacturer
DA regimen	Daunorubici	40 mg/m ² /d, d1-d3	Zhejiang Hisun pharmaceutical Co. Ltd., Taizhou, Zhejiang, China.
	Cytarabine	150 mg/m ² /d, d1-d7	Actavis Italy SpA, Nerviano, Milano, Italy.
A course of high-dose cytosine arabinoside treatment	Cytosine arabinoside	4.5 g/d, d1, d3, d5	Actavis Italy SpA, Nerviano, Milano, Italy.
MA regimen	Mitoxantrone	10 mg/m ² /d, d1-d3	Shangdong Luoxin Biotechnology Co., Ltd., Linyi, Shandong, China.
	Cytarabine	150 mg/m ² /d, d1-d7	Actavis Italy SpA, Nerviano, Milano, Italy.
Triple intrathecalinjection	Cytarabine	50 mg	Actavis Italy SpA, Nerviano, Milano, Italy.
	Methotrexate	10 mg	Jiangsu Hengrui Medicine Co., Ltd., Lianyungang, Jiangsu, China.
	Dexamethasone	5 mg	Guangzhou Baiyunshan Tianxin pharmaceutical Co. Ltd., Guangzhou, Guangdong, China.
Conditioning regimen before Allo-HSCT	Busulfan	3.2 mg/kg/d, d-7~d-4	Ben Venue Laboratories Inc., Bedford, Ohio, USA.
	Cyclophosphamide	60 mg/kg/d, d-3~d-2	Baxter Oncology GmbH, Halle, Germany.
	Antithymocyte globulin	2.5 mg/kg/d, d-4~d-1	Neovii Biotech GmbH, Munich, Germany
IA regimen	Idarubicin	8 mg/m ² /d, d1-d3	Zhejiang Hisun pharmaceutical Co. Ltd., Taizhou, Zhejiang, China.
	Cytarabine	150 mg/m ² /d, d1-d7	Actavis Italy SpA, Nerviano, Milano, Italy.