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Chronic myeloid leukemia management during pregnancy: a case report

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Abstract

Chronic Myeloid Leukemia (CML) is characterized by the increased and unregulated growth of myeloid cells in bone marrow and accumulation of these cells in blood. Its occurrence during pregnancy is a very rare condition and the correct management is not well stablished yet. We present a case of a 21-year-old female diagnosed with CML during pregnancy. The protocol chose by the doctor was hydroxyurea on second trimester, and interferon-alpha on third trimester. The baby was born healthy and at the expected time. After giving birth, the patient started Imatinib Mesilate (IM) 400mg/day treatment and was able to control the disease.

Keywords: Pregnancy, Chronic Myeloid Leukemia, Management.

Introduction

The management of Chronic Myeloid Leukemia (CML) during pregnancy is quite not elucidated yet [1, 2]. Although many patients are diagnosed after the reproductive age, patients under 29 years old comprise 7.5–12% of all CML cases [3]. Nowadays, the treatment options available are mainly tyrosine kinase

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inhibitors (TKIs), interferon-alpha (IFN-α), leukapheresis and hydroxyurea (HU) [4]. If the patient planned the pregnancy, TKI treatment must be replaced for another one before conceiving, due to its comproved side effects to the fetus development [5, 6].

On the other hand, if the pregnancy is not planned, each case must be looked in an independent way, giving special attention to the pregnancy period, leukocyte and plateles account and pregnancy history.

In this case report, a patient received a CML diagnose at 7 weeks pregnancy. The treatment conduct choosen for her was able to keep disease under control during pregnancy and did not affect fetal development. This article aims to contribute to the better pregnancy management for patients diagnosed with CML.

Case report

A 19-year-old woman at gestacional age of seven weeks and no prior medical history of familiar cancer was admitted to the Maternidade Escola Assis Chateaubriand (MEAC/UFC) located at Fortaleza State, northeast Brazil, in November 2017. Physical examination indicated an enlarged spleen and hemogram as follows: White blood cell count of 250,39 × 103/mm3 with 2% blasts, 15% metamyelocytes, 23% bands, 63% neutrophils, and 2% lymphocytes; hemoglobin concentration of 9 g/dL; and platelet count of 1,035 × 106/mm3.

The exams showed leukocytosis with a left shift (presence of metamielocytes and bands), thrombocytosis and anemia. The patient reported asthenia and malaise, had no comorbidities, and had had another pregnancy with eclampsia, four years before.

Qualitative Real-Time Polymerase Chain Reaction (qPCR) analysis was performed in a peripheral blood sample and led to a BCR-ABL1 fusion transcript e14a2 positive result and to CML diagnoses, at the end of the 8th gestational week. At this time, patient reported front-occipital headache and the fetus presented tachycardia. After 12 weeks of pregnancy (December 2017), the patient started cytoreductive therapy with HU (1g/day) and sodium enoxaparin.

At 27 weeks of pregnancy (February 2018), patient showed dyspnea to great efforts and throbbing headache during morning, wield with paracetamol. At this time (end of the second trimester), HU was suspended, and the patient remained without any citorreductive medication for one month. IFN-α treatment (3.000.000 UI, three times/week) was administered from March to May 2018.

The Gestational Ultrasound (GUS) was performed every month and showed no alterations in fetus development. Leukocytes and platelets levels were monitored during pregnancy and medication changes, and the levels were back to normal, as can be observed in Figure 1.

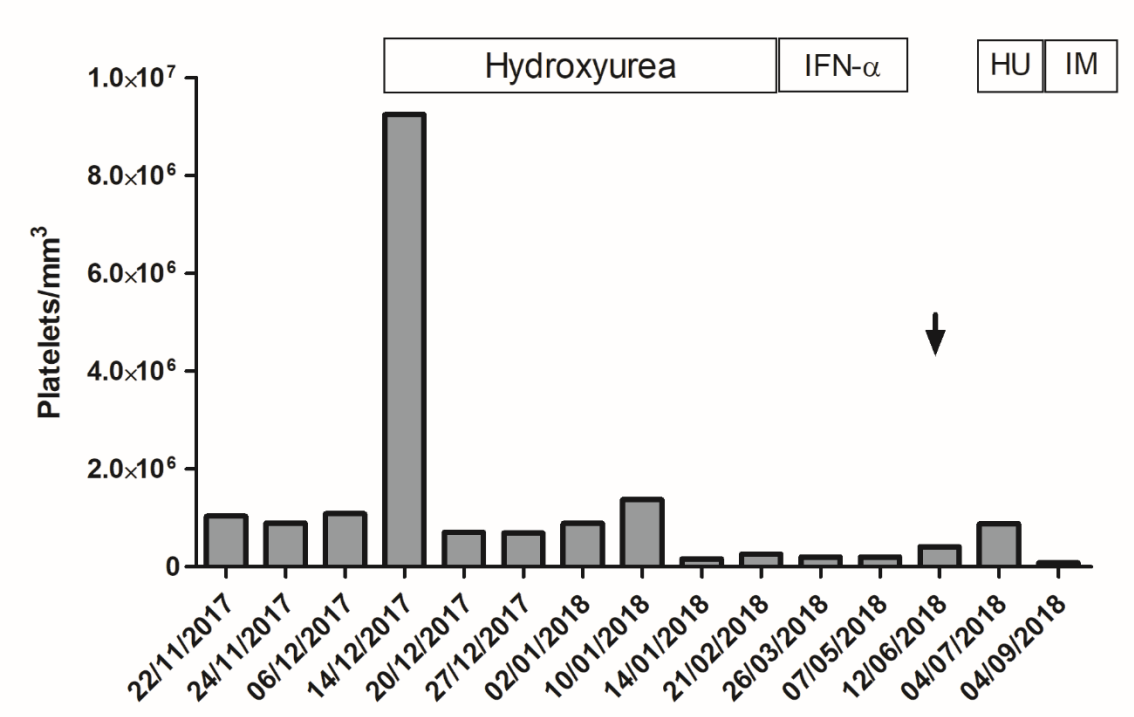

Figure 1. Leukocyte and platelet variation during pregnancy and post-partum period. The arrow indicated the childbirth. HU = Hydroxyurea; IFN-α = Interferon-alpha; IM = Imatinibe Mesilate.

The cytoreductive treatment was interrupted from May 30, 2018, until 37 weeks of pregnancy (June, 2018), when the patient gave birth to a healthy child with 3165g and APGAR score 9/10, through Caesarean section. After the baby was born, the patient took HU again, due to the lack of IM in the hospital. The IM (400mg/day) was available only one month and 14 days after the child was born (Figure 1). The patient tried to breast feeding her son during the first 24 hours, but the newborn developed cyanosis, which led to an interruption of breast-feeding.

After the patient started IM and oral contraceptives, the patient reported some adverse effects such as nausea, diarrhea, vomiting and severe epigastric pain, with one episode of hematemesis. These adverse effects were reported from fourth to ninth month after given birth. The patient stops taking oral

contraceptive pills and showed a pain reduction.

Discussion and Conclusion

Chronic Myeloid Leukemia (CML) is a hematological neoplasia, which accounts for approximately 15% to 20% of all leukemias, with incidence of one to two cases per 100,000 individuals. It presents a higher frequency in adults between 40 and 60 years, mainly males. However, it can affect individuals of all age groups, with less than 10% of cases corresponding to patients up to 20 years of age. [8]

The occurrence rate of leukemia during pregnancy is 1-2/100,000, being described as a very rare condition [5, 9]. In general, malignancies during the pregnancy have been considered a challenge for oncologists due to limited treatment options [10]. Most of the available anticancer agents are cytotoxic and have many potential embryo and fetus side effects, interfering in the implantation process or blocking the totipotent cell's DNA synthesis, compromising normal development [11].

Considering the lack of a standard protocol for the management of leukemia during pregnancy, different treatment options may be more appropriate in each case, depending on the moment of diagnosis. For example, according to Mikhael (2017), if pregnancy occurs after two years after the patient has reached remission, discontinuation of TKI becomes safer for eventual pregnancy. However, if the patient receives the diagnosis during the pregnancy, the use of TKIs as initial treatment should be avoided due to their higher toxicity, and other forms of management should be considered [12].

Nowadays, the available options for CML treatment during pregnancy includes tyrosine kinase inhibitors (TKIs), IFN-α, leukapheresis and HU [4]. HU have been used as initial therapy before confirmation of the BCR-ABL1 fusion and in high leukocyte counts or clinical symptoms. Although HU is effective in inducing clinical and hematological remission, this medication is not as effective as TKIs in cytogenetic remission [12, 13].

Some successful cases have been reported of pregnant woman being treated with HU during pregnancy [5, 14], indicating that this medication might be considered to treat leukocytosis after fetal organogenesis [9]. Besides, this treatment caused a great response to the patient in this article, measured by it effects in platelets down regulation, which was set to normal values in one month (150000-450000 cels/mm^3).

On the other hand, HU potentiates DNA and chromosomal damages, which may promote carci-

nogenesis, genomic instability, and mutation occurrence [15]. However, the incidence of HU-related leukemia remains undetermined and leukemogenic risk of HU remains controversial partially due to lack of long-term follow-up [16].

Regarding the use of TKIs during pregnancy, it is already known that these medications can inhibit diverse proteins, such as KIT proto-oncogene (c-KIT), platelet derived growth factors receptors α and β (PDGFR-α/β), arginase 1 (ARG1) and colony stimulating factor 1 receptor (c-FMS) which are known to have functions that may be important on gonadal development, implantation and fetal development [5- 7].

Although some successful cases have being reported with the use of TKIs during pregnancy [10, 17], those drugs increase toxicity risks to embryo and to mother and their use is contraindicated during pregnancy [6, 9].

On the other hand, the use of HU during pregnancy has some side effects reported, like an increased risk of pre-eclampsia and embryotoxic/teratogenic effects in animal models, and the fact that its excretion occurs through human milk, leading to severe side effects in new births [1]. Nevertheless, HU and IFN-α has been reported as fewer toxic medications, being recommended for the second and third trimesters of pregnancy [12]. Besides that, IFN-α has no association with congenital malformation, although toxicities associations have been described [1, 2, 5, 9].

The use of TKIs after giving birth is encouraged once this medication is more effective in controlling the disease. However, the literature discourages breastfeed for woman taking IM, since it has already been proved that approximately 1.5% of maternal dose is excreted into milk and can cause impaired bone growth and growth retardation in children [1, 5].

The treatment combination chose in this case was able to control the disease during pregnancy and to deliver a healthy baby. The parameters used to follow the disease course was leukocytes and platelets. HU has shown to be a good treatment option during the pregnancy first semester, and IFN-α showed good results during second and third trimesters. We hope to contribute to the elucidation of the best treatment option for patients in this situation and endorse the relevance to disclosure cases like this one, since the CML diagnosis during pregnancy is a very rare condition, especially at such a young age.

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