Acute lymphoblastic leukemia in pregnancy

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Abstract

The diagnosis of a hematologic malignancy such as acute leukemia is uncommon in pregnancy; such disease carries important risks for both the mother and fetus well-being. Acute lymphoblastic leukemia (ALL) presents mainly in childhood and adolescence; consequently, the coexistence of ALL and pregnancy is uncommon, which leads to scarce information related to treatment in this particular population. The present review tries to highlight important data regarding ALL treatment in pregnancy.

Key words: Acute leukemia. Pregnancy. Treatment.

Introduction

Oncology disorders during pregnancy are rare and occur only in 0.1% of pregnancies, mostly are related to non-hematological etiologies¹. A leukemia diagnosis during pregnancy occurs in 1 out of every 1000 pregnancies, corresponding mostly to the myeloid cell line^{2,3}.

Management of acute leukemia during pregnancy places the physician into multiple challenges where it is necessary to balance the risk of teratogenicity and complications in the mother in case of delays in treatment. The low incidence of this condition prevents the possibility of making high-quality studies; however, the majority of recommendations of treatment came from case reports and retrospective cohort studies. The highest incidence of acute lymphoblastic leukemia (ALL) is during childhood and adolescence; therefore, toxicity and complications observed during the administration of essential medication (i.e., L-asparaginase and rituximab) are not well-known³. The treatment of pregnant women with ALL requires multidisciplinary care and a close relationship between physician, patient, and family.

Clinical case

A 14-year-old female without a relevant medical background was referred from another institution due to a 4-week history of progressive dyspnea, paleness, and weight loss. The previous clinic identified the patient with a pregnancy of 24 weeks of gestation, accompanied by high-output heart failure; hence, the patient was referred immediately. During the initial evaluation, the patient was observed with tegument paleness, bilateral basal crackles, and edema in the lower limbs. Her heart rate was of 120 beats per minute (bpm), respiratory rate of 24 breaths per minute, blood pressure of 120/80 mmHg, partial oxygen saturation of 95% with supplementary oxygen.

Her initial laboratory studies reported Hb 2.4 g/dl, leukocytes $2.7 \times 10^3/\text{mL}$, neutrophils $413 \times 10^3/\text{mL}$, lymphocytes $1.47 \times 10^3/\text{mL}$, and platelets $97 \times 10^3/\text{mL}$; a bone marrow aspiration was performed obtaining a diluted sample. However, the presence of L1 type lymphoblasts was identified; therefore, a flow cytometry using the Euroflow system was performed; confirming a positive result for ALL CD10+, CD19+, CD20+, CD22+, CD34+, and CD79acy+. Furthermore, we tried to

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identify the chimeric gene BCR/ABL through *in situ* hybridization technique, which was negative.

Discussion

In the treatment of ALL during pregnancy, it is necessary to remark the priority of the mother well-being over the fetus; however, knowing the different phases of the embryonic-fetal development, measures can be adopted to reduce the risk of teratogenicity without sacrificing effectiveness of treatment. The development of the product can be divided into two periods: pre-embryonic and embryonic phase, which are from conception until week 8 of gestation, and the fetal period, which begins at 8 weeks of gestation until conception. Treatment during both periods can be linked to congenital defects; however, during the embryonic and pre-embryonic periods, the risk is much greater and abortion is the most frequent complication³.

Due to the fact that acute leukemias have an aggressive course, prompt treatment is required which is why therapeutic abortion is recommended before week 20 of gestation; however, each case must be assessed individually. Although it is accepted that after the 20 weeks, the patient can be treated as usual (non-pregnant patient)^{1,3,4}. It is important to highlight the fact that as gestational age advances the possibility of congenital defects decreases remarkably, being lower in the third trimester of gestation. Chemotherapy agents can be related to adverse obstetric results (i.e. fetal death, preterm delivery, and delay in intrauterine growth)^{1,4}.

The use of combined therapy is the cornerstone of ALL treatment. Drugs such as vinca alkaloids (i.e., vincristine), anthracyclines (i.e., daunorubicin, mitoxantrone, and doxorubicin), cytosine arabinoside (AraC), L-asparaginase, methotrexate, and rituximab are part of the standard treatment. It is important to remark the toxicity of methotrexate and its absolute contraindication during pregnancy³⁻⁵. Choosing the appropriate treatment for a patient, different factors ought to be considered, from the chosen medication itself, like the molecular weight of the drug and its binding to proteins, and other factors related to the fetus and mother like permeability of the placental barrier, as well as the physiological increase of the vascular volume of the mother¹⁻⁴. There is little understanding of the pharmacokinetic and pharmacodynamic mechanisms of the drugs during pregnancy; thus, it is important to decide treatment in the available information to choose the

medications with less toxicity for the product without sacrificing effectiveness for the mother²⁻⁴.

In the case of vinca alkaloids, the most used is vincristine which strongly binds to proteins reducing the possibility of teratogenicity. Despite this, there are reports of delay in intrauterine growth as well as preterm delivery and pre-eclampsia⁶. Concerning the use of AraC, its teratogenic dose is unknown; however, it is linked to limb malformations^{6,7}. The use of anthracyclines may cause cardiotoxicity in the fetus, but its toxicity decreases after the third trimester due to a decrease in the permeability of the placental barrier of molecules >500 Da. The two most utilized anthracyclines are doxorubicin (580 Da) and daunorubicin (564 Da)⁸. It is important to note that during pregnancy, there is an increase in plasmatic volume up to 50%, which is accompanied by an increase in renal and hepatic anthracycline depuration; therefore, “attenuating” dosing is not recommended^{2,8}.

Regarding the use of L-asparaginase, it is necessary to highlight the possibility of thrombotic events during its use which in addition with transitory thrombophilia of pregnancy could theoretically increase the possibility of thrombotic events⁹. Rituximab, a monoclonal anti-CD20 antibody, is not recommended during gestation due to the risk of neonatal cytopenia and selective depletion of B lymphocytes⁴. Less common side effects involve the heart as well as limb deformities (i.e., club foot) which were observed in 2.2% of pregnancies¹⁰. It is important to highlight that side effects increase when rituximab is administered in the 12 weeks previous to delivery; mainly because after the 26 weeks of gestation, the permeability of the medication increases, reaching its maximum in the past 4 weeks of gestation¹⁰. Another essential element of management is support treatment, in which prophylaxis with quinolones and antifungal (i.e., amphotericin, itraconazole, posaconazole, and voriconazole) is contraindicated. The use of antiemetics such as ondansetron and metoclopramide as well as antibiotics such as penicillin, cephalosporin, aminoglycosides, and metronidazole is allowed during gestation³. We ought to remark the evidence in favor of safety using cotrimoxazole during pregnancy¹¹.

In the case of acute myeloblastic leukemia (AML), similar outcomes among pregnant and non-gravida patients are extensively described. Such outcomes could be linked to early treatment onset. In the case of ALL, the evidence is scarce; however, extrapolating AML outcomes, early treatment seems imperative to improve outcomes¹².

Clinical case

We decided to begin treatment with steroids and vincristine in our patient as a bridge therapy until reaching the third trimester of gestation, after which a standard induction scheme was set in place with weekly doxorubicin and vincristine, accompanied by hydrocortisone and AraC-based intrathecal chemotherapy. During the administration of chemotherapy, the mother and the fetus were monitored weekly, without eventualities. The patient completed a standard induction regimen; afterward, a reevaluation of bone marrow by flow cytometry was performed and reported positive. Due to this, a change in the chemotherapy scheme was performed; also, we intensified the assessment of fetal well-being, with the plan of performing an induction of labor reaching 34 weeks of gestation.

Conclusion

ALL during pregnancy is a therapeutic challenge for the hematologist, in which the risk of teratogenicity and the well-being of the mother ought to be balanced. Due to this, a multidisciplinary team of specialists is required, with the intention of obtaining the best obstetric and maternal results.

Conflicts of interest

The authors have no conflicts of interest to report.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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