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Acute lymphoblastic leukaemia in pregnancy

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ABSTRACT

Two cases of pregnant patients with acute lymphoblastic leukaemia (ALL) are presented. ALL is rare in pregnancy. The basic principle of ALL treatment is combination chemotherapy with sequential administration of induction, consolidation and maintenance therapy, and this also holds for ALL in pregnancy. The prognosis of ALL in pregnancy is poor and termination of the pregnancy needs to be considered.

KEYWORDS

Acute lymphoblastic leukaemia, pregnancy, termination

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is rare in pregnancy. The overall incidence of ALL is 1.3 per 100,000, with a slight male predominance.[1] In nonpregnant adult patients treatment results in a complete remission in 80% of the cases. Forty percent of adults are cured by modern treatment strategies (disease-free survival for at least ten years). In the past 20 years major advances in terms of biological characterisation and outcome of adult ALL have been achieved. The basic principle of ALL treatment is combination chemotherapy with sequential administration of induction, consolidation and maintenance therapy.[2]
We present two cases of pregnant patients with ALL.

CASE REPORT

Patient A
A 30-year-old female patient presented to the emergency department because of a collapse. An acute lymphoblastic leukaemia (common B cell type) was diagnosed, and a pregnancy test was positive. The white blood cell (WBC) count was 206,000/μl. Vaginal ultrasound revealed an intact intrauterine pregnancy of six weeks gestation. It was her third pregnancy; she had two children from two uneventful pregnancies, the youngest ten months old. Furthermore she had a negative medical history.

Treatment for ALL with prednisone, vincristine, asparaginase, daunorubicin and methotrexate (intrathecal) was started. Cytogenetic analysis revealed a t(9;22) (Philadelphia chromosome). At day 28 after the start of the first course, bone marrow analysis showed persistent leukaemia. After five weeks a missed abortion was diagnosed by abdominal ultrasound. Because of bone marrow depression due to the chemotherapy with concomitant strict isolation, medical rather than surgical treatment for the missed abortion was considered to be the first option, since especially profuse bleeding due to a surgical procedure was feared. Misopristol (800 μg) was given vaginally followed by mifepristone (600 mg) orally. Within 12 hours a complete abortion with little blood loss occurred which was confirmed by vaginal ultrasound. After the second course of high-dose cytarabine, the patient reached a complete remission (CR). An HLA-identical sib was found. Awaiting allogenic transplantation, we prescribed imatinib 800 mg once daily. Three weeks after CR, she was admitted for an allogenic stem cell transplantation. This procedure was complicated by severe sepsis and

adult respiratory distress syndrome (ARDS). The patient died in the ICU.

Patient B

A 37-year-old patient was admitted to the haematology department, where an acute lymphoblastic leukaemia was diagnosed. The WBC was 166,000/μl. The patient was treated with the same high-dose chemotherapy schedule as patient A. Cytogenetic analysis revealed a t(9;22) (Philadelphia chromosome). At the time of diagnosis she was 15 weeks pregnant in her first pregnancy. Termination of the pregnancy was discussed and rejected. Three weeks after the first course of chemotherapy the peripheral blood smear showed 3% lymphoblasts. She was given high-dose cytarabine. At 22 weeks gestation she started having abdominal cramps with the loss of clear fluid and the same day a spontaneous delivery of a stillborn foetus of 400 g occurred. The placenta followed spontaneously and was complete, the blood loss was 500 cc. Because of low platelets (24,000/μl) a platelet transfusion was given. At day 28 after the start of cytarabine we found 65% lymphoblasts in the bone marrow smear. No HLA-identical sib or matched unrelated donor was found. At the patient started imatinib 400 mg twice a day and was discharged. She died a few weeks later.

DISCUSSION

The prognosis of ALL depends on several clinical and biological features. Younger age (<30 years), WBC <30,000/μl, the presence of a mediastinal mass, T-cell or TMy immunophenotype, and absence of the Philadelphia chromosome are positive prognostic factors. Both our patients had Ph+ ALL, WBC >30,000/μl and were ≥30 years. Without any adverse features three-year survival is 91%. Philadelphia chromosome + ALL (Ph+ ALL) has a 76% chance of CR after chemotherapy; of this 76%, only 17% remain in remission after three years.[3] Allogenic transplantation results in higher survival rates.[4] With regard to pregnancy the overall literature is moderately positive about acute leukaemia, but a recent report shows a less favourable outcome.[5] In the first trimester a teratogenic effect of the chemotherapeutic agents used for the treatment of leukaemia can occur.[6] In the second and third trimester of pregnancy, chemotherapy may provide a greater risk of stillbirth, growth retardation, premature birth and maternal and foetal myelosuppression.[7] The treatment during pregnancy does not appear to have a significant impact on the future growth and development of the child.[8]

However, most of the literature deals with acute myeloblastic leukaemia (AML) instead of ALL. Both of our patients suffered from ALL. Some pregnancies have ended uneventfully, although there are few data on long-term follow-up, but severe pre-eclampsia, sudden intra-uterine death, pancytopenia and normal karyogram with a ring chromosome and gaps without clinical consequence have also been reported in pregnant patients with ALL.[9]

Acute leukaemia requires immediate treatment, irrespective of the gestational age.[10] Pregnancy does not alter the course of acute leukaemia, but the outcome is far worse when treatment is delayed.[11] Pregnant women should receive weight-based doses similar to those given to women who are not pregnant, adjusted to the continuing weight gain.[10] Because of the high risk of teratogenic effects of chemotherapy during the first trimester, termination of the pregnancy should be considered. After the first trimester the decision to terminate the pregnancy needs to be discussed with the patient. Vinca alkaloids, anthracyclines, cytarabine and steroids are the cornerstone of remission induction regimens. Vinca alkaloids are not potent teratogens. During pregnancy, 111 exposures have been reported. With administration after the first trimester 8% intrauterine growth retardation (IUGR), 6% preterm delivery and 2% pre-eclampsia occurred. In 28 pregnancies exposed to anthracyclines, 21 were uneventful. Cytarabine can induce limb abnormalities when used in the first trimester. Eighty-nine cases have been reported in which cytarabine was used in all trimesters, with six intrauterine foetal deaths (IUFD) and two neonatal deaths.[10]

A dilatation and curettage is usually considered the first option, but to terminate pregnancies of up to 63 days of amenorrhoea, and increasingly at all gestations, the antiprogesterone mifepristone in combination with a prostaglandin analogue (misoprostol) provides a suitable nonsurgical method.[12-14]

In our first patient timely induction was needed, because she had a high-risk ALL. In patients in the middle of chemotherapy with a very low platelet count, a spontaneous abortion might result in profuse bleeding. Platelets are given if their numbers fall to less than 10,000/μl; in pregnancy transfusions are required at higher levels.[1] In our second patient an immature delivery occurred spontaneously. But again, also in the case of a viable pregnancy, termination of the pregnancy can be considered because of the adverse effects of the chemotherapeutic agents.

CONCLUSION

Our two cases show the poor prognosis of ALL in pregnancy. Both patients had Ph+ ALL, WBC >30,000/μl and were ≥30 years, which are all negative prognostic factors. Acute leukaemia requires immediate treatment, irrespective of the gestational age. Termination of the pregnancy and the risks of chemotherapy during pregnancy, especially in the first trimester, need to be discussed with the patient with ALL. The combination of oral mifepristone and vag-

inally inserted misoprostol is a safe and effective method for abortion. Our first case showed that this method can also be used in patients less suitable for surgical treatment and might be considered the first choice for these patients. Although the literature is moderately positive about the prognosis of acute leukaemia, this does not seem to be the case for ALL in pregnancy. More studies are required to establish the prognosis of acute (lymphoblastic) leukaemia in pregnancy, but this is difficult, because of the low prevalence.

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