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Case Report

Successful Pregnancy and Delivery in a Patient with Chronic Myelogenous Leukemia (CML), and Management of CML with Leukapheresis during Pregnancy: a Case Report and Review of the Literature

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Although infrequently seen, the management of cancer during pregnancy can be difficult for patients, their families and physicians. The concomitant occurrence of pregnancy and chronic myelogenous leukemia is uncommon. We describe the successful management of a 26-year-old woman in the first trimester of her pregnancy with chronic myelogenous leukemia (CML) in chronic phase by using only leukapheresis. She was treated with leukapheresis until her delivery at 36 weeks of gestation. The procedure was without significant adverse effects on the patient or fetus. We applied a total of 15 leukapheresis treatments throughout the pregnancy. The patient gave birth vaginally to a healthy 2800 g boy at 36 weeks of gestation. We conclude that leukapheresis may provide an alternative treatment to chemotherapy, α-interferon or imatinib in pregnant patients with CML, particularly with concern over their potential teratogenic and other adverse effects.

Key words: chronic myelogenous leukemia – pregnancy – leukapheresis

INTRODUCTION

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder with clonal expansion of transformed primitive hematopoietic progenitor cells. It is characterized by a biphasic or triphasic clinical course in which a terminal blastic phase follows a chronic phase of variable duration. It affects predominantly older individuals, although all age groups may be affected (1,2).

The coincidence of CML and pregnancy is an uncommon event, in part because CML occurs mostly in older age groups. The management of CML during pregnancy is a difficult problem because of the potential effects of the therapy on the mother and fetus (3–5). While CML may not need to be treated immediately, and pregnancy does not appear to affect the course of CML, there is still a risk of leukostasis, as well as the risk of placental insufficiency with consequent below-normal fetal birth weight, increased fetal prematurity, and increased mortality if CML is left untreated for the duration of the pregnancy (6–8).

Leukapheresis has been demonstrated to have some value in the management of CML. However, since chronic mechanical cytoreduction does not prolong survival in these patients, and is inconvenient, costly and time consuming, leukapheresis is not currently recommended as maintenance therapy for CML (6,9).

We describe the successful management of a patient with CML in chronic phase by using leukapheresis throughout her pregnancy as the sole modality of treatment.

CASE REPORT

A 26-year-old patient was referred to our hospital at 12 weeks of gestation because of increased white blood cell (WBC) and platelet counts that were detected during the first antenatal visit. She was asymptomatic except for mild fatigue, which she had attributed to her pregnancy. On initial examination, she was found to have an intrauterine pregnancy of 12 weeks' gestation and a spleen palpable 3-cm below the left costal margin.

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WBC count was 131×10^9/l with 35% neutrophils, 15% bands, 20% metamyelocytes, 9% myelocytes, 2% basophils, 8% lymphocytes and 10% monocytes. Hemoglobin was 9.8 g/dl and platelet count was 944×10^9/l. A bone marrow specimen demonstrated marked granulocytic hyperplasia, and marrow cells contained the Philadelphia (Ph) chromosome. Based on the clinical findings and microscopic analyses of her peripheral blood and bone marrow, CML was diagnosed. The patient was admitted to the hospital, and informed consent was obtained for therapeutic leukapheresis. Therapeutic leukapheresis was administered to maintain the patient's WBC below 100×10^9/l. Vascular access was obtained via a 17-gauge needle placed in the antecubital vein; blood return was via an 18-gauge angiocatheter. A COBE SPECTRA continuous-flow pheresis machine was used. Anticoagulation during the procedure was obtained by the use of heparin and acid-citrated dextrose in a ratio of 13:1. Fluid replacement, if needed, was with normal saline (10). Leukapheresis was initiated at the 12th week of gestation and two procedures were carried out over two weeks. The WBC was reduced to 60×10^9/l and remained stable at this level until the 22nd gestational week. At the 23rd week a progressive rise in the WBC count (166×10^9/l) occurred. Leukapheresis was administered and subsequently performed on a weekly outpatient basis until the time of delivery. A total of 15 leukapheresis treatments were performed. An average of 8 l of whole blood was processed in each leukapheresis. *Ex vivo* blood volume was ~200 ml during the harvesting in each pass. Each procedure took ~3 h. During each procedure, an average of 1.3×10^{11} WBC were removed. The patient was kept on her left side to prevent hypotension due to inferior vena cava compression by gravid uterus. The platelet count and spleen size were not decreased by the leukapheresis procedures. Therapeutic leukapheresis was well tolerated by the mother and the fetus in our case and no adverse effects were observed.

Labor was induced at 36 weeks of gestation. A healthy baby boy, weighing 2800 g, 51 cm, with Apgar score of 9, was delivered vaginally. The patient's WBC at that time was 54×10^9/l and hemoglobin was 10.7 g/dl. The infant's examinations and blood count were normal. There were no perinatal complications. Macroscopic examination of the placenta was normal. Two weeks after delivery, α-interferon was started for treatment of CML, because there was no suitable donor for stem cell transplantation. The baby's growth and development have been normal to date (2 years).

DISCUSSION

The pregnancy of a patient with a neoplastic disease requiring cytotoxic treatment poses a very difficult therapeutic dilemma. A related problem arises when a woman becomes pregnant during or shortly after receiving chemotherapy or radiotherapy, due to the side effects of most cytotoxic agents and radiotherapy (4,5,11). Most information on this subject stems from animal experiments, but there is relatively little data on human abnormalities. Data in humans, to a large extent, depend on case reports. The effects of cytotoxic drugs on the fetus may be studied from two perspectives: (i) immediate effects, which are well known in terms of abortive and teratogenic effects; and (ii) late effects, which are less well known, the most important ones are gonadal and other endocrinological disorders, growth and development problems which involve the central nervous system, immunosuppression and genetic and teratogenic disorders that may affect future generations. These risks are concentrated in the first trimester and depend on the chemotherapeutic agents or combinations of agents used (4,5,11–13).

The therapeutic approach to leukemia complicated with pregnancy is likely to be different to that usually used to treat this disease. Differences are modified by several variables, including time of diagnosis, clinical tolerance of the disease, and the toxic effects of the drugs on mother and child (4,5,13,14).

Conventional therapeutic options of chronic phase CML include hydroxyurea, busulfan, interferon-based regimens and stem cell transplantation, with stem cell transplantation being the only curative therapy (1,2). Through rational drug development, imatinib, Gleevec (formerly STI571), a bcr-abl tyrosine kinase inhibitor, offers a new hope for expanded options for patients with CML. Imatinib entered clinical trials in 1998 and has since been shown to induce dramatic hematologic and cytogenetic responses (2,15–19). However, despite its remarkable efficacy and toxicity profile, little is known about the potential for long-term toxicity. In preclinical studies imatinib was teratogenic in rats, but not rabbits, and impaired spermatogenesis occurred in rats, dogs and monkeys. Because of the teratogenicity data in rats, it is recommended that women treated with imatinib should be aware of the potential teratogenicity of imatinib and effective contraception should be used during imatinib therapy to prevent pregnancy. There is no data concerned with continued imatinib therapy during pregnancy (16). Several reports have appeared that describe clonal cytogenetic abnormalities in Ph-negative cells of CML patients treated with imatinib. The long-term significance of these abnormalities remains to be determined (17–19). Both hydroxyurea and busulfan inhibit DNA synthesis and therefore have the potential to cause abortion, intrauterine growth retardation and congenital malformations. However, neither teratogenic effects nor hematologic consequences to the fetus have been reported with hydroxyurea treatment (20–25). Busulfan crosses the placenta and causes severe stunting of growth and gonadal aplasia in the offspring of pregnant rats (6,7). Busulfan has been used successfully in CML during pregnancy, but fetal malformations have been reported (4,5,20,26).

α-Interferon has been used for the treatment of CML with variable success (1,2). Laboratory evidence suggests that it crosses the placental barrier and increases the incidence of abortion in rhesus monkeys (27,28). There are no reports about its adverse effects on pregnancy and the developing fetus in humans, but there are reports of normal infants delivered following treatment with α-interferon during pregnancy (8,20,26–30). But α-interferon therapy may decrease fertility

due to decreases in serum estradiol and progesterone levels (28).

Leukapheresis has been successfully used in both acute and chronic leukemia for the rapid reduction of high WBC counts in patients with impending vascular occlusion. Since chronic mechanical cytoreduction does not prolong survival in these patients, and because it is inconvenient, costly and time-consuming, leukapheresis is not currently recommended as maintenance therapy for these diseases. However, this form of treatment does offer an attractive short-term alternative to chemotherapy for the pregnant patient, since exposure to the potentially hazardous effects of alternative chemical agents can be avoided (6,14,31–35). We applied a total of 15 leukapheresis treatments throughout the pregnancy. Therapeutic leukapheresis was well tolerated by the mother and the fetus in our case and no adverse effect was observed.

In conclusion, in light of other successfully treated cases reported in the literature and our own we would suggest that leukapheresis can be considered for treatment of CML as early as the first trimester of pregnancy and that it can be successfully continued throughout the pregnancy. Because of the lack of teratogenic and other adverse effects, it may be the optimal treatment for pregnant patients with CML who tolerate and respond to the procedure.

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