LETTER TO THE EDITOR

Successful Pregnancy following Busulfan and Cyclophosphamide Conditioning and Allogeneic Bone Marrow Transplantation for Chronic Myeloid Leukemia

Recovery of gonadal function in patients after allogeneic stem cell transplantation for hematologic malignancies is uncommon, and only a few cases have been reported. We report the case of a 39-year-old woman who had a normal full-term delivery 8 years after allogeneic bone marrow transplantation for chronic myeloid leukemia. Conditioning consisted of cyclophosphamide 120 mg/kg over 2 days and Busulfan 16 mg/kg over 4 days (BuCy). To our knowledge, this is the second reported case of pregnancy after BuCy conditioning.

An increasing number of young women suffering from leukemia and other malignant and nonmalignant disorders are being cured by stem cell transplantation (SCT), raising the concern of late adverse effects of this procedure. These young people often wish to resume a high quality of life, and usually wish to have children. Most pretransplant conditioning protocols include alkylating agents, irradiation, or both, either of which can cause germinal epithelium depletion and infertility [1]. In the nontransplant setting, the frequency of early menopause, azoospermia and germ cell destruction varies with the type and total dose of alkylating agent or irradiation, as well as patient sex and age at the time of treatment administration [2,3]. Despite the gonadal toxicity of SCT, the literature documents successful pregnancies after therapy; however, the true incidence of pregnancy and pregnancy-related complications after transplantation are unknown [4-11]. We report a successful pregnancy and delivery after allogeneic bone marrow transplantation for chronic myeloid leukemia (CML) conditioned with busulfan and cyclophosphamide.

A 31-year-old woman was diagnosed with Philadelphia positive CML in the chronic phase in April 1998 after routine admission blood cell count. Clinical examination was normal, without splenomegaly. Hematologic values were: hemoglobin 10.9 g/dL, white blood cells: 105 × 10^9/L (8% promyelocytes, 15% myelocytes, 15% metamyelocytes, 50% band cells, and 3% segmented cells), platelets: 1128 × 10^9/L. Bone marrow examination was hypercellular without excess of blasts. Karyotype showed 46, XX, t(9;22) with no other abnormalities. Cytoreduction with hydroxyurea was started followed by Interferon-alpha-2b 5,000,000 UI 5 times per week from May 1998 to December 1999, achieving hematologic remission. Allogeneic bone marrow transplantation from her HLA identical sister was performed in July 2000 after conditioning with busulfan 16 mg/kg over 4 days and cyclophosphamide 120 mg/kg over 2 days (BuCy). Anti-GVHD prophylaxis included methotrexate and cyclosporine A. She presented acute grade I skin and chronic grade I liver GVHD. In 2006, during follow-up with no evidence of disease, she was found to be pregnant, and in October 2006 she gave birth to a term, normal-weight healthy boy. She was at that time 39 years old. There were no complications during pregnancy and no evidence of recurrence of CML after delivery.

Recovery of gonadal function in patients after SCT for hematologic malignancies is uncommon, and only a few cases have been reported. In allogeneic SCT, recovery of ovarian function ranges from 14% to 24%, and the major factors that influence posttransplant fertility are total body irradiation (TBI) and age [12,13]. Sanders et al. [8] described from a population of 1522 transplant survivors 146 pregnancies in 76 allograft patients conditioned with cyclophosphamide with or without busulfan or TBI. Of 73 women treated with BuCy only 1 recovered ovarian function, but she did not become pregnant after SCT. They also found that partners of male patients had uncomplicated pregnancies and normal children, whereas female recipients of allografts had a high incidence of miscarriage, premature labor, and low birthweight babies. However, the infants were apparently not at risk for increased incidence of congenital anomalies.

Salooja et al. [11] assessed the outcome of conception in women and partners of men relating to 19,412 allogeneic and 17,950 autologous transplant patients. 232 (0.6%) conceived after SCT. Seventy-four were women after allo-SCT, including only 1 patient receiving BuCy as conditioning regimen (described separately in a case report [7]). Rates of congenital anomalies, developmental delay, and malignant disease were not higher than normal in the offspring of SCT patients. Three CML patients relapsed after
pregnancy with embryo transfer, raising the concern of a theoretic disturbance of the graft-versus-leukemia effect as a consequence of pregnancy [11,14].

To our knowledge, this is the second reported case of successful pregnancy after BuCy conditioning and allogeneic bone marrow transplantation in a female patient and the first reported case of pregnancy after SCT and BuCy in CML receiving chemotherapy before transplant (hydroxyurea). The first reported case was in a thalassemia patient [7].

The effect of BuCy on fertility remains unclear, and deserves further study and continued follow-up evaluation with pregnancy outcome on transplant recipients to determine the actual incidence of fertility, pregnancy-related complications, leukemia relapse, as well as mutational injury that could affect their offspring.

The erratic gastrointestinal absorption of busulfan as a result of oral administration may lead to intra- and interindividual variability, bioavailability, and pharmacokinetics [15,16], and the impact of intravenous administration or different dosing schedules (eg, once daily) in fertility needs further investigation.

In vitro fertilization (IVF) with embryo cryopreservation constitutes a valid alternative for young women cured after SCT with some successful reported cases in the literature [17,18]. On the other hand, cryopreservation of mature oocytes following IVF/intracytoplasmic sperm injection offers some advantages, but it is still limited by its low success rate. Emerging and exciting techniques of germ cell/gonadal tissue cryopreservation (banking) followed by autotransplantation have been clinically explored but it should be considered experimental in humans for the present time until greater evidence regarding efficacy and safety is accrued [19].

REFERENCES

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