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Successful Pregnancy After Conditioning With Cyclophosphamide and Fractionated Total Body Irradiation

Louis Letendre[1]* and S. Breanndan Moore[1]

We report the case of a 24-year-old man who received high-dose cyclophosphamide (CY) 120mg/kg over 2 days and twice daily fractionated total body irradiation (TBI) over 3 days(1,320 cGy) prior to allogeneic bone marrowtransplantation. Seven and one-half years later he fathered a normal child who has developed normally so far. **Med. Pediatr. Oncol. 28: 147–148** © 1997 Wiley-Liss, Inc.

Key words: successful pregnancy after CY and TBI conditioning

INTRODUCTION

There is an increasing number of long-term survivors of autologous and allogeneic bone marrow transplantations. A variety of complications have been described, resulting from aggressive conditioning regimen, immunosuppressive therapy, or the effect of graft-vs.-host disease (GVHD). At our institution, nearly all patients receiving allogeneic bone marrow transplantation for hematologic malignancies are conditioned with high-dose cyclophosphamide (CY) 60 mg/kg/d on days −5 and −4 followed by twice daily fraction of total body irradiation (TBI) 220 cGy per fraction on days −3, −2, and −1. Radiation is administered at a dose rate of 8 cGy/min and homogeneity of dose distribution falls within 5–15%. This program was expected to invariably result in sterility, but we hereby report the case of a young man who fathered a healthy daughter $7\frac{1}{2}$ years after receiving this regimen. Among 26 other males who underwent allogeneic transplantation for hematologic malignancy, and who survived more than 3 years posttransplant, he is the only one to have fathered a child.

CASE REPORT

The patient was 24 years old when he was referred in June 1985 with a 2-week history of sore throat, tonsillar enlargement, cervical adenopathy, and unresponsiveness to oral antibiotics. His peripheral white blood cell count (WBC) was 35,000 with 74% blasts. His bone marrow was consistent with acute nonlymphocytic leukemia classified as M_4 by FAB criteria. The cytogenetic analysis of 20 metaphases was normal.

He was induced in complete remission with only one course of daunorubicin (DNR 60 mg/m^2 days 1, 2, 3), cytosine arabinoside (Ara-C 200 mg/m^2 continuous infusion for 5 days), and 6-thioguanine (6-TG 100 mg/m^2 po bid for 5 days). Because of his high WBC count at presentation, it was decided to proceed with immediate allogeneic bone marrow transplantation from his HLA-identical and mixed lymphocyte culture-compatible brother.

In late July 1985 he received conditioning with CY/TBI. Review of his hospital course was uneventful with good engraftment documented on day 19 (Absolute Neutrophil Count (ANC) >500 and platelet > 50,000). Despite prophylactic treatment of GVHD with methotrexate, he developed a characteristic skin rash and liver function test abnormality on day 28. He responded dramatically and rapidly to prednisone 1.5 mg/kg/d and the medication was rapidly tapered.

Other complications included *Pneumocystis carinii* pneumonia on day 300 and streptococcus pneumonia sepsis on day 330. During the second year posttransplant, he presented with signs of localized cutaneous chronic GVHD with subcutaneous sclerosis at the wrists, elbows, and knees. He was treated with penicillamin from April 1987 to April 1992. Because his course remained fairly indolent and without functional impairment, the medication was discontinued.

In September 1992 his wife became pregnant. An ultrasound at 4 and 6 months showed a normal fetus. An amniocentesis was done at 4 months of pregnancy and was also normal. The pregnancy was allowed to proceed to term. In June 1993 she delivered a normal baby girl. No congenital malformation was detected and the baby has developed normally during the last 2 years.

With parental informed consent we obtained detailed HLA typing, as well as red cell antigen determination of the baby, the mother, and the patient. From all the avail-

[1]Departments of Hematology and Internal Medicine and Transfusion Medicine, Mayo Foundation, Rochester, Minnesota.

*Correspondence to: L. Letendre, Division of Hematology and Internal Medicine, Mayo Foundation, Rochester, MN 55905.

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able information we are reasonably confident that this patient is the biological father. We found Fy^a, Le^a, and Jk^a antigens on the child's red cells which could not have been inherited from the mother. These antigens had to be of biological paternal origin, but we cannot prove that they came from the patient, as we had no pretransplantation red cells from the bone marrow transplantation patient. The baby's HLA typing demonstrates an obligatory A1-B8 paternal haplotype which the transplant patient and his donor possess. However, red cell antigen typing of the marrow donor clearly excludes him as the biological father of the child since the marrow donor lacks all three of the red cell antigens listed above. All three of these antigens are easily typed for using standard blood banking procedures.

The patient agreed to submit a semen analysis which showed a low sperm count (3.0×10^6 sperm/cc), poor motility (47%), and abnormal morphology (93%).

DISCUSSION

The recovery of gonadal function after bone marrow transplantation is dependent on the patient's age, type of conditioning regimen, and time elapsed since transplantation. In the experience of the Fred Hutchinson Cancer Center in Seattle [1], most women older than age 26 years will experience permanent ovarian failure, especially if conditioned with a combination of CY and busulfan (BU) or CY and TBI. In younger patients ($\leq$26 years), the recovery of the menstrual cycle will occur in nearly all cases treated with CY alone and sporadically in women receiving CY + TBI, at an average of 3–5 years post transplantation. Successful pregnancies have been reported by the Seattle group and others after CY + TBI, but the dose of radiation has been less than 10 Gy [1–4].

In humans, Leydig cell function is resistant to various conditioning regimens and spermatogenesis is preserved after single-agent CY. The addition of BU or TBI usually results in sterility. It came as a surprise to us that five patients in the Seattle experience [1] did recover spermatogenesis after CY + TBI and conceived nine normal children. In all these cases, however, the radiation was given as a single fraction of 10 Gy or less. No patient treated with fractionated radiation recovered fertility.

Recently Pakkala et al. [5] reported the case of a 28-year-old man who received CY and fractionated TBI at the same dose range as our patient. This man also conceived a child 4 years after transplantation despite apparent aspermia.

It is of interest that all children fathered after bone marrow transplantation have so far presented no specific congenital malformation, and that women who have conceived posttransplantation, the greatest risk seemed to be spontaneous abortion rather than congenital malformation. This information should be extremely helpful to reassure patients that a normal pregnancy and fetus can be expected, although additional follow-up of these children will be needed.

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