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Case report

Successful pregnancy following very high-dose total body irradiation (1575 cGy) and bone marrow transplantation in a woman with acute myeloid leukemia

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Summary:

A 22-year-old woman had a normal full-term delivery 6 years after a successful allogeneic bone marrow transplantation (BMT) for acute myeloid leukemia (AML). Conditioning therapy consisted of cyclophosphamide (120 mg/kg) and total body irradiation (TBI) to a total of 1575 cGy in seven fractions (225 cGy × 7, at a dose rate of 3.5 cGy/min). Graft-versus-host disease prophylaxis was with methotrexate and cyclosporin A. Grade I acute GVHD developed after BMT but there was no chronic GVHD. She became amenorrhoeic after BMT and serial gonadal testing indicated hypergonadotrophic hypogonadism. She became pregnant and delivered a full-term, healthy baby 6 years after BMT. Successful pregnancy after TBI of more than 1200 cGy is extremely rare. This case, to the best of our knowledge, is the second patient who received a higher dose of TBI (1575 cGy) to have a successful pregnancy. This and previous reports indicate that normal pregnancy is possible after BMT with TBI in excess of 1200 cGy.
Keywords: pregnancy; total body irradiation

Bone marrow transplantation (BMT) is an established treatment for certain types of leukemia, producing an approximately 50% cure rate in first complete remission.[1] The use of total body irradiation (TBI), an integral part of the transplant conditioning therapy, has been reported to be associated with ovarian failure.[2] A number of successful pregnancies have been reported in patients with severe aplastic anemia who have received high-dose chemotherapy alone.[3] There are, however, only a few reports of those who received TBI as conditioning and the majority of these cases received TBI to total doses of between 500 and 800 cGy.[4,5] Successful pregnancies following TBI of more than 1000 cGy are extremely rare.[6–9] Sanders *et al*[10] reported a women with ovarian function recovery after cyclophosphamide and 1575 cGy TBI who became pregnant. We report a successful pregnancy after BMT for acute myeloid leukemia (AML) following high-dose cyclophosphamide and fractionated TBI of 1575 cGy.

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Case report

A 16-year-old Chinese female was diagnosed as having AML (FAB M2) in April 1989. Complete remission was achieved using a combination of cytosine arabinoside and daunorubicin. Following consolidation therapy with high-dose Ara-C and mitoxantrone, she received an HLA-matched, mixed lymphocyte culture non-reactive sibling BMT in September 1989. Cyclophosphamide 60 mg/kg/day was administered for 2 days and TBI to a total dose of 1575 cGy in seven fractions (225 cGy per fraction per day, at a dose rate of 3.5 cGy/min) was given by ^{60}Co machine. Prophylaxis against graft-versus-host disease (GVHD) was with methotrexate and cyclosporin A. Engraftment was rapid and post-transplant condition was uneventful. She exhibited grade I acute GVHD of the skin, but there was no evidence of chronic GVHD.

She became completely amenorrhoeic after BMT. Serial measurement of serum gonadotrophins indicated hypergonadotrophic hypogonadism (Table 1). After 5 years of post-transplant amenorrhea, menstruation recommenced spontaneously, but irregularly. In March 1996, she was found to be pregnant and the pregnancy proceeded normally. She gave birth to a healthy boy at 38 weeks gestation in October

Table 1 Serum gonadotrophin levels after BMT

Date	*FSH*	*LH*	*E2*
Before BMT	18	7.2	62
12 m after BMT	141	95.8	<25
24 m after BMT	130	102	<25
66 m after BMT	116	95.6	<25
93 m after BMT	22	16.2	45

BMT = bone marrow transplantaton; m = month(s); FSH = follicle stimulating hormone; LH = luteinizing hormone; E2 = oestradiol.
Normal ranges for follicular phase menstrual cycle: FSH and LH 1–30 IU/l; E2 25–120 pg/ml.

Table 2 Prior reports of pregnancies after BMT following high-dose TBI

Diagnosis	*Age*		*Conditioning*	*TBI*			*Ref.*
	At BMT	*At pregnancy*		*Dose*	*Fraction*	*Rate*	
NHL	24	26	Cy/TBI	1200	6	2	6
AML	20	25	Cy/TBI	1200	6	10	6
ALL	16	22	Ara-C+Cy/TBI	1250	5	3.5	7
ALL	29	34	Cy/TBI	1000	5	—	8
CML	28	34	Cy/TBI	950	—	—	9
ALL	—	—	Cy/TBI	1400	7	—	10
NHL	—	—	Cy/TBI	1575	7	—	10
AML	16	22	Cy/TBI	1575	7	3.5	This study

BMT = bone marrow transplantation; TBI = total body irradiation; Cy = cyclophosphamide; Ara-C = cytosine arabinoside; Dose = total dose of TBI (in cGy); Rate = dose rate of TBI (in cGy/min); Ref. = reference.

1996. There were no complications during pregnancy and the delivery proceeded smoothly. The birth weight of the boy was 2890 g. The boy is now 6 months old and is developing normally. Hematologic complete remission was noted in the mother after delivery.

Discussion

Recovery of gonadal function in patients transplanted for hematologic malignancies is uncommon and only a few cases have been reported. The dose of irradiation is an important determinant affecting the recovery of ovarian function. Lower doses of TBI are associated with a higher incidence of recovery of ovarian function after BMT. A number of patients with aplastic anemia have had successful pregnancies following TBI to a total dose of between 300 and 800 cGy,[4,5] but it is extremely rare for patients to became pregnant following TBI of more than 1000 cGy.

The patient's age was another important factor influencing recovery of ovarian function after TBI. Sanders *et al*[4] reported the return of normal gonadotrophin levels and menstruation in 32 of 43 women who had cyclophosphamide alone as preconditioning regimen, but return of ovarian function was less likely over the age of 26 years. In a study conducted by Ash[11] the author observed that 400 cGy of TBI may cause a 30% incidence of sterility in young women (20–30 years of age), but in women aged above 40 years, it resulted in 100% sterility. Our patient received BMT at the age of 16 and became pregnant at the age of 22. Table 2 shows reports of pregnancies after BMT following high-dose TBI. The majority of these patients who had successful pregnancies were transplanted below 30 years of age and were compatible with the observations by Ash.

A number of successful pregnancies has been reported in patients with aplastic anemia when high-dose cyclophosphamide alone was used as conditioning therapy.[3] The possibility that conditioning regimens for leukemia which do not include TBI may be associated with preservation of fertility is of interest. A recent report on pregnancies with successful outcomes following BMT for leukemia using high-dose cyclophosphamide-containing regimens as conditioning therapy is encouraging.[12] The combination of high-dose busulfan and cyclophosphamide without TBI is now commonly used as the conditioning regimen before BMT and is reported to have comparable anti-leukemic activity as compared with regimens containing TBI.[13] The effect on fertility of BuCy remains unclear and deserves further study. In summary, successful pregnancy after TBI of more than 1200 cGy is extremely rare. This case, to the best of our knowledge, is the second case receiving a higher dose of TBI (1575 cGy) to have a successful pregnancy. This and previous reports indicate that normal pregnancy is possible after BMT with TBI in excess of 1200 cGy.

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