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Successful Pregnancy and Delivery After Radiation With Ovarian Shielding for Acute Lymphocytic Leukemia Before Menarche

Naoya Ishibashi, MD, PhD, Toshiya Maebayashi, MD, PhD,**
Takuya Aizawa, MD, Masakuni Sakaguchi, MD,* Osamu Abe, MD, PhD,**
Tsutomu Saito, MD, PhD,† Yoshiaki Tanaka, MD, PhD,‡
Motoaki Chin, MD, PhD,§ and Hideo Mugishima, MD, PhD§

Summary: Total body irradiation is performed as a preconditioning regimen to inhibit graft-versus-host disease after bone marrow transplantation and to eradicate remaining tumor cells. However, these regimens result in delayed secondary sex characteristics and failure of ovarian function recovery, leading to amenorrhea and infertility. Herein, we report a case of an 11-year-old girl diagnosed with acute lymphocytic leukemia who received induction chemotherapy and prophylactic cranial irradiation. For bone marrow transplantation, she received total body irradiation of 12 Gy with uterine and ovarian shielding at 13 years of age. The patient remained in remission and menarche began at 14 years of age. At 23, she became pregnant and delivered a baby naturally with no abnormalities.

Key Words: acute lymphocytic leukemia (ALL), ovarian function preservation, ovarian shielding, pregnancy, total body irradiation (TBI)

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Hematopoietic stem cell transplantation is a radical, curative treatment for hematological malignancies, such as leukemia and malignant lymphoma. Total body irradiation (TBI), as well as chemotherapy, is widely performed as a preconditioning regimen, with the aim of inhibiting graft-versus-host disease (GVHD) after transplantation and to eradicate remaining tumor cells. However, these preconditioning regimens result in delayed secondary sex characteristics in childhood and adolescence, and failure of normal ovarian function recovery in women, leading to a high incidence of amenorrhea and infertility.

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From the Departments of *Radiology; §Pediatrics and Child Health, Nihon University School of Medicine, Itabashi; †Radiology Clinic, Saonoda Medical Corporations, Adachi, Tokyo; and ‡Department of Radiation Oncology, Kawasaki Saiwai Hospital, Kawasaki, Kanagawa, Japan.

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Reprints: Naoya Ishibashi, MD, PhD, Department of Radiology, Nihon University School of Medicine, 30-1, Oyaguchi Kami-cho, Itabashi-ku, Tokyo 173-8610, Japan (e-mail: ishibashi.naoya@nihon-u.ac.jp).

CASE REPORT

In April 1997, an 11-year-old girl visited a pediatric clinic for evaluation of repeated febrile episodes and was found to have a low white blood cell count of 2800/μL. Her bone marrow biopsy showed that blasts accounted for 94.1% of white blood cells, peroxidase staining was negative, and the cells were positive for CD10, CD19, and HLA-DR. She was subsequently diagnosed with acute lymphocytic leukemia (ALL; French-American-British Class L1, common ALL). On the basis of the high-risk protocol of the Children's Cancer & Leukemia Study Group (CCLSG; ALL 941 Protocol Study; ages 10 to 19 y),[1] she was administered tetrahydropyranyl adriamycin, vincristine, prednisone, and 6-mercaptopurine and

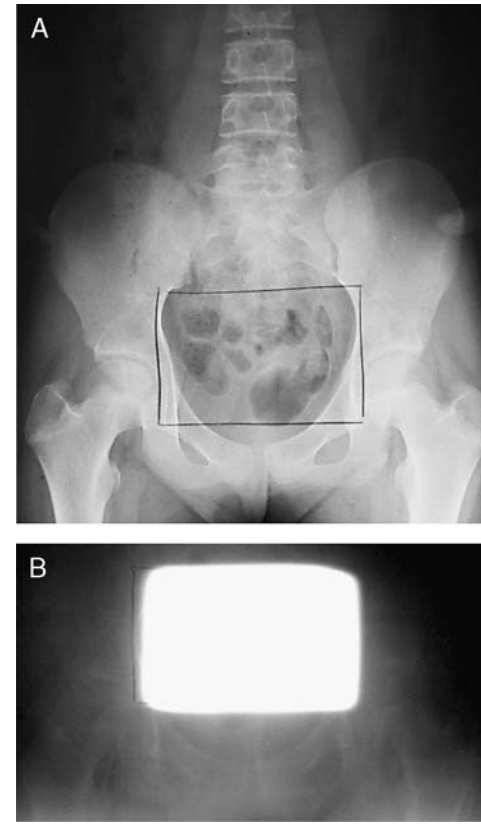

FIGURE 1. A, Radiograph for confirmation of the uterine and ovarian shielding location. The box shows the location of the lead block. B, A portal image obtained at the location of the uterine and ovarian shielding in TBI. TBI indicates total body irradiation.

achieved complete remission. Thereafter, she received intensification therapy using the same drug regimen.

Systemic chemotherapy is usually ineffective as a central nervous system treatment because of the inability to cross the blood-brain barrier. To prevent central nerve recurrence, the high-risk protocol recommends prophylactic cranial irradiation (PCI). Thus, in October of the same year, the patient received PCI of 18 Gy in 12 fractions. From March to September 1998, she remained in remission and was administered maintenance therapy consisting of cyclophosphamide (CY), cytarabine, and 6-mercaptopurine. In October, the patient was admitted to receive bone marrow transplant from her brother who was a complete HLA match. As preconditioning chemotherapy, she received etoposide (60 mg/kg) for 24 hours, followed by the administration of CY (60 mg/kg) for 2 days. Thereafter, at 13 years of age, she received TBI with uterine and ovarian shielding; a total dose of 12 Gy with a fraction dose of 3 Gy, once a day, for 4 days. The following day (day 0), she received 6.37×10^7/kg of bone marrow from her HLA-matched brother. On day 30, graft survival was confirmed by bone marrow biopsy. Methotrexate (short-MTX) and cyclosporine A were administered for GVHD prevention. As the patient had neither GVHD nor other complications, she was discharged on day 41.

The patient was treated with radiotherapy using 2 anteroposterior opposed fields with 10 MV x-rays from a linear accelerator (PRIMUS; Toshiba Medical Systems Corp., Tokyo, Japan). A dose of 3 Gy per fraction was delivered once daily 4 times during the 4-day period (total: 12 Gy), and the dose rate was 10 cGy/min. For ovarian shielding, pelvic computed tomography was performed before TBI to identify the locations of the uterus and ovaries. Next, pelvic radiographs were obtained and using pelvic computed tomography images for reference, the locations of the uterus and ovaries were identified and shielding was performed with an 80 mm thick lead block (Fig. 1). The attenuation rate of the lead block was measured using a water-equivalent phantom corresponding to the size measured in the patient; it was one eighth. Accordingly, the ovarian dose was reduced to approximately 1.5 Gy.

Ovarian function before and after bone marrow transplantation was evaluated using the luteinizing hormone-releasing hormone (LH-RH) loading test. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels at baseline before transplantation were 8.6 and 6.2 mIU/mL, respectively, both of which were normal premenarche levels. Levels 30 minutes after LH-RH administration were 12.2 and 20.6 mIU/mL for FSH and LH, respectively, which represent normal responses. FSH and LH levels at baseline 2 months after transplantation were 114.8 and 25.2 mIU/mL, respectively. As only the FSH level was abnormally high, secondary ovarian dysfunction was suspected (Fig. 2). Thirty minutes after LH-RH administration, FSH and LH levels were 143.7 and 25.2 mIU/mL, respectively, which represent normal responses. The patient remained in remission and experienced no chronic GVHD or other complications. In March 2000, menarche began at 14 years of age. Thereafter, she had a slightly irregular menstrual cycle. However, in January 2003 her FSH was 6.3 mIU/mL, LH 7.7 mIU/mL, and estradiol (E2) 73.4 pg/mL, which were all normal. In July 2009, she was confirmed pregnant at 23 years of age and had a favorable course thereafter. In April 2010, at 24 years of age, she naturally delivered a baby girl weighing 3182 g at 40 weeks and 3 days gestation. The mother and baby have been well ever since, with no apparent abnormalities nor complications.

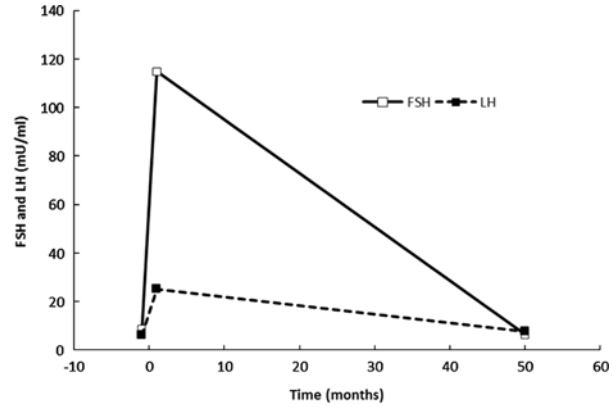

FIGURE 2. Ovarian function evaluated using luteinizing hormone-releasing hormone (LH-RH) before and after TBI. Month zero is the day of bone marrow transplantation. FSH indicates follicle-stimulating hormone; LH, luteinizing hormone; TBI, total body irradiation.

DISCUSSION

TBI and CY are often administered as preconditioning regimens for bone marrow transplantation to achieve effective immunosuppression and to eradicate tumor cells. In girls, however, such preconditioning regimens are highly likely to result in ovarian dysfunction and infertility. When CY alone is used for preconditioning, ovarian function recovers at a high rate even if the CY concentration was high.[2] Meanwhile, ovarian function recovery is only observed in 6.25% of patients treated with CY plus TBI.[3] An irradiation dose of 3 Gy reportedly causes ovarian complications in 5% of patients,[4] and the recovery rate in patients who receive TBI without ovarian shielding is no more than 15%.[5] Moreover, TBI can cause uterine hypoplasia and disturb blood flow.[6] Thus, even if patients become pregnant, they may experience miscarriages or preterm delivery. However, fertility may be preserved if the uterus and ovaries are shielded during TBI. From previous reports, ovarian function recovery was reported in 6 of 8 patients undergoing TBI with ovarian shielding, and 2 of the 6 ultimately gave birth to a baby.[7,8] Table 1 shows a summary of the reports in which pregnancies were obtained after TBI with ovarian shielding. Among the patients who underwent TBI with ovarian shielding, ours was the youngest at only 13 years old and in premenarche. Ovarian function recovery is influenced by CY dose and irradiation dose. The most important factor is reportedly age, with better results obtained in younger patients.[9] As our patient showed transiently elevated FSH levels 2 months after bone marrow transplantation, ovarian dysfunction was suspected (Fig. 2). This was attributed to preconditioning, because ovarian function immediately before transplantation had been normal. As the CY dose for preconditioning regimen was a total of 120 mg, and therefore not especially high, the FSH elevation might have been due to TBI as a preconditioning agent. A past report on TBI with ovarian shielding described a patient with high FSH level and transient amenorrhea.[7] The irradiation dose to the ovary in our patient was approximately 1.5 Gy with 8 fractioning times for 4 days due to performing TBI with ovarian shielding, but transient ovarian dysfunction still occurred. This is the first report of a patient giving birth to a baby after receiving PCI plus TBI, as she underwent an 18 Gy dose of PCI before TBI. When cranial plus spinal radiotherapy is performed to treat leukemia, the risk of miscarriage is approximately doubled owing to the effect of direct spinal cord irradiation or scattered rays, though the risk reportedly increases by 1.4-fold with cranial radiotherapy alone.[10] Our patient had normal menarche at 14 years of age, normal menstruation. There is a model predicting the age of ovarian failure after radiotherapy.[11] In this model, at the age of 13 years our patient received TBI, when ovarian dose is 12 Gy, the predicted age at ovarian failure is 13.6 to 21.4. Our patient had an uneventful pregnancy and delivery. The

TABLE 1. A Summary of Reports Presenting Pregnancies After TBI With Ovarian Shielding

Disease	Age at TBI	Conditioning	TBI		References
			Dose (cGy)	No. Fractionation	
CML	25	CY + TBI	1200	6	8
MDS	22	CY + TBI	1200	6	8
ALL	13	CY + TBI	1200	4	This study

ALL indicates acute lymphocytic leukemia; CML, chronic myelogenous leukemia; CY, cyclophosphamide; MDS, myelodysplastic syndrome; TBI, total body irradiation.

mother and baby have been healthy since with no leukemia recurrence or GVHD. Therefore, we consider uterine and ovarian shielding with TBI to be effective for preserving fertility. Recently, technologies in delivery of external beam of radiotherapy advance and intensity-modulated radiotherapy is used to concentrate dose into target tumors with sparing normal tissue. Total marrow irradiation using intensity-modulated radiotherapy to reduce doses to normal organs is reported[12] and this technique may be used to TBI instead of ovarian shielding. Although advances in the field of reproductive endocrinology have made it possible to perform in vitro fertilization and to store frozen embryos, the clinical application of these procedures to children is difficult. In addition, it may delay treatment owing to ovarian stimulation and there is a high risk that collected cells may contain tumor cells.[13] Uterine and ovarian shielding in TBI is a useful technique and can be performed relatively easily. However, as uterine and ovarian shielding may result in shielding tumor cells present in the pelvic bone, it should only be performed when patients and their family request fertility preservation and provide sufficient informed consent.

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