Endocrine late effects following allogeneic hematopoietic stem cell transplantation with non-myeloablative conditioning

Emiko Miyashita1,2, Yoko Miyoshi1, Noriyuki Namba1,3, Hideaki Ohta4, Hisao Yoshida1,5, Takako Miyamura1, Yoshiko Hashii1, Keiichi Ozono1

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) has been established for the treatment of various diseases such as leukemia/lymphoma, hematological disease, congenital bone marrow failure, and immunodeficiency. The improvement of therapeutic outcomes following HSCT has led to an increasing number of children, adolescents, and adults surviving.1,2

Myeloablative stem cell transplantation (MAST) was, in the past, intended to maximize the antitumor effect, but was associated with severe and frequent late effects including endocrine disorders.3,7 Reduced intensity stem cell transplantation (RIST) is a method that employs reduced intensity of conditioning; its indication has even been expanded to pediatric diseases due to the potential reduction of late effects.8 However, there are a few reports which support the decrease in late effects associated with RIST.

In this study, we retrospectively examined the difference of late effects and their severity, particularly endocrine disorders, in pediatric patients after RIST versus MAST.

Methods

This study was approved by the Ethical Review Board of Osaka University Hospital (approval no. 14440). A total of...
161 patients underwent HSCT for benign and malignant hematological neoplasms, malignant solid tumors, metabolic disorders, or immunological disorders at a single center between March 2001 and February 2012. Of these, 76 were still alive and followed continuously. We selected patients who received allogeneic HSCT once only and were in remission for ≥2 years. Thirty-five patients met these criteria (Figure 1). Twenty-three patients (14 females, 9 males) received RIST and 12 patients (2 females, 10 males) received MAST. The conditioning regimen containing >8 Gy or single dose >5 Gy of total body irradiation (TBI) and >8 mg/kg of busulfan orally or intravenous equivalent was defined as a myeloablative regimen. A non-myeloablative regimen was defined as below: TBI ≤2 Gy with or without a purine analog, fludarabine+cyclophosphamide+/- antithymoglobulin, fludarabine+cytosine arabinoside+idarubicin, or total lymphoid irradiation+antithymoglobulin. The fludarabine-based conditioning regimen without the definition of myeloablative or non-myeloablative was considered as a reduced intensity conditioning regimen.9,10

The patients were retrospectively analyzed based on their medical records. Basic data collected were age at disease onset, gender, underlying disease, height, weight, presence or absence of puberty, age at the time of transplantation, transplant information (conditioning regimen, donor, human leukocyte antigen [HLA] matching, presence or absence of acute or chronic graft-versus-host disease [GvHD]), and duration of post-transplant follow-up. Collection of data regarding post-transplant late effects were related to systemic evaluations such as performance status, liver function, renal function, and endocrine function. Endocrinological evaluation was performed based on data as follows: growth abnormality from stature and obesity, thyroid function (thyroid-stimulating hormone, free thyroxine, free triiodothyronine, and thyroid autoantibodies), gonadal function for girls (Tanner stage, menstruation, luteinizing hormone [LH], follicle-stimulating hormone [FSH], estrogen, and anti-Müllerian hormone [AMH]); and gonadal function for boys (Tanner stage, LH, FSH, testosterone, and presence or absence of hormone replacement therapy). The onset of puberty was defined as detectable LH. AMH was measured only in the patients with informed consent.

Performance status was evaluated by using the Eastern Cooperative Oncology Group Performance Status. CTCAE version 4.0 was used to evaluate the severity of late effects: grade I was defined as mild, grade II was moderate, grade III was severe, and grade IV was life-threatening.3,11-13

Current height was expressed as the standard deviation score (SDS) for age and gender. Short stature was defined as a stature < −2 SD for chronological age or slow growth as growth velocity 1.5 SD below the mean for more than 2 years. Emaciation was defined as <20% lean for ideal weight. Primary hypothyroidism was defined as TSH ≥10 U/mL. Central hypothyroidism was defined as FT4 < 0.8 ng/dL and abnormally elevated TSH. Hypogonadism was defined as the delayed development of Tanner stage or elevated FSH without high estradiol or testosterone. In addition, low level AMH ranging from the lower limit of normal to below the sensitivity threshold was used as an evaluation point in females. AMH levels were measured by using highly sensitive ELISA (AMH Gen II, Beckman Coulter Company) from SRL Inc. (Tokyo, Japan). The concentrations were compared to the normal values in healthy pediatric female patients as reported by Hagen et al., with a cutoff value <2.5th percentile being defined as low AMH.14 The conversion formula offered by SRL Inc. was as follows: AMH Gen II (ng/mL) = 0.189 × EIA AMH (pmol/L) − 0.334.

Statistical analysis was performed using the Statcel2 program. A non-parametric Mann-Whitney test was used to com-
pare data between RIST and MAST. The chi-square test was used for the comparison of the qualitative variables between RIST and MAST. A value of $P<0.05$ was considered to be statistical significant.

Results

Patients characteristics

Table 1 summarizes the characteristics of the 23 patients (14 girls, 9 boys) with RIST and the 12 patients (2 girls, 10 boys) with MAST. Eight patients who underwent RIST were diagnosed with malignancy (1 each with acute lymphoblastic leukemia [ALL], acute myeloid leukemia [AML], relapsed AML, treatment-related AML, relapsed Hodgkin’s disease, peripheral T-cell lymphoma, relapsed atypical large cell lymphoma, and refractory Langerhans cell histiocytosis). Eleven patients who underwent RIST were diagnosed with hematological disease (7 aplastic anemia, 3 myelodysplastic syndrome, and 1 congenital bone marrow failure with radio-ulnar synostosis) and 4 patients with immunodeficiency (3 familial hemophagocytic syndrome, and 1 leukocyte adhesion deficiency). All 12 patients who underwent MAST were diagnosed with malignancy (9 high risk or relapsed ALL, 2 AML, 2

| Characteristic | Group | P value |
|---------------|-------|---------|
| Gender, n (%) |       |         |
| Male          | 9 (39) | 10 (83) | 0.034 |
| Female        | 14 (61) | 2 (17) |
| Median age at SCT (range) | 4y0m (0y3m-14y8m) | 12y6m (2y12m-15y11m) | 0.06 |
| Median duration of follow-up (range) | 4y5m (2y2m-10y8m) | 8y4m (4y6m-13y4m) | 0.07 |
| Disease, n (%) |       |         |
| Malignancy    | 8 (34.8) | 12 (100) | 0.002 |
| Hematological | 11 (47.8) | 0 |
| Immunodeficiency | 4 (17.4) | 0 |
| Donor and HLA compatibility, n (%) |       |         |
| Related       | 14 (60.9) | 4 (33.3) | 0.35 |
| HLA compatible | 6 (26.1) | 2 (16.7) |
| HLA incompatible | 8 (34.8) | 2 (16.7) |
| Unrelated     | 9 (39.1) | 8 (66.7) |
| HLA compatible | 3 (13.1) | 5 (41.7) |
| HLA incompatible | 6 (26.1) | 3 (25) |
| Stem cell source, n (%) |       |         |
| Bone marrow   | 19 (82.6) | 9 (75.0) | 0.65 |
| Peripheral blood | 3 (13.1) | 1 (8.3) |
| Cord blood    | 1 (4.4) | 2 (16.7) |
| Conditioning regimen, n (%) |       |         |
| Fludarabine-based | 23 (100) | 0 |
| + low-dose TLI/TAI | 9 (39.1) | 0 |
| + low-dose BU-based | 3 (13.1) | 0 |
| + cytotoxic drugs | 11 (47.8) | 0 |
| High-dose chemotherapy-based | 0 | 12 (100) |
| + TBI | 0 | 10 (83.3) |
| − TBI | 0 | 2 (16.7) |
| GvHD, n (%) |       |         |
| Acute GvHD (grade III-IV) | 4 (17.4) | 0 |
| Chronic GvHD | 11 (47.8) | 2 (16.7) |
| Limited | 8 (34.8) | 1 (8.3) |
| Extensive | 3 (13.1) | 1 (8.3) |

BU, busulfan; GvHD, graft-versus-host disease; HLA, human leukocyte antigen; m, month; MAST, myeloablative stem cell transplantation; RIST, reduced intensity stem cell transplantation; SCT, stem cell transplantation; TAI, thoraco-abdominal irradiation; TBI, total body irradiation; TLI, total lymphoid irradiation; y, year.
The conditioning regimen of RIST consisted of fludarabine 150 mg/m² and another drug (melphalan 140 or 180 mg/m², busulfan 6-8 mg/m², or cyclophosphamide 300 mg/m²). With respect to irradiation therapy, the dose of lymphoid or thoraco-abdominal irradiation was 2-4 Gy (in 2 fractions) and ovarian or testicular shielding was performed. In MAST, 10 patients had a conditioning regimen consisting of TBI (12 Gy) plus melphalan 180 mg/m² and two patients had a non-TBI regimen (busulfan 16 mg/m² and thiopeta 800 mg/m², respectively).

Late effects

In the RIST group, seven of the 23 patients (30.4%) had no late effects. Sixteen of the 23 patients (69.6%) experienced a late effect of some description, e.g. endocrine disorders, dry eye, dental/mouth problem, skin problem, renal failure, secondary pulmonary hypertension, secondary immunodeficiency, which was severe and life-threatening in one. Seven patients (30.4%) had one late effect, five patients (21.7%) had two late effects, four patients (17.4%) had three to five late effects. In the MAST group, all patients had a late effect. Three patients (25%) had one late effect, four patients (33.3%) had two late effects, and five patients (41.7%) had above four late effects. According to the classification of late effect severity (Table 2), the RIST patients clearly had less severe effects than MAST patients. One patient was classified as very severe in the RIST group with life-threatening late effects, i.e. renal failure and secondary pulmonary hypertension. One patient was classified as very severe in the MAST group, i.e. severe weight loss and multiple osteonecrosis. Both patients had prolonged steroid therapy for severe chronic GvHD. No secondary malignancy considered as a late effect was seen in either group.

Endocrine late effects

Table 3 shows the frequency of the endocrine late effects in the RIST and MAST groups. There was no significant difference between the RIST and MAST groups according to the frequency of growth problems and thyroid dysfunction as late effects.
All patients with thyroid dysfunction had hormone replacement therapy. Twenty-six patients (15 RIST and 11 MAST) had reached the onset of puberty. All patients in the MAST group who had reached puberty were diagnosed with hypogonadism and two patients (1 male and 1 female) had hormone replacement therapy. In the RIST group, one female alone received sex hormone replacement therapy. The frequency of hypogonadism as a late effect was clearly higher for MAST than for RIST.

Table 4 shows the analysis of correlation between transplant-related factors and the prevalence of endocrine late effects in the RIST group. The incidence of endocrine late effects was higher in patients who underwent RIST at ≥10 years of age \( (P = 0.03) \). However, evaluation of specific kinds of endocrine disorder (growth, thyroid, and gonadal) only showed that the incidence of gonadal dysfunction was higher in patients who underwent RIST at ≥10 years of age with a significant difference \( (P = 0.01, \text{data not shown}) \).

Gonadal function

Fifteen patients had puberty (6 boys and 9 girls) and gonadal function was evaluated in these patients (Table 5). Five of the boys were in the early stage of puberty and ovarian or testicular shielding were performed. All patients with thyroid dysfunction had hormone replacement therapy. Twenty-six patients (15 RIST and 11 MAST) had reached the onset of puberty. All patients in the MAST group who had reached puberty were diagnosed with hypogonadism and two patients (1 male and 1 female) had hormone replacement therapy. In the RIST group, one female alone received sex hormone replacement therapy. The frequency of hypogonadism as a late effect was clearly higher for MAST than for RIST.

Table 5. Gonadal function

| Disease          | Age at SCT | Age at evaluation | Conditioning regimen | FSH (mIU/mL) | LH (mIU/mL) | T (ng/mL) | Testis volume (mL) | Tanner stage |
|------------------|------------|-------------------|----------------------|--------------|-------------|-----------|-------------------|--------------|
| Male (\(n=6\))  |            |                   |                      |              |             |           |                   |              |
| Patient 1        | AA         | 11y1m             | 15y2m                | TLI*+Flu+CY  | 9.6         | 6.3       | 4.3               | 3            |
| Patient 2        | AA         | 3y10m             | 10y11m               | TAL*+Flu+CY  | 0.9         | 0.4       | <0.05             | <0.5         |
| Patient 3        | ALCL rel   | 4y0m              | 10y11m               | TLI*+Flu+CY  | 5.1         | 1         | 0.5               | 1-2          |
| Patient 4        | AML        | 2y10m             | 12y9m                | BU+Flu       | 1.3         | 1.3       | 0.07              | 3            |
| Patient 5        | t-AML      | 7y2m              | 9y4m                 | Flu+CA+MEL   | 5.4         | 0.6       | <0.05             | 1-2          |
| Patient 6        | HD rel     | 14y8m             | 25y7m                | BU+Flu       | 19.3        | 5.3       | 4.51              | 5-6          |
| Female (\(n=9\))|            |                   |                      |              |             |           |                   |              |
| Patient 7        | AA         | 13y11m            | 18y8m                | TAI*+Flu+CY  | 1.9         | 1         | 32                | Normal       |
| Patient 8        | AA         | 12y0m             | 13y9m                | TLI*+Flu+CY  | 10.2        | 12.1      | 45                | ND           |
| Patient 9        | AA         | 12y10m            | 15y8m                | TLI*+Flu+CY  | 4.9         | 7.7       | <10               | Normal       |
| Patient 10       | AA         | 8y3m              | 15y9m                | TAI*+Flu+CY  | 16          | 3.9       | 11                | Normal       |
| Patient 11       | AA         | 4y6m              | 10y10m               | TAI*+Flu+CY  | 5.2         | 10.4      | 16                | Normal       |
| Patient 12       | MDS        | 12y1m             | 14y1m                | Flu+MEL      | 4.8         | 3         | 21                | 0.26         |
| Patient 13       | MDS        | 10y2m             | 13y5m                | Flu+MEL      | 6.8         | 3.8       | 56                | 0.27         |
| Patient 14       | MDS        | 10y0m             | 12y0m                | Flu+MEL      | 9.4         | 5.6       | 15                | <0.01        |
| Patient 15       | PTCL       | 13y4m             | 18y2m                | Flu+MEL      | 6.1         | 4.1       | 32                | Normal       |

AA, aplastic anemia; ALCL rel: atypical large cell lymphoma relapse; AMH, anti-Müllerian hormone; AML, acute myeloid leukemia; BU, busulfan; CY, cyclophosphamide; E2, estradiol; Flu, fludarabine; FSH, follicle-stimulating hormone; HD rel, Hodgkin's lymphoma relapse; LH, luteinizing hormone; m, month; MDS, myelodysplastic syndrome; MEL, melphalan; ND, not done; PTCL, peripheral T-cell lymphoma; SCT, stem cell transplantation; T, testosterone; TAI, thoraco-abdominal irradiation; t-AML: treatment-related acute myeloid leukemia; TLI, total lymphoid irradiation; y, year. *Irradiation dose was 3-4 Gy (in 2 fractions) and ovarian or testicular shielding were performed.

discussion

We present data on late effects after RIST and MAST, especially endocrine disorders of childhood cancer survivors (CCSs). In 2008, we reported endocrinological analysis of 122 CCSs in a single institute.\(^5\) In that report, 82 of 122 (67%) CCSs had endocrinological abnormalities, including
of 26 (96%) patients with brain tumors. In the present study, 60.9% of CCSs after RIST had either no late effects or just one late effect. The severity of late effects after RIST was almost always classified as mild. In addition, only 4.3% of CCSs after RIST had life-threatening late effects. On the other hand, 75% of CCSs after MAST had more than one late effects. Their severity was almost always severe. One of 12 patients (8.3%) after MAST had life-threatening late effects (Table 2). Regarding the incidence of the endocrine late effects, there was no significant difference between RIST and MAST in growth failure and thyroid dysfunction (Table 3).

These data indicate that RIST reduced the prevalence and severity of late effects in comparison with published reports on HSCT. Madden et al. reported that RIST recipients for non-malignant diseases had few late effects during long-term follow-up but late effects were not absent. In our report, similarly, the incidence of late effects was reduced but not absent, with endocrine late effects especially still accounting for a large proportion of the late effects. However, we need to consider the pretreatment before HSCT, i.e. the influence of GvHD and prednisolone for GvHD treatment. The frequency of GvHD, in particular, was higher in the RIST group compared to the MAST group in our study. To some degree, some of the late effects, e.g. short stature, might be influenced strongly by GvHD or steroid therapy as well as by the intensity of the conditioning regimen.

In 2010, Bresters et al. reported late effects in 162 children (149 MAST, 13 RIST). We note that the frequency of each endocrine disorder in their study was higher than that of the RIST patients in our report. Furthermore, we found that age ≥ 10 years at the time of RIST in childhood is a significant risk factor for endocrine late effects, especially gonadal dysfunction. This is in agreement with previous studies that showed late effects following MAST in childhood were related to patient age. It has been shown that the risk for ovarian failure after chemotherapy or irradiation is higher in girls who are post-pubertal at the time of treatment as compared to those who are pre-pubertal. In our study, all patients diagnosed with ovarian dysfunction were ≥ 10 years of age at RIST. They had not received any treatment before RIST and received a conditioning regimen consisting of melphalan and fludarabine. This implies that further improvement of RIST regimens is necessary, especially in older patients.

Recently, attention has been given to fertility after treatment as the number of CCSs has increased and reach adolescence. In female CCSs, fertility is an important matter of concern, especially with respect to correct evaluation of ovarian function. As noted previously, FSH, the traditional marker for menopause, does not rise until ovarian function has significantly diminished. Also, there is a report that AMH is an informative and practical predictor of menopause and ovarian dysfunction in adults because AMH values decrease before FSH increases.

In 2013, we have previously reported a prospective study measuring AMH in 53 female CCSs. This showed a discrepancy between the low AMH group and the high FSH group and suggested that conventional evaluation of ovarian functional reserve using menstruation and FSH levels is inadequate. Another report has revealed that the measurement of serum AMH shows promise as a reliable clinical marker for determining ovarian reserve in CCSs. Recently, the International Late Effects of Childhood Cancer Guideline Hormonization Group reported that a low AMH in females < 25 years did not always indicate reduced fertility or low ovarian reserve. On the other hand, some reports have shown that AMH testing is a useful method to evaluate gonadal function in females < 25 years. The optimal timing to measure serum AMH levels for evaluating ovarian reserve is important. Ovarian function after RIST has been discussed by Shimizu et al., who concluded that RIST is an effective means of preserving ovarian function. Panasiuk et al. likewise reported ovarian function seems to be preserved in females after RIST. However, in their report, ovarian functional recovery was defined by traditional markers, which may not be sufficiently sensitive to detect ovarian function failure.

In summary, late effects following RIST, particularly endocrine disorders, were analyzed in a single hospital. Though we must pay attention to some points such as the small number of cases or the short observation period when evaluating results in this study, we still observed a high incidence of endocrine disorders including gonadal dysfunction after RIST. Further improvement of transplantation conditioning is therefore needed. A multicenter study is necessary to resolve this issue with continuous long-term multidisciplinary follow-up by hematologists, endocrinologists, gynecologists, and urologists.

Authors’ contributions

EM, YM, and KO designed the study. EM performed the study, analyzed the data, and wrote the paper. NN, HO, HY,
Conflict of interest disclosure

The authors declare no competing financial interests.

References

1. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the Children’s Oncology Group. J Clin Oncol. 2012; 30: 1663–1669.
2. Ko RH, Ji L, Barnette P, et al. Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: a Therapeutic Advances in Childhood Leukemia Consortium study. J Clin Oncol. 2010; 28: 648–654.
3. Oeffinger KC, Mertens AC, Sklar CA, et al. Childhood Cancer Survivor Study. Chronic health conditions in adult survivors of childhood cancer. N Eng J Med. 2006; 355: 1572–1582.
4. Ranke MB, Schwarze CP, Dopfer R, et al. PDWP of the BMT. Late effects after stem cell transplantation (SCT) in children: growth and hormones. Bone Marrow Transplant. 2005; 35: S77–81.
5. Couto-Silva AC, Trivin C, Thibaud E, Espereu H, Michon J, Brauner R. Factors affecting gonadal function after bone marrow transplantation during childhood. Bone Marrow Transplant. 2001; 28: 67–75.
6. Chemaitilly W, Sklar CA. Endocrine complications in long-term survivors of childhood cancers. Endocr Relat Cancer. 2010; 17: R141–159.
7. Bresters D, van Gils IC, Kollen WJ, et al. High burden of late effects after haematopoietic stem cell transplantation in childhood: a single-centre study. Bone Marrow Transplant. 2010; 45: 79–85.
8. Satwani P, Cooper N, Rao K, Veys P, Amrolia P. Reduced intensity conditioning and allogeneic stem cell transplantation in childhood malignant and nonmalignant diseases. Bone Marrow Transplant. 2008; 41: 173–182.
9. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant. 2009; 15: 1628–1633.
10. Giralt S, Thall PF, Khouri I, et al. Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. Blood. 2001; 97: 631–637.
11. Common Toxicity Criteria, Version 2.0. 30 Apr 1999. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf [accessed 7 Nov 2017].
12. Geenen MM, Cardous-Ubbink MC, Kremer LC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA. 2007; 297: 2705–2715.
13. Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA. 2013; 309: 2371–2381.
14. Hagen CP, Aksglaede L, Sørensen K, et al. Serum levels of anti-Müllerian hormone as a marker of ovarian function in 926 healthy females from birth to adulthood and in 172 Turner syndrome patients. J Clin Endocrinol Metab. 2010; 95: 5003–5010.
15. Miyoshi Y, Ohta H, Hashii Y, et al. Endocrinological analysis of 122 Japanese childhood cancer survivors in a single hospital. Endocr J. 2008; 55: 1055–1063.
16. Madden LM, Hayashi RJ, Chan KW et al. Long-term follow-up after reduced-intensity conditioning and stem cell transplantation for childhood nonmalignant disorders. Biol Blood Marrow Transplant. 2016; 22: 1467–1472.
17. Sanders JE. The impact of marrow transplant preparative regimens on subsequent growth and development. The Seattle Marrow Transplant Team. Semin Hematol. 1991; 28: 244–249.
18. Nakayama K, Liu P, Detry M, et al. Receiving information on fertility- and menopause-related treatment effects among women who undergo hematopoietic stem cell transplantation: changes in perceived importance over time. Biol Blood Marrow Transplant. 2009; 15: 1465–1474.
19. Liu J, Malhotra R, Voltarelli J, et al. Ovarian recovery after stem cell transplantation. Bone Marrow Transplant. 2008; 41: 275–278.
20. Miyoshi Y, Yorifuji T, Horikawa R, et al. Gonadal function, fertility, and reproductive medicine in childhood and adolescent cancer patients: a national survey of Japanese pediatric endocrinologists. Clin Pediatr Endocrinol. 2016; 25: 45–57.
21. Green DM, Kawashima T, Stovall M, et al. Fertility of female survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol. 2009; 27: 2677–2685.
22. Hagen CP, Aksglaede L, Sørensen K, et al. Serum levels of anti-Müllerian hormone as a marker of ovarian function in 926 healthy females from birth to adulthood and in 172 Turner syndrome patients. J Clin Endocrinol Metab. 2010; 95: 5003–5010.
23. Miyoshi Y, Ohta H, Namba N, et al. Low serum concentrations of anti-Müllerian hormone are common in 53 female childhood cancer survivors of childhood cancer. JAMA. 2007; 297: 2705–2715.
24. Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA. 2013; 309: 2371–2381.
25. Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA. 2013; 309: 2371–2381.
26. van Dorp W, Mulder RL, Kremer LC, et al. Recommendations for premature ovarian insufficiency surveillance for female survivors of childhood, adolescent, and young adult cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. J Clin Oncol. 2016; 34: 3440–3450.
27. Salih SM, Elsarrag SZ, Prange E, et al. Evidence to incorporate
inclusive reproductive health measures in guidelines for childhood and adolescent cancer survivors. J Pediatr Adolesc Gynecol. 2015; 28: 95–101.

27. Miyoshi Y, Yasuda K, Tachibana M, et al. Longitudinal observation of serum anti-Müllerian hormone in three girls after cancer treatment. Clin Pediatr Endocrinol. 2016; 25: 119–126.

28. Shimizu M, Sawada A, Yamada K, et al. Encouraging results of preserving ovarian function after allo-HSCT with RIC. Bone Marrow Transplant. 2012; 47: 141–142.

29. Panasiuk A, Nussey S, Veys P, et al. Gonadal function and fertility after stem cell transplantation in childhood: comparison of a reduced intensity conditioning regimen containing melphalan with a myeloablative regimen containing busulfan. Br J Haematol. 2015; 170: 719–726.