

1 **ORIGINAL ARTICLES**

2 **Effect of conditioning intensity on late complications in AYA who underwent allogeneic HCT**
3 **during childhood**

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20 **ABSTRACT**

21 We retrospectively analyzed the effect of conditioning intensity on 22 late complications in 145
22 adolescent and young adults who underwent allogeneic hematopoietic cell transplantation (HCT) in
23 childhood. Seventy-six patients received myeloablative conditioning (MAC), while 69 received
24 reduced-intensity conditioning (RIC). Incidence rates of late complications (≥ 1), organ dysfunction,
25 endocrine/metabolic abnormalities, and psychosocial issues in evaluable patients were 71.0%,
26 17.2%, 66.2%, and 9.0%, respectively. The prevalence of short stature, impaired glucose tolerance,
27 dyslipidemia, and gonadal dysfunction was significantly higher in the MAC group than in the RIC
28 group. Multivariate analyses identified conditioning regimen as an independent factor for gonadal
29 dysfunction and impaired glucose tolerance, but not for short stature. In contrast, inverse probability
30 of treatment weighting analysis revealed that the prevalence of not only gonadal dysfunction and
31 impaired glucose tolerance, but also of short stature, was significantly higher in the MAC group
32 than in the RIC group. The prevalence of organ dysfunction, secondary malignancies, and
33 psychological issues did not differ significantly between the two groups. Reducing conditioning
34 intensity significantly influenced various endocrine complications but not organ dysfunction or
35 psychosocial issues. These findings will inform selection of optimal conditioning regimens and
36 development of practical long-term follow-up systems for pediatric HCT recipients.

37 **Keywords:** Late complications, adolescent and young adult, allogeneic hematopoietic cell
38 transplantation, childhood, long-term follow-up

39 **INTRODUCTION**

40 Recent advances in transplantation methods and supportive therapies have improved the clinical
41 outcomes of allogeneic hematopoietic cell transplantation (allo-HCT) for malignant and non-
42 malignant diseases (NMDs), resulting in an increasing number of long-term survivors. Late
43 complications have become one of the most serious issues in adult recipients, strongly affecting the
44 life expectancy of HCT survivors [1,2]. In contrast, pediatric recipients receive intensive
45 chemotherapy and/or irradiation during important stages of physical and mental development and
46 can survive longer after HCT, which might be associated with a higher risk of various late
47 complications and decreased quality of life (QOL). A comprehensive understanding of the late
48 complications unique to pediatric recipients might aid in the selection of optimal conditioning
49 regimens and facilitate the development of transition systems from pediatric to adult health care for
50 the long-term follow-up (LTFU) of HCT survivors.

51 Allo-HCT using high-dose total body irradiation (TBI) and/or alkylator-based
52 myeloablative conditioning (MAC) has been performed as curative therapy for pediatric patients
53 with malignant diseases and NMDs, particularly those with a high risk of relapse or graft rejection.
54 However, TBI and alkylator-associated late complications are among the most serious in long-term
55 HCT survivors. Reduced-intensity conditioning (RIC) has been developed to reduce the occurrence
56 of late MAC-related complications [3]; however, only few studies have investigated the effects of
57 conditioning intensity on late complications in pediatric recipients [4-9]. In the current study, we

58 comprehensively investigated late complications in adolescent and young adult (AYA) patients who
59 underwent allo-HCT during childhood, focusing on the impact of conditioning intensity.

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61 **SUBJECTS AND METHODS**

62 **Study design and data collection**

63 This study was approved by the institutional ethics committees of Kyoto University Hospital and
64 the local ethics committees of Hiroshima University Hospital, St. Luke's International Hospital, and
65 Tokyo Medical and Dental University Hospital. Informed consent was obtained from participants in
66 the form of an opt-out option on the website. Clinical data were extracted from medical records at
67 the four institutions. Candidate patients were selected according to the following criteria: (1)
68 patients who underwent their first HCT between January 1990 and December 2017 at < 19 years of
69 age, (2) patients who survived for ≥ 5 years without relapse, (3) patients aged 15–39 years at the
70 time of study registration, and (4) patients who had a medical history within 3 years at the time of
71 study registration. Data from 215-patients was analyzed; of these, 70 who underwent autologous
72 peripheral blood stem cell transplantation (auto-PBSCT, n = 47), auto-PBSCT and allo-HCT (n =
73 6), or multiple allo-HCT (n = 17) were excluded. A total of 145 patients were included in the final
74 analysis (Fig. 1).

75 NMDs were classified as congenital and acquired; congenital NMDs included inborn errors of
76 immunity, inborn metabolic disease, and inherited bone marrow failure syndrome, while acquired
77 NMDs included acquired aplastic anemia and non-familial hemophagocytic lymphohistiocytosis.
78 According to previous reports [10,11], MAC was classified as a regimen, including 5 Gy or more of
79 TBI, total abdominal radiation (TAI), or total lymphoid irradiation (TLI) as a single fraction,

80 TBI/TAI/TLI of 8 Gy or more in fractionated doses, or oral or intravenous busulfan (BU) at > 8
81 mg/kg. Other conditioning regimens were classified as RIC. Human leukocyte antigen (HLA)
82 matching was assessed using serological data for HLA-A, HLA-B, and HLA-DR loci. Acute and
83 chronic graft-versus-host disease (GVHD) were diagnosed and graded by attending physicians at
84 each hospital according to consensus criteria [12,13]. Twenty-two question items, consisting of late
85 complications of organ dysfunction (n = 10), endocrine/metabolic abnormalities (n = 7), secondary
86 malignancy (n = 1), and psychosocial issues (n = 4), were basically selected according to the
87 guidelines of the Japanese Society for Transplantation and Cellular Therapy (Table 1) [14]. Patients
88 with organ dysfunction that was difficult to distinguish from chronic GVHD were excluded.

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90 **Statistical analysis**

91 The characteristics of the patients in the two groups were compared using Fisher's exact test for
92 categorical variables and the Mann–Whitney U test for continuous variables. The prevalence of late
93 complications was compared between the two groups using Fisher's exact test. The logistic
94 regression analysis was used for multivariate analyses of factors affecting major
95 endocrine/metabolic abnormalities. The factors included in the analysis were patient age at HCT (0–
96 5 vs. ≥ 6 years), sex, diagnosis (malignant diseases vs. NMDs), conditioning regimen (MAC vs.
97 RIC), use of TBI/TAI/TLI, use of BU, melphalan (MEL) dose (≤ 140 vs. > 140 mg/m²), treatment
98 history prior to allo-HCT (cumulative exposure of alkylators, anthracyclines, and etoposide; use of

99 platinum agents; radiation therapy; surgery), and presence of chronic GVHD. Cumulative alkylator
100 exposure prior to allo-HCT was quantified as cyclophosphamide equivalent dose (CED), calculated
101 using the following equation: $CED (mg/m^2) = 1.0 \times [\text{cumulative cyclophosphamide dose } (mg/m^2)] +$
102 $0.244 \times [\text{cumulative ifosfamide dose } (mg/m^2)]$ [15]. Cumulative anthracycline exposure prior to
103 allo-HCT was quantified as doxorubicin equivalent dose in which conversions are idarubicin $\times 5$,
104 daunorubicin $\times 0.5$, mitoxantrone $\times 10$, and epirubicin $\times 0.6$ [16]. Factors with $P < 0.1$ in the
105 univariate analysis were included in the multivariate analysis.

106 Inverse probability of treatment weighting (IPTW) method using stabilized weights was
107 conducted to assess the impact of conditioning regimen on major endocrine/metabolic abnormalities
108 while addressing other biases [17]. To reduce selection bias, propensity score methods were used to
109 ensure that the MAC and RIC groups were as similar as possible. The propensity score was
110 calculated using a logistic regression model with conditioning regimen (MAC vs. RIC) as the
111 dependent variable and the following observed baseline characteristics as the independent variables:
112 patient age at HCT (0–5 vs. ≥ 6 years), sex, diagnosis (malignant diseases vs. NMDs), CED prior to
113 allo-HCT ($< 4,000$ vs. $\geq 4,000$ mg/m^2), anthracycline dose prior to allo-HCT (< 250 vs. ≥ 250
114 mg/m^2), and etoposide dose prior to allo-HCT ($< 2,000$ vs. $\geq 2,000$ mg/m^2). To explore whether
115 IPTW yielded a balance of covariates between the two groups, the standardized mean differences
116 (SMDs) were calculated after weighting the data with the IPTWs. SMD values < 0.2 indicated low
117 levels of covariate imbalances [18]. All analyses were conducted by the authors with the use of

118 EZR (version 1.61, Saitama Medical Center, Jichi Medical University), which is a graphical user
119 interface for R (the R Foundation for Statistical Computing) [19]. *P*-values were two-sided, and *P* <
120 0.05 was considered significant for all analyses except for univariate analyses.

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122 **RESULTS**

123 **Patient characteristics**

124 The clinical data for the 145 patients are presented in Table 2. Seventy-six patients received MAC
125 while 69 received RIC. The median age at HCT and at the time of study registration were 9 years
126 (range 0–18) and 23 years (range 15–39), respectively. The follow-up period was significantly
127 longer in the MAC group than in the RIC group. Diseases included malignant diseases (*n* = 81),
128 acquired NMDs (*n* = 24), and congenital NMDs (*n* = 40). The treatment history prior to allo-HCT is
129 shown in Table 3. Cumulative exposure of anthracyclines, alkylators, and etoposide were
130 significantly higher in the MAC group than in the RIC group. The principal diagnoses of each
131 disease group are presented in Supplementary Table 1; patients in the MAC group were more likely
132 to have malignant disease. Grade II–IV acute GVHD and chronic GVHD occurred in 46 (31.7%)
133 and 17 (11.7%) patients, respectively.

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135 **Late complications**

136 The prevalence of late complications after allo-HCT is shown in Fig. 2, Fig. 3, and Supplementary
137 Table 2. Of the evaluable 145 patients, 103 (71.0%) experienced at least one late complication of
138 any type, the prevalence of which in the MAC group (86.8 %) was significantly higher than that in
139 the RIC group (53.6%, $P < 0.01$).

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141 **Organ dysfunction**

142 Of the evaluable 145 patients, 25 (17.2%) experienced at least one organ dysfunction, with no
143 significant differences in prevalence between the two groups. The prevalence of dental
144 abnormalities (6.9%) was the highest among organ dysfunctions, and younger patients (0–5 years at
145 HCT) developed them more frequently than older patients (≥ 6 years at HCT, 18.9% vs. 2.8%, $P =$
146 0.003). The prevalence of any other organ dysfunction was less than 5%.

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148 **Endocrine/metabolic abnormalities**

149 Of the evaluable 145 patients, 96 (66.2%) experienced at least one endocrine/metabolic
150 abnormalities. Regarding major endocrine/metabolic abnormalities, the prevalence of short stature,
151 impaired glucose tolerance, dyslipidemia, and gonadal dysfunction in evaluable patients were
152 24.8%, 9.8%, 15.3 %, and 61.5%, respectively. The prevalence of gonadal dysfunction in male
153 patients (61.0%) was almost equivalent to that in female patients (62.1%). The prevalence of at least
154 one endocrine/metabolic abnormalities and major endocrine/metabolic abnormalities in the MAC

155 group (85.5 and 82.9%, respectively) were significantly higher than those in the RIC group (44.9
156 and 43.5%, respectively, $P < 0.001$ for both comparisons). Univariate and multivariate analyses
157 showed that conditioning regimen was an independent factor associated with gonadal dysfunction
158 and impaired glucose tolerance, whereas age at HCT and chronic GVHD were independently
159 associated with short stature (Supplementary Table 3 and Table 4). No significant risk factors for
160 dyslipidemia were identified.

161 We used the IPTW method to further investigate the impact of conditioning regimen
162 intensity on major endocrine/metabolic abnormalities, the prevalence of short stature, impaired
163 glucose tolerance, dyslipidemia, and gonadal dysfunction. The clinical characteristics after applying
164 IPTW were summarized in Supplementary Tables 4-7. Five cases receiving radiation therapy (one
165 each to the cranial, head/neck, mediastinum, eyeball, and chest/abdomen) prior to allo-HCT were
166 excluded from the analysis since they could have a significant impact on endocrine complications.
167 After applying the IPTW method, modest changes in the apparent sample size were noted and the
168 SMDs between the MAC and RIC groups were less than 0.2 for almost all factors, except for a few,
169 indicating that the baseline characteristics were balanced. The logistic regression was then
170 performed on the weighted cohort and showed that the risk of gonadal dysfunction [odds ratio (OR),
171 0.28; 95% confidence interval (CI), 0.12-0.67; $P = 0.004$], short stature (OR, 0.39; 95%CI, 0.17-
172 0.90; $P = 0.026$), and impaired glucose tolerance (OR, 0.04; 95%CI, 0.00-0.74; $P = 0.029$) was
173 lower in the RIC group compared to the MAC group (Table 5).

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Psychosocial issues

Of the evaluable 144 patients, 13 (9.0%) experienced at least one psychosocial issues, including social issues (n = 10), mental health issues requiring psychiatric intervention (n = 12), and being unable to work or attend school (n = 3) (Supplementary Table 2). There was no significant difference in the prevalence between the two groups.

Secondary malignancy

Four patients (2.8%) were diagnosed with secondary malignancies, consisting of oral cancer (n = 2), medulloblastoma (n = 1), and post-transplant lymphoproliferative disorder (n = 1). There was no significant difference in the prevalence between the two groups.

DISCUSSION

MAC has strong therapeutic effects on allo-HCT for malignant diseases and NMDs, which can be counteracted by various late complications that occur after HCT. The current study multidimensionally analyzed the impact of conditioning intensity on late complications in AYA patients who underwent allo-HCT in childhood, finding that effect varied by complication type.

Endocrine/metabolic abnormalities were the most common late complication in both pediatric and adult recipients. High-dose TBI or alkylators, particularly BU, are associated with

193 irreversible gonadal dysfunction in both male and female patients [20,21]. In line with previous
194 reports [22-26], the current study demonstrated that gonadal dysfunction was observed in a
195 considerable proportion of pediatric recipients receiving high-dose TBI and/or BU-based MAC,
196 which is comparable to that in adult recipients [27,28]. High-dose TBI also significantly affects the
197 development of impaired glucose tolerance and dyslipidemia [29,30]. The use of RIC significantly
198 reduced the risk of complications.

199 Short stature is a child-specific late complication caused by growth hormone deficiency
200 (GHD), spine irradiation, and systemic steroid therapy for GVHD [31]. A younger age at HCT and
201 single-dose TBI were risk factors for GHD [32,33]. Multivariate analysis demonstrated that a
202 younger age at HCT and chronic GVHD significantly affected short stature. Furthermore, the IPTW
203 method identified MAC as an independent risk factor for short stature.

204 A lower prevalence of organ dysfunction has been found in pediatric recipients than adult
205 recipients [34,35], strongly suggesting that MAC is generally well tolerated in most pediatric
206 recipients [6]. Additionally, the use of recent HCT methods, such as organ shielding and TBI
207 fractionation schedules [36,37], as well as therapeutic drug monitoring-guided dosing of BU [38],
208 may contribute to a further reduction in organ dysfunction prevalence in pediatric recipients
209 compared with previous reports [9]. In such situations, the benefits of RIC may be insignificant for
210 most organ dysfunction. Dental abnormalities, a specific late complication in developing children,
211 are significantly associated with a younger age at treatment and intensive chemotherapy [39-41].

212 The current study demonstrated that younger age at HCT, but not conditioning intensity,
213 significantly affects dental abnormality occurrence.

214 In addition to late physical complications, including organ dysfunction,
215 endocrine/metabolic abnormalities, and secondary malignancies, late psychosocial complications
216 can influence the QOL of HCT survivors. Various late psychosocial complications, such as anxiety,
217 depression, impairment of interpersonal relationships, and post-traumatic stress disorder, may
218 persist for a long time after HCT [42]. However, the experience of HCT itself can often positively
219 affect late psychosocial complications in HCT survivors, despite the presence of unresolved late
220 physical complications [43]. Compared to adult recipients, academic delay, unemployment,
221 unmarried status, and non-independent living are more concerning socioeconomic problems facing
222 pediatric recipients [44,45]. In the current study, the prevalence of psychosocial issues was 9% in
223 pediatric recipients and was not significantly associated with conditioning intensity. Thus, large-
224 scale surveys, including patient-reported outcomes, are required for a more realistic analysis in this
225 field [46].

226 The current study had several limitations. First, this was a retrospective analysis of data
227 from a heterogeneous group of patients. Second, late complications were diagnosed by attending
228 physicians at each hospital using different methods, which might have led to an underestimation of
229 the prevalence of each complication. Third, this study also analyzed only long-term survivors,
230 meaning we could not evaluate the impact of various factors on late lethal complications,

231 particularly organ dysfunction. Finally, the follow-up period was relatively short and the upper limit
232 of patient age at the time of registration was limited to 39 years, which hampered a more extensive
233 evaluation of late complications, such as infertility, premature ovarian insufficiency, and secondary
234 malignancies.

235 In conclusion, the current study found that reducing conditioning intensity exerted a
236 significant influence on reducing the occurrence of various endocrine/metabolic abnormalities, but
237 not of organ dysfunction or psychosocial issues in pediatric recipients reaching AYA. The
238 knowledge gained from this study will contribute not only to the selection of optimal conditioning
239 regimens but also to the development of practical LTFU tools and the facilitation of the efficient
240 transition of AYA HCT survivors from pediatric to adult health care.

241

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244

245 **AUTHOR CONTRIBUTIONS**

246 MS, MA, and KU designed the research, organized the project, performed the statistical analysis,
247 and analyzed the data. MS, KU, MA, IK, TK and HK collected the data from the medical records of
248 the institution. NT, TA, and YO assisted with the statistical analysis. MS and KU wrote the

249 manuscript. KU, MA, IK, TK, and HK assisted with data interpretation and provided insightful
250 comments. All authors interpreted the data and reviewed and approved the manuscript.

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252 **COMPETING INTERESTS**

253 None

254

255 **DATA AVAILABILITY STATEMENT**

256 The datasets generated during and/or analyzed during the current study are available from the
257 corresponding author on reasonable request.

258

259 **Figure legends**

260 Figure 1. Flow chart of patient disposition

261 Figure 2. Prevalence of late complications after allo-HCT in MAC and RIC

262 Figure 3. Prevalence of late complications (a) organ dysfunction (b) endocrine/metabolic
263 abnormalities (c) psychosocial issue (d) secondary malignancy

264 GHD, growth hormone deficiency

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TABLE 1. List of 22 questionnaire items used to assess late complications of allogenic HCT

Late complication	Diagnostic criteria
Organ dysfunction	
Cataracts	Diagnosed by an ophthalmologist
Hearing loss	Impairments that interfere with daily life
Dental abnormalities	Dental developmental defects
Invasive pneumococcal disease	N.A.
Immunoglobulin replacement	Requiring regular replacement
Cardiac dysfunction	LVEF < 50%
Myocardial infarction	N.A.
Renal dysfunction	eGFR < 60 mL/min/1.73 m ²
Cerebrovascular disorders	Cerebral infarction caused by stenosis of cerebral blood vessels, moyamoya disease, cerebral arterial dissection, and cerebral venous thrombosis
Avascular necrosis	N.A.
Endocrine/metabolic abnormalities	
Adult GHD	Requiring GH supplementation (including cases of transition from childhood)
Short stature	< -2.0 standard deviations
Thyroid dysfunction	Requiring treatment
Impaired glucose tolerance	Meeting any of the following criteria: fasting blood glucose ≥ 126 mg/dL, 75 g OGTT 2-hour value ≥ 200 mg/dL, random blood glucose ≥ 200 mg/dL, and HbA1c ≥ 6.5%
Dyslipidemia	Meeting any of the following criteria based on fasting blood samples: LDL-cholesterol ≥ 140 mg/dL, HDL-cholesterol < 40 mg/dL, triglycerides ≥ 150 mg/dL, and non-HDL cholesterol ≥ 170 mg/dL
Obesity	≥20% for individuals aged 6 to under 18 years and BMI ≥ 25 kg/m ² for individuals aged ≥18 years
Gonadal dysfunction (female)	Abnormal female hormone levels requiring intervention by a gynecologist
Gonadal dysfunction (male)	Abnormal male hormone levels in individuals aged ≥16 (FSH ≥ 10 mIU/mL, or FSH below the reference value, or testicular volume ≤ 10 mL, or testosterone < 3 ng/mL) or undergoing HRT.

Psychosocial issues

Cognitive dysfunction	Impairments that interfere with daily life
Social or school life issues	Impairments that interfere with daily life
No work or study	Not employed and not attending school
Mental issues	Symptoms requiring intervention by a psychiatrist
Secondary malignancy	Therapy-related malignancies (including PTLD, AML/MDS, and solid tumors)

HCT, hematopoietic cell transplantation; N.A., not available; LVEF, left ventricle ejection fraction; eGFR, estimated glomerular filtration rate; GH, growth hormone; OGTT, oral glucose tolerance test; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein; BMI, body mass index; FSH, follicle-stimulating hormone; HRT, hormone replacement therapy; -PTLD, post-transplant lymphoproliferative disorder; AML, acute myeloblastic leukemia; MDS, myelodysplastic syndrome

TABLE 2 Characteristics of the 145 patients included in the study

Variables	Factors	All (n = 145)	MAC (n = 76)	RIC (n = 69)	P-value
Age at HCT (years), median (range)		9 (0–18)	9 (0–17)	10 (0–18)	0.153
Age at study registration (years), median (range)		23 (15–39)	23 (15–39)	23 (15–37)	0.454
Follow-up (years), median (range)		14 (5–28)	15 (5–28)	13 (6–28)	0.018
Sex, n (%)	Male	84 (57.9)	39 (51.3)	45 (65.2)	0.151
	Female	61 (42.0)	37 (48.7)	24 (34.8)	
Diagnosis, n (%)	Malignant diseases	81 (55.9)	67 (88.2)	14 (20.3)	<0.001
	NMDs	64 (44.1)	9 (11.8)	55 (79.7)	
Year of HCT, n (%)	–2009	84 (57.9)	46 (60.5)	38 (55.0)	0.614
	2010–	61 (42.0)	30 (39.4)	31 (44.9)	
Donor source, n (%)	BM	116 (80.0)	57 (75.0)	59 (85.5)	0.107
	CB	25 (17.2)	15 (19.7)	10 (14.4)	
	PBSC	4 (0.70)	4 (5.2)	0 0	
HLA match, n (%)	Match	100 (68.9)	48 (63.2)	52 (75.3)	0.15
	Mismatch	45 (31.0)	28 (36.8)	17 (24.6)	
Acute GVHD, n (%)	II–IV	46 (31.7)	28 (36.8)	18 (26.0)	0.211
Chronic GVHD, n (%)	Yes	17 (11.7)	6 (7.9)	11 (15.9)	0.313

MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; NMD, non-malignant diseases; HCT, hematopoietic cell transplantation; BM, bone marrow; CB, cord blood; PBSC, peripheral blood stem cell; NM, non-malignant; GVHD, graft-versus-host disease

TABLE 3 The main treatment history prior to allo-HCT

Variables	Factors	All (n = 145)	MAC (n = 76)	RIC (n = 69)	<i>P</i> -value
Anthracycline dose, mg/m ² (%)	None	73 (50.3)	12 (15.8)	61 (88.4)	<0.001
	1-250	31 (21.4)	27 (35.5)	4 (5.8)	
	≥ 250	41 (28.3)	37 (48.7)	4 (5.8)	
CED, mg/m ² (%)	< 4,000	121 (83.4)	55 (72.4)	66 (95.7)	<0.001
	4,000-8,000	15 (10.3)	13 (17.1)	2 (2.9)	
	≥ 8,000	9 (6.2)	8 (10.5)	1 (1.4)	
Use of platinum agent (%)	Yes	4 (2.8)	1 (1.3)	3 (4.3)	0.347
	No	141 (97.2)	75 (98.7)	66 (95.7)	
Etoposide dose, mg/m ² (%)	< 2,000	117 (80.7)	53 (69.7)	64 (92.8)	<0.001
	≥ 2,000	28 (19.3)	23 (30.3)	5 (7.2)	
Radiation prior to allo-HCT (%)	Yes	5 (3.4)	4 (5.3)	1 (1.4)	0.369
	No	140 (96.6)	72 (94.7)	68 (98.6)	
Surgery (%)	Yes	4 (2.8)	1 (1.3)	3 (4.3)	0.347

MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; CED, cyclophosphamide equivalent dose

TABLE 4 Multivariate analyses of factors affecting the prevalence of major late endocrine complications

Endocrine complication	Variables	Factors	Total	Prevalence		Univariate analysis	Multivariate analysis	
			No.	No.	%	<i>P</i> -value	OR (95% CI)	<i>P</i> -value
Gonadal dysfunction	Disease	Malignant diseases	69	49	71	0.012	Ref	0.415
		NMDs	47	22	46.8		1.69 (0.48-5.92)	
	Anthracycline dose prior to allo-HCT, mg/m ²	< 250	80	42	52.5	0.004	Ref	0.186
		≥ 250	36	29	80.5		2.2 (0.684-0.706)	
	Conditioning	MAC	61	48	78.7	<0.001	Ref	0.02
		RIC	55	23	41.8		0.219 (0.06-7.91)	
	Use of BU	No	102	59	57.8	0.076	Ref	0.38
		Yes	14	12	85.7		2.12 (0.395-11.4)	
Short stature	Age	0-5 years	39	19	48.7	<0.001	Ref	<0.001
		≥ 6 years	102	16	15.6		0.199 (0.079-0.499)	
	Anthracycline dose prior to allo-HCT, mg/m ²	< 250	101	20	19.8	0.033	Ref	0.23
		≥ 250	40	15	37.5		1.96 (0.652-5.92)	
	Conditioning	MAC	75	25	33.3	0.018	Ref	0.378
		RIC	66	10	15.2		0.587 (0.18-1.92)	
	Use of BU	No	118	13	11	0.034	Ref	0.747
		Yes	23	10	43.4		1.23 (0.35- 4.31)	

Impaired glucose tolerance	Chronic GVHD	No	124	24	19.4	<0.001	Ref	0.001
		Yes	17	11	64.7		7.62 (2.22-26.2)	
	Sex	Female	59	10	16.9	0.022	Ref	0.036
		Male	84	4	4.8		0.244 (0.06-0.916)	
	Conditioning	MAC	76	13	17.1	0.001	Ref	0.024
		RIC	67	1	1.4		0.092 (0.01-0.738)	
Dyslipidemia	Chronic GVHD	No	126	13	10.3	0.065	Ref	0.053
		Yes	17	4	23.5		4.31 (0.98-19.0)	
	Disease	Malignant diseases	81	18	22.2	0.009	Ref	0.673
		NMDs	63	4	8.3		0.703 (0.137-3.61)	
	Anthracycline dose prior to allo-HCT, mg/m ²	< 250	103	12	11.6	0.072	Ref	0.731
		≥ 250	41	10	24.4		1.21 (0.409-3.57)	
	Etoposide dose prior to allo-HCT, mg/m ²	0-2,000	116	14	12.1	0.04	Ref	0.293
		≥ 2,000	28	8	28.6		1.80 (0.602-5.36)	
	Conditioning	MAC	76	18	23.7	0.005	Ref	0.116
		RIC	68	4	5.8		0.312 (0.073-1.33)	

OR, odds ratio; CI, confidence interval; NMDs, non-malignant diseases; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; BU, busulfan; GVHD, graft-versus-host disease

TABLE 5 Logistic regression analysis on the cohort after applying stabilized IPTW

Variables	Factors	Gonadal dysfunction		Short stature		Impaired glucose tolerance		Dyslipidemia	
		OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value
Conditioning	MAC	Ref		Ref		Ref		Ref	
	RIC	0.28 (0.12-0.67)	0.004	0.39 (0.17-0.90)	0.026	0.04 (0.00-0.74)	0.029	0.37 (0.127-1.08)	0.068

IPTW, Inverse probability of treatment weighting; OR, odds ratio; CI, confidence interval; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning

Between January 1990 and December 2017, 215 patients aged 15 to 39 who underwent their first HCT under the age of 19 and survived for more than five years without relapse

Patients who underwent auto-PBSCT (n = 47) were excluded

Patients who underwent auto-PBSCT and allo-HCT (n = 6) were excluded

Patients who underwent multiple allo-HCT (n = 17) were excluded

A total of 145 patients were included in the final analysis.





