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ORIGINAL ARTICLE

Comparable outcomes between autologous and allogeneic transplant for adult acute myeloid leukemia in first CR

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Although allogeneic hematopoietic stem cell transplantation from an HLA-matched sibling donor (MSD) is a potentially curative post-remission treatment for adults with acute myeloid leukemia (AML) in their first CR, transplant-related morbidity and mortality remains a major drawback. We retrospectively compared the outcomes of patients who underwent autologous peripheral blood stem cell transplantation (auto-PBSCT; $n = 375$) with those who underwent allogeneic bone marrow transplantation (allo-BMT; $n = 521$) and allo-PBSCT ($n = 380$) from MSDs for adults with AML/CR1, in which propensity score models were used to adjust selection biases among patients, primary physicians and institutions to overcome ambiguity in the patients' background information. Both the multivariate analysis and propensity score models indicated that the leukemia-free survival rate of auto-PBSCT was not significantly different from that of allo-BMT (hazard ratio (HR), 1.23; 95% confidence interval (CI), 0.92 to 1.66; $P = 0.16$) and allo-PBSCT (HR, 1.13; 95% CI, 0.85–1.51; $P = 0.40$). The current results suggest that auto-PBSCT remains a promising alternative treatment for patients with AML/CR1 in the absence of an available MSD.

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INTRODUCTION

Despite a CR rate as high as 70–80% for adult patients with AML, 60% of the patients in their first CR (CR1) relapsed on conventional post-remission chemotherapy, such as high-dose cytarabine.[1–4] Allogeneic (allo) hematopoietic stem cell transplantation (SCT) with bone marrow (BM) or peripheral blood (PB) from an HLA-matched sibling donor (MSD) is a potentially curative post-remission treatment for patients with AML/CR1. However, transplant-related morbidity and mortality due to regimen-related toxicities, severe infections and GvHD are drawbacks of allo-SCT, and there is an increased risk and severity of these adverse effects associated with using an alternative donor graft in the absence of a MSD. Autologous (auto) SCT using BM or PB is also effective for patients with AML/CR1, allowing for the intensification of chemotherapy with the expectation of a lower rate of relapse than conventional chemotherapy, and offering the advantage of the availability of a transplant graft, unlike that of allo-SCT. The major obstacle associated with auto-SCT is a higher rate of relapse because of the lack of a GvL effect by allogeneic cells, although this can be offset by a lower transplant-related mortality (TRM) after auto-SCT.[1,5–12]

The aim of this study was to retrospectively compare the outcomes of autologous peripheral blood stem cell transplantation (auto-PBSCT) with those of allogeneic bone marrow transplantation (allo-BMT) and allo-PBSCT from MSD for adults with AML/CR1 using the national registry-based data of the Transplant Registry Unified Management Program (TRUMP) in Japan.

PATIENTS AND METHODS

Data collection

The data for 6884 Japanese patients with *de novo* AML aged ⩾16 years at the time of the transplant who underwent SCT were obtained from the TRUMP[13] in Japan (Supplementary Figure 1). Inclusion was based on the following criteria: CR1 at transplant, first transplant with auto-PBSCT or MSD allo-BMT or MSD allo-PBSCT. The selection of these treatments was based on the attending physician's discretion. Patients with acute promyelocytic leukemia, AML with myelodysplasia-related changes, secondary AML from myelodysplastic syndrome, myeloid sarcoma or a previous history of malignancy, and those who received T-cell-depleted or cord blood grafts, were excluded. The study was designed by the Adult AML Working Group of the JSHCT (Japan Society for Hematopoietic Cell Transplantation), and was approved by the TRUMP Data Management Committee of the JSHCT and the Institutional Review Board of Aichi Medical University School of Medicine, where this study was organized.

End points and definitions

The primary end point was the 5-year leukemia-free survival (LFS). The secondary end points were the 5-year overall survival (OS), relapse and TRM. The classification of conditioning regimens (myeloablative vs reduced-intensity) was based on the report by the CIBMTR (Center for International Blood Marrow Transplant Research).[14] Cytogenetic subgroups were classified according to the National Comprehensive Cancer Network Guidelines.[15] The OS rate was defined as the number of days from transplantation to death from any cause. Relapse was defined as clinical or hematological recurrence after transplantation. TRM was defined as death without relapse. The LFS was defined as survival without disease relapse. Any patients who were alive at the last follow-up date were censored. The data regarding the causative microbes of infections, postmortem changes in the causes of death and supportive care, including prophylaxis for

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infections and therapy for GvHD given on an institutional basis, were not available for this cohort.

Statistical analysis

All statistical analyses were performed using the EZR software package (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0),[16] as described in a previous report.[17] The variables according to univariate and multivariate analyses included the recipient's age at the time of transplantation, sex, initial performance status (PS), days from diagnosis to SCT, disease characteristics (the FAB subtypes, WBC count at diagnosis, myeloperoxidase (MPO) positivity of blasts, cytogenetic risk groups,[15] presence of extramedullary disease, the number of chemotherapy cycles required to achieve CR) and the transplant characteristics (myeloablative conditioning (MAC) vs reduced-intensity and non-MCA (RIC/NMA),[18] tacrolimus vs cyclosporine and the year of transplantation). The cutoff points for the continuous variables were determined according to the Japan Adult Leukemia Study Group scoring system, showing a $>20\,000/\mu L$ initial WBC count as unfavorable prognostic factor,[4] and the National Comprehensive Cancer Network guidelines,[15] and the median was used for all other data. The χ^2-test and the Wilcoxon rank sum test were used to compare the data between two groups, and the Kruskal–Wallis test was also used to compare the data among three groups. The probability of LFS and OS was calculated using the Kaplan–Meier method and was compared using the log-rank test. The probabilities of TRM and relapse were compared using the Gray test[19] and were analyzed using a cumulative incidence analysis,[20] whereas considering relapse and death without disease relapse as respective competing risks. A multivariate analysis was then performed using the covariates that were identified as significant ($P<0.1$) according to a univariate analysis (Supplementary Table 1). Cox proportional models and Fine-Gray competing risk regression models were used to evaluate the hazard ratio (HR) associated with the stem cell source. The inverse probability of treatment weighting (IPTW) as the propensity score method[21–23] using the same variables was performed to reduce the effects of selection biases in the stem cell source. For both the univariate and multivariate analyses, *P*-values were two-sided and statistical significance was considered to exist at values of $P\leqslant 0.05$.

RESULTS

Patient characteristics

A total 1276 patients met the criteria for study inclusion, 375 of whom underwent auto-PBSCT, 521 underwent allo-BMT and 380 underwent allo-PBSCT (Table 1). With a median follow-up of the respective groups of 1568 (8–3650), 1212 (0–3650) and 942 (0–3650) days among survivors, 117 (32%), 129 (25%) and 100 (27%) patients had relapsed, and 131 (35%), 191 (37%) and 169 (45%) patients had died, respectively. The auto-PBSCT group included more patients who were older, female, had a worse PS, were M2 subtype-predominant, had reduced MPO positivity, favorable risk cytogenetics, had been less frequently treated with two or more chemotherapy cycles to attain CR, and had a longer duration from diagnosis to transplant than the allo-BMT and allo-PBSCT groups. The allo-PBSCT group comprised transplants in more recent years of the study compared with the auto-PBSCT group.

Transplant outcomes according to the stem cell source

The transplant outcomes according to the stem cell source are shown in Figure 1 and Table 2. The 5-year LFS after transplantation was 60% (95% confidence interval (CI), 54–65%; reference) in the auto-PBSCT group, 59% (95% CI, 54–63%; $P=0.759$) in the allo-BMT group and 51% (95% CI, 46–57%; $P=0.145$) in the allo-PBSCT group (Figure 1a). The 5-year OS after transplantation was 65% (95% CI, 59–70%) in the auto-PBSCT group and 62% (95% CI, 57–66%; $P=0.422$) in the allo-BMT group, and was significantly lower in the allo-PBSCT group (55%; 95% CI, 49–60%; $P=0.004$) (Figure 1b). The 5-year cumulative incidence of relapse after transplantation was 33% (95% CI, 28–38%) in the auto-PBSCT group, 26% (95% CI, 22–30%; $P=0.079$) in the allo-BMT group and 28% (95% CI, 24–33%; $P=0.226$) in the allo-PBSCT group (Figure 1c), whereas the 5-year cumulative incidence of TRM was significantly lower in the auto-PBSCT group (8%; 95% CI, 5–11%) compared with that in the allo-BMT group (15%; 95% CI, 12–18%; $P=0.016$) and that in the allo-PBSCT group (21%; 95% CI, 16–25%; $P<0.001$) (Figure 1d).

In the multivariate models adjusted for the clinical factors, the LFS did not differ significantly between the auto-PBSCT and allo-BMT groups (HR, 1.27; 95% CI, 0.94–1.72; $P=0.114$) or between the auto-PBSCT and allo-PBSCT groups (HR, 1.09; 95% CI, 0.80–1.47; $P=0.559$), which was also true of the OS for auto-PBSCT compared with the allo-BMT (HR, 1.02; 95% CI, 0.74–1.41; $P=0.886$) and with allo-PBSCT (HR, 0.86; 95% CI, 0.62–1.20; $P=0.383$) (Table 2). In multivariate models, auto-PBSCT was associated with a significantly higher incidence of relapse compared with allo-BMT (HR, 1.83; 95% CI, 1.29–2.58; $P<0.001$) and allo-PBSCT (HR, 2.11; 95% CI, 1.46–3.05; $P<0.001$), which was offset by the significantly lower TRM compared with allo-BMT (HR, 0.53; 95% CI, 0.29–0.96; $P=0.036$) and allo-PBSCT (HR, 0.29; 95% CI, 0.16–0.53; $P<0.001$). When an adjustment analysis based on IPTW using the propensity score was performed to reduce the selection biases of patients, the effects of auto-PB on the LFS and OS were not significantly different from those of allo-BMT and allo-PBSCT.

Although it is outside the scope of the present study, when the allo-BMT and allo-PBSCT groups were compared by the same multivariate models, no significant difference was found in either the LFS or OS, irrespective of whether IPTW adjustment was used (Supplementary Table 2).

Subgroup analysis

Figure 2 shows a forest plot comparing the relative effects of auto-PBSCT with allo-BMT and allo-PBSCT on the LFS in each subgroup. Of note, the patients with a PS of 2–4 benefited from auto-PBSCT more than allo-BMT in terms of the LFS (*P* for interaction = 0.015). Conversely, auto-PBSCT was associated with a worse LFS compared with allo-BMT in patients with a $>20\,000/\mu L$ initial WBC count (*P* for interaction = 0.020). In all other groups of patients, such as those of an older age, with a high-risk FAB subtype, extramedullary disease or who required two or more chemotherapy cycles to attain CR, auto-PBSCT did not show a significantly different LFS to allo-BMT (Figure 2a). Auto-PBSCT showed no inferior effects on the LFS compared with allo-PBSCT in any subgroups, and instead, auto-PBSCT exhibited a better LFS than allo-PBSCT in patients with an initial WBC count $\leqslant 20\,000/\mu L$ (*P* for interaction = 0.026) or >50% MPO-positive blasts (*P* for interaction = 0.033) (Figure 2b). The CD34-positive cell count did not significantly influence LFS in patients who received auto-PBSCT (Supplementary Figure 2). The conditioning regimen (MAC vs RIC/NMA) did not significantly influence LFS in patients who received allo-BMT or allo-PBSCT (Supplementary Figure 3).

DISCUSSION

The main disadvantages of auto-PBSCT are the possibility of greater contamination of leukemic cells in the stem cell product, as suggested by a study from the European Group Blood and Marrow Transplantation,[24] and the absence of a GvL effect, which is considered to lead to a lower curative potential compared with allo-SCT. Contrary to expectation, the current nation-wide study showed that the 5-year LFS after auto-PBSCT for adult patients with AML/CR1 was as high as 60%, which was not significantly different from those after allo-BMT and allo-PBSCT using MSD. These findings were confirmed by a multivariate analysis and IPTW analyses after adjusting for any patient selection bias using the propensity score models. Auto-PBSCT was associated with a 5-year relapse rate of 33%, which was

Table 1. The characteristics of the patients

Characteristics	*Total*	*NA*	*auto-PBSCT*	*allo-BMT*	*allo-PBSCT*	P-*value*	*P-value (allo-BMT* vs *auto-PBSCT)*	*P-value (allo-PBSCT* vs *auto-PBSCT)*
Number of patients (%)	1276 (100)	0	375 (29.4)	521 (40.8)	380 (29.8)			
Year of transplant (%)		0						
1995–1999	353 (27.7)		153 (40.8)	180 (34.5)	20 (5.3)	< 0.001	0.075	< 0.001
2000–2004	357 (28.0)		95 (25.3)	128 (24.6)	134 (35.3)			
2005–2011	566 (44.4)		127 (33.9)	213 (40.9)	226 (59.5)			
Age at transplant (%)		0						
Median	41		47	37	43	< 0.001	< 0.001	0.004
(Range)	(16–80)		(17–80)	(16–73)	(16–74)			
> 50	323 (25.3)		144 (38.4)	74 (14.2)	105 (27.6)	< 0.001	< 0.001	0.002
Gender (%)		0						
Male	740 (58.0)		241 (64.3)	284 (54.5)	215 (56.6)	0.011	0.003	0.031
PS at the initial visit (%)	110							
2–4	215 (18.4)		77 (22.8)	82 (17.2)	56 (16.0)	0.046	0.047	0.023
WBC count at diagnosis, × cells/μL (%)		53						
Median	14 800		12 300	15 300	15 900	0.207	0.559	0.083
(Range)	(200–1 063 000)		(600–387 800)	(200–680 000)	(500–1 063 000)			
> 20 000	535 (43.7)		148 (40.4)	214 (43.4)	173 (47.5)	0.152	0.383	0.054
FAB subtypes (%)		0						
M0	100 (7.8)		15 (4.0)	47 (9.0)	38 (10.0)	< 0.001	< 0.001	< 0.001
M1	254 (19.9)		78 (20.8)	97 (18.6)	79 (20.8)			
M2	473 (37.1)		174 (46.4)	182 (34.9)	117 (30.8)			
M4	204 (16.0)		69 (18.4)	78 (15.0)	57 (15.0)			
M5	166 (13.0)		32 (8.5)	79 (15.2)	55 (14.5)			
M6	45 (3.5)		4 (1.1)	22 (4.2)	19 (5.0)			
M7	13 (1.0)		2 (0.5)	7 (1.3)	4 (1.1)			
Unclassified	21 (1.6)		1 (0.3)	9 (1.7)	11 (2.9)			
MPO-positive blasts (%)		298						
⩽ 50%	415 (42.4)		88 (31.0)	176 (46.4)	151 (47.9)	< 0.001	< 0.001	< 0.001
Cytogenetics (%)		51						
Favorable	176 (14.4)		95 (26.4)	45 (9.2)	36 (9.6)	< 0.001	< 0.001	< 0.001
Intermediate	796 (65.0)		231 (64.2)	320 (65.2)	245 (65.5)			
Poor	202 (16.5)		17 (4.7)	104 (21.2)	81 (21.7)			
Unclassified	51 (4.2)		17 (4.7)	22 (4.5)	12 (3.2)			
Extramedullary disease, × region(s) (%)		2						
⩾ 1	58 (4.6)		10 (2.7)	25 (4.8)	23 (6.1)	0.077	0.106	0.023
Chemotherapy cycles to achieve CR1 (%)		26						
⩾ 2	358 (28.6)		72 (19.8)	148 (29.1)	138 (36.6)	< 0.001	0.002	< 0.001
Days from diagnosis to transplant (%)		0						
Median	184		207	180	168	< 0.001	< 0.001	< 0.001
(Range)	(7–1270)		(12–979)	(67–1270)	(7–1229)			
⩾ 185	633 (49.6)		235 (62.7)	243 (46.6)	155 (40.8)	< 0.001	< 0.001	< 0.001
Preparative regimen (%)		375[a]						
MAC	462 (51.3)		—	259 (49.7)	203 (53.4)	0.271	—	—
RIC/NMA	439 (48.7)		—	262 (50.3)	177 (46.6)			
GvHD prophylaxis (%)		383[a]						
CSA+MTX	754 (84.4)		—	453 (87.8)	301 (79.8)	0.005	—	—
CSA without MTX	58 (6.5)		—	25 (4.8)	33 (8.8)			
TAC+MTX	55 (6.2)		—	29 (5.6)	26 (6.9)			
TAC without MTX	11 (1.2)		—	5 (1.0)	6 (1.6)			
Others	10 (1.1)		—	4 (0.8)	6 (1.6)			
No prophylaxis	5 (0.6)		—	0 (0.0)	5 (1.3)			

Abbreviations: CR1 = first CR; CSA = cyclosporine; FAB = the French-American-British classification; GVHD = graft-versus-host disease; MAC = myeloablative conditioning; MPO = myeloperoxidase staining; MTX = methotrexate; NA = not available; NMA = non-myeloablative conditioning; PBSCT = autologous peripheral blood stem cell transplantation; PS = performance status; RIC = reduced-intensity conditioning; TAC = tacrolimus. [a]Include number of auto-PBSCT.

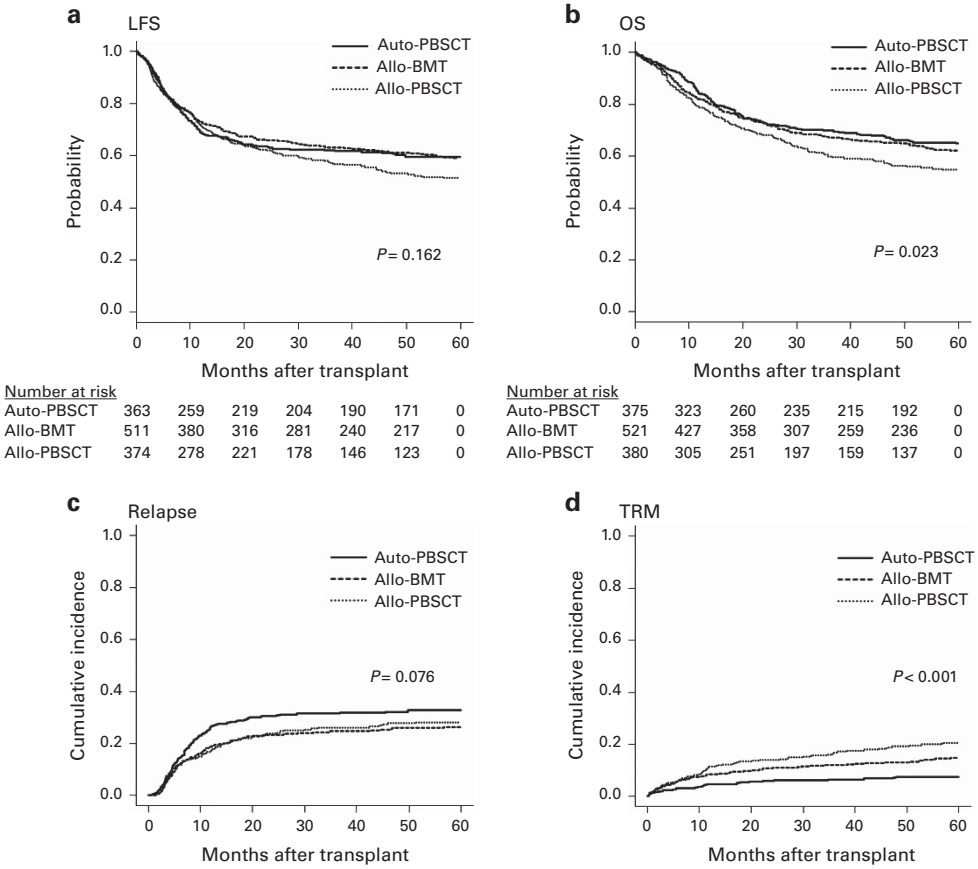

Figure 1. The results of the Kaplan–Meier analysis of the LFS (**a**) and OS (**b**), and the estimated cumulative incidence curves of relapse (**c**) and TRM (**d**) after SCT in patients with AML in their first CR, according to the stem cell source. The solid lines represent auto-PBSCT, the dashed lines represent allo-BMT and the dotted lines represent allo-PBSCT.

Table 2. Comparison of the transplant outcomes between auto-PBSCT and allo-BMT and between auto-PBSCT and allo-PBSCT

	auto-PBSCT vs *allo-BMT*		P-*value*	*auto-PBSCT* vs *allo-PBSCT*		P-*value*
	Number of patients	*Hazard ratio (95% CI)*		*Number of patients*	*Hazard ratio (95% CI)*	
LFS						
Univariate	363 vs 511	1.02 (0.82–1.26)	0.892	363 vs 374	0.84 (0.67–1.06)	0.137
Multivariate	259 vs 338	1.23 (0.92–1.66)	0.161	271 vs 301	1.13 (0.85–1.51)	0.403
IPTW	258 vs 332	1.23 (0.87–1.74)	0.246	258 vs 290	1.21 (0.87–1.70)	0.263
OS						
Univariate	375 vs 521	0.91 (0.72–1.14)	0.402	375 vs 380	0.73 (0.58–0.92)	0.009
Multivariate	266 vs 344	1.07 (0.78–1.48)	0.658	279 vs 310	0.88 (0.65–1.19)	0.401
IPTW	265 vs 337	0.98 (0.69–1.40)	0.910	265 vs 293	0.96 (0.66–1.40)	0.830
Relapse						
Univariate	363 vs 511	1.33 (1.03–1.71)	0.027	363 vs 374	1.25 (0.96–1.63)	0.100
Multivariate	259 vs 338	1.64 (1.17–2.28)	0.004	271 vs 306	1.92 (1.37–2.69)	< 0.001
TRM						
Univariate	363 vs 511	0.50 (0.32–0.79)	0.003	363 vs 374	0.36 (0.23–0.57)	< 0.001
Multivariate	349 vs 482	0.54 (0.33–0.89)	0.016	349 vs 369	0.36 (0.20–0.62)	< 0.001

Abbreviations: CI = confidence interval; ITPW = inverse probability of treatment weighting; LFS = leukemia-free survival; OS = overall survival; PBSCT = autologous peripheral blood stem cell transplantation; TRM = transplant-related mortality.

compensated for by a 5-year TRM of 8%, thus suggesting that, in addition to allo-BMT/PBSCT from a MSD, auto-PBSCT can also be a curative option as post-remission treatment in many adult patients with AML/CR1.

These findings are in contrast to those of previous non-randomized prospective trials conducted in the 1990 s,[1,11,12,25] in which auto-SCT offered a lower survival benefit to patients with AML/CR1 than allo-SCT. One potential explanation for these

differences is that the previous studies primarily used auto-BM grafts rather than auto-PB grafts for transplantation, resulting in a TRM of 10–20%. However, the stem cell source has since shifted from BM to PB for both auto- and allo-SCT. Engraftment using a PB graft may be beneficial for preventing fatal infections, resulting in TRM in as low as 5–10% of patients after auto-PBSCT,[9,26,27] as observed in the present study. However, these beneficial effects may be counterbalanced by the increased risk and severity of GVHD after allo-PBSCT, as observed in previous studies.[23,28–30] This may result in a comparable survival outcome among auto-PBSCT, allo-BMT and allo-PBSCT.

This hypothesis may be supported by a recent report[5] in which auto-PBSCT for AML/CR1 showed a 5-year TRM of 8%. The preferred use of BM in the past may also account for the lack of a clear survival advantage of auto-SCT for AML/CR1 over intensive chemotherapy in trials conducted until the early 2000 s.[1,31–33] Indeed, in recent reports,[34–37] auto-PBSCT showed a better long-term LFS compared with chemotherapy in patients with AML/CR1 having favorable or intermediate cytogenetics.

The subgroup analyses showed that the LFS rate after auto-PBSCT was not inferior to the rates after allo-BMT or allo-PBSCT, with the exception of allo-BMT in patients with an initial WBC count of $>20\,000/\mu L$. Furthermore, the LFS after auto-PBSCT was found to be superior to that after allo-BMT in patients with a PS of 2–4 and the LFS after allo-PBSCT in patients with an initial WBC count of $\leqslant 20\,000/\mu L$ or $>50\%$ MPO-positive blasts. These findings may differ from those in previous studies from the Haemato Oncology Foundation for Adults in the Netherlands and CIBMTR,[5,35] in which a similar OS, but worse LFS, was observed between auto-SCT and allo-BMT/PBSCT using patient cohorts predominantly comprising patients with AML/CR1 with intermediate-risk cytogenetics. The risk cytogenetics category of AML blasts is a key prognostic factor that determines the post-remission therapy.[15,38] The subgroup analyses showed that the LFS rates after auto-PBSCT and allo-BMT were not significantly different in patients with favorable or intermediate-risk cytogenetics, but were significantly different in patients with poor-risk cytogenetics. A difference in the LFS was not observed between auto-PBSCT and allo-PBSCT in any of the cytogenetic risk categories. Nevertheless, the preferred post-remission treatment for AML/CR1 as indicated by the cytogenetic risk category might change over time or vary among institutions, potentially due to institutional experience, and inherent limitations in the patient selection are suggested of previously reported comparisons between auto-SCT and allo-SCT. We herein attempted to overcome such selection biases by using risk stratification IPTW models with the propensity scores, in addition to the conventional multivariate analysis, to reduce the effects of preferences among institutions in selecting a stem cell source. A propensity scoring system and IPTW model was devised to estimate the effects of treatments by comparing the outcomes of those subjects who were not randomly assigned to experimental or control groups in an observational study, and thus has the benefit of overcoming such selection biases through risk stratification to adjust for preferences among institutions.[21–23] However, the propensity score model used in the present study does not take into account information regarding donor availability, depth of remission or the molecular aberrations of AML because these data were unavailable in the present cohort. This is one of limitations of the present study. For the purpose of overcoming such limitations and

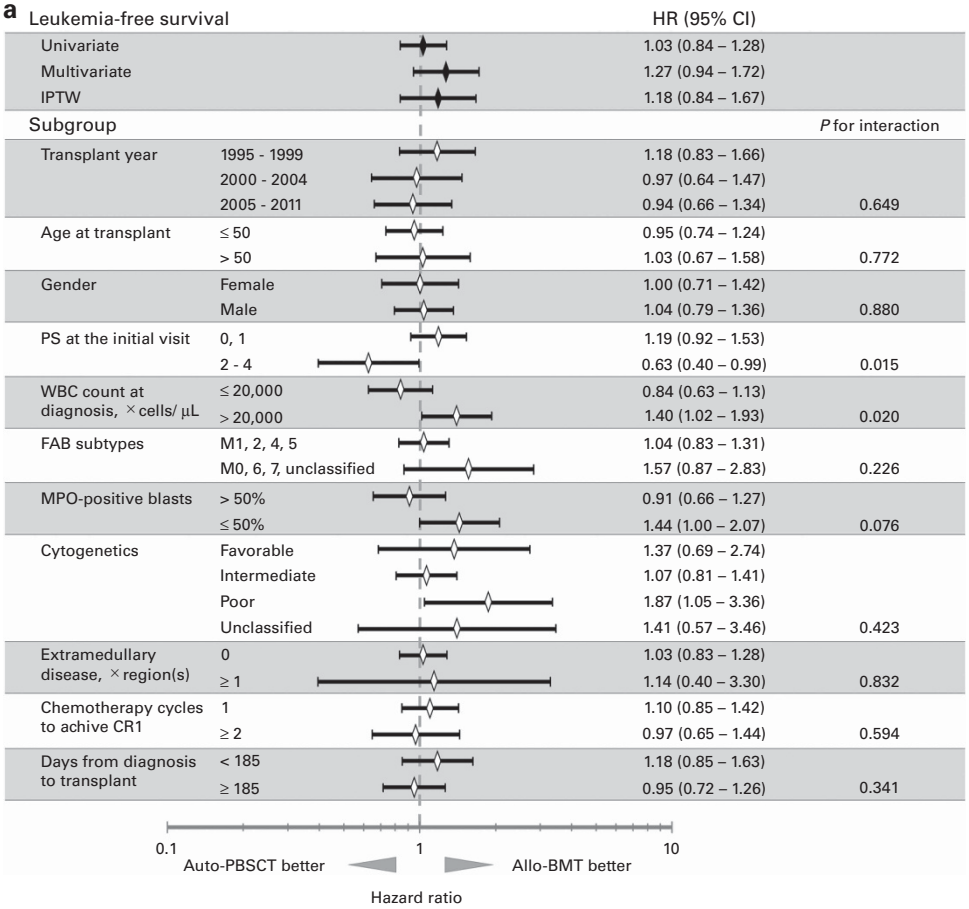

Figure 2. A forest plot of the LFS in the different subgroups. Hazard ratios (HRs) from the subgroup analyses of the LFS between auto-PBSCT and allo-BMT (**a**) and between auto-PBSCT and allo-PBSCT (**b**) are shown. HRs < 1.00 indicate a better LFS after auto-PBSCT.

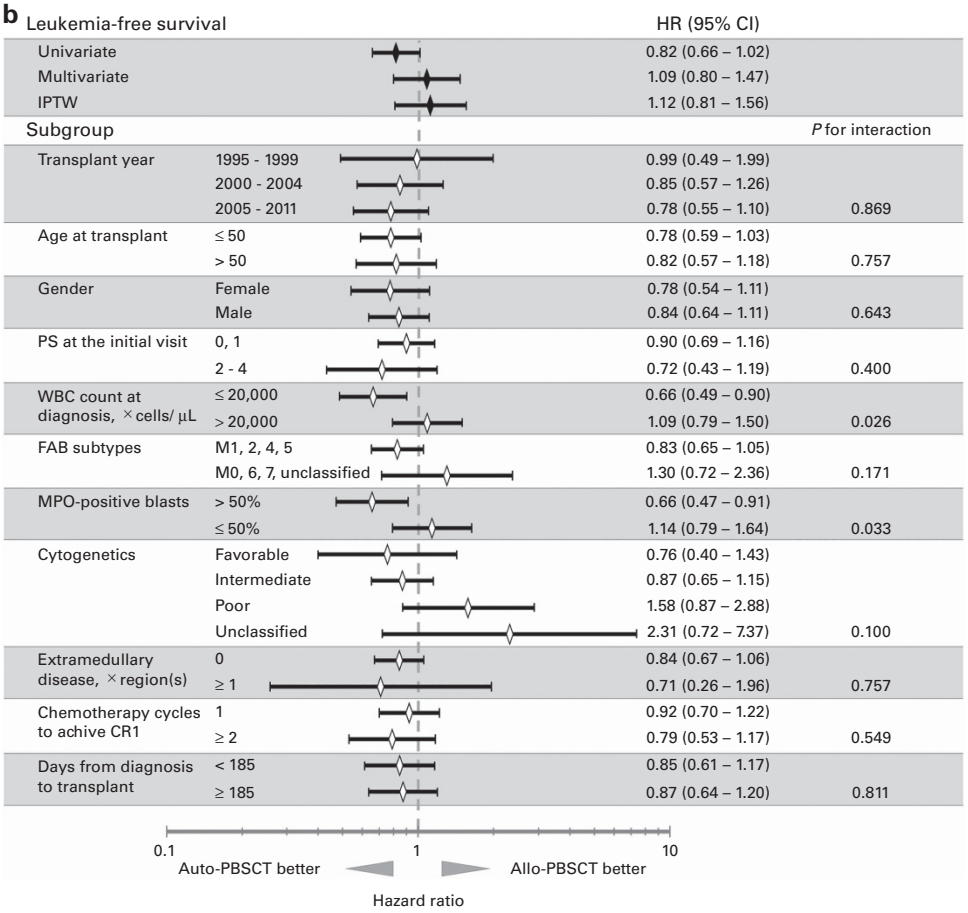

Figure 2. Continued.

strengthening our conclusions, we added an analysis using the receiver operating characteristic curve to determine the extent to which the variables used in the IPTW analysis reflect the LFS, the primary end point (Supplementary Figure 4). The area under the curve surpassed 0.7 for both comparisons of auto-PB vs allo-BM and auto-PB vs allo-PB, indicating that the variables used in the IPTW analysis adequately reflected the LFS in the present study with minimal effects of other factors, including donor availability, depth of remission and the molecular aberrations of AML. The IPTW model can only be applied to statistics using two-valued variables, such as the survival and death, and does not accommodate for an analysis of competing risks such as the relapse rate and TRM. First, the effects of the conditioning regimen used for auto-PBSCT could also account for the favorable LFS, considering that 274 (76%) patients who received a conditioning regimen containing high-dose cytarabine followed by auto-PBSCT showed a 5-year LFS of 62%, which showed a slight improvement compared with the 5-year LFS of 54% ($P = 0.131$) in the remaining 86 (24%) patients with auto-PBSCT. Evidence can also be observed in previous reports showing a favorable long-term LFS of 61–71% after auto-SCT using a high-dose cytarabine-containing regimen.[39,40] Second, the use of consolidation chemotherapy prior to auto-PBSCT could have positively affected the outcome. Although this possibility is highly speculative due to the lack of information on the type and cycle number of consolidation chemotherapy, a longer duration from the diagnosis to transplant in the present auto-PBSCT group compared with those in the allo-BMT and allo-PBSCT groups may imply that patients with auto-PBSCT received more cycles of consolidation chemotherapy prior to transplantation. Although the possibility of patient selection biases remains unclear, this hypothesis may be supported by previous studies[40–42] in which two or more consolidation chemotherapy cycles prior to transplantation was the most favorable factor for the LFS and relapse after auto-SCT, but not after allo-SCT. This is in addition to the current finding that a longer duration from the diagnosis to transplant showed a trend toward improving the LFS after auto-PBSCT.

The use of auto-PBSCT as a post-remission treatment for AML/CR1 may compromise the safety and effectiveness of subsequent allo-SCT in patients who relapse and are candidates for this procedure.[43,44] However, unlike the case of salvage by MAC allo-SCT,[44,45] RIC/NMA allo-SCT using a MSD or alternative donors has been suggested to be effective in rescuing patients with AML who relapse following auto-ACT.[35,46,47] In a study published by the CIBMTR,[46] unrelated donor allo-SCT using RIC/NMA after auto-SCT relapse resulted in a 5-year OS of 37% and a 1-year TRM of 28%, contrary to the 5-year OS of 19% and 1-year TRM of 48% following that with MAC. This suggests that the failure of previous auto-SCT could be overcome by allo-SCT using RIC/NMA. One important fact related to this issue is that the treatment success for AML relapse after initial allo-SCT is limited, with a 3-year OS of 10–20% in previous studies,[17,48,49] indicating that the counter-measure used for post-transplant relapse remains critical, regardless of whether an auto-graft had been used for initial transplantation.

A previous study[50] showed that AML patients with a PS of 2–4, comparable with a Karnofsky PS of 70 or lower, had a lower probability of achieving an event-free survival after allo-SCT mainly due to a higher TRM compared with those with a PS of 0–1 (event-free survival 9% vs 33%; $P < 0.0001$), and were thus considered to be poor candidates for allo-SCT. Auto-PBSCT may

be available for such patients ineligible for allo-SCT, as suggested in the present study. As another aspect of the present findings, allo-PBSCT could be considered to be overtreatment for patients with an initial WBC $\leqslant$20 000/μL or $>$50% MPO-positive blasts as they are expected to have a low relapse rate,[4] and auto-PBSCT may be prioritized over allo-PBSCT for the long-term LFS.

The nature of a retrospective, registry-based analysis leads to several limitations. First, there was no available information regarding the chemotherapeutic agents used in induction and consolidation chemotherapy, the number of cycles of consolidation chemotherapy, the quantification of minimal-residual disease (MRD) or the molecular markers. Previous studies have demonstrated that MRD at the time of auto- or allo-SCT is a significant, independent predictor of subsequent relapse and a shorter survival for AML/CR1.[51–57] The presence of adverse-risk molecular markers, such as internal tandem duplications of the fms-related tyrosine kinase 3 gene (*flt3-ITD*), could compromise the outcome of auto-SCT, although the predictive values of the molecular markers with regard to the outcome of auto- and allo-SCT have varied among studies and thus remain unclear.[58–62] Accordingly, there is a possibility that in the present cohort auto-PBSCT was not favored for high-risk patients with AML/CR1 due to the presence of MRD and molecular markers, leading to the artificial appearance of an improved outcome after auto-PBSCT. However, the present findings in which the LFS of auto-PBSCT was not significantly different from that of allo-BMT and allo-PBSCT, regardless of the year of the transplant, in the subgroup analysis may discount this possibility, as the detection of MRD and molecular markers for leukemic cells became popular as predictors of the prognosis in the early 2000 s in Japan. The collection of data on the MRD and gene mutation profiles is outside the scope of the present study, and further studies are warranted to determine the importance of these factors. Another limitation is that the present study did not adjust for multiple testing because the analyses were conducted in an exploratory context; thus, the interpretation of the analyses in the subgroups should be carefully considered.

The present data suggest that in the absence of an available MSD, auto-PBSCT remains a promising alternative for AML patients. The present findings may also raise questions about whether, in the absence of a MSD, allo-BMT or allo-PBSCT from alternative donors should be prioritized over auto-PBSCT. However, care should be taken before drawing any conclusions because validation studies, including the collection of information regarding previous consolidation chemotherapy, the MRD status at transplant and molecular markers, are required to confirm the efficacy of auto-PBSCT for AML/CR1. Further studies are also warranted to ascertain whether the findings of this study can be extended to auto-PBSCT vs alternative donor transplantation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Akiyoshi Takami, Motonori Mizutani and Masahiko Hara designed the research and wrote the manuscript. Motonori Mizutani, Masahiko Hara and Akiyoshi Takami analyzed the data. Motonori Mizutani and Masahiko Hara performed the statistical analyses. All the authors contributed to the collection of the data and samples and critically reviewed and approved the final manuscript.

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