Annals of Hematology (2019) 98:2179–2186
https://doi.org/10.1007/s00277-019-03736-5

ORIGINAL ARTICLE

Allogeneic hematopoietic cell transplantation for patients with a history of multiple relapses of acute myeloid leukemia

Masamitsu Yanada[1] · Jinichi Mori[2] · Jun Aoki[3] · Masayoshi Masuko[4] · Kaito Harada[5] · Naoyuki Uchida[6] · Noriko Doki[7] · Takahiro Fukuda[8] · Toru Sakura[9] · Heiwa Kanamori[10] · Masashi Sawa[11] · Tadakazu Kondo[12] · Yuta Katayama[13] · Junya Kanda[12] · Tatsuo Ichinohe[14] · Yoshiko Atsuta[15,16] · Shingo Yano[17]

Received: 4 October 2018 / Accepted: 10 June 2019 / Published online: 15 June 2019

Abstract

The prognosis of patients with acute myeloid leukemia (AML) is dismal after experiencing multiple relapses. This study retrospectively analyzed outcomes of allogeneic hematopoietic cell transplantation (HCT) for 192 adults with AML in third or subsequent complete remission (CR3+), 300 in second relapse (REL2), and 50 in third or subsequent relapse (REL3+) who were enrolled in a Japanese nationwide transplantation registry. The study population included patients undergoing umbilical cord blood transplantation, but not those undergoing haploidentical HCT. Patients transplanted in CR3+ had better survival than those transplanted in REL2 and REL3+ (48%, 21%, and 12% at 4 years; $P < 0.001$), and this was due to a reduction in post-transplant relapse (23%, 57%, and 52%; $P < 0.001$). The corresponding cumulative incidence of non-relapse mortality was 33%, 26%, and 36% ($P = 0.022$). Multivariate analysis revealed significantly lower relapse and overall mortality for those in CR3+ and significantly lower non-relapse mortality for those in REL2. Hazard ratios (95% confidence intervals) for overall mortality were 2.02 (1.56–2.64) for REL2+ versus CR3+ ($P < 0.001$) and 2.12 (1.40–3.19) for REL3+ versus CR3+ ($P < 0.001$). Our analysis demonstrates the curative potential of allogeneic HCT for patients with a history of multiple AML relapses and suggests the potential benefits and risks of reinduction attempt before transplantation, highlighting the need for an individualized approach in determining whether to give reinduction therapy in this setting.

Keywords Acute myeloid leukemia · Allogeneic hematopoietic cell transplantation · Relapsed · Multiple relapses

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00277-019-03736-5) contains supplementary material, which is available to authorized users.

✉ Masamitsu Yanada
myanada@aichi-cc.jp

[1] Department of Hematology and Cell Therapy, Aichi Cancer Center, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan

[2] Jyoban Hospital Tokiwa Foundation, Fukushima, Japan

[3] Yokohama City University Medical Center, Yokohama, Japan

[4] Niigata University Hospital, Niigata, Japan

[5] Tokai University School of Medicine, Isehara, Japan

[6] Toranomon Hospital, Tokyo, Japan

[7] Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan

[8] National Cancer Center Hospital, Tokyo, Japan

[9] Saiseikai Maebashi Hospital, Maebashi, Japan

[10] Kanagawa Cancer Center, Yokohama, Japan

[11] Anjo Kosei Hospital, Anjo, Japan

[12] Graduate School of Medicine, Kyoto University, Kyoto, Japan

[13] Hiroshima Red Cross Hospital and Atomic-Bomb Survivors Hospital, Hiroshima, Japan

[14] Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan

[15] Nagoya University Graduate School of Medicine, Nagoya, Japan

[16] Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya, Japan

[17] Jikei University School of Medicine, Tokyo, Japan

Introduction

Allogeneic hematopoietic cell transplantation (HCT) can provide a cure for a subset of patients with acute myeloid leukemia (AML) who are deemed unlikely to be cured with conventional chemotherapy [1, 2]. The efficacy of allogeneic HCT is, however, compromised by a high risk of treatment-related morbidity and mortality, making it crucial to evaluate whether the benefits of transplantation outweigh its risk. Although this evaluation is primarily based on cytogenetic and molecular profiles of leukemic cells of patients in first complete remission (CR) [3], the use of allogeneic HCT is more actively pursued for patients with relapsed disease owing to anticipated poor prognosis with chemotherapy alone [1].

It is generally agreed that post-transplant outcome depends largely on disease status at the time of transplantation [4–9], and patients in first or second CR are considered standard risk. However, those with a history of multiple relapses are high risk, irrespective of whether or not they subsequently achieve CR. One question that remains unanswered is whether and to what extent an attempt to achieve CR before transplantation is worthwhile, given the low likelihood of achieving CR as well as a concern about chemotherapy-related complications which may possibly compromise post-transplant outcomes and even preclude a conduct of transplantation altogether. To address this issue, we analyzed a cohort of AML patients who had a history of multiple relapses before allogeneic HCT and were enrolled in a Japanese nationwide transplantation registry.

Patients and methods

Study population

All data were collected through the Transplant Registry Unified Management Program sponsored by the Japanese Society for Hematopoietic Cell Transplantation and the Japanese Data Center for Hematopoietic Cell Transplantation. This registration program covers nearly all transplantation centers nationwide, and each participating center is required to report annually follow-up information for consecutively registered HCTs [10–12].

Patients with AML (excluding acute promyelocytic leukemia) were selected from the database if they had undergone their first allogeneic HCT between 2002 and 2015, were aged 16 years or older at the time of transplantation, and had experienced two or more relapse episodes prior to transplantation. Patients who underwent haploidentical HCT were excluded, as were those who had previously undergone autologous HCT. The institutional review board of the Fujita Health University School of Medicine approved this study and granted waivers for informed consent because of demonstration of adequate privacy safeguards. This study was conducted in accordance with the Declaration of Helsinki.

Definitions

CR was defined as the presence of all of the following conditions: less than 5% of blasts in the bone marrow, no leukemic blasts in the peripheral blood or extramedullary sites, recovery of blood counts, and relapse as loss of CR. Cytogenetic risk was classified in accordance with the criteria provided by the National Comprehensive Cancer Network Guidelines [13, 14]. The conditioning intensity was determined in line with the consensus criteria [15, 16]: myeloablative conditioning (MAC) included (1) single-dose of total body irradiation (TBI) > 5 Gy or fractionated TBI > 8 Gy, (2) oral busulfan > 9 mg/kg or intravenous busulfan > 7.2 mg/kg, and (3) melphalan > 140 mg/m^2. Reduced intensity conditioning (RIC) included regimens that did not meet the criteria for MAC or non-myeloablative conditioning (i.e., (1) TBI ≤2 Gy with or without purine analog; (2) fludarabine and cyclophosphamide-based regimen; (3) fludarabine, cytarabine, and idarubicin; and (4) cladribine and cytarabine). For this study, non-myeloablative conditioning was included in RIC because of the very small number of patients receiving it. Neutrophil engraftment was defined as the first of three consecutive time points with a neutrophil count of 0.5×10^9/L or greater. Acute and chronic graft-versus-host disease (GVHD) were assessed according to the standard criteria [17, 18]. For the analysis of chronic GVHD, only patients who survived 100 days post-transplant without relapse were included.

Statistical analysis

Distribution of patient characteristics among groups was compared by using Fisher's exact test for categorical variables, and the Kruskal–Wallis test for continuous variables. Overall survival (OS) was defined as the time from transplantation to death or last visit. The probability of OS was estimated with the aid of the Kaplan–Meier estimator, and differences among groups were analyzed with the log-rank test. To evaluate the independent effect of the time period, multivariate analysis was performed with the inclusion of all covariates listed in Table 1 in the final model. We did not use a model selection approach because of the concern about a potentially confounding effect of each of these variables. The Cox proportional hazards regression model was constructed for multivariate analysis, and hazard ratios (HRs) were calculated together with the corresponding 95% confidence intervals (CIs). Relapse and non-relapse mortality were considered to be competing risk events. Incidence of relapse and non-relapse mortality was estimated with the aid of the cumulative incidence estimator, and univariate and multivariate analyses were performed by using the model of Fine and Gray. For the analysis of relapse, patients who never achieved CR after transplantation were categorized as relapse cases at time 0. Cumulative incidence of neutrophil engraftment and GVHD was also

Table 1 Characteristics of patients by disease status at the time of transplantation

	CR3+ (*N* = 192)		REL2 (*N* = 300)		REL3+ (*N* = 50)		*P* value
Age							*P* = 0.335
Median (range) (years)	52	(16–74)	49	(16–79)	51	(19–70)	
< 50 years	88	(46%)	155	(52%)	24	(48%)	
≥ 50 years	104	(54%)	145	(48%)	26	(52%)	
Sex							*P* = 0.142
Male	79	(41%)	118	(39%)	13	(26%)	
Female	113	(59%)	182	(61%)	37	(74%)	
ECOG performance status							*P* = 0.010
0–1	169	(92%)	235	(82%)	38	(84%)	
≥ 2	15	(8%)	51	(18%)	7	(16%)	
Missing	8		14		5		
Donor							*P* = 0.001
Related donor	62	(32%)	54	(18%)	7	(14%)	
Unrelated donor	78	(41%)	142	(47%)	21	(42%)	
Umbilical cord blood	51	(27%)	104	(35%)	22	(44%)	
Conditioning							*P* = 0.015
Myeloablative	95	(56%)	199	(67%)	25	(51%)	
Reduced-intensity	74	(44%)	97	(33%)	24	(49%)	
Missing	23		4		1		
GVHD prophylaxis							*P* = 0.098
Cyclosporine-based	86	(47%)	109	(37%)	21	(42%)	
Tacrolimus-based	96	(53%)	183	(63%)	29	(58%)	
Missing	10		8		–		
Cytogenetic risk							*P* = 0.153
Favorable	60	(31%)	81	(27%)	7	(14%)	
Intermediate	99	(52%)	159	(53%)	29	(58%)	
Poor	18	(9%)	33	(11%)	5	(10%)	
Unevaluable	15	(8%)	27	(9%)	9	(18%)	
Year of transplantation							*P* = 0.041
2002–2009	141	(73%)	190	(63%)	37	(74%)	
2010–2015	51	(27%)	110	(37%)	13	(26%)	

CR3+ third or subsequent complete remission, *REL2* second relapse, *REL3+* third or subsequent relapse, *ECOG* Eastern Cooperative Oncology Group, *GVHD* graft-versus-host disease

calculated by accommodating competing risks (death for neutrophil engraftment and death and relapse for GVHD). All statistical analyses were performed with Stata version 14.2 software (StataCorp. LP, College Station, TX, USA).

Results

Patients

A total of 542 patients were eligible for analysis. Disease status at the time of transplantation was third or subsequent CR (CR3+) for 192 patients, second relapse (REL2) for 300, and third or subsequent relapse (REL3+) for 50. Median follow-up for surviving patients was 4.2 years (range, 0.1 to 14.2 years). Table 1 summarizes the characteristics of patients stratified by disease status. There were statistically significant differences among the cohorts with respect to performance status, donor type, conditioning intensity, and year of transplantation. Specifically, patients in CR3+ were more likely to have better performance status and to have received transplantation from a related donor, those in REL2 were more likely to have undergone myeloablative conditioning and to have received transplantation during the later period, and those in REL3+ were more likely to have received umbilical cord blood transplantation (UCBT). For GVHD prophylaxis, 483 patients received methotrexate (MTX)-included regimens, and 42 mycophenolate mofetil (MMF)-included regimens.

As MMF was used almost exclusively for UCBT (39/42), we categorize the cohort into cyclosporine or tacrolimus groups rather than into MTX or MMF groups. Anti-thymocyte globulin (ATG) was used in only 5.2% of the overall study population. Owing to the limited number, the use of ATG was not considered for further analyses.

Engraftment and GVHD

The cumulative incidence of neutrophil engraftment at day 30 was 89%, 83%, and 69% for patients in CR3+, REL2, and REL3+, respectively ($P < 0.001$). Multivariate analysis demonstrated that patients in REL3+ tended to show slower neutrophil engraftment than those in CR3+ ($P = 0.052$) and in REL2 ($P = 0.054$). There was no difference among the cohorts in either the cumulative incidence of grades II–IV acute GVHD (39% for CR3+, 40% for REL2, and 32% for REL3+ at day 100; $P = 0.590$) or the chronic GVHD (35% for CR3+, 44% for REL2, and 34% for REL3+ at 1 year; $P = 0.350$). Multivariate analysis confirmed lack of any significant associations between disease status and either type of GVHD (data not shown).

Overall survival

Figure 1 compares OS by disease status at the time of transplantation. Patients in CR3+ had significantly better survival than those in REL2 and REL3+ (48%, 21%, and 12% at 4 years, respectively; $P < 0.001$ for the comparison among the three groups, $P < 0.001$ for CR3+ vs REL2, $P < 0.001$ for CR3+ vs REL3+, and $P = 0.212$ for REL2 vs REL3+).

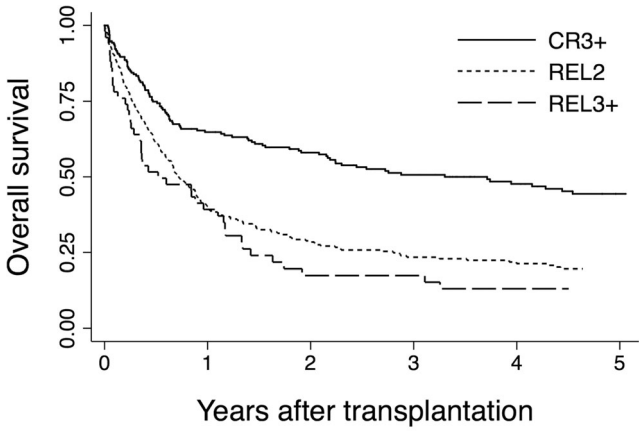

Fig. 1 Overall survival for patients undergoing allogeneic HCT in third or subsequent complete remission (CR3+, $N = 192$), second relapse (REL2, $N = 300$), and third or subsequent relapse (REL3+, $N = 50$). P values were < 0.001 for the comparison among the three groups: < 0.001 for CR3+ vs REL2, < 0.001 for CR3+ vs REL3+, and 0.212 for REL2 vs REL3+

This effect remained significant after adjustment for confounding effects of other covariates (Table 2). Multivariate analysis showed that HRs (95% CIs) for overall mortality were 2.02 (1.56–2.64) for REL2+ versus CR3+ ($P < 0.001$), 2.12 (1.40–3.19) for REL3+ versus CR3+ ($P < 0.001$), and 1.04 (0.72–1.51) for REL3+ versus REL2 ($P = 0.816$). Besides disease status, performance status of 0–1 and favorable cytogenetics were significantly associated with lower risk of overall mortality ($P = 0.005$ and $P = 0.021$, respectively).

Relapse

Figure 2 compares cumulative incidence of relapse by disease status at the time of transplantation. Patients in CR3+ showed a significantly lower rate of relapse than those in REL2 and REL3+ (23%, 57%, and 52% at 4 years, respectively; $P < 0.001$ for the comparison among the three groups, $P < 0.001$ for CR3+ vs REL2, $P < 0.001$ for CR3+ vs REL3+, and $P = 0.311$ for REL2 vs REL3+). This effect remained significant after adjustment for confounding effects of other covariates (Table 2). Multivariate analysis showed that HRs (95% CIs) for relapse were 3.77 (2.61–5.43) for REL2+ versus CR3+ ($P < 0.001$), 2.62 (1.51–4.55) for REL3+ versus CR3+ ($P = 0.001$), and 0.70 (0.44–1.10) for REL3+ versus REL2 ($P = 0.123$). Besides disease status, only favorable cytogenetics was significantly associated with lower risk of relapse ($P = 0.016$).

Non-relapse mortality

Figure 3 compares non-relapse mortality by disease status at the time of transplantation. Patients in REL2 showed significantly lower non-relapse mortality than those in CR3+ and REL3+; the cumulative incidence of non-relapse mortality at 4 years was 33% for patients in CR3+, 26% for those in REL2, and 36% for those in REL3+ ($P = 0.022$ for the comparison among the three groups, $P = 0.015$ for CR3+ vs REL2, $P = 0.643$ for CR3+ vs REL3+, and $P = 0.047$ for REL2 vs REL3+). This effect remained significant after adjustment for confounding effects of other covariates (Table 2). Multivariate analysis showed that HRs (95% CIs) for non-relapse mortality were 0.63 (0.44–0.91) for REL2+ versus CR3+ ($P = 0.013$), 1.08 (0.58–1.99) for REL3+ versus CR3+ ($P = 0.815$), and 1.86 (1.07–3.24) for REL3+ versus REL2 ($P = 0.029$). Besides disease status, only performance status of 0–1 was significantly associated with lower risk of non-relapse mortality ($P = 0.015$).

Conditioning regimens and outcomes

As shown in Table 2, conditioning intensity did not affect overall mortality, relapse, or non-relapse mortality. There was no evidence that the effect of conditioning intensity on each of these outcomes varied according to patient age (test

Table 2 Results of multivariate analysis

	Overall mortality			Relapse			Non-relapse mortality		
	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
Disease status									
REL2 vs CR3+	2.02	(1.56–2.64)	< 0.001	3.77	(2.61–5.43)	< 0.001	0.63	(0.44–0.91)	0.013
REL3+ vs CR3+	2.12	(1.40–3.19)	< 0.001	2.62	(1.51–4.55)	0.001	1.08	(0.58–1.99)	0.815
REL3+ vs REL2	1.04	(0.72–1.51)	0.816	0.70	(0.44–1.10)	0.123	1.86	(1.07–3.24)	0.029
Age									
≥ 50 vs < 50 years	1.23	(0.95–1.59)	0.111	0.93	(0.68–1.28)	0.661	1.27	(0.84–1.91)	0.251
Sex									
Male vs female	0.95	(0.76–1.19)	0.651	1.06	(0.80–1.40)	0.680	0.81	(0.56–1.17)	0.259
ECOG performance status									
2–4 vs 0–1	1.51	(1.13–2.02)	0.005	0.81	(0.53–1.24)	0.326	1.69	(1.11–2.58)	0.015
Donor									
Unrelated donor vs related donor	0.99	(0.71–1.38)	0.953	1.03	(0.67–1.58)	0.887	0.88	(0.55–1.41)	0.601
Umbilical cord blood vs related donor	0.97	(0.69–1.36)	0.851	0.77	(0.51–1.19)	0.240	1.20	(0.74–1.94)	0.460
Conditioning									
Reduced-intensity vs myeloablative	1.10	(0.86–1.42)	0.442	1.14	(0.83–1.56)	0.419	1.03	(0.69–1.52)	0.894
GVHD prophylaxis									
Tacrolimus- vs cyclosporine-based	0.95	(0.73–1.23)	0.707	0.94	(0.66–1.32)	0.706	1.05	(0.72–1.54)	0.788
Cytogenetic risk									
Favorable vs intermediate	0.72	(0.55–0.95)	0.021	0.65	(0.46–0.92)	0.016	1.02	(0.68–1.54)	0.907
Poor vs intermediate	1.14	(0.81–1.61)	0.442	1.06	(0.69–1.63)	0.785	1.05	(0.59–1.86)	0.862
Unevaluable vs intermediate	1.48	(0.99–2.21)	0.052	1.15	(0.71–1.87)	0.569	1.21	(0.58–2.51)	0.611
Year of transplantation									
2002–2009 vs 2010–2015	0.96	(0.75–1.23)	0.741	0.92	(0.67–1.26)	0.612	0.99	(0.69–1.42)	0.949

HR hazard ratio, *CI* confidence interval, *REL2* second relapse, *CR3+* third or subsequent complete remission, *REL3+* third or subsequent relapse, *ECOG* Eastern Cooperative Oncology Group, *GVHD* graft-versus-host diseases

for interaction $P = 0.131$ for overall mortality; $P = 0.414$ for relapse; and $P = 0.844$ for non-relapse mortality). Details of the conditioning regimens used are summarized in Supplementary Table. Incorporating the fludarabine plus melphalan regimen into MAC did not change the results ($P = 0.959$ for overall mortality, $P = 0.854$ for relapse, and $P = 0.917$ for non-relapse mortality). We used TBI at a dose of > 8 Gy (hereafter referred to as high-dose TBI) for 178 (35%) of 514 patients. The use of high-dose TBI correlated with the declined overall mortality for those in CR3+ (HR [95% CI], 0.60 [0.36–0.99]; $P = 0.048$), which was caused by a non-significant reduction in relapse (HR [95% CI], 0.78 [0.37–1.65]; $P = 0.516$) and non-relapse mortality (HR [95% CI], 0.75 [0.42–1.36]; $P = 0.354$). For those in REL2 and REL3+, however, the use of high-dose TBI did not affect any of the outcomes (data not shown).

Subgroup analysis of patients not in CR

For patients in REL2 and REL3+, we assessed the prognostic relevance of disease burden as well as time to transplantation. The percentage of blasts in the bone marrow before transplantation was obtained from 204 patients; of these, 76 (37%) presented with ≥ 20% or more blasts. Bone marrow blasts ≥ 20% correlated with a trend for higher relapse (HR [95% CI], 1.75 [0.97–3.17]; $P = 0.064$) and a significantly higher overall mortality (HR [95% CI], 1.76 [1.28–2.46]; $P < 0.001$). In addition, the time elapsed from the latest relapse to transplantation was known for 229 patients; of these, 135 (59%) underwent transplantation within 2 months from the latest relapse. Patients transplanted 2 months or later exhibited significantly higher risks of non-relapse mortality (HR [95% CI], 2.22 [1.26–3.89]; $P = 0.006$) and overall mortality (HR [95% CI], 1.38 [1.01–1.87]; $P = 0.040$).

Discussion

Patients who have gone through multiple AML relapses have extremely poor prognosis [3]. To pursue a cure for such patients, it is a matter of clinical concern how best to proceed to allogeneic HCT. Although it is intuitive that allogeneic HCT

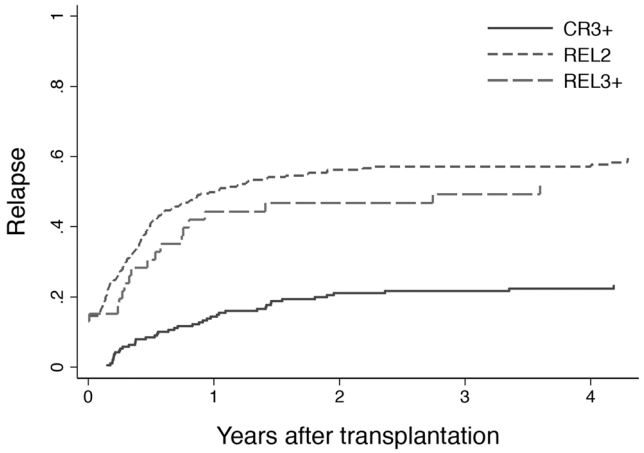

Fig. 2 Cumulative incidence of relapse for patients undergoing allogeneic HCT in third or subsequent complete remission (CR3+, $N = 192$), second relapse (REL2, $N = 300$), and third or subsequent relapse (REL3+, $N = 50$). Those who never achieved CR after transplantation were categorized as relapse cases at time zero. P values were < 0.001 for the comparison among the three groups: < 0.001 for CR3+ vs REL2, < 0.001 for CR3+ vs REL3+, and 0.311 for REL2 vs REL3+

yields a better disease control when performed during CR, patients in second or subsequent relapse are unlikely to respond to salvage chemotherapy [19]. Furthermore, intensive chemotherapy could result in toxicity that may hamper the success of a future transplantation. This situation shows the importance of investigating the risks and benefits of reinduction attempts for patients with multiple relapses. This prompted us to conduct the study presented here.

Our analysis on 542 adults with multiple pre-transplant relapses of AML demonstrated that allogeneic HCT still offers a potential cure for this group of patients with an otherwise incurable disease. Furthermore, outcomes were shown to differ significantly according to disease status at the time of transplantation. Patients transplanted in CR3+ had better OS than those transplanted in REL2 or REL3+, and this was obviously due to reduced risk of post-transplant relapse. Relapse was the main cause for treatment failure in a non-CR setting, as more than 50% of our patients in REL2 and REL3+ relapsed after transplantation. In contrast, the relapse rate for those transplanted in CR3+ was only 23%, which was even lower than their non-relapse mortality of 33%. These results support the use of salvage induction therapy as a bridge to allogeneic HCT even for patients with multiple relapses. As our registry data did not secure information on measurable residual disease (MRD), we were not able to expand our analysis by considering MRD data. However, some recent studies have reported that the absence of MRD at the time of transplantation correlated with lower relapse and better OS for patients with AML transplanted during first CR [20, 21], making it a subject of future investigation to elucidate how the MRD status affects post-transplant outcomes for patients in second or further CR. In terms of non-relapse mortality, univariate and multivariate analyses showed that patients in REL3+ and CR3+ were at higher risk than those in REL2. Although it was unclear whether the inclusion of chemotherapy increases the vulnerability to subsequent allogeneic HCT, our results raise concern regarding this potential risk.

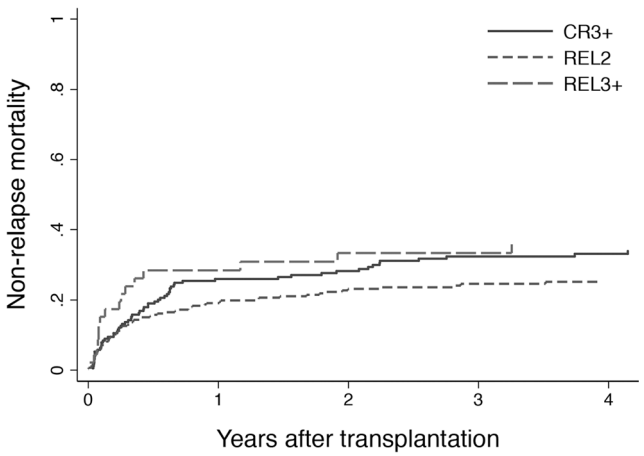

Fig. 3 Cumulative incidence of non-relapse mortality for patients undergoing allogeneic HCT in third or subsequent complete remission (CR3+, $N = 192$), second relapse (REL2, $N = 300$), and third or subsequent relapse (REL3+, $N = 50$). P values were 0.022 for the comparison among the three groups: 0.015 for CR3+ vs REL2, 0.643 for CR3+ vs REL3+, and 0.047 for REL2 vs REL3+

Besides disease status, cytogenetics and performance status were identified as factors significantly affecting survival after transplantation. Favorable cytogenetics was associated with lower risk of relapse and performance status above 1 with higher risk of non-relapse mortality. In the cohort of patients not in CR, lower bone marrow blasts before transplantation and more rapid transition to transplantation correlated with better outcomes. These may provide guidance for the choice whether and when to proceed to allogeneic HCT. Regarding the donor source, a high rate of UCBT (33% of all the patients) merits special attention, which could signify transplantation practice in Japan; > 1000 UCBTs were performed per year, accounting for one-third of all allogeneic HCTs [22]. Our analysis could not detect significant impact of donor sources on overall mortality, relapse, or non-relapse mortality, and the outcomes with UCBT were comparable to those with related HCT. Owing to the immediate availability, UCBT could be a beneficial option for patients at very high risk of early relapse or disease progression.

Because of the retrospective registry-based design, this study suffers from some limitations. The primary limitation is derived from the fact that the decision of when to choose allogeneic HCT for an individual patient could have been confounded by multiple factors, and there may have been other effects of several unknown and unmeasured factors. Although we did not observe any significant impact of donor type or conditioning intensity on

post-transplant outcomes, these results are also susceptible to bias because which patients received which procedures was the result of non-randomized selection. In addition, our database did not consistently record detailed information on chemotherapy administered before allogeneic HCT. It should also be noted that our study did not consider the information on specific gene mutations such as those of *FLT3* and *NPM1*. Although the prognostic impact of such mutations is unclear in patients with relapsed disease, several studies have reported that the presence or absence of these mutations provides relevant prognostic information on patients undergoing allogeneic HCT during first CR [23, 24].

While our results should be interpreted cautiously with these limitations in mind, this is the largest study to date to investigate patients with a history of multiple relapses of AML before allogeneic HCT, for whom conducting a prospective study is unfeasible. Some may argue that better outcomes for our patients in CR3+ could represent not only prognostic relevance of disease status itself but also intrinsic responsiveness of leukemia. Even if the latter was the case, attempts to induce CR would still be useful in the selection of patients most likely to be salvaged with allogeneic HCT. In this regard, however, it is worth emphasizing that allogeneic HCT is feasible in selected patients with second or greater relapse, and some of them achieve long-term disease control following allogeneic HCT. To ascertain the true effects of conducting reinduction chemotherapy before transplantation, a larger study is warranted enrolling not only patients who underwent HCT but also those who failed to proceed to HCT. In the absence of such data, our findings should provide valuable insights into pursuing a cure for this kind of patients with extremely poor prognosis.

Last of all, high relapse rates noted especially in patients transplanted beyond CR necessitate the development of strategies to prevent post-transplant relapse; these might include the prophylactic use of donor lymphocyte infusion, azacitidine, or novel agents, but we could not assess the effects of these interventions because of incomplete data. Regarding conditioning, our analysis did not display prominent advantage with any type of conditioning regimen except for high-dose TBI for patients in CR3+. However, a high demand exists for the establishment of conditioning regimens that yield more potent antileukemic activity without elevating toxicity, such as those including ^{131}I-labeled anti-CD45 antibody [25, 26]. Reduction of the risk of post-transplant relapse signifies a key challenge to enhance transplant outcomes.

In summary, this study demonstrates the curative potential of allogeneic HCT for patients with a history of multiple AML relapses. The potential benefits and risks of reinduction attempt before transplantation noted in our patients highlight the need for an individualized approach in determining whether to give reinduction therapy in this setting.

Funding information This work was supported in part by the Practical Research Project for Allergic Diseases and Immunology (Research Technology of Medical Transplantation) from Japan Agency for Medical Research and Development (AMED) under the grant number 18ek0510023h0002.

Compliance with ethical standards This study was approved by the institutional review board of the Fujita Health University School of Medicine and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients for being included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Forman SJ, Rowe JM (2013) The myth of the second remission of acute leukemia in the adult. Blood 121:1077–1082
2. Thol F, Schlenk RF, Heuser M, Ganser A (2015) How I treat refractory and early relapsed acute myeloid leukemia. Blood 126: 319–327
3. Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Buchner T, Dombret H, Ebert BL, Fenaux P, Larson RA, Levine RL, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz M, Sierra J, Tallman MS, Tien HF, Wei AH, Lowenberg B, Bloomfield CD (2017) Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 129:424–447
4. Greinix HT, Nachbaur D, Krieger O, Eibl M, Knobl P, Kalhs P, Lutz D, Linkesch W, Niederwieser D, Hinterberger W, Lechner K, Rosenmayr A, Gritsch B (2002) Factors affecting long-term outcome after allogeneic haematopoietic stem cell transplantation for acute myelogenous leukaemia: a retrospective study of 172 adult patients reported to the Austrian Stem Cell Transplantation Registry. Br J Haematol 117:914–923
5. Sierra J, Storer B, Hansen JA, Martin PJ, Petersdorf EW, Woolfrey A, Matthews D, Sanders JE, Storb R, Appelbaum FR, Anasetti C (2000) Unrelated donor marrow transplantation for acute myeloid leukemia: an update of the Seattle experience. Bone Marrow Transplant 26:397–404
6. Michallet M, Thomas X, Vernant JP, Kuentz M, Socie G, Esperou-Bourdeau H, Milpied N, Blaise D, Rio B, Reiffers J, Jouet JP, Cahn JY, Bourhis JH, Lioure B, Leporrier M, Sotto JJ, Souillet G, Sutton L, Bordigoni P, Dreyfus F, Tilly H, Gratecos N, Attal M, Leprise PY, Demeocq F, Michel G, Buzyn A, Delmas-Marsalet B, Bernaudin F, Ifrah N, Sadoun A, Guyotat D, Cavazzana-Cavo M, Caillot D, De Revel T, Vannier JP, Baruchel A, Fegueux N, Tanguy ML, Thiebaut A, Belhabri A, Archimbaud E (2000) Long-term outcome after allogeneic hematopoietic stem cell transplantation for advanced stage acute myeloblastic leukemia: a retrospective study of 379 patients reported to the Societe Francaise de Greffe de Moelle (SFGM). Bone Marrow Transplant 26:1157–1163
7. Sayer HG, Kroger M, Beyer J, Kiehl M, Klein SA, Schaefer-Eckart K, Schwerdtfeger R, Siegert W, Runde V, Theuser C, Martin H, Schetelig J, Beelen DW, Fauser A, Kienast J, Hoffken K, Ehninger G, Bornhauser M, Cooperative German Transplant Study G (2003) Reduced intensity conditioning for allogeneic hematopoietic stem cell transplantation in patients with acute myeloid leukemia: disease status by marrow blasts is the strongest prognostic factor. Bone Marrow Transplant 31:1089–1095
8. Kurosawa S, Miyawaki S, Yamaguchi T, Kanamori H, Sakura T, Moriuchi Y, Sano F, Kobayashi T, Yasumoto A, Hatanaka K,

Yanada M, Nawa Y, Takeuchi J, Nakamura Y, Fujisawa S, Shibayama H, Miura I, Fukuda T (2013) Prognosis of patients with core binding factor acute myeloid leukemia after first relapse. Haematologica 98:1525–1531

9. Weisdorf DJ, Millard HR, Horowitz MM, Hyare PS, Champlin R, Ho V, Mielcarek M, Rezvani A, Stockerl-Goldstein K, Khoury HJ, De Lima M, Saber W, Sandmaier B, Zhang MJ, Eapen M (2017) Allogeneic transplantation for advanced acute myeloid leukemia: the value of complete remission. Cancer 123:2025–2034
10. Atsuta Y, Suzuki R, Yoshimi A, Gondo H, Tanaka J, Hiraoka A, Kato K, Tabuchi K, Tsuchida M, Morishima Y, Mitamura M, Kawa K, Kato S, Nagamura T, Takanashi M, Kodera Y (2007) Unification of hematopoietic stem cell transplantation registries in Japan and establishment of the TRUMP System. Int J Hematol 86:269–274
11. Atsuta Y (2016) Introduction of Transplant Registry Unified Management Program 2 (TRUMP2): scripts for TRUMP data analyses, part I (variables other than HLA-related data). Int J Hematol 103:3–10
12. Kanda J (2016) Scripts for TRUMP data analyses. Part II (HLA-related data): statistical analyses specific for hematopoietic stem cell transplantation. Int J Hematol 103:11–19
13. O'Donnell MR, Tallman MS, Abboud CN, Altman JK, Appelbaum FR, Arber DA, Bixby D, Blum W, Borate U, Coutre SE, De Lima M, Fathi AT, Foran JM, Gore SD, Lancet J, Maness LJ, Marcucci G, Martin MW, Martin MG, Moore JO, National Comprehensive Cancer Network (2016) NCCN clinical practice guidelines in oncology. Acute Myeloid Leukemia. Version 1.2016. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed 26 Feb 2016
14. Yanada M, Mori J, Aoki J, Harada K, Mizuno S, Uchida N, Kurosawa S, Toya T, Kanamori H, Ozawa Y, Ogawa H, Henzan H, Iwato K, Sakura T, Ota S, Fukuda T, Ichinohe T, Atsuta Y, Yano S (2018) Effect of cytogenetic risk status on outcomes for patients with acute myeloid leukemia undergoing various types of allogeneic hematopoietic cell transplantation: an analysis of 7812 patients. Leuk Lymphoma 59:601–609
15. Giralt S, Logan B, Rizzo D, Zhang MJ, Ballen K, Emmanouilides C, Nath R, Parker P, Porter D, Sandmaier B, Waller EK, Barker J, Pavletic S, Weisdorf D (2007) Reduced-intensity conditioning for unrelated donor progenitor cell transplantation: long-term follow-up of the first 285 reported to the national marrow donor program. Biol Blood Marrow Transplant 13:844–852
16. Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, Apperley J, Slavin S, Pasquini M, Sandmaier BM, Barrett J, Blaise D, Lowski R, Horowitz M (2009) Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant 15:1628–1633
17. Sullivan KM, Agura E, Anasetti C, Appelbaum F, Badger C, Bearman S, Erickson K, Flowers M, Hansen J, Loughran T et al (1991) Chronic graft-versus-host disease and other late complications of bone marrow transplantation. Semin Hematol 28:250–259
18. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, Thomas ED (1995) 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 15:825–828
19. Kantarjian HM, DiNardo CD, Nogueras-Gonzalez GM, Kadia TM, Jabbour E, Bueso-Ramos CE, O'Brien SM, Konopleva M, Jain NB, Daver NG, Shpall EJ, Champlin RE, Simkins A, Garcia-Manero G, Keating MJ, Huang X, Cortes JE, Pierce SA, Ravandi F, Freireich EJ (2018) Results of second salvage therapy in 673 adults with acute myelogenous leukemia treated at a single institution since 2000. Cancer 124:2534–2540
20. Araki D, Wood BL, Othus M, Radich JP, Halpern AB, Zhou Y, Mielcarek M, Estey EH, Appelbaum FR, Walter RB (2016) Allogeneic hematopoietic cell transplantation for acute myeloid leukemia: time to move toward a minimal residual disease-based definition of complete remission? J Clin Oncol 34:329–336
21. Oran B, Jorgensen JL, Marin D, Wang S, Ahmed S, Alousi AM, Andersson BS, Bashir Q, Bassett R, Lyons G, Chen J, Rezvani K, Popat U, Kebriaei P, Patel K, Rondon G, Shpall EJ, Champlin RE (2017) Pre-transplantation minimal residual disease with cytogenetic and molecular diagnostic features improves risk stratification in acute myeloid leukemia. Haematologica 102:110–117
22. Activities and outcomes of hematopoietic cell transplantation in Japan (2016). http://www.jdchct.or.jp/en/data/slide/2016/. Accessed 21 Nov 2018
23. Schmid C, Labopin M, Socie G, Daguindau E, Volin L, Huynh A, Bourhis JH, Milpied N, Cornelissen J, Chevallier P, Maertens J, Jindra P, Blaise D, Lenhoff S, Ifrah N, Baron F, Ciceri F, Gorin C, Savani B, Giebel S, Polge E, Esteve J, Nagler A, Mohty M, Acute Leukemia Working Party of the European Group of B, Bone Marrow T (2015) Outcome of patients with distinct molecular genotypes and cytogenetically normal AML after allogeneic transplantation. Blood 126:2062–2069
24. Song Y, Magenau J, Li Y, Braun T, Chang L, Bixby D, Hanauer DA, Chughtai KA, Gatza E, Couriel D, Goldstein S, Pawarode A, Reddy P, Riwes M, Connelly J, Harris A, Kitko C, Levine J, Yanik G, Parkin B, Choi SW (2016) FLT3 mutational status is an independent risk factor for adverse outcomes after allogeneic transplantation in AML. Bone Marrow Transplant 51:511–520
25. Pagel JM, Gooley TA, Rajendran J, Fisher DR, Wilson WA, Sandmaier BM, Matthews DC, Deeg HJ, Gopal AK, Martin PJ, Storb RF, Press OW, Appelbaum FR (2009) Allogeneic hematopoietic cell transplantation after conditioning with 131I-anti-CD45 antibody plus fludarabine and low-dose total body irradiation for elderly patients with advanced acute myeloid leukemia or high-risk myelodysplastic syndrome. Blood 114:5444–5453
26. Mawad R, Gooley TA, Rajendran JG, Fisher DR, Gopal AK, Shields AT, Sandmaier BM, Sorror ML, Deeg HJ, Storb R, Green DJ, Maloney DG, Appelbaum FR, Press OW, Pagel JM (2014) Radiolabeled anti-CD45 antibody with reduced-intensity conditioning and allogeneic transplantation for younger patients with advanced acute myeloid leukemia or myelodysplastic syndrome. Biol Blood Marrow Transplant 20:1363–1368