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Efficacy of Total-Body Irradiation-based Intensified Myeloablative Regimens for Acute Leukemia—An International Collaborative Study

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Keywords: acute leukemia | international collaborative study | myeloablative conditioning

ABSTRACT

Background: In this study, we compared outcomes of intensified myeloablative conditioning regimens using large registry data from Japan (Japanese Society for Transplantation and Cellular Therapy) and the United States (Center for International Blood and Marrow Transplant Research).

Methods: Adult patients who underwent their first myeloablative allogeneic hematopoietic stem cell transplantation (HSCT) for acute leukemia in remission between 2010 and 2018 using conditioning regimens of cyclophosphamide plus total-body irradiation (CY/TBI), CY/TBI+cytarabine (AraC), or CY/TBI+etoposide (VP16) were included.

Results: The acute myeloid leukemia (AML) cohort (N = 480, 38.8%) indicated that overall survival (OS) was poorer in CY/TBI+AraC (hazard ratio [HR] 1.46, $p < 0.001$) and CY/TBI+VP16 (HR 1.39, $p = 0.059$) compared to CY/TBI. Relapse was not suppressed, while treatment-related mortality (TRM) was significantly higher (HR 1.78 and 1.74, $p < 0.001$ and 0.018, respectively). In the acute lymphoblastic leukemia (ALL) cohort ($N = 3901$, 61.2%), OS was comparable among these regimens. With intensified

regimens, relapse was significantly suppressed in CY/TBI+VP16 (HR 0.74, $p = 0.005$), while TRM was higher (HR 1.21, $p = 0.077$). No interactions were observed regarding the country.

Conclusion: In AML adding AraC and VP16 to CY/TBI had an adverse effect on OS. Conversely, in ALL, adding VP16 or AraC to CY/TBI did not affect survival, but the addition of VP16 reduced the risk of relapse.

Clinical Trial Registration: The authors have confirmed clinical trial registration is not needed for this submission.

1 | Introduction

In allogeneic hematopoietic stem cell transplantation (HSCT) for acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), intensified myeloablative conditioning regimens have been explored in order to reduce the frequency of post-HSCT relapse [1, 2]. These regimens do reduce post-transplant relapse; however, they may induce higher treatment-related toxicity, leading to poorer overall survival (OS) [3, 4].

Our group previously analyzed leukemia cases using the Japanese registry database and found that the addition of high-dose cytarabine (AraC) showed superior OS compared with the conventional myeloablative regimen (cyclophosphamide plus total-body irradiation [CY/TBI]) with decreased post-HSCT relapse and the same level of TRM in cord blood transplantation (CBT) [1, 2], but not with other sources like bone marrow or peripheral blood stem cell (BMT/PBSCT) [3]. Moreover, the addition of etoposide (VP16) to CY/TBI improved the outcome in bone marrow (BM) or peripheral blood stem cell (PBSC) transplants in patients with high-risk ALL in Japan [5].

These results had certain limitations, due to heterogenous donor sources, variable conditioning regimens, and time-frame bias (older vs. more recent years of HSCT). Moreover, CBT outcomes in Japan are relatively better, partly because of the genetic homogeneity of the Japanese population. These limitations led us to validate previous results using a large international cohort from the Center for International Blood and Marrow Transplant Research (CIBMTR) in the United States (US) and the Japanese Society for Transplantation and Cellular Therapy (JSTCT) to compare the benefits and drawbacks of these regimens between cohorts.

2 | Patients and Methods

2.1 | Study Cohort and Inclusion Criteria

We included adult patients (18 years or older at transplantation) who underwent their first myeloablative allogeneic HSCT (BM or PBSC) for acute leukemia in remission (CR1 or 2) between 2010 and 2018, either in Japan or the US using conditioning regimens of CY/TBI, CY/TBI+AraC, or CY/TBI+VP16 without any ex vivo T-cell depletion or post-transplant CY. The two datasets from the US and Japan were merged for analysis.

The primary endpoint was OS, and secondary endpoints included disease-free survival (DFS), treatment-related mortality (TRM), disease relapse/progression, acute and chronic graft-versus-host disease (GVHD), cumulative incidence of infections (bacterial and viral) and veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) by day 100 post-HSCT.

This study was approved by the Institutional Review Board of Kyoto University and was conducted according to the principles of the Declaration of Helsinki.

2.2 | Generation of the Merged Database and Definition of Variables

Two datasets from the US (through CIBMTR) and Japan (JSTCT and Japanese Data Center for Hematopoietic Cell Transplantation [JDCHCT]) were merged for analysis. The JSTCT/JDCHCT database contained information on all hematopoietic cell transplantations performed in Japan, including pre-transplant patient characteristics, (underlying disease, previous treatments and their outcomes, patient performance status, etc.), transplantation procedures (conditioning regimens, donor sources, GVHD prophylaxis, etc.), and post-transplant status obtained by periodic follow-ups (various complications such as infection, GVHD, disease status, and survival) [6]. Overall, the JSTCT/JDCHCT database has a very similar structure to the CIBMTR database.

Regarding the US database, data were reported prospectively to the CIBMTR. CIBMTR is a working group of more than 500 transplant centers worldwide that provide detailed patient, disease, transplant characteristics, and outcomes of consecutive allogeneic transplantations. The CIBMTR collects both Transplant Essential Data (TED) and Comprehensive Report Form (CRF) data before transplantation, 100 days and 6 months after transplantation, and annually after that. CRF data are collected only in a subset of patients determined by an algorithm adjusted biannually to ensure representative samples. All subjects whose data were included in this study provided institutional review board-approved consent to participate in the CIBMTR Research Database and to have their data included in observational research studies [7]. Observational studies with this database are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in the researchers' capacity as a public health authority under the Health Insurance Portability and Accountability Act Privacy Rule.

All necessary data regarding pre- and post-transplant data were extracted from the JSTST/JDCHCT database and linked to the

CIBMTR database. The de-identified dataset was forwarded from JDCHCT and the included variables were modified to match those used in CIBMTR. The modified dataset was simply added to the CIBMRT database.

Types and doses of chemotherapeutants added to conventional conditioning (CY/TBI) were summarized and categorized into several groups. Each group was compared with conventional regimens in terms of prognosis and regimen-related complications.

2.3 | Statistical Analyses

Patients were grouped based on the conditioning they received: CY/TBI, CY/TBI+AraC, and CY/TBI+VP16. For each of the three groups, OS and DFS probabilities were calculated using the Kaplan-Meier method. The log-rank test was used to compare survival curves between the CY/TBI and CY/TBI+AraC groups and the CY/TBI and CY/TBI+VP16 groups. Cumulative incidence of TRM was calculated considering relapse as a competing risk. Cumulative incidence of acute and chronic GVHD was calculated considering death as a competing risk. After computing cumulative incidence probabilities in the three patient groups, Gray's test was used to compare the CY/TBI and CY/TBI+AraC groups and the CY/TBI and CY/TBI+VP16 groups over time [8].

Multivariable analyses were performed using the Cox proportional hazards model. Conditioning regimens (CY/TBI, CY/TBI+AraC, and CY/TBI+VP16) and country (US/Japan) were included in the model at all times. A stepwise model selection procedure was used to identify other significant factors to be included in the final model. Interactions between conditioning regimens and each of the variables included in the final model were checked in order to identify patient groups in which conditioning regimens had a different effect. This approach was used to model OS, DFS, relapse, TRM, acute GVHD, and chronic GVHD.

The cumulative incidence of post-transplant toxicities was calculated in each of the three patient groups defined by conditioning regimens. Death was considered a competing risk.

3 | Results

3.1 | Patient Characteristics

In total, 6381 patients were included in this study (3469 from the US, and 2912 from Japan) (Table 1). CY/TBI was most commonly used (N = 5374, 84.2%), while CY/TBI+AraC was used in 389 patients and CY/TBI+VP16 in 618 patients. The median ages of patients were 40, 36, and 35 years in CY/TBI, CY/TBI+AraC, and CY/TBI+VP16, respectively. The majority of patients (N = 5007, 78.4%) were transplanted in CR1. The most frequently used donor sources included HLA-matched unrelated donors (N = 2546, 39.8%), followed by HLA-matched siblings (N = 2522, 39.5%). TBI dose distribution indicated that the median dosage was 1200 cGy.

TABLE 1 | Patient characteristics.

Characteristic	CY/TBI	CY/TBI +AraC	CY/TBI +VP16
No. of patients	54	389	618
Country—no. (%)			
US	3167 (59)	113 (29)	189 (31)
Japan	2207 (41)	276 (71)	429 (69)
Recipient age—no. (%)			
Median (min–max)	40 (18–72)	36 (18–72)	35 (18–67)
−29	1380 (26)	141 (36)	228 (37)
30–39	1326 (25)	112 (29)	170 (28)
40–49	1646 (31)	81 (21)	154 (25)
50–59	946 (18)	42 (11)	61 (10)
60-	76 (1)	15 (4)	5 (1)
Recipient gender—no. (%)			
Male	3022 (56)	226 (58)	367 (59)
Female	2352 (44)	163 (42)	251 (41)
Karnofsky score prior to HCT—no. (%)			
<90	1243 (23)	62 (16)	88 (14)
≥90	4100 (76)	327 (84)	526 (85)
Disease—no. (%)			
AML	2189 (41)	223 (57)	68 (11)
ALL	3185 (59)	166 (43)	550 (89)
Disease status—no. (%)			
AML CR1	1598 (30)	160 (41)	57 (9)
CR2	591 (11)	63 (16)	11 (2)
ALL CR1	2609 (49)	130 (33)	453 (73)
CR2	576 (11)	36 (9)	97 (16)
HCT-CI—no. (%)			
AML 0–2	1714 (31)	199 (51)	57 (9)
3+	468 (9)	24 (6)	11 (2)
ALL 0–2	2350 (54)	135 (34)	471 (76)
3+	821 (15)	30 (8)	76 (12)
Cytogenetic score—no. (%)			
AML Favorable	286 (5)	37 (10)	7 (1)
Intermediate	1109 (21)	120 (31)	26 (4)
Poor	282 (5)	33 (8)	15 (2)
ALL Normal	608 (11)	35 (9)	149 (24)
Poor	1748 (33)	82 (21)	315 (51)
Graft type—no. (%)			
Bone Marrow	2252 (42)	241 (62)	365 (59)
Peripheral Blood	3122 (58)	148 (38)	253 (41)

(Continues)

TABLE 1 | (Continued)

Characteristic	CY/TBI	CY/TBI +AraC	CY/TBI +VP16
Donor type—no. (%)			
HLA-identical sibling	2114 (39)	170 (44)	238 (39)
Well-matched unrelated (8/8)	2207 (41)	131 (34)	208 (34)
Partially-matched unrelated (7/8)	800 (15)	68 (17)	125 (20)
Mis-matched unrelated (≤ 6/8)	129 (2)	12 (3)	30 (5)
Follow-up—median (range), month	63 (0-151)	60 (1-139)	62 (0-143)

Abbreviations. ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; AraC, cytarabine; CR, complete remission; CY, cyclophosphamide; HCT, hematopoietic cell transplantation; HCT-CI, HCT commodity index; TBI, total body irradiation; VP16, etoposide.

3.2 | Post-HSCT Outcomes in AML According to Conditioning Regimens

In the AML cohort (N = 2480, 38.8%), OS at 1 year was 76.9% (95% confidence interval [CI] 75.1%–78.7%) in the CY/TBI group while 73.0% (66.9%–78.8%) in the CY/TBI+AraC group and 67.6% (56.1%–78.2%) in CY/TBI+VP16 group (p = 0.139) (Figure 1A). The cumulative frequencies of relapse at 1 year in each group were 20.3% (18.6%–22.0%), 15.7% (11.1%–20.8%), and 23.5% (14.2%–34.4%), respectively (p = 0.166) (Figure 2A). TRM at 1 year was significantly higher in the CY/TBI+AraC group (17.5% [12.7%–22.8%]) and CY/TBI+VP16 group (19.1% [10.7%–29.3%]) than in the CY/TBI group (11.2% [9.9%–12.5%]) (p = 0.018) (Figure 3A).

Multivariable analyses indicated that OS was inferior in CY/TBI+AraC (hazard ratio [HR] 1.46, p < 0.001) and CY/TBI+VP16 (HR 1.39, p = 0.059) compared to CY/TBI, where country, recipient age, cytogenetic score, donor, HCT-CI, and year of HSCT were included in the model. DFS was significantly inferior in these intensified regimens (HR 1.32 and 1.39, p = 0.008 and 0.049, respectively). Relapse was not suppressed (HR 0.98 and 1.16, p = 0.913 and 0.528), while TRM was significantly higher (HR 1.78 and 1.74, p < 0.001 and 0.018, respectively) (Table 2).

Frequencies of other complications were also calculated (Table 3). Incidence of GVHD (acute grades 2–4 and 3–4, and chronic) and infections (viral, bacterial, fungal) were comparable among the regimens. VOD/SOS could not be evaluated due to the small number of events. Interactions regarding the country were not observed.

3.3 | Post-HSCT Outcomes in ALL According to each Conditioning Regimen

In the ALL cohort (N = 3901, 61.2%), OS at 1 year was 79.5% (95% CI 78.0%–80.9%) in the CY/TBI group while 79.1% (72.5%–85.0%) in the CY/TBI+AraC group and 79.6% (76.1%–82.9%) in the CY/TBI+VP16 group (p = 0.991) (Figure 1B). The cumulative incidence of relapse at 1 year in each group was 17.4% (16.1%–18.7%) in CY/TBI and 15.9% (10.7%–21.9%) in CY/TBI+AraC, which is significantly higher than that in CY/TBI+VP16 (13.0% [10.3%–16.0%] (p = 0.024) (Figure 2B). TRM at 1 year was 12.7% (11.6%–13.9%) in CY/TBI, 14.7% (9.7%–20.5%) in CY/TBI+AraC, and 13.8% (11.0%–16.8%) in CY/TBI+VP16, respectively (p = 0.665) (Figure 3B).

TABLE 2 | Multivariate analyses for various outcome measures in acute myelogenous leukemia (AML).

Outcomes	N	HR (95% CI)	p
Overall survival			
CY/TBI	2187	Reference	
CY/TBI+AraC	223	1.46 (1.17–1.82)	<0.001*
CY/TBI+VP16	68	1.39 (0.99–1.95)	0.059
Disease-free survival			
CY/TBI	2174	Reference	
CY/TBI+AraC	223	1.32 (1.07–1.63)	0.008*
CY/TBI+VP16	68	1.39 (1.00–1.92)	0.049*
Relapse			
CY/TBI	2174	Reference	
CY/TBI+AraC	223	0.98 (0.73–1.33)	0.913
CY/TBI+VP16	68	1.16 (0.74–1.81)	0.528
TRM			
CY/TBI	2174	Reference	
CY/TBI+AraC	223	1.78 (1.32–2.39)	<0.001*
CY/TBI+VP16	68	1.74 (1.10–2.75)	0.018*

Abbreviations: CI, confidence interval; HR, hazard ratio; TRM, treatment-related mortality.
* indicates statistically significant.

Multivariate analyses demonstrated that OS was comparable among the regimens (HR 1.02, p = 0.880 in CY/TBI+AraC and HR 1.02, p = 0.841 in CY/TBI+VP16, compared to CY/TBI), where country, recipient age, cytogenetic score, disease status, donor/recipient sex match, HCT-CI, and year of HSCT were included in the model. DFS was also comparable. Benefits of intensified regimens were observed in relapse, which was significantly reduced in CY/TBI+VP16 (HR 0.74, p = 0.005), while TRM was higher with borderline significance (HR 1.21, p = 0.077) (Table 4).

Frequencies of post-HSCT complications are shown in Table 5. Viral infection was significantly less frequent in the cohort with CY/TBI+VP16. No interactions were observed regarding the country.

4 | Discussion

Our analyses using international datasets from the US and Japan provided three new insights regarding intensified myeloablative conditioning regimens for patients undergoing BMT or PBSCT.

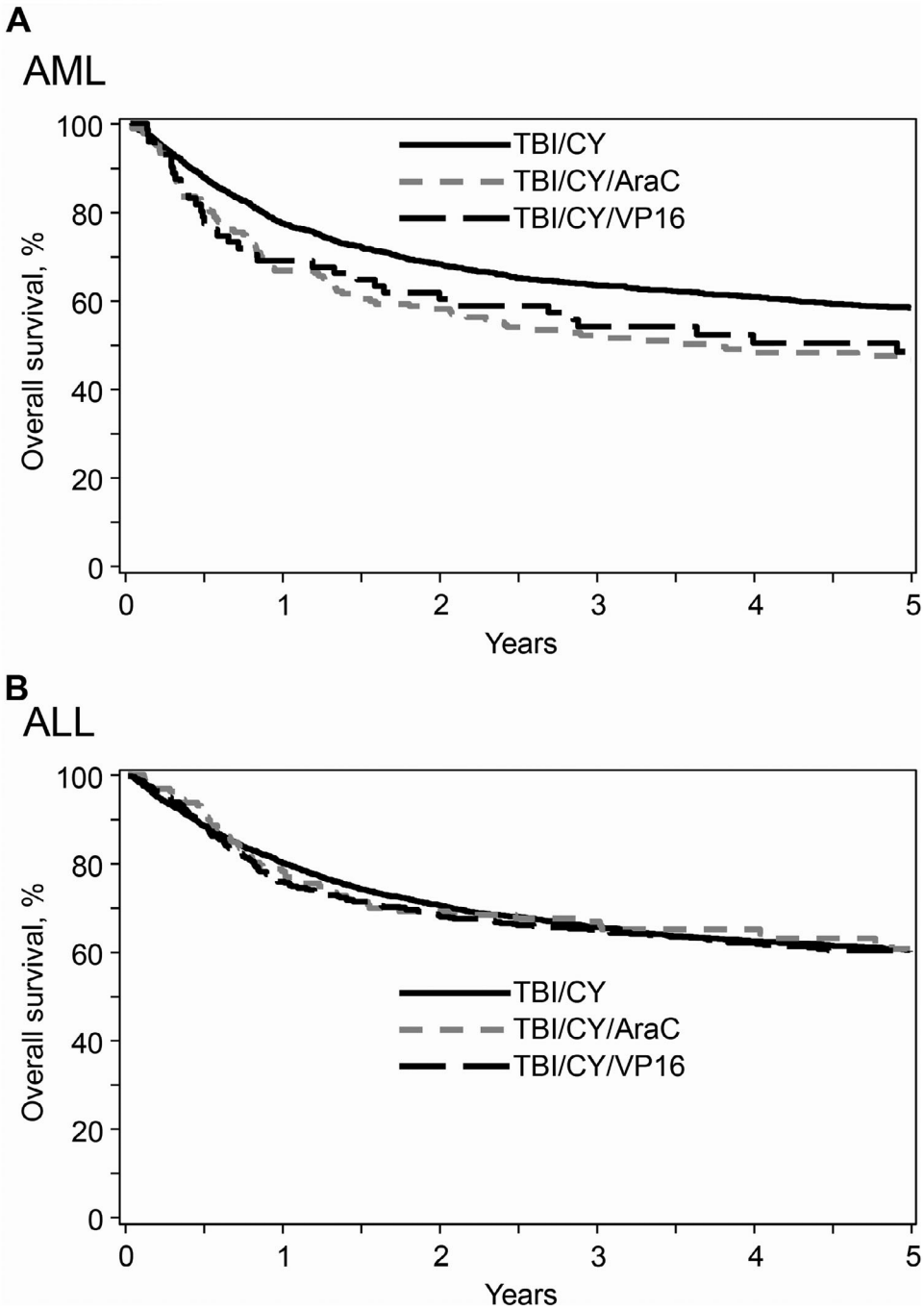

FIGURE 1 | Overall survival: OS in (A) acute myelogenous leukemia (AML) and (B) acute lymphoblastic leukemia (ALL) conditioned with CY/TBI, CY/TBI+AraC, and CY/TBI+VP16 are shown separately.

(1) In AML, adding AraC to CY/TBI increased TRM without reducing the relapse rate; thus, it had an adverse effect on OS. (2) In ALL, adding VP16 or AraC to CY/TBI did not affect survival, but the addition of VP16 reduced the risk of relapse. (3) These trends were comparable between the US and Japanese cohorts.

The negative impacts of intensified regimens are compatible with those previously shown in the Japanese registry database analysis [3]. Detailed analyses for various post-HSCT complications indicated no significant correlation between the specific complications and the intensity of conditioning regimens. However, mucosal damage, including stomatitis, enterocolitis, and cystitis, is expected to increase in accordance with the intensity of conditioning regimens [9]. This damage, if not resolved early, can induce infections, which may ultimately lead to significantly higher TRM for both AML and ALL [10]. In addition, high-dose AraC used in conditioning regimens can cause pulmonary complications, such as interstitial pneumonitis [11]. Post-transplant pneumonitis can lead to respiratory failure or can increase the incidence of pulmonary infections, which may result in significantly higher TRM [12].

On the other hand, additional anti-leukemic effects of intensified regimens were only partially demonstrated in this study, which

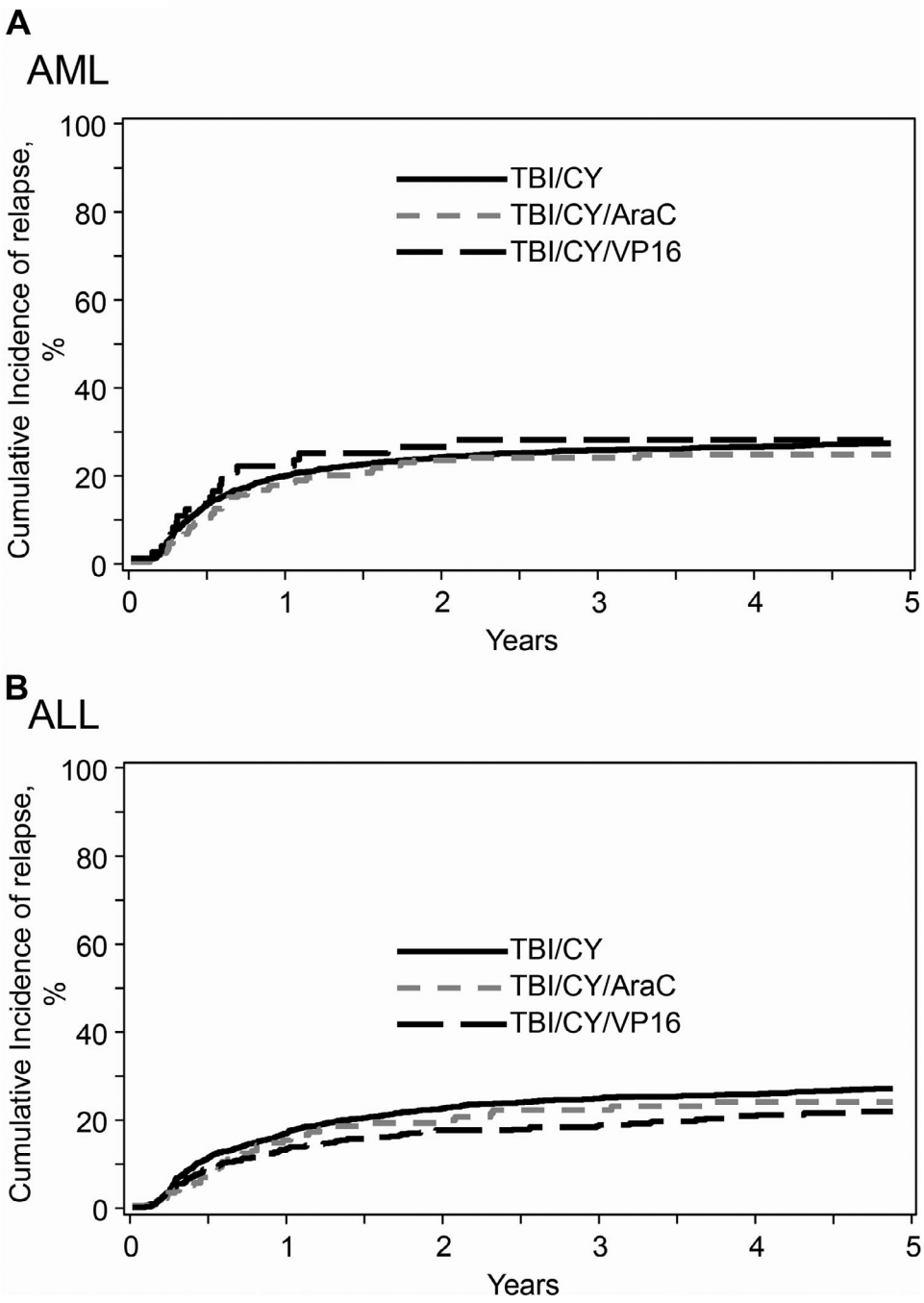

FIGURE 2 | Relapse: The cumulative incidence of relapse in (A) acute myelogenous leukemia (AML) and (B) acute lymphoblastic leukemia (ALL) conditioned with CY/TBI, CY/TBI+AraC, and CY/TBI+VP16 are shown separately.

differs from our original hypothesis that intensified regimens can reduce relapse in all situations. High-dose AraC or VP16 can induce greater marrow ablation; thereby eliminating surviving leukemia cells [13, 14]. However, post-HSCT relapse risk reduction is more likely dependent on graft-versus-leukemia (GVL) effects after transplant, rather than intensification of MAC regimens that perhaps can be overcome by leukemia cells in the absence of GVL [14, 15]. In spite of the limited effects of conditioning regimens on post-HSCT relapse, an additional benefit of VP16 in ALL was clearly shown, and this is compatible with recent reports from Japan [16, 17] and reported for the first time using the large cohort data. Augmentation of the dose of TBI to 1320 cGy as opposed to 1200 cGy might overcome the risk of relapse [18], but in our study, almost all TBI dosages were 1200 cGy, so no further analyses were possible. Non-TBI MAC regimens were not included in this study.

The final, but most important finding in this study is that the impacts of intensified conditioning regimens were comparable between the US and Japanese cohorts because there were no statistically significant interactions. It is often asserted that the Japanese people are more "genetically homogeneous" than populations of the US and European countries and that they may experience a lower incidence of GVHD and related adverse events

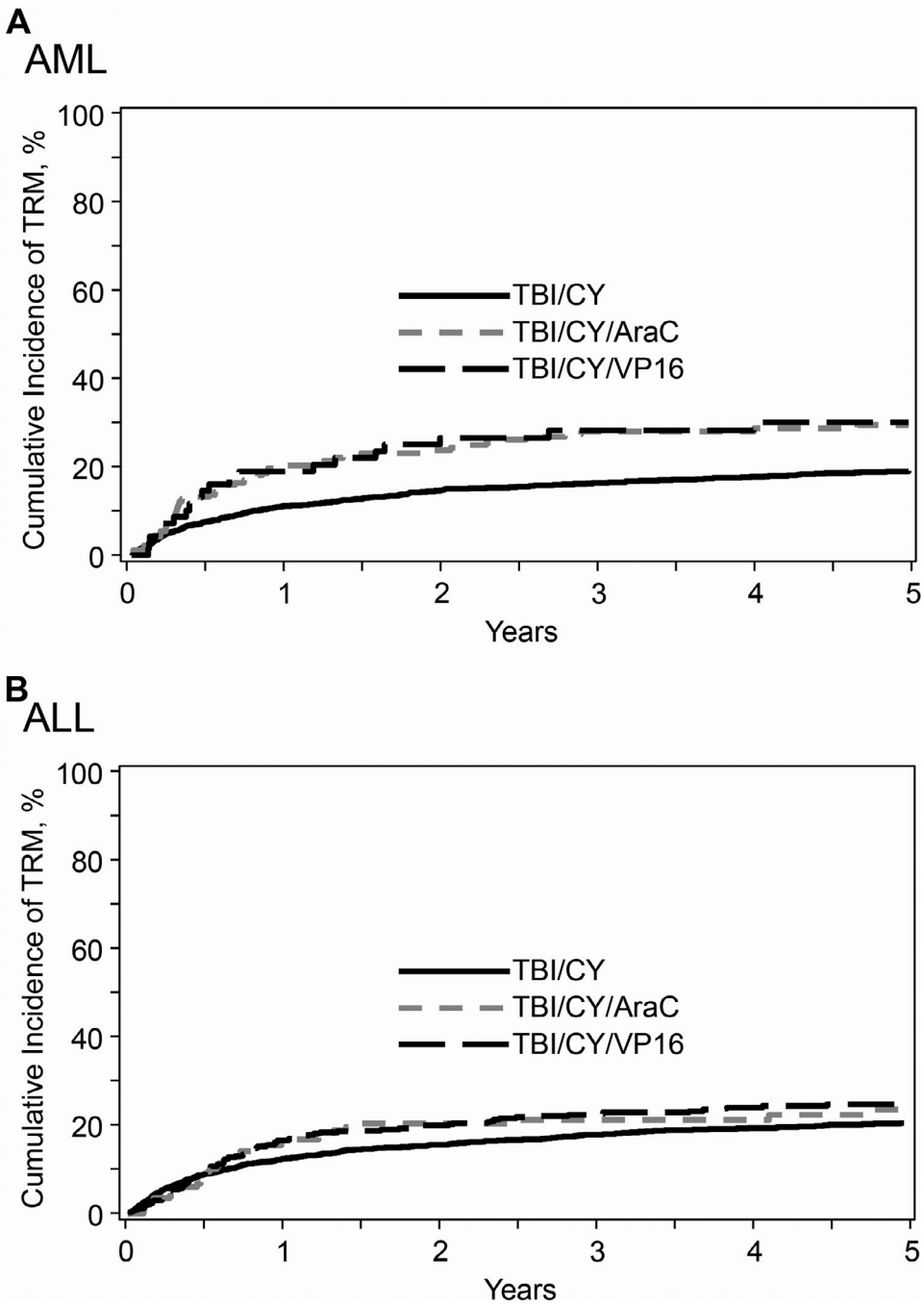

FIGURE 3 | TRM: Cumulative incidence of treatment-related mortality (TRM) in (A) acute myelogenous leukemia (AML) and (B) acute lymphoblastic leukemia (ALL) conditioned with CY/TBI, CY/TBI+AraC, and CY/TBI+VP16 are shown separately.

[2, 14]. Our study, merging both the Japanese and American registry databases, suggests that the results of the HSCT registry are interchangeable between the two countries. A previous study, performed in a similar manner [19], also indicated a similarity between the two cohorts.

There are some limitations in this study due to the retrospective nature of data from both registries. Bias in regard to the selection of conditioning regimens for acute leukemia patients and at different HSCT centers is an important limitation. The choice of conditioning regimen depends on the attending physicians in each institution, indicating that the clinical experiences of each transplant center can be a source of bias. In our analysis, we adjusted for country, however, the use of intensified MAC was significantly higher in Japan compared to the US, which might indicate that residual confounding might be present despite the regression analysis. It is possible that patients who received AraC and VP16 were given an intensified regimen due to the perceived high risk of relapse or the perceived low TRM risk or due to institutional protocol. Given the nonrandomized nature of the study, a degree of selection bias cannot be ruled out. Furthermore, the dose of radiation and each chemotherapeutic drug were not analyzed in this study, but it can have an impact on relapse risk and TRM (usually inverse-related) [20]. Only TBI-based regimens

TABLE 3 | Incidence of post-hematopoietic stem cell transplantation (post-HSCT) complications in acute myelogenous leukemia (AML).

	CY/TBI	CY/TBI+AraC	CY/TBI+VP16	*p*
	Incidence (95% CI), %			
aGVHD (grades 2–4)	35.9 (33.6–38.3)	40.8 (34.1–47.7)	40.4 (26.8–54.9)	0.353
(grades 3–4)	10.7 (9.3–12.3)	10 (6.2–14.5)	14.9 (6.2–26.5)	0.686
cGVHD				
100-day	5.4 (4.5–6.4)	6.8 (3.9–10.5)	3.1 (0.3–8.7)	0.398
6 months	25.0 (23.2–26.8)	22.5 (17.2–28.3)	21.5 (12.4–32.4)	0.595
Viral infection	10.6 (9.1–12.1)	7.0 (3.9–10.9)	12.8 (4.8–23.8)	0.157
Bacterial infection	51.8 (49.3–54.2)	49.7 (42.8–56.7)	50 (35.2–64.8)	0.851
Fungal infection	3.9 (3–4.9)	5.6 (2.8–9.3)	8.5 (2.3–18.2)	0.339
SOS/VOD	1.9 (1.3–2.6)	2.0 (0.5–4.4)	0.0 (0.0–0.0)	<0.001*

Abbreviations. GVHD, graft-versus-host disease; SOS/VOD, sinusoidal obstruction syndrome/veno-occlusive disease. The incidence of various infections is reported on Day 100.

TABLE 4 | Multivariate analyses for various outcome measures in acute lymphoblastic leukemia (ALL).

Outcomes	*N*	HR (95%CI)	*p*
Overall survival			
CY/TBI	3185	Reference	
CY/TBI+AraC	166	1.02 (0.79–1.32)	0.880
CY/TBI+VP16	550	1.02 (0.86–1.20)	0.841
Disease-free survival			
CY/TBI	3185	Reference	
CY/TBI+AraC	166	1.00 (0.79–1.27)	0.967
CY/TBI+VP16	548	0.94 (0.81–1.10)	0.458
Relapse			
CY/TBI	3185	Reference	
CY/TBI+AraC	166	0.85 (0.61–1.18)	0.337
CY/TBI+VP16	548	0.74 (0.60–0.92)	0.005*
TRM			
CY/TBI	3185	Reference	
CY/TBI+AraC	166	1.20 (0.85–1.69)	0.297
CY/TBI+VP16	548	1.21 (0.98–1.49)	0.077

were included, and busulfan-based regimens were excluded due to the small number of patients with intensified MAC regimens. Therefore, the conditioning regimens in this study do not mirror the current most frequently used regimens in the US. Increasingly prevalent GVHD prophylaxis regimens, such as post-transplant cyclophosphamide, and to a lesser degree, the use of abatacept, were not included in this study. Pediatric patients were not included. Moreover, minimal residual disease (MRD) data were not available; MRD data can influence the choice of conditioning regimen in the real-world setting.

In conclusion, this international collaborative study indicated that intensified myeloablative regimens are inferior in BM or PBSC HSCT, except for CY/TBI+VP16 in ALL. There may be a limit to the intensification of conditioning in AML beyond CY/TBI, but some gains can be made in ALL with such. This goes along with the long-held belief that AML relies more on GVL relative to ALL, and we should view these diseases differently from an HSCT standpoint in how to reduce disease relapse. The emergence of novel molecularly targeted drugs, antibody-based drugs, or cytotherapies, but not intensification of cytotoxic chemotherapies with off-target toxicities, can be game changers in induction, consolidation, and conditioning regimens. Therefore, our results should be revisited in the future.

Author Contributions

YArai, RB, NH, WS, and YAtsuta designed the research, organized the project, and performed statistical analyses. MY, SY, and SK interpreted data. All other authors critically reviewed the draft and approved the final version of the manuscript.

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TABLE 5 | Incidence of post-hematopoietic stem cell transplantation (post-HSCT) complications in acute lymphoblastic leukemia (ALL).

	CY/TBI	CY/TBI+AraC	CY/TBI+VP16	*p*
	Incidence (95% CI), %			
aGVHD (grades 2–4)	38.3 (35.9–40.6)	47.9 (38–58)	40.9 (36.2–45.6)	0.139
(grades 3–4)	11 (9.5–12.5)	7.4 (3–13.6)	12.1 (9.2–15.4)	0.334
cGVHD				
100-day	5.8 (5.0–6.7)	5.5 (2.5–9.5)	6.5 (4.6–8.8)	0.813
6 months	24.1 (22.6–25.6)	24.4 (18.1–31.3)	25.5 (21.9–29.3)	0.767
Viral infection	14.7 (13.1–16.5)	12.5 (6.6–19.8)	8.5 (6.1–11.4)	<0.001*
Bacterial infection	52.4 (50–54.9)	53.9 (43.8–63.8)	53.9 (49.1–58.7)	0.852
Fungal infection	4.6 (3.6–5.6)	2.1 (0.2–5.9)	3.8 (2.2–5.9)	0.254
SOS/VOD	1.9 (1.3–2.7)	5.1 (1.6–10.4)	1.4 (0.5–2.8)	0.252

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Clinical Trial Registration

The authors have confirmed clinical trial registration is not needed for this submission.

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