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ORIGINAL ARTICLE

# Outcomes of allogeneic stem cell transplantation for DLBCL: a multi-center study from the Kyoto Stem Cell Transplantation Group

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## Abstract

Allogeneic hematopoietic stem cell transplantation (allo-SCT) has been considered as a potentially curative treatment option for refractory or relapsed diffuse large B cell lymphoma (DLBCL) patients. However, there is little information available, especially for Japanese patients and in cord blood transplantation (CBT). We aimed to determine treatment outcomes of allo-SCT for DLBCL in the Kyoto Stem Cell Transplantation Group, a multi-institutional joint research group. Sixty-eight DLBCL patients who underwent their first allo-SCT between 2003 and 2016 were included. The median time from diagnosis to transplantation was 13.5 months. Thirty-one patients were in CR/PR at transplantation. Twenty-seven patients underwent CBT. The median follow-up for survivors was 44.2 months. Four-year overall survival (OS) and relapse-free survival (RFS) rates were 23% (95% CI, 13–35%) and 20% (95% CI, 11–31%), respectively. Cumulative incidences of non-relapse mortality and relapse were 23% and 57%, respectively. Patients in CR/PR at allo-SCT had better OS (4-year, 46% vs 4%, $P < 0.001$) and RFS (4-year, 36% vs 7%, $P = 0.005$). The source of the stem cell did not significantly affect OS (4-year, bone marrow vs cord blood vs peripheral blood, 28.6% vs 27.2% vs 6.5%, $P = 0.193$). In multivariate analysis, non-remission status at SCT associated with inferior OS and RFS. Duration from diagnosis to transplantation of less than 1 year associated with inferior RFS. Allo-SCT, including CBT, may be a promising therapeutic modality for DLBCL patients who have good disease control at transplantation.

**Keywords** Diffuse large B cell lymphoma · Treatment outcome · Allo-SCT · Cord blood transplantation

## Introduction

High-dose chemotherapy followed by autologous stem cell transplantation (auto-SCT) is the standard treatment option for relapsed diffuse large B cell lymphoma (DLBCL) patients who show chemosensitivity. However, a significant proportion of patients experience relapse after auto-SCT or cannot proceed to auto-SCT. In a recent analysis of patients included

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in the CORAL study, the median survival time of patients who relapsed after auto-SCT was 10 months (95% CI, 6.6–12.6 months), and 1-year overall survival (OS) was 39.1% [1]. In particular, patients who relapsed within 6 months after auto-SCT and patients who did not respond to salvage regimens had a poor prognosis.

In such patients, allogeneic stem cell transplantation (allo-SCT) has been considered. A graft-versus-lymphoma effect has also been observed in DLBCL patients as well as in low-grade lymphoma patients [2]. Thus, allo-SCT can be viewed as a potentially curative treatment option for relapsed or refractory DLBCL patients.

To date, several groups have conducted retrospective cohort studies on allo-SCT for DLBCL patients [3–12]. The reported outcomes are similar and all of these groups suggest that allo-SCT can provide durable remission in a subset of patients with refractory or relapsed DLBCL. According to a review by Klyuchnikov et al. [13], allo-SCT in relapsed or refractory DLBCL patients can result in a 3-year progression-free survival of 30 to 40%.

These results may not be directly translatable into clinical practice in Japan, because the choices of the stem cell sources are different from those in Western countries. In Japan, cord blood is frequently chosen as an alternative stem cell source. Although two research groups have reported treatment outcomes after allo-SCT in Asian patients with DLBCL [14, 15], the cohort sizes were relatively small. There is still a paucity of available data regarding the role of allo-SCT in DLBCL patients, particularly Japanese patients. In addition, these previous studies did not include [3–9, 12, 15] or included only a few [10, 11, 14] patients who underwent cord blood transplantation (CBT), and little information is available about the outcome of CBT for DLBCL patients.

In this study, we evaluated treatment outcomes for 68 Japanese patients with DLBCL who underwent allo-SCT including CBT. We also aimed to elucidate risk factors associated with the treatment efficacy and adverse events after allo-SCT.

## Patients and methods

### Data source

The Kyoto Stem Cell Transplantation Group (KSCTG) is a multi-center group of 17 transplantation centers in Japan. This retrospective study was performed using clinical data for 68 adult patients who underwent their first allogeneic stem cell transplantation (allo-SCT) between 2003 and 2016 in KSCTG hospitals. This study was approved by the institutional review boards at Kyoto University Hospital and all other participating centers.

### Endpoints

The primary endpoint of the study was overall survival. Other endpoints were relapse-free survival, relapse, non-relapse mortality, and acute GVHD. The physicians who performed transplantation at each center diagnosed and graded acute GVHD according to the traditional criteria [16]

### Statistical analysis

The probabilities of overall survival and relapse-free survival were estimated according to the Kaplan-Meier method, and groups were compared using the log-rank test. The probabilities of relapse, non-relapse mortality, and acute GVHD were estimated on the basis of cumulative incidence curves [17]. For patients who did not achieve CR after allo-SCT, we defined the date of relapse as day 0. Competing events were death without relapse for relapse, relapse for non-relapse mortality, and death before acute GVHD for acute GVHD. The groups were compared using Gray's test [18]. The Cox proportional hazards model was used to evaluate the effects of confounding variables on overall survival and relapse-free survival, whereas Fine and Gray's proportional hazards model was used for other endpoints [19]. Based on the reports from CIBMTR, we classified the conditioning regimens as myeloablative or reduced-intensity [20].

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [21]. EZR is a graphical user interface for R (The R Foundation for Statistical Computing, version 3.3.2, Vienna, Austria). More precisely, it is a modified version of R commander (version 2.3-0) designed to add statistical functions that are frequently used in biostatistics.

## Results

### Patient characteristics

Table 1 shows patient and transplant characteristics. The median age of the patients at transplantation was 52 years (range, 32 to 67). Twenty-three patients were males and 45 patients were females. Twenty-two patients (32.4%) had received high-dose chemotherapy with auto-SCT. Thirty-one (45.6%) were CR/PR and 37 (54.4%) were not in remission at transplantation. The source of stem cells was peripheral blood (PB) in 19 (27.4%) patients, bone marrow (BM) in 22 (32.8%), and cord blood (CB) in 27 (39.7%). The most frequently used stem cell source was CB. Twenty-four (35.3%) patients received myeloablative conditioning and 43 (63.2%) received reduced-intensity conditioning. Fifty-one patients were conditioned with regimens containing total body irradiation (TBI).

**Table 1** Patient characteristics

| Patient characteristics ($n$ = 68) | | $n$ (%) |
|---|---|---|
| Age | Median | 52 years |
| | Range | 32~67 years |
| | < 50 | 30 (44.1) |
| | ≥ 50 | 38 (55.9) |
| Male:Female | | 23:45 |
| Stage | I | 2 (2.9) |
| | II | 15 (22.1) |
| | III | 4 (5.9) |
| | IV | 47 (69.1) |
| IPI | Low | 18 (26.5) |
| | Low-I | 15 (22.1) |
| | High-I | 19 (27.9) |
| | High | 12 (17.6) |
| | Unknown | 4 (5.9) |
| First-line treatment | R-CHOP/CHOP | 50 (73.5) |
| | R-HyperCVAD/HyperCVAD | 6 (8.8) |
| | DA-EPOCH-R | 4 (5.9) |
| | Others[1] | 4 (5.9) |
| | Unknown | 4 (5.9) |
| Response to the first-line treatment | CR | 33 (48.5) |
| | PR | 8 (11.8) |
| | Refractory | 23 (33.8) |
| | Unknown | 4 (5.9) |
| Time from diagnosis to the first relapse (among 31 CR/PR patients)[2] | Median | 12.2 months |
| | Range | 0.75~67.4 months |
| | < 1 year | 15 (48.4) |
| | ≥ 1 year | 16 (51.6) |
| Time from diagnosis to transplantation | Median | 13.5 months |
| | Range | 2.2~169.5 months |
| | < 1 year | 28 (41.2) |
| | ≥ 1 year | 40 (58.8) |
| Previous history of autologous stem cell transplantation | Yes | 22 (32.4) |
| | No | 46 (67.6) |
| Treatment year | 2003–2010 | 31 (45.6) |
| | 2011–2016 | 37 (54.4) |
| Disease status at transplantation | CR/PR | 31 (45.6) |
| | 1st CR | 2 (2.9) |
| | 2nd CR | 4 (5.9) |
| | ≥ 3rd CR | 7 (10.3) |
| | 1st PR | 8 (11.8) |
| | 2nd PR | 10 (14.7) |
| | NIR | 37 (54.4) |
| | Primary refractory | 13 (19.1) |
| | 1st relapse | 15 (22.1) |
| | 2nd relapse | 7 (10.3) |
| | ≥ 3rd relapse | 2 (2.9) |

**Table 1** (continued)

| Patient characteristics ($n$ = 68) | | $n$ (%) |
|---|---|---|
| Chemosensitivity at transplantation (among 24 relapsed patients) | Resistant | 10 (41.7) |
| | Sensitive | 6 (25.0) |
| | Unknown | 8 (33.3) |
| Stem cell source | BM | 22 (32.8) |
| | PB | 18 (26.9) |
| | CB | 27 (39.7) |
| | BM+PB | 1 (1.5) |
| Donor type[3] | Related donor | 25 (36.8) |
| | Matched related | 13 (19.1) |
| | Mismatched related | 12 (17.6) |
| | Unrelated donor | 16 (23.5) |
| | Matched unrelated | 7 (10.3) |
| | Mismatched unrelated | 9 (13.2) |
| | Unrelated cord blood | 27 (39.7) |
| | Matched cord | 3 (4.4) |
| | Mismatched cord | 24 (35.3) |
| Conditioning | Myeloablative | 24 (35.3) |
| | Reduced-intensity | 43 (63.2) |
| | Unetermined[4] | 1 (1.5) |
| MAC regimen | CY+TBI | 15 (22.1) |
| | Others | 9 (13.2) |
| RIC regimen | Flu-Bu-based[5] | 11 (16.2) |
| | Flu-Mel-based[6] | 28 (41.1) |
| | Others | 4 (5.9) |
| GVHD prophylaxis | CyA-based | 18 (26.9) |
| | Tac-based | 49 (73.1) |
| Median follow-up time in survivors (range) | | 3.8 years (0.4 to 8.7) |

*IPI*, International Prognostic Index; *R-CHOP*, rituximab, cyclophosphamide, adriamycin, vincristine, prednisolone; *CHOP*, cyclophosphamide, adriamycin, vincristine, prednisolone; *R-HyperCVAD*, rituximab, hyperfractionated cyclophosphamide, adriamycin, vincristine, dexamethasone; *HyperCVAD*, hyperfractionated cyclophosphamide, adriamycin, vincristine, dexamethasone; *DA-EPOCH-R*, dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, adriamycin, rituximab; *CR*, complete remission; *PR*, partial remission; *NIR*, not in remission; *BM*, bone marrow; *PB*, peripheral blood; *CB*, cord blood; *MAC*, myeloablative conditioning; *RIC*, reduced-intensity conditioning; *CY*, cyclophosphamide; *TBI*, total body irradiation; *Flu*, fludarabine; *Bu*, busulfan; *Mel*, melphalan; *GVHD*, graft-versus-host disease; *CyA*, cyclosporine A; *Tac*, tacrolimus

[1] Other regimens were as follows: *CHASER*, cyclophosphamide, high-dose cytarabine, methylprednisolone, etoposide, rituximab; *R-CVP*, rituximab, cyclophosphamide, vincristine, prednisolone; *R-THP-COP*, rituximab, epirubicin, cyclophosphamide, vincristine, prednisolone; High-dose methotrexate

[2] Among 41 patients who achieved CR/PR after their first-line therapy, 40 patients had a relapse. The date of the first relapse was unknown in 9 patients

[3] HLA disparities were determined by antigen-level HLA-A, B, and DR typing in all related donors, one unrelated donor, and all cord blood units, and by allele-level HLA-A, B, C, and DRB1 typing in other unrelated donors

[4] This patient received a conditioning regimen with fludarabine, busulfan, cytarabine, and TBI 4Gy. The dose of busulfan was unknown

[5] The doses of busulfan were as follows: 3.2 mg/kg, 2 patients; 6.4 mg/kg, 6 patients; 8 mg/kg (orally), 3 patients

[6] The doses of melphalan were as follows: 80 mg/m$^2$, 10 patients; 100 mg/m$^2$, 7 patients; 140 mg/m$^2$, 11 patients

## Overall survival

The median follow-up time in survivors was 3.8 years (range, 0.4 to 8.7). The 4-year overall survival rate for the entire cohort was 23.1% (95% CI, 13.3–34.5%). The 4-year overall survival rate was 46.2% (95% CI, 27.6–63.2%) in patients who were CR/PR at transplantation and 4.3% (95% CI, 0.37–17.2%) in patients who were not in remission ($P$ < 0.001, Fig. 1a). We analyzed overall survival according to the stem cell source. The 4-year overall survival rate was

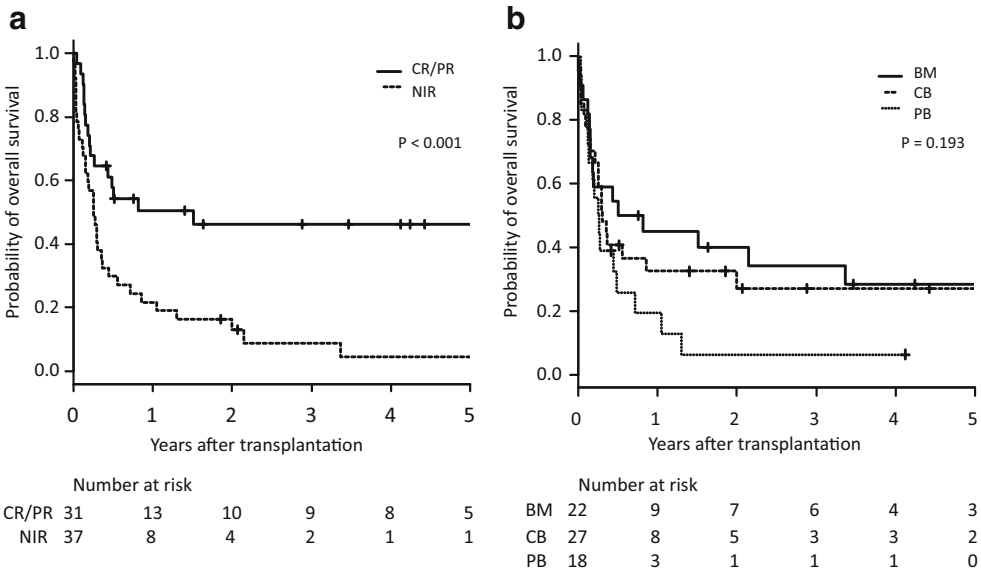


**Fig. 1** Overall survival (OS). **a** OS was stratified according to the disease status at allo-SCT. CR/PR, complete remission/partial remission; NIR, not in remission. **b** OS was stratified according to the stem cell source. BM, bone marrow; CB, cord blood; PB, peripheral blood

28.6% (95% CI, 11.2–48.9%) in patients who received BM, 27.2% (95% CI, 11.6–45.5%) in patients who received CB, and 6.5% (95% CI, 0.43–25.3%) in patients who received PB ($P = 0.193$, Fig. 1b). In a univariate analysis, early treatment period (treatment year, 2003–2010), not in remission at transplantation, and cyclosporine A-based GVHD prophylaxis were identified as adverse prognostic factors. In a multivariate analysis, all these factors remained adverse prognostic factors. The results of the multivariate analysis for overall survival are summarized in Table 2.

## Relapse-free survival

The 4-year relapse-free survival rate for the entire cohort was 19.9% (95% CI, 11.0–30.7%). The 4-year relapse-free survival rate was 35.8% (95% CI, 18.8–53.2%) in patients who achieved CR/PR at transplantation and 7.2% (95% CI, 1.5–19.2%) in patients who were not in remission ($P = 0.005$, Fig. 2a). According to the stem cell source, the 4-year relapse-free survival rate was 28.6% (95% CI, 11.2–48.9%) in the BM group, 27.2% (95% CI, 11.6–45.5%) in the CB group, and 6.5% (95% CI, 0.43–25.3%) in the PB group ($P = 0.193$, Fig. 2b). In a univariate analysis, significant adverse factors were time from diagnosis to transplantation (TDT) < 1 year, not in remission at transplantation, and cyclosporine A-based GVHD prophylaxis. In a multivariate analysis, TDT < 1 year and not in remission at transplantation were identified as significant adverse prognostic factors. Table 3 shows the results of a multivariate analysis for relapse-free survival.

## Relapse

Thirty-eight (55.9%) patients relapsed after transplantation. In a multivariate analysis, treatment period (2011–2016 versus 2003–2010, HR 0.55; 95% CI, 0.33–0.92), TDT (≥ 1 year versus < 1 year, HR 0.38; 95% CI, 0.22–0.66), and disease status at transplantation (not in remission versus CR/PR, HR 2.06; 95% CI, 1.18–3.6) were identified as significantly correlated factors. Patients who underwent allo-SCT within 1 year from diagnosis had a higher relapse rate (Fig. 3a). Regarding the stem cell source, the PB group had a higher relapse rate than the CB and BM groups (Fig. 3b). The cumulative incidence of 4-year relapse was 46.6% (95% CI, 23.9–66.5%) in the BM group, 59.3% (95% CI, 38.0–75.4%) in the

**Table 2** Results of a multivariate analysis for overall survival

| Variable | Hazard ratio (95% confidence interval) | *P* value |
|---|---|---|
| Treatment year | | |
| 2011–2016 versus 2003–2010 | 0.56 (0.30–0.99) | 0.047 |
| Disease status at transplantation | | |
| NIR versus CR/PR | 2.88 (1.56–5.31) | 0.0007 |
| GVHD prophylaxis | | |
| Tac-based versus CyA-based | 0.50 (0.27–0.93) | 0.027 |

*CR*, complete remission; *PR*, partial remission; *NIR*, not in remission; *GVHD*, graft-versus-host disease; *CyA*, cyclosporine A; *Tac*, tacrolimus

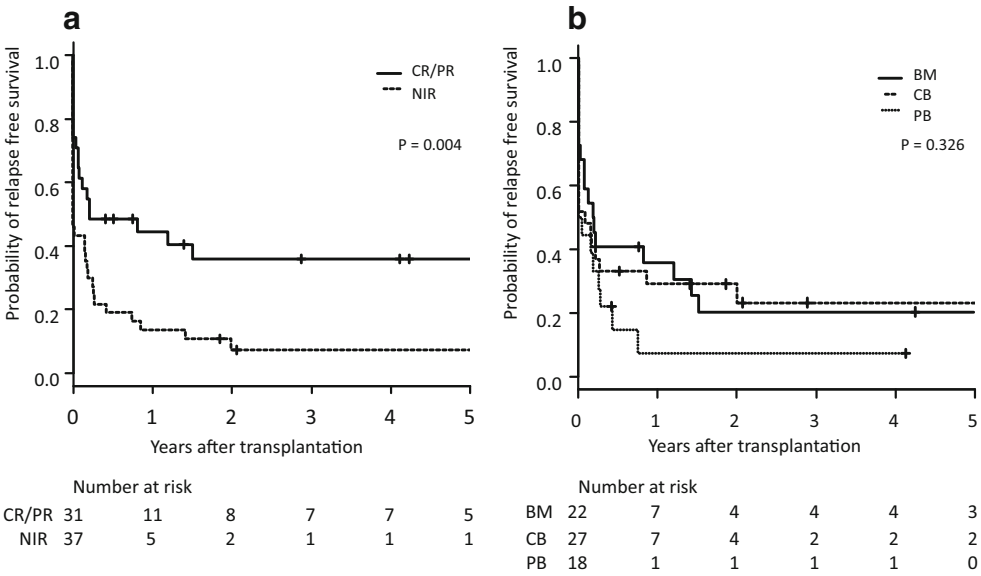


**Fig. 2** Relapse-free survival (RFS). **a** RFS was stratified according to the disease status at allo-SCT. CR/PR, complete remission/partial remission; NIR, not in remission. **b** RFS was stratified according to the stem cell source. BM, bone marrow; CB, cord blood; PB, peripheral blood

CB group, and 70.4% (95% CI, 37.6–88.2%) in the PB group, but these differences were not statistically significant ($P$ = 0.309). The type of conditioning regimen had no effect on relapse. However, in the RIC regimen group, patients who had a Flu-Bu-based conditioning regimen had higher relapse rates than those with Flu-Mel-based conditioning or other conditioning (Fig. 3c). The cumulative incidences of 4-year relapse were 72.7% (95% CI, 29.7–92.0%) in the Flu-Bu-based conditioning group and 42.9% (95% CI, 24.1–60.4%) in the Flu-Mel-based conditioning group and this difference was not statistically significant ($P$ = 0.108). Also, in patients who underwent RIC regimen, patients receiving TBI-containing regimen had lower relapse incidence than those receiving non-TBI regimen. The cumulative incidences of 4-year relapse were 37.6% (95% CI, 20.1–55.1%) in the TBI-containing regimen and 76.9% (95% CI, 39.3–92.9%) in the non-TBI regimen ($P$ = 0.008).

## Acute GVHD and non-relapse mortality

The cumulative incidence of grades II to IV acute GVHD at day 100 was 33.8% (95% CI, 22.8–45.2%). The cumulative incidence of 4-year non-relapse mortality was 23.4% (95% CI 13.7–34.6%). The incidences of 4-year non-relapse mortality in patients who received myeloablative conditioning and reduced-intensity conditioning were 14.4% (95% CI, 3.0–34.5%) and 28.9% (95% CI, 15.7–43.4%), respectively ($P$ = 0.193). The incidence of non-relapse mortality did not differ among patients with BM (33.0%, 95% CI 13.7–53.7%), CB (17.4%, 95% CI 4.7–36.7%), and PB (22.2%, 95% CI 6.1–44.5%) grafts ($P$ = 0.364). A previous history of auto-SCT did not affect non-relapse mortality. The incidences of 4-year non-relapse mortality in patients who had previous auto-SCT or no history of auto-SCT were 14.2% (95% CI, 3.2–33.2%) and 27.6% (95% CI, 15.0–41.9%), respectively ($P$ = 0.232).

## Discussion

In the present study, we evaluated the treatment outcomes for 68 Japanese patients with DLBCL who underwent allo-SCT. The 4-year overall survival rate was 46.2% in patients who achieved CR/PR at transplantation. This result indicates that allo-SCT is useful as a salvage therapy, considering the poor

**Table 3** Results of a multivariate analysis for relapse-free survival

| Variable | Hazard ratio (95% confidence interval) | $P$ value |
|---|---|---|
| Time from diagnosis to transplantation | | |
| ≥ 1 year versus < 1 year | 0.43 (0.24–0.78) | 0.0052 |
| Disease status at transplantation | | |
| NIR versus CR/PR | 2.41 (1.34–4.35) | 0.0035 |
| GVHD prophylaxis | | |
| Tac-based versus CyA-based | 0.59 (0.33–1.06) | 0.079 |

*CR*, complete remission; *PR*, partial remission; *NIR*, not in remission; *GVHD*, graft-versus-host disease; *CyA*, cyclosporine A; *Tac*, tacrolimus

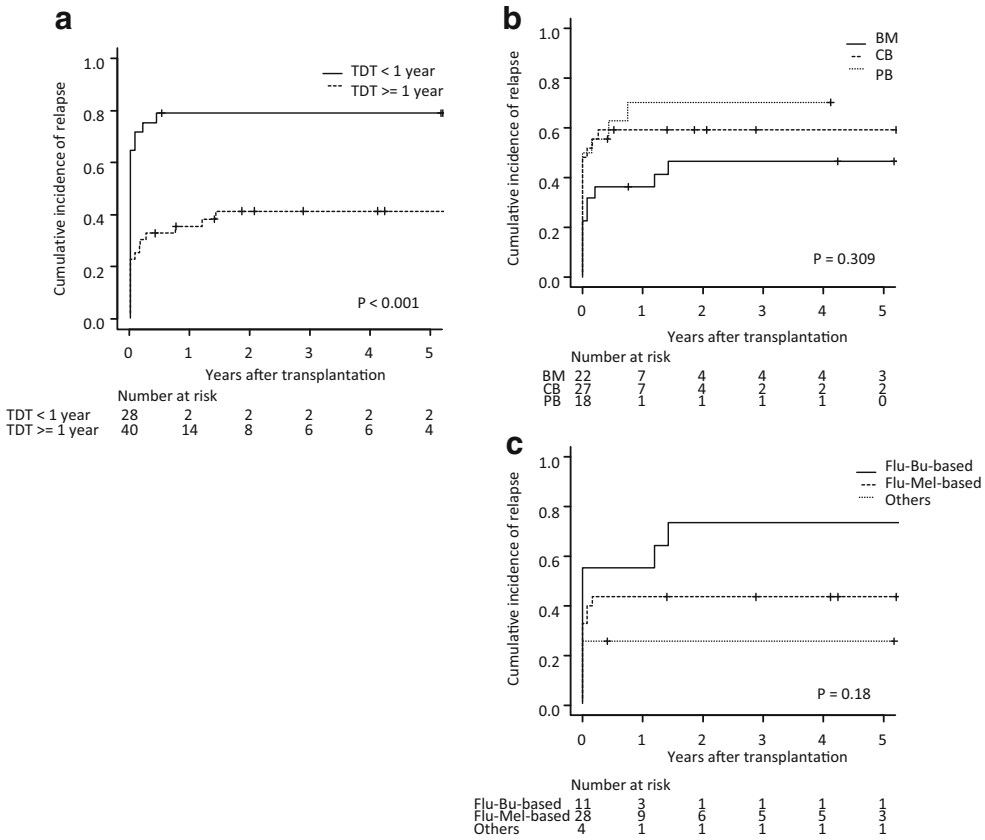


**Fig. 3** Cumulative incidence of relapse. **a** The cumulative incidence of relapse was stratified according to the time from diagnosis to transplantation (TDT). **b** The cumulative incidence of relapse was stratified according to the stem cell source. BM, bone marrow; CB, cord blood; PB, peripheral blood. **c** The cumulative incidence of relapse in RIC-conditioned patients was examined according to the conditioning regimen

outcome of refractory or relapsed DLBCL patients. In the SCOLAR-1 study [22], which retrospectively evaluated outcomes in patients with refractory DLBCL, the median overall survival from the start of salvage therapy was 6.3 months, and 1-year OS was 28%, although we cannot simply compare these outcomes. As in previous reports, patients who were PR/CR at transplantation had better OS and RFS than those who were not in remission. This result supports the notion that allo-SCT can be considered as a salvage therapy for relapsed or refractory patients when they have good disease control at transplantation. Patients who were not in remission at allo-SCT had a dismal outcome. Novel drugs and therapies including CAR-T therapy can be preferred treatment options for these patients. If they achieve CR/PR after the treatment with novel therapeutic agents, they can be good candidates for allo-SCT.

We also demonstrated that TDT less than 1 year was an adverse prognostic factor for RFS. Also, this group experienced a higher relapse rate than the other group. However, this result should be interpreted with caution considering the retrospective nature of the present study. In our cohort, 67.6% of patients did not undergo auto-SCT before allo-SCT. Upfront allo-SCT for DLBCL patients is not the standard in Japan. Although CR/PR rates were not different between these groups (50.0% in the TDT < 1 year group, 42.5% in the TDT ≥ 1 year group), we could not exclude the possibility that patients who underwent allo-SCT within 1 year from diagnosis had a more aggressive clinical course. Therefore, we could not determine whether delayed allo-SCT was better than immediate allo-SCT based solely on this finding.

Most previous studies excluded patients who underwent CBT. Although a few retrospective cohort studies have examined CBT for lymphoid malignancies [23–25], these studies included Hodgkin lymphoma, low-grade B cell lymphomas or T cell lymphomas other than DLBCL. Therefore, little information is available regarding CBT for DLBCL patients. In contrast, our cohort included 27 (39.7%) patients who underwent CBT. In this study, CBT was not an adverse factor for OS, PFS, or relapse. The outcome of CBT patients was comparable with that of patients with other stem cell sources. Therefore, CBT can be considered a feasible treatment option for relapsed or refractory DLBCL patients, especially those who need immediate transplantation. In our cohort, outcomes of peripheral blood stem cell transplantation (PBSCT) were worse than those of transplantations with other stem cell sources. Although the reason is not clear, the higher percentage of elder patients (age ≥ 50) in the PB group (54.5% in the BM group, 48.1% in the CB group, and 72.2% in the PB group) partly explains the worse outcome in this group.

Regarding the conditioning regimen, we did not find any difference between myeloablative and reduced-intensity conditioning regimens. However, in patients who underwent RIC, use of TBI resulted in lower relapse rate and Flu-Mel-based

conditioning tended to be associated with lower relapse. Recently, Yoon et al. [26] reported that RIC-allo-HSCT using Flu+Mel+800 cGy TBI gave favorable survival outcomes in a cohort of relapsed or refractory non-Hodgkin lymphoma patients, including DLBCL patients. Our study supports their results and a Flu-Mel-based TBI regimen may be a better choice, also in DLBCL.

This study has several limitations. First, our cohort lacked cytogenetic data and immunohistochemical data, and we could not tell how many patients in our cohort were double-hit lymphomas or double-expressor lymphomas. Second, the choice of chemotherapeutic regimens and the addition of local radiotherapy before allo-SCT depended on the treating physicians and were not uniform among the centers. Therefore, we could not tell whether a patient who achieved CR by radiation of bulky lesions could also expect a favorable prognosis.

In conclusion, our analysis showed that allo-SCT including CBT can be a promising therapeutic option for relapsed or refractory DLBCL patients, especially those who have achieved CR/PR.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

**Ethical approval** This study was approved by the institutional review board of each participating institution. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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