Attaining Complete Remission May Confer a Better Outcome after Allogeneic Hematopoietic Stem Cell Transplantation in Adult Patients with Acute B-cell Lymphoblastic Leukemia

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Introduction : Treatment outcome of adult patients with acute B-cell lymphoblastic leukemia (ALL) is suboptimal even after an allogeneic hematopoietic stem cell transplantation (allo-HSCT). To maximize the efficacies of this treatment strategy, risk stratification is crucial.

Methods : We retrospectively collected clinical data of the adult patients with allo-HSCT for ALL at a single insitiution in Japan between 2003 and 2022. Univariate and multivariate analyses were performed to identify risk factors for overall survival (OS), progression-free survival (PFS) and GVHD-free-and-relapse-free survival (GRFS) at 3 years.

Results : A total of 58 patients were included with 34 females and a median age of 39. Sixty-two percent of patients harbored high-risk cytogenetic features or Philadelphia chromosome (Ph). Hematologic complete response (CR) rate was 93 % after a first induction, but 75.9 % were in CR at allo-HSCT. Blinatumomab was used in 1.7 % of patients. A chimeric mRNA had been detected in 4 of 26 patients at allo-HSCT. The 3-year OS, PFS and GRFS were 72.7 %, 54.7 % and 46.2 %, respectively. Pre-transplantation CR was an independent risk factor.

Discussion/Conclusions : Our results imply that a better OS may potentially be achieved by improved pre-transplantation CR rate with more frequent application of novel agents. *Shinshu Med J 71 : 257—267, 2023*

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Key words : acute lymphoblastic leukemia, allogeneic stem cell transplantation, prognostic risk factor, adult patient

I Introduction

Acute B-cell lymphoblastic leukemia (ALL) in adult patients remains a challenging disease to treat, with suboptimal long-term survival rates, lagging behind those in pediatric patients, where 90 % of cure rates are seen[1)2)]. The increased risk of relapse has led to poorer treatment outcomes in ALL[3)], and consolidative allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been considered historically as a curative approach for all eligible adult patients with ALL with high-risk features or ALL in second complete remission (CR2) or greater[4)-7)]. Indeed, up to 50 % of adult patients with ALL received allo-HSCT according to real-world data[8)]. However, despite recent advances in the prevention and control of toxicities of allo-HSCT[9)-19)], many cases still fail to be cured after transplantation, emphasizing the need to identify pre-transplantation prognostic risk factors in patients who receive allo-HSCT.

We herein report the result of a retrospective study of allo-HSCT in adult patients with ALL performed at a single institution over the past 20 years. These

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retrospective data will provide a database for a historical control to advance the field of treatment for ALL in the adult population.

Ⅱ Patients and Methods

A Patients

Patients who received allo-HSCT for ALL at the Department of Hematology of Shinshu University Hospital, Matsumoto, Japan, between 2003 and 2022 were enrolled. Patients under 16 years old were excluded. The diagnosis of ALL was confirmed in accordance with the Revised 4th Edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues[20]. Real-time quantitative polymerase chain reaction (RT-PCR) was performed with mRNA from the bone marrow (BM) cells, if available, to screen for chimeric mRNA (Major *BCR-ABL1*, minor *BCR-ABL1*, *PML-RARA*, *RUNX1-RUNX1T1*, *CBFB-MYH11*, *DEK-NUP214*, *NUP98-HOXA9*, *ETV6-RUNX1*, *TCF3-PBX1*, *STIL-TAL1*, *KMT2A-AFF1*, *KMT2A-AFDN*, *KMT2A-MLLT3*, and *KMT2A-MLLT1*). Patients with T-cell acute lymphoblastic leukemia, mixed lineage leukemia, and lymphoid blastic crisis from chronic myelogenous leukemia were excluded from this study. If a patient underwent multiple transplantations, only the data obtained during the first allo-HSCT procedure were included in the analysis. Relevant clinical data were retrieved from their charts. Hematologic complete remission (CR) was defined as meeting all of the following responses: <5 % blasts in the BM, absolute neutrophil count >1,000/μL in the peripheral blood, platelets >100,000/μL without transfusion support, and no extramedullary disease. The BM cells before allo-HSCT were subjected to the RT-PCR to detect residual disease if a sample was available in a patient with measurable chimeric mRNA at the diagnosis.

B Transplantation

All transplantation procedures were performed at the Department of Hematology, Shinshu University Hospital. Myeloablative conditioning (MAC) regimens were generally preferred for tolerable patients, but reduced intensity conditioning (RIC) regimens were also adopted at the discretion of the transplantation team members of the department. Total-body irradiation (TBI) of 2 Gy was allowed to be added to a conditioning regimen to augment the likelihood of engraftment. Any disagreement on treatment plans was resolved by discussion among the team. Prophylaxis for graft-versus-host disease (GVHD) was either a combination of calcineurin inhibitor and short methotrexate for BM or peripheral blood (PB) transplantations, or a combination of tacrolimus and mycophenolate mofetil (MMF) for cord blood (CB) transplantation. A rabbit anti-thymocyte immunoglobulin (ATG) at 2 mg/kg was allowed to be administered on day -1 or -2 if severe GVHD was anticipated because of an HLA disparity between donor and recipient. Prophylaxis for infections included Levofloxacin 500 mg daily from day -7 until neutrophil engraftment, and Acyclovir 200 mg twice daily and Fluconazole 200 mg daily from day -7 until a month after the cessation of GVHD prophylaxis or treatment. Fluconazole was replaced by Voriconazole 200 mg twice daily or Posaconazole 300 mg twice daily when renovations were started at different wards in the same hospital building in August 2021. Sulfamethoxazole 400 mg and Trimethoprim 80 mg daily were prescribed soon after the day of neutrophil engraftment until a month after the cessation of GVHD prophylaxis or treatment. Anti-epileptic agents were administered prophylactically when busulfan was included in a conditioning regimen.

C Statistical analyses

The primary endpoints were the 3-year overall survival (OS), 3-year progression-free survival (PFS), and GVHD-free and relapse-free survival (GRFS) at 3 years after allo-HSCT. The OS was defined as the period of time between the date of allo-HSCT and the date of death due to any cause, and the PFS was defined as the period of time between the date of allo-HSCT and the date of disease progression. The GRFS was defined as the time after allo-HSCT in the absence of grade Ⅲ-Ⅳ acute GVHD, chronic GVHD that required systemic treatment, relapse, and death[21]. The probabilities of the OS, PFS and GRFS were estimated with the Kaplan-Meier method. A log-rank test was

Table 1 Patient characteristics (n = 58)

Median Age [range]		39.5 [17–70] years old
Sex	Male	24 (41.4%)
	Female	34 (58.6%)
Median WBC at Dx [range]		8,725 [660–575,550]
	< 30,000/μL	36 (62.1%)
	≥ 30,000/μL	16 (27.6%)
	NA	6 (10.3%)
Chromosomal Abnormality		
	Ph1	23 (39.7%)
	high risk	13 (22.4%)
Pre-HSCT Treatment		
	TKIs	20 (34.5%)
	Blinatumomab	1 (1.7%)
ALL at allo-HSCT		
	1st CR	40 (69.0%)
	2nd CR	4 (6.9%)
	non-CR	9 (15.5%)
	NA	5 (8.6%)
Median months from Dx to HSCT [range]		6.5 [3.2–113.2]
Median years of Observation [range]		3.7 [0.2–19.2]

Dx, diagnosis ; Ph1, Philadelphia chromosome ; HSCT, hematopoietic stem cell transplantation ; TKI, tyrosin kinase inhibitor ; CR, complete remission ; NA, data not available

used to perform univariate comparisons among subgroups. The Cox proportional hazard model with a backward selection method was used to identify independent variables for the OS, PFS and GRFS. As the secondary endpoints, cumulative incidences of non-relapse mortality (NRM), ALL relapse, and acute and chronic GVHD were estimated. The results were described with hazard ratios and their 95 % confidence intervals (95 % CIs). All tests were two-sided, and a p value <0.05 was considered to indicate statistical significance.

All statistical analyses were performed with EZR version 1.61, available at Saitama Medical Center, Jichi Medical University, Saitama, Japan (https://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics[22].

D Ethical considerations

Patients who did not agree to be included in the present study were excluded from the dataset using an opt-out method. This study was conducted with approval by the institutional review board of Shinshu University School of Medicine (Approval number : 5748).

Ⅲ Results

A Patients

A total of 58 patients were included in this analysis **(Table 1)**. They were 24 males and 34 females with a median age (range) of 39.5 (17.0–70.0) years old at the time of allo-HSCT. The median (range) of the white blood cell (WBC) count at the diagnosis was 8,725 (660–575,550) /μL. High-risk genetic features for ALL were found in 13 patients (22.4 %), including harboring 11q23 abnormality (n = 3), hypodiploidy (chromosomes < 45) (n = 1), and a complex karyotype (presence of ≥ 5 aberrations) (n = 9). Twenty-three patients tested positive for Philadelphia chromosome p210 (n = 2), p190 (n = 20), and unknown (n = 1). Before allo-HSCT, 20 patients were treated with tyrosine kinase inhibitors (imatinib [n = 8], dasatinib [n = 10], ponatinib

Table 2 Characteristics of HSCT

Variables			n (%)
Stem Cell Source			
	Bone Marrow		39 (67.2)
	Peripheral Blood		6 (10.3)
	Cord Blood		13 (22.4)
Relationship of Donor			
	related		15 (25.9)
	unrelated		43 (74.1)
Donor-Recipient Sex			
	F to M		10 (17.2)
	M to F		16 (27.6)
	matched		32 (55.2)
HLA Disparity			
	matched		31 (53.5)
	mismatched		24 (41.4)
	unknown		3 (5.2)
Conditioning Intensity			
	MAC		49 (84.5)
		TBI-CY	22
		intensified TBI-CY	18
		Flu-Bu4 ± MEL/TBI	9
	RIC		9 (15.5)
		Flu-Bu2 ± TBI	2
		Flu-MEL ± TBI	7
GVHD Prophylaxis			
	CsA + short MTX		19 (32.8)
	Tac + short MTX		33 (56.9)
	CsA + MMF		7 (12.1)
	Tac + MMF		1 (1.7)
ATG			6 (10.3)

HSCT, hematopoietic stem cell transplantation ; MAC, myeloablative conditioning ; RIC, reduced intensity conditioning ; TBI, total body irradiation ; CY, cyclophosphamide ; Flu, fludarabine ; Bu, busulfan ; MEL, melphalan ; CsA, cyclosporin A ; MTX, methotrexate ; Tac, tacrolimus ; MMF, micofenolate mofetil ; ATG, anti-thymocyte gammaglobulin

[n = 2]), and 1 patient was treated with blinatumomab. Fifty-four patients (93.1 %) achieved CR after a single course of induction therapy. The disease status at the time of allo-HSCT was hematological CR in 44 patients (75.9 %), non-CR in 9 patients (15.5 %) and unknown in 5 patients (8.6 %). An analysis of the chimeric mRNA had been available at the diagnosis in 26 patients with *ETV6-RUNX1* (n = 1), *TCF3-PBX1* (n = 3), *KMT2A-AFF1* (n = 3), major *BCR-ABL1* (n = 2) and minor *BCR-ABL1* (n = 17). The chimeric mRNA was detected at the time of transplantation in one patient with *TCF3-PBX1*, who was in hematological non-CR, and three patients with minor *BCR-ABL1*, who were in hematological CR (n = 1), in non-CR (n = 1) and with an unknown hematological status (n = 1).

B Transplantation (Table 2)

The transplantation graft was from the BM in 39 patients (67.2 %), the PB in 6 patients (10.3 %), and the CB in 13 patients (22.4 %). The donor and recipient were unrelated in 43 transplantations (74.1 %). The donor-to-recipient sex parings were female-to-male in 10 transplantations (17.2 %), male-to-female in 16 transplantations (27.6 %) and same-sex pairings in 32 transplantations (55.2 %). Thirty-one transplantations (53.5 %) were performed from 8/8 allele-matched do-

nors. The MAC regimen (n = 49, 84.5 %) was either a TBI-CY-based regimen (n = 40) or Flu-Bu4-based regimen (n = 9). RIC regimens (n = 9, 15.5 %) were either a Fu-Bu2-based regimen (n = 2) or Flu-Mel-based regimen (n = 7). TBI (2 Gy) was added as a conditioning regimen in 6 patients (10.3 %). ATG was included in GVHD prophylaxis in 6 patients (10.3 %).

C The OS

The median [range] period of observation was 3.7 [0.2-19.2] years. The 3-year OS was 72.7 % (95 % CI : 58.1 %-82.9 %) **(Fig. 1a)**. A log-rank univariate analysis showed that age of ≥40 years old at the time of transplantation (p = 0.0324) and non-CR at the time of transplantation (p = 0.0166) were identified as risk factors for the OS **(Fig. 1b,c)**. There were no statistical differences in the OS between patients with allo-HSCT performed before (n = 35) and after 2013 (n = 23) (p = 0.406). The results of the multivariate analysis showed that non-CR at allo-HSCT was an independent risk factor for the OS with a hazard ratio of 3.254 (95 % CI : 1.119-9.459, p = 0.03022).

D The PFS and GRFS

The 3-year PFS was 54.7 % (95 % CI : 40.6 %-66.7 %) **(Fig. 1d)**. Patients with residual disease at allo-HSCT showed a significantly poorer PFS than patients without residual disease (p = 0.00154) **(Fig. 1e)**. A multivariate analysis indicated that non-CR at the time of transplantation was an independent risk factor for a poor PFS with a hazard ratio of 3.562 (95 % CI : 1.539-8.24, p = 0.002998).

The 3-year GRFS was 46.2 % (95 % CI : 23.6 %-58.7 %) **(Fig. 1f)**. Univariate analyses showed that the stem cell source and non-CR at transplantation were associated with the outcome with a statistical significance (p = 0.00598 and p = 0.00005, respectively) **(Fig. 1g,h)**. A multivariate analysis indicated that non-CR at transplantation was an independent risk factor for a GRFS with a hazard ratio of 4.746 (95 % CI : 2.081-10.82, p = 0.000213).

E Cumulative incidence rates of GVHD, relapse and NRM

The cumulative incidence rates of grade Ⅱ-Ⅳ acute GVHD and grade Ⅲ-Ⅳ acute GVHD were 46.7 % (95 % CI : 34.9 %-60.4 %) and 5.1 % (95 % CI : 0.2 %-1.3 %), respectively **(Fig. 2a)**. No significant differences were found between the groups in the incidence rates of acute GVHD. The cumulative incidence rates of chronic GVHD and chronic GVHD requiring systemic therapy were 48.7 % (95 % CI : 7.6 %-34.4 %) and 21.4 % (95 % CI : 11.2 %-38.8 %), respectively **(Fig. 2b)**. No significant differences were found between groups in the incidence rates of chronic GVHD.

The cumulative incidence of relapse was 28.8 % (95 % CI : 17.4 %-41.1 %) at 3 years **(Fig. 2c)**. Patients without CR at transplantation had a tendency toward an association with an increased rate of relapse, but the difference did not reach statistical significance (p = 0.07).

The cumulative incidence of non-relapse mortality (NRM) was 16.7 % at 3 years (95 % CI : 8.1 %-27.8 %) **(Fig. 2d)**. A higher rate of NRM was significantly associated with age ≥40 years old at the time of allo-HSCT (p = 0.0209) and male sex (p = 0.00795) **(Fig. 2e,f)**.

F Post-transplantation anti-leukemic therapy

Among the 20 patients with relapsed ALL after allo-HSCT, 17 received anti-leukemic therapies, including 3 with chemotherapy, 9 with tyrosine kinase inhibitors (imatinib [n = 2], dasatinib [n = 3], ponatinib [n = 5]), and 1 with blinatumomab. Three patients with Ph-positive ALL and six patients with Ph-negative ALL underwent a second allo-HSCT procedure.

Ⅳ Discussion

The recent development of pediatric-inspired regimens, novel anti-leukemic agents, and MRD-driven treatment strategies might potentially reduce the dependence of patients with standard-risk ALL on allo-HSCT, but an increasing number of adult patients with ALL harboring higher-risk features still undergo the transplantation seeking a cure[6)23)-28)]. Our results showed a 3-year OS of 72.7 %, which confirmed the challenges faced by adult patients with ALL compared with the more favorable outcomes in pediatric patients. Our results also suggested that achieving higher CR rates before allo-HSCT is associated with a better OS in adult recipients.

A recent study has suggested that adult patients with ALL who are MRD-negative prior to allo-HSCT

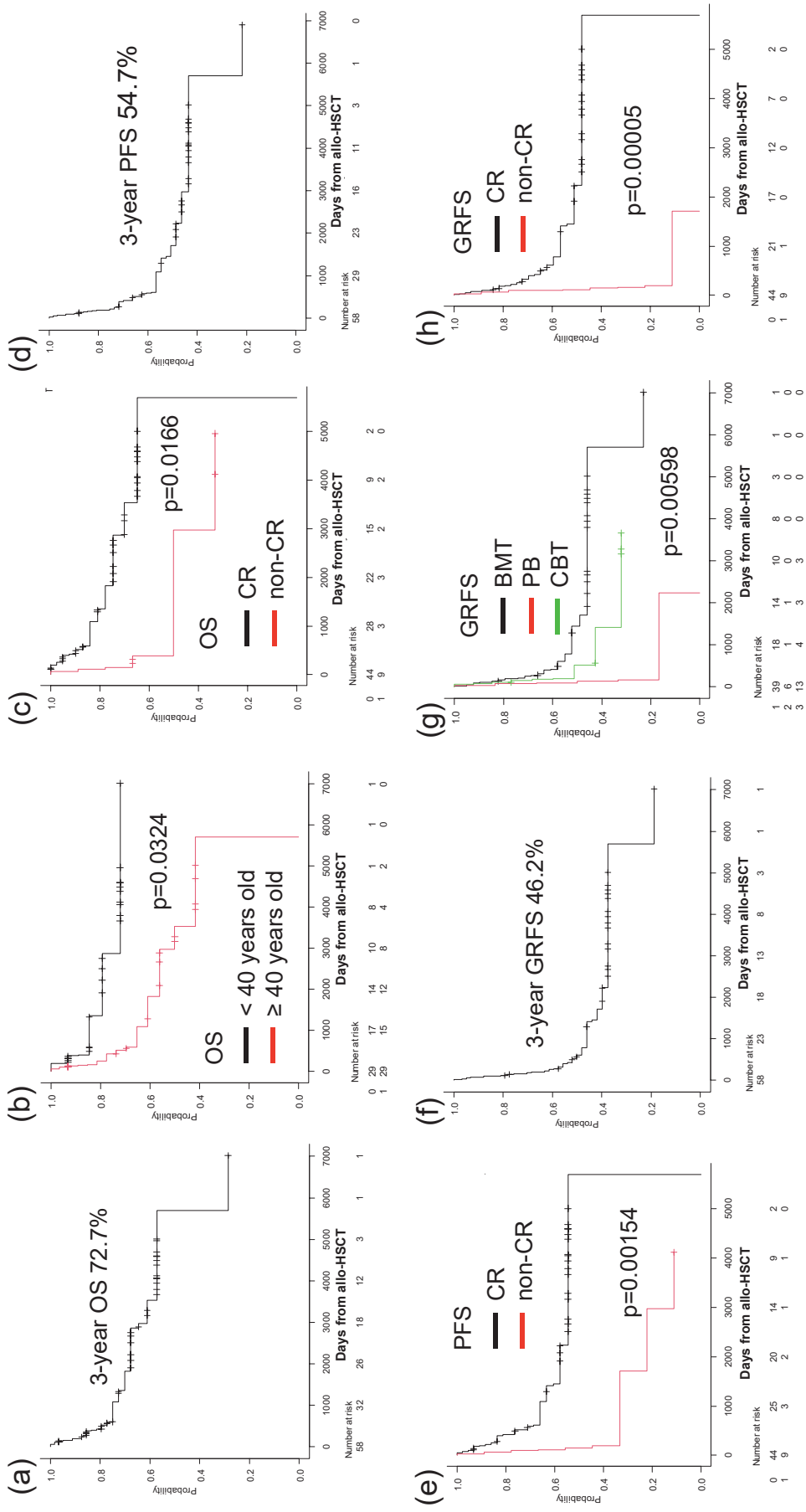

Fig. 1 Kaplan–Meier curves of the overall survival (OS), progression–free survival (PFS), and GVHD–free and relapse–free survival (GRFS).
(a) The 3–year OS was 72.7 % (95 % CI : 58.1 %–82.9 %) ; a superior OS was observed in (b) relatively young patients (<40 years old) and (c) patients with hematological CR at the time of transplantation, with statistical significance (p = 0.0324 and p = 0.0166, respectively). (d) The 3–year PFS was 54.7 % (95 % CI : 40.6 %–66.7 %), and a relatively better PFS was observed in (e) younger patients than in older patients (p = 0.00154). (f) The 3–year GRFS was 46.2 % (95 % CI : 23.6 %–58.7 %) ; a subgroup analyses showed that the GRFS differed (g) among stem cell sources (p = 0.00598) and (h) by CR status (p = 0.00005). The median [range] period of observation was 3.7 [0.2–19.2] years.

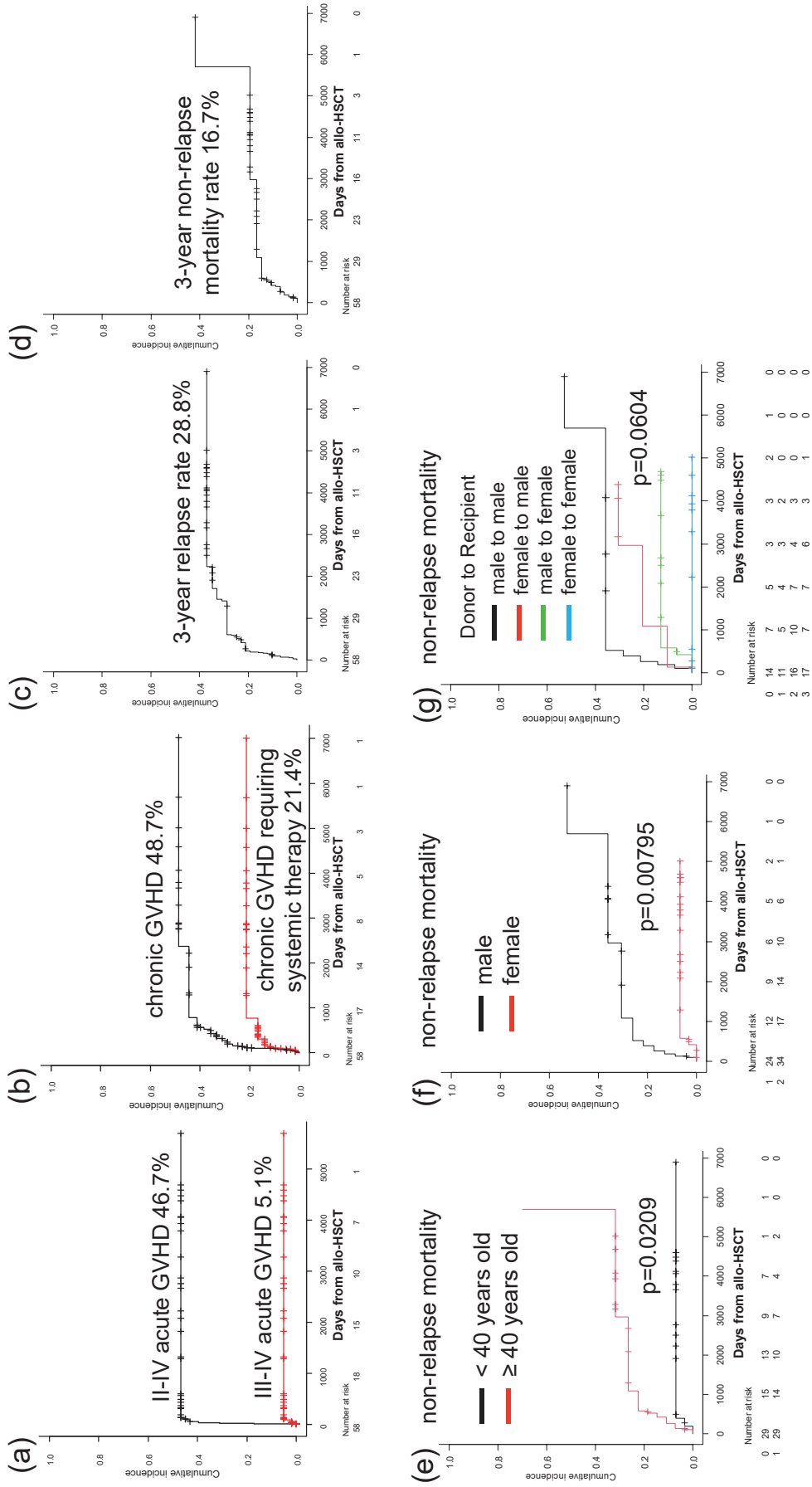

Fig. 2 Cumulative incidence curves of GVHD, disease relapse, and non-relapse mortality (NRM).

(a) Grade Ⅱ-Ⅳ acute GVHD was observed in 46.7 %, and grade Ⅲ-Ⅳ acute GVHD was observed in 5.1 % of the patients. (b) Chronic GVHD was reported in 48.7 %, and chronic GVHD requiring systemic therapy occurred in 21.4 %. (c) ALL relapse was observed in 28.8 % of cases at 3 years after allo-HSCT, while (d) NRM was seen in 16.7 %. Subgroup comparisons of the cumulative incidence of NRM showed that older age (e) and male sex (f) were associated with a significantly increased NRM ($p = 0.0209$ and $p = 0.00795$, respectively). Regarding donor-recipient sex pairings (g), there was a tendency toward a higher NRM in male-to-male pairs, followed by female-to-male pairs, male-to-female pairs, and female-to-female pairs, but the differences were not statistically significant ($p = 0.0604$).

achieve superior outcomes[29]. In our cohort, however, the OS, PFS, and GRFS did not differ markedly between the patients (n = 17) who tested negative with PCR for chimeric mRNA before transplantation and the patients (n = 41) in whom the test was not performed at all or the test result was positive (p = 0.83, p = 0.231 and p = 0.328, respectively). One possible explanation for the lack of an association is that PCR findings were not available in 17 % of patients with Ph-positive ALL and 72 % of patients with Ph-negative ALL in our cohort due to the retrospective nature of the present study. It should be noted, however, that the methods used for MRD analysis, either PCR-based or immunophenotyping-based techniques, may vary among institutions worldwide, and that the cut-off values are not standardized[29]. Nevertheless, recent studies have suggested that a deeper response to an MRD-negative level may be expected with novel agents such as blinatumomab[30][31]. Only one of the patients with Ph-negative ALL received blinatumomab in our cohort. With the increasing availability of novel therapies MRD negativity is likely to become achievable for more patients, hopefully leading to improved treatment outcomes among adult ALL patients with or without allo-HSCT[31][32].

A significant difference between the OS and PFS was also recognized in our cohort, suggesting that a number of patients refractory to allo-HSCT might have been salvaged by post-HSCT therapies. Indeed, tyrosine kinase inhibitors (TKIs) or blinatumomab were administered after post-HSCT relapses in nine patients with Ph-positive ALL and one with Ph-negative ALL. Second transplantation procedures were performed in three and six patients with Ph-positive and Ph-negative ALL, respectively. Increasing evidence suggests the efficacy of TKIs following allo-HSCT for patients with Ph-positive ALL, while a suitable agent has not been identified as maintenance therapy for Ph-negative ALL[33][34]. The establishment of maintenance and/or preemptive therapies is eagerly awaited for transplant recipients with Ph-negative ALL.

Of note, a significantly increased rate of NRM was found in male patients compared with female patients in our cohort, although the difference did not translate into a sex-based difference in the OS, PFS, or GRFS. We did not find a significant difference between male and female patients in such pre-transplantation factors as age distribution (p = 0.907 with a Mann-Whitney test), the WBC count at the diagnosis (p = 0.269), frequency of high-risk chromosomal abnormality (p = 1.0), frequency of Philadelphia chromosome (p = 0.586), CR rate at transplantation (p = 0.154), HLA disparity (p = 1.0), or conditioning (p = 0.467). Nakasone et al. reported that a donor-recipient sex difference may confer different risks of GVHD, different risks of relapse and non-relapse mortality and a poor OS, and the contribution of the risks varies according to conditioning regimens[35]. In our cohort, the cumulative incidence of NRM seemed highest in male-to-male transplantation, followed by female-to-male, male-to-female, and female-to-female cases, although the difference did not reach statistical significance (p = 0.0604) **(Fig. 2g)**.

Several limitations associated with the present study warrant mention. Because of the retrospective nature of the analysis, a detailed description of the genetic lesions of ALL was lacking in more than 70 % of the patients with Ph-negative ALL. It is desirable to perform genetic analysis of ALL in all patients at the diagnosis, ideally including a genetic lesion such as the Ph-like pattern, which may be incorporated in the assessment of the disease risks as well as in exercising an MRD-driven treatment strategy[2][7][23]. However, despite all these limitations, this retrospective study may provide some historical control data for performing a comparative analysis at our institution in the future.

V Conclusion

In this retrospective analysis of allo-HSCT in 58 adult patients with ALL, our results show that attaining CR before transplantation may be an independent risk factor for an improved OS, PFS, and GRFS. Treatment outcomes with the incorporation of novel agents before and after transplantation should be retrospectively compared with this dataset in the future.

Conflict of Interest

The authors declare that they have no competing interests.

References

1) Kantarjian H, Thomas D, O'Brien S, et al : Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer 101 : 2788-2801, 2004
2) Faderl S, O'Brien S, Pui CH, et al : Adult acute lymphoblastic leukemia : concepts and strategies. Cancer 116 : 1165-1176, 2010
3) Pui CH, Evans WE : Acute lymphoblastic leukemia. N Engl J Med 339 : 605-615, 1998
4) Künz T, Hauswirth AW, Hetzenauer G, Rudzki J, Nachbaur D, Steiner N : Changing Landscape in the Treatment of Adult Acute Lymphoblastic Leukemia (ALL). Cancers 14 : 2022 (Accessed Feb 23, 2023, at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9454969/)
5) Arslan S, Pullarkat V, Aldoss I : Indications for Allogeneic HCT in Adults with Acute Lymphoblastic Leukemia in First Complete Remission. Curr Treat Options Oncol 22 : 2021 (Accessed Feb 23, 2023, at https://link.springer.com/article/10.1007/s11864-021-00860-1
6) Dholaria B, Savani BN, Huang XJ, Nagler A, Perales MA, Mohty M : The evolving role of allogeneic haematopoietic cell transplantation in the era of chimaeric antigen receptor T-cell therapy. Br J Haematol 193 : 1060-1075, 2021
7) Oliansky DM, Larson RA, Weisdorf D, et al : The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of adult acute lymphoblastic leukemia : update of the 2006 evidence-based review. Biol Blood Marrow Transplant 18 : 16-17, 2012
8) Juliusson G, Karlsson K, Lazarevic V, et al : Hematopoietic stem cell transplantation rates and long-term survival in acute myeloid and lymphoblastic leukemia : real-world population-based data from the Swedish Acute Leukemia Registry 1997-2006. Cancer 117 : 4238-4246, 2011
9) Penack O, Marchetti M, Ruutu T, et al : Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies : updated consensus recommendations of the European Society for Blood and Marrow Transplantation. Lancet Haematol 7 : e157-e167, 2020
10) Zeiser R, von Bubnoff N, Butler J, et al : Ruxolitinib for Glucocorticoid-Refractory Acute Graft-versus-Host Disease. N Engl J Med 382 : 1800-1810, 2020
11) Maertens JA, Girmenia C, Brüggemann RJ, et al : European guidelines for primary antifungal prophylaxis in adult haematology patients : summary of the updated recommendations from the European Conference on Infections in Leukaemia. J Antimicrob Chemother 73 : 3221-3230, 2018
12) Asano-Mori Y : Fungal infections after hematopoietic stem cell transplantation. Int J Hematol 91 : 576-587, 2010
13) Ben-Ami R, Lewis RE, Kontoyiannis DP : Invasive mould infections in the setting of hematopoietic cell transplantation : current trends and new challenges. Curr Opin Infect Dis 22 : 376-384, 2009
14) Groll AH, Tragiannidis A : Recent advances in antifungal prevention and treatment. Semin Hematol 46 : 212-229, 2009
15) Mohty M, Malard F, Abecasis M, et al : Prophylactic, preemptive, and curative treatment for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients : a position statement from an international expert group. Bone Marrow Transplant 55 : 485-495, 2020
16) Carreras E : How I manage sinusoidal obstruction syndrome after haematopoietic cell transplantation. Br J Haematol 168 : 481-491, 2015
17) Bonifazi F, Barbato F, Ravaioli F, et al : Diagnosis and Treatment of VOD/SOS After Allogeneic Hematopoietic Stem

Cell Transplantation. Front immunol 11 : 2020 (Accessed Feb 23, 2023, at https://www.frontiersin.org/articles/10.3389/fimmu.2020.00489/full)

18) Ljungman P, de la Camara R, Robin C, et al : Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). Lancet Infect dis 19 : e260–e272, 2019

19) Boeckh M, Murphy WJ, Peggs KS : Reprint of : Recent advances in cytomegalovirus : an update on pharmacologic and cellular therapies. Biol Blood Marrow Transplant 21 : S19–S24, 2015

20) Swerdlow SH, Campo E, Harris NL, et al : WHO Classification of Tumours of Haematoopoietic and Lymphoid Tissues. Revised 4th Edition, pp 200–208, International Agency for Research on Cancer, Lyon, 2017

21) Holtan SG, DeFor TE, Lazaryan A, et al : Composite end point of graft–versus–host disease–free, relapse–free survival after allogeneic hematopoietic cell transplantation. Blood 125 : 1333–1338, 2015

22) Kanda Y : Investigation of the freely available easy–to–use software 'EZR' for medical statistics. Bone Marrow Transplant 48 : 452–458, 2013

23) Samra B, Jabbour E, Ravandi F, Kantarjian H, Short NJ : Evolving therapy of adult acute lymphoblastic leukemia : state–of–the–art treatment and future directions. J Hematol Oncol 13 : 2020 (Accessed Feb 25, 2023, at https://jhoonline.biomedcentral.com/articles/10.1186/s13045–020–00905–2)

24) Ghobadi A, Slade M, Kantarjian H, et al : The role of allogeneic transplant for adult Ph + ALL in CR1 with complete molecular remission : a retrospective analysis. Blood 140 : 2101–2112, 2022

25) Short NJ, Kantarjian H, Jabbour E : SOHO State of the Art Updates & Next Questions : Intensive and Non–Intensive Approaches for Adults With Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia. Clin Lymphoma Myeloma Leuk 22 : 61–66, 2022

26) Zhang Y, Feng S : The impact of tyrosine kinase inhibitors on allogeneic hematopoietic stem cell transplantation for adult patients with Philadelphia chromosome–positive acute lymphoblastic leukemia. Leuk Res 109 : 2021 (Accessed Feb 25, 2023, at https://www.sciencedirect.com/science/article/pii/S014521262100148X?via%3Dihub)

27) Nagafuji K, Miyamoto T, Eto T, et al : Prospective evaluation of minimal residual disease monitoring to predict prognosis of adult patients with Ph–negative acute lymphoblastic leukemia. Eur J Haematol 103 : 164–171, 2019

28) Giebel S, Boumendil A, Labopin M, et al : Trends in the use of hematopoietic stem cell transplantation for adults with acute lymphoblastic leukemia in Europe : a report from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). Ann Hematol 98 : 2389–2398, 2019

29) Pavlů J, Labopin M, Niittyvuopio R, et al : Measurable residual disease at myeloablative allogeneic transplantation in adults with acute lymphoblastic leukemia : a retrospective registry study on 2780 patients from the acute leukemia working party of the EBMT. J Hematol Oncol 12 : 2019 (Accessed Feb 28, 2023, at https://jhoonline.biomedcentral.com/articles/10.1186/s13045–019–0790–x)

30) Martinelli G, Boissel N, Chevallier P, et al : Long–term follow–up of blinatumomab in patients with relapsed/refractory Philadelphia chromosome–positive B–cell precursor acute lymphoblastic leukaemia : Final analysis of ALCANTARA study. Eur J Cancer 146 : 107–114, 2021

31) Gökbuget N, Dombret H, Bonifacio M, et al : Blinatumomab for minimal residual disease in adults with B–cell precursor acute lymphoblastic leukemia. Blood 131 : 1522–1531, 2018

32) Gökbuget N, Zugmaier G, Dombret H, et al : Curative outcomes following blinatumomab in adults with minimal residual disease B–cell precursor acute lymphoblastic leukemia. Leuk Lymphoma 61 : 2665–2673, 2020

33) DeFilipp Z, Advani AS, Bachanova V, et al : Hematopoietic Cell Transplantation in the Treatment of Adult Acute Lymphoblastic Leukemia : Updated 2019 Evidence–Based Review from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant 25 : 2113–2123, 2019

34) DeFilipp Z, Chen YB : Strategies and Challenges for Pharmacological Maintenance Therapies after Allogeneic

Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant 22 : 2134-2140, 2016

35) Nakasone H, Remberger M, Tian L, et al : Risks and benefits of sex-mismatched hematopoietic cell transplantation differ according to conditioning strategy. Haematologica 100 : 1477-1485, 2015

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