Ther Adv Hematol
2021, Vol. 12: 1–10
DOI: 10.1177/20406207211001135

Should patients receive consolidation chemotherapy before reduced intensity allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia in first complete remission?

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Abstract

Background: For acute myeloid leukemia (AML) patients, the role of bridging consolidation chemotherapy after achieving first complete remission (CR1) in the transplant setting is a frequently debated issue. The lack of data from Asian patients led us to conduct this study.

Methods: We retrospectively studied outcomes of 106 patients in CR1 undergoing allogeneic stem cell transplantation (alloSCT) with reduced intensity conditioning (RIC) based on their exposure to pre-transplant consolidation chemotherapy. There were 35 in the no consolidation group *versus* 71 in the consolidation group.

Results: The median relapse free survival (RFS) was 9 months for the no consolidation group and 51 months for consolidation group ($p = 0.023$). The median overall survival was 32 months for the no consolidation group and not reached for the consolidation group ($p = 0.034$). Multivariate analysis recognized consolidation and poor cytogenetics as adverse prognostic factors for RFS. Moreover, RFS was better in patients with a shorter time lapse between last chemotherapy and alloSCT in both the no consolidation group and the consolidation group. Consolidation chemotherapy did not negatively affect neutrophil and platelet engraftment, infection rates, or acute graft-*versus*-host disease (GVHD) incidence. On the other hand, patients undergoing consolidation chemotherapy showed trends towards a more severe degree of chronic GVHD.

Conclusion: The exposure to consolidation chemotherapy in CR1 prior to alloSCT with RIC conditioning did not negatively impact the outcomes in Korean AML patients, for whom a suitable donor is rarely immediately available. Therefore, post-remission consolidation chemotherapy is a reasonable option if required.

Keywords: acute myeloid leukemia, allogeneic hematopoietic stem cell transplantation, complete remission, post-remission chemotherapy, reduced intensity

Received: 15 January 2021; revised manuscript accepted: 10 February 2021.

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Introduction

Allogeneic stem cell transplantation (alloSCT) remains an integral part of acute myeloid leukemia (AML) treatment due to its curative potential.[1] After achieving first complete remission (CR1), the role of consolidation chemotherapy is solid in non-transplant settings.[2,3] However in the transplant setting, the role of bridging consolidation chemotherapy is a frequently debated issue. Following the studies from the European Group for Bone Marrow Transplantation (EBMT)[4] and Center for International Blood and Marrow Transplant Research[5] in 2000, which showed no significant difference in relapse rates, relapse free

survival (RFS), and overall survival (OS) between patients undergoing alloSCT with myeloablative conditioning regimen after consolidation *versus* no consolidation, prompt transition to transplant is the accepted standard of care. For reduced intensity conditioning (RIC) on the other hand, evidence has been less concrete. Some advocate the theoretical additive benefits of consolidation chemotherapy for more stringent disease control in alloSCT with RIC,[6,7] while others report similar transplant outcomes regardless of conditioning intensity.[8,9]

In Korea, consolidation chemotherapy in CR1 is commonly offered prior to alloSCT while clearing insurance to prevent early relapse. As for the conditioning regimen, RIC is predominantly used due to reduced susceptibility and tolerability to chemotherapeutic agents and radiotherapy. The treatment of AML is costly, and therefore is inevitably heavily influenced by regional health regulations. Sometimes such discrepancies, along with ethnic disparities, can lead to different outcomes.[10] In this regard, we thought it appropriate to address the rather surprising lack of data on the effects of post-remission chemotherapy before alloSCT for AML in CR1 in an Asian population. A Korean population was selected for this study, because Korea has a sole public medical insurance system that is mandatory and covers approximately 98% of the overall Korean population.[11] Also, as the range of coverage is strictly controlled, the first line AML treatment algorithm is relatively uniform throughout the population. Here, we report the outcomes of 106 patients in CR1 undergoing alloSCT with RIC based on their exposure to pretransplant consolidation chemotherapy.

Methods

Study design and subjects

This was a multi-center retrospective, longitudinal cohort study of AML patients over 18 years old consecutively treated at Seoul National University Hospital and Seoul National University Bundang Hospital. The study period was set between January 2013 and December 2018. Non-acute promyelocytic leukemia AML patients achieving CR1 induction therapy and undergoing alloSCT with RIC were included for analyses. RIC conditioning was chosen per attending physician's choice based on the patient's age, co-morbidities, prior treatment tolerability, and associated complications. Only those achieving cytogenetic complete remission (CR) per 2017 European LeukemiaNet recommendations[12] were considered. If the patient harbored specific mutation trackable by real-time quantitative polymerase chain reaction (PCR) or direct sequencing, molecular CR had to be confirmed before alloSCT. Those achieving CR with incomplete recovery or morphologic leukemia-free state were not counted as CR.[12] Biphenotypic leukemias were also excluded. During the study period, a total of 106 patients (35 in the no consolidation group *versus* 71 in the consolidation group) were deemed eligible. Their medical records were reviewed and analyzed for demographics, baseline disease characteristics, chemotherapy, factors related to alloSCT, response to alloSCT, adverse events, and survival outcomes. This study was conducted according to the Declaration of Helsinki and was approved by the institutional review board of participating hospitals (Seoul National University Hospital IRB number H-1911-042-107 and Seoul National University Bundang Hospital IRB number B-1509-314-108). The informed consent was waived in light of the retrospective nature of the study and the anonymity of the subjects.

Definitions

The diagnosis of AML was made according to the World Health Organization Classification of Hematopoietic Neoplasms, which requires identification of 20% or more leukemic blasts in the bone marrow. Secondary AML was defined as AML following myelodysplastic syndrome or myeloproliferative neoplasms confirmed prior to the diagnosis of AML, or AML secondary to proven leukemogenic exposure. Complex karyotype was defined as any karyotype with at least three chromosome aberrations, regardless of their type and the individual chromosomes involved.[13] Prognostic grouping of cytogenetics was performed according to Southwest Oncology Group criteria.[14] Fms-related tyrosine kinase 3 (*FLT3*) internal tandem duplication (ITD), mutations in exons 8 and 17 of *c-KIT*, *RUNX1-RUNX1T1*, *CEBPA* and nucleophosmin-1 (*NPM1*) mutations were analyzed using DNA samples obtained at initial diagnosis and multiplex PCR and direct sequencing.

Acute graft-*versus*-host disease (GVHD) grading was performed according to the standard criteria.[15]

Chronic GVHD was classified as mild, moderate, or severe according to the 2014 National Institutes of Health consensus criteria.[16] Transplant-related mortality (TRM) was defined as death without progression of underlying AML. Relapse was defined by the morphologic evidence of disease in the peripheral blood, bone marrow, or extra-medullary sites. The RFS was defined as the time from stem cell infusion to relapse or death from any cause. The OS was defined as the time from stem cell infusion to death of any cause. Neutrophil engraftment was defined as an absolute neutrophil count $>0.5\times10^9$/L on three consecutive measurements. Platelet recovery was defined as seven consecutive measurements of 20.0×10^9/L without transfusion.

Treatment schema

One cycle of chemotherapy was required for remission induction in the majority of the patients (71/106, 67.0%), while 35 (33.0%) required two cycles. Most received standard 3 + 7 induction as first line chemotherapy, which consisted of idarubicin 12 mg/m^2 for 3 days plus cytarabine 100 mg/m^2 for 7 days. There were seven patients who underwent cytarabine (100 mg/m^2 for 7 days) + daunorubicin (90 mg/m^2 for 3 days).

Up until 2015, anthracycline based consolidation chemotherapy regimens were used: (1) DA, consisting of daunorubicin 45 mg/m^2 on days 1–3 plus cytarabine 2 g/m^2 on days 1–4; (2) IA, consisting of idarubicin 12 mg/m^2 on days 1–3 plus cytarabine 2 g/m^2 on days 1–4; and (3) high dose cytarabine (6 g/m^2 on days 1–3) plus idarubicin (12 mg/m^2 on days 1–3). The center's policy for consolidation was DA $\rightarrow$ IA $\rightarrow$ high dose cytarabine based regimen. However, the sequence of consolidation regimens and dose reduction was modified at the discretion of the attending physician. From 2015, consolidation with three cycles of HDAC (3 g/m^2 twice daily over 3 days) was uniformly used.

All of the RIC regimen was BuFlu (busulfan 3.2 mg/kg on days −7 to −6, fludarabine 30 mg/m^2 on days −7 to −2) with either antithymocyte globulin or post-transplant cyclophosphamide. All patients received recombinant granulocyte colony-stimulating factor from day 1 of the stem cell transplantation until the absolute neutrophil counts were $>1.0\times10^9$/L for three consecutive days or $>3.0\times10^9$/L. Patients were treated with cyclosporine (3 mg/kg) or tacrolimus (0.04 mg/kg per day) with or without a short course of methotrexate (15 mg/m^2 on day 1 and 10 mg/m^2 on days 3, 6, and 11). Total body irradiation was not used.

Statistical analysis

Differences between groups were assessed using a Student's *t*-test or one-way analysis of variance for continuous variables, and Pearson chi-square test for categorical variables, as indicated. The RFS and OS curves were estimated using the Kaplan–Meier method. If patients survived without death or progression, the survival was censored at the latest date of follow-up when no death or progression was confirmed. Cumulative incidence curves were used in the competing-risk setting to calculate the probability of acute and chronic GVHD and TRM. For GVHD, death without an event was considered as the competing event. For TRM, relapse was considered as the competing event. Associations between potential prognostic factors and survival outcomes were evaluated using the Cox's proportional hazard regression models. A stepwise backward procedure was used, and predictors achieving a p-value below 0.05 were considered then sequentially removed if the p-value in the multiple model was above 0.05. All data were analyzed using the Statistical Package for the Social Sciences software (IBM® SPSS® Statistics, version 22.0). p values of <0.05 were considered statistically significant.

Results

Patient characteristics

The baseline characteristics of all patients are shown in Table 1. When patients were stratified according to exposure to consolidation chemotherapy, there were more secondary AML in patients in the no consolidation group ($p=0.026$) compared with the consolidation group. The median number of consolidation cycles was 1 (range 1–3 cycles) for patients in the consolidation group. There were no differences between the two groups with regard to age, sex, cytogenetic risk group, donor source, modified EBMT risk score, number of induction chemotherapy, infused CD34 count, and GVHD prophylaxis regimens.

Table 1. Baseline characteristics.

n, %	No consolidation *n* = 35	Consolidation *n* = 71	*p*
Age, years*	54 (18–65)	52 (22–68)	0.499
Sex, male	13 (37.1)	36 (50.7)	0.188
Cytogenetic risk group			
Favorable	7 (20.0)	13 (18.3)	0.939
Intermediate	24 (68.6)	51 (71.8)	
Poor	4 (11.4)	7 (9.9)	
AML type			
De novo	25 (71.4)	63 (88.7)	0.026
Secondary	10 (28.6)	8 (11.3)	
Induction to alloSCT, days*	110 (52–208)	145 (87–319)	<0.001
CR1 to alloSCT, days*	52 (15–120)	101 (7–294)	<0.001
Last CTX to alloSCT, days*	110 (52–208)	65 (28–259)	<0.001
No. of induction cycles before CR1			
1	21 (60.0)	50 (70.4)	0.283
2	14 (40.0)	21 (29.6)	
Consolidation cycles			
0	35 (100)	0	N/A
1	0	52 (73.2)	
2	0	16 (22.5)	
3	0	3 (4.2)	
Donor source			
Matched related donor	17 (48.6)	33 (46.5)	0.106
Matched unrelated donor	5 (14.3)	17 (23.9)	
Partially matched unrelated donor	4 (11.4)	1 (1.4)	
Haplo-identical	9 (25.7)	20 (28.2)	
Sex matching			
Female donor to male recipient	5 (14.3)	11 (15.5)	0.870
mEBMT risk score			
1–2	23 (65.7)	34 (47.9)	0.083
3–6	12 (34.3)	37 (52.1)	
Infused CD34, $\times 10^6$/kg*	4.62 (1.87–13.13)	5.45 (1.00–12.91)	0.670
GVHD prophylaxis			
ATG use	34 (97.1)	69 (97.2)	0.991
Post-CY use	1 (2.9)	2 (2.8)	0.991

*Represented as median (range).
alloSCT, allogeneic stem cell transplantation; AML, acute myeloid leukemia; ATG, anti-thymoglobulin; CR1, first complete remission; CTX, chemotherapy; CY, cyclophosphamide; GVHD, graft-*versus*-host disease; mEBMT, modified European group for blood and marrow transplantation; N/A, not applicable; No., number.

The interval between CR1 and alloSCT was significantly longer in the consolidation group (median 52 days in the no consolidation group *versus* median 101 days in the consolidation group, $p < 0.001$). However, the interval between last chemotherapy and alloSCT was also significantly longer in the no consolidation group [median 110 days (range 52–208 days) in the no consolidation group *versus* median 65 days (range 28–259 days) in consolidation, $p < 0.001$].

Outcomes of alloSCT

There were no differences in neutrophil and platelet engraftment rates between the two groups, as shown in Table 2. There was no difference in median time to neutrophil engraftment and platelet recovery with regard to exposure to consolidation chemotherapy.

Median follow-up for the whole group was 33 months (range 4–83 months). The median RFS was 9 months for the no consolidation group and 51 months for the consolidation group [$p = 0.023$; Figure 1(a)]. Poor cytogenetic group and no consolidation were recognized as adverse prognostic factors in multivariate analysis (Table 3). The median OS was 32 months for the no consolidation group and not reached for the consolidation group [$p = 0.034$; Figure 1(b)]. There were 17 deaths in the no consolidation group and the most common cause of death was disease progression. In the consolidation group, there were 22 deaths and the most common cause of death was also disease progression (Table 2). No consolidation was the only prognostic factors recognized for OS (Table 3), thus multivariate analysis was not carried out.

GVHD and other complications

The cumulative incidence of grades II–IV acute GVHD at day 100 was 29.0% for the no consolidation group *versus* 20.5% for the consolidation group ($p = 0.201$; Table 2). The cumulative incidence of moderate to severe chronic GVHD at 1 year was 27.1% for the no consolidation group *versus* 24.3% for the consolidation group ($p = 0.988$). There was no difference between the two groups regarding infection rates, and cytomegalovirus reactivation. The cumulative incidence of TRM at 2 years was 14.7% for the no consolidation group *versus* 4.9% for the consolidation group ($p = 0.056$).

During the median follow-up of 33 months, there was no incidence of veno-occlusive disease/sinusoidal obstruction syndrome or post-transplant lymphoproliferative disease.

Discussion

The purpose of this study was to address a frequently encountered clinical dilemma of whether there is a need for post-remission consolidation chemotherapy in CR1 before alloSCT, specifically for Asian AML patients, who have been underrepresented in previous studies.[17] To the best of our knowledge, this is the first study focusing on an Asian population.

The hypothetical advantage of pre-transplant consolidation therapy lies in the possibility of inducing further minimal residual disease (MRD) prior to RIC conditioning. As shown in Table 4, as the use of RIC regimens continues to expand, several retrospective studies have investigated this potential benefit in efforts to optimize the efficacy and safety of the treatment. These previous studies[18–20] uniformly reported that post-remission consolidation does not improve the outcomes of subsequent alloSCT, but does increase transplant treatment-related mortality, thus is a reasonable choice if and when required. Our results not only resonate this sentiment, but also showed that bridging consolidation therapy leads to better survival outcomes without increasing adverse events. It is difficult to exactly define "immediately suitable" donors, but in Korea insurance clearance regarding alloSCT takes approximately 2 months after CR1 achievement, as evident in our study (median time from CR1 to alloSCT 52 days for the no consolidation group). It is also worth noting that there were more patients with higher modified EBMT risk score in the consolidation group compared with the no consolidation group, indicating that the patients in the consolidation group probably did not have readily available donors. Given this background, while it is true that our findings require careful interpretation, it seems also true that bridging consolidation chemotherapy at least does not negatively impact alloSCT outcomes and may actually be helpful in selected RIC-alloSCT setting. Moreover, RFS was better in patients with a shorter time lapse between last chemotherapy and alloSCT in both the no consolidation group and the consolidation group (Figure 2). For the no consolidation group, patients undergoing alloSCT within 110 days of

Table 2. Transplantation outcomes.

n, %	No consolidation *n* = 35	Consolidation *n* = 71	*p*
Neutrophil engraftment	33 (94.3)	69 (97.2)	0.462
Time to neutrophil engraftment, days*	12 (3–32)	12 (3–34)	0.466
Platelet recovery	33 (94.3_	69 (97.2)	0.462
Time to platelet recovery, days*	17 (6–54)	15 (6–127)	0.984
Cumulative incidence of any acute GVHD at day 100*	29.0	20.5	0.201
Grade II–IV acute GVHD	5 (14.3)	7 (9.9)	0.499
Cumulative incidence of any chronic GVHD at 1 year	27.1	24.3	0.988
Moderate–severe chronic GVHD	1 (2.9)	13 (18.3)	0.027
Any infection within 100 days of alloSCT	13 (37.1)	22 (31.0)	0.526
CMV reactivation	12 (34.3)	22 (31.0)	0.732
VOD/SOS	0	0	N/A
PTLD	0	0	N/A
Cumulative incidence of TRM at 2 years	14.7	4.9	0.056
Cause of death			
Disease progression	6 (37.5)	8 (36.4)	0.639
Infection	5 (31.3)	4 (18.2)	
GVHD related	4 (25.0)	6 (27.3)	
Others	1 (6.3)	4 (18.2)	

*Represented as median (range).
alloSCT, allogeneic stem cell transplantation; CMV, cytomegalovirus; GVHD, graft-*versus*-host disease; N/A, not applicable; PTLD, post-transplant lymphoproliferative disease; TRM, transplant related mortality; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

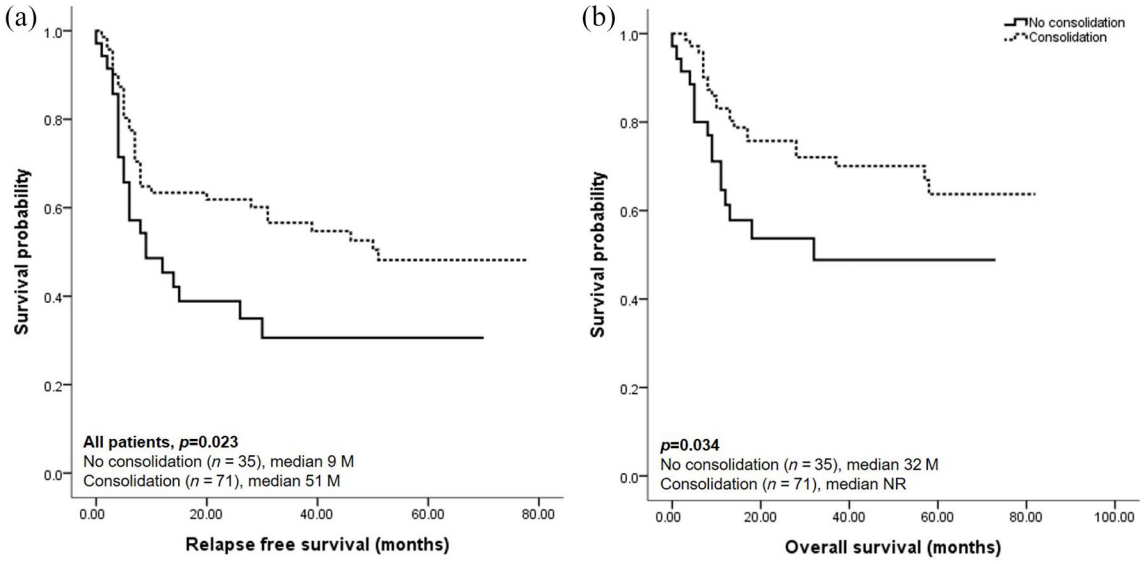

Figure 1. (a) Relapse free survival. (b) Overall survival.
M, months; NR, not reached.

Table 3. Risk factors for transplantation outcomes for patients undergoing allogeneic stem cell transplantation with reduced intensity conditioning.

Variables		Univariate		Multivariate	
		HR (95% CI)	***p***	**HR (95% CI)**	***p***
Relapse free survival					
Cytogenetic risk group	Favorable	1			
	Intermediate	2.377 (1.011–5.589)	0.047	2.775 (1.162–6.628)	0.022
	Poor	4.308 (1.481–12.536)	0.007	5.048 (1.679–15.172)	0.004
Consolidation	No	1			
	Yes	0.549 (0.322–0.937)	0.028	0.543 (0.371–0.929)	0.026
Age	<60 years	1			
	⩾60 years	1.566 (0.900–2.690)	0.113		
AML subtype	*De novo*	1			
	Secondary	1.317 (0.681–2.546)	0.413		
Sex	Male	1			
	Female	1.233 (0.733–2.074)	0.430		
mEBMT risk score	1–2	1			
	3–6	0.831 (0.493–1.403)	0.489		
Last chemo to alloSCT	⩽72 days*	1			
	>72 days	0.676 (0.401–1.139)	0.141		
Overall survival					
Cytogenetic risk group	Favorable	1			
	Intermediate	2.349 (0.827–6.671)	0.109		
	Poor	2.433 (0.607–9.762)	0.210		
Consolidation	No	1			
	Yes	0.506 (0.265–0.967)	0.039		
Age	<60 years	1			
	⩾60 years	1.913 (0.963–3.801)	0.064		
AML subtype	de novo	1			
	Secondary	1.854 (0.877–3.922)	0.106		
Sex	Male	1			
	Female	1.047 (0.554–1.980)	0.888		
mEBMT risk score	1–2	1			
	3–6	0.953 (0.503–1.807)	0.884		
Last chemo to alloSCT	⩽72 days	1			
	>72 days	0.693 (0.365–1.313)	0.261		

*Median time from last chemotherapy to allogeneic stem cell transplantation for the entire cohort.
alloSCT, allogeneic stem cell transplantation; AML, acute myeloid leukemia; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; mEBMT, modified European group for blood and marrow transplantation.

Table 4. Comparative studies.

	Current	McCormack *et al.*[20]	Warlick *et al.*[19]	Yeshurun *et al.*[18]
	No consol./consol.	No consol./consol.	No consol./consol.	No consol./consol.
Study period	2013–2018	2001–2008	2001–2008	2001–2010
Ethnicity/population	Korean	USA	North America/Europe	Europe
Conditioning	RIC	RIC	RIC	RIC
Patients, number	35 *versus* 71	35 *versus* 25	202 *versus* 402	151 *versus* 222
Median age, years	54 *versus* 52	55 *versus* 57	60 *versus* 59	58 *versus* 56
Relapse	At 2 years, 38.9% *versus* 39.9%	At 2 years, 32.0% *versus* 40.0%	At 2 years, 33.0% *versus* 37.0%	At 3 years, 36.0% *versus* 38.0%
TRM	At 2 years, 14.7% *versus* 4.9%	At 2 years, 26.0% *versus* 4.0%	At 1 year 23% *versus* 16%	At 3 years, 19.0% *versus* 14.0%
Overall survival	At 2 years, 53.7% *versus* 72.0%	At 2 years, 51.0% *versus* 55.0%	At 2 years, 42.0% *versus* 47.0%	At 3 years, 48.0% *versus* 51.0%

consol, consolidation; RIC, reduced intensity conditioning; TRM, transplant-related mortality.

last chemotherapy showed better RFS compared with those undergoing alloSCT after 110 days (median 30 months *versus* 6 months, respectively, $p = 0.056$). For the consolidation group, patients undergoing alloSCT within 65 days of last chemotherapy showed better RFS compared with those undergoing alloSCT after 65 days (median not reached *versus* 31 months, respectively, $p = 0.078$). Although the difference did not reach statistical significance, this finding supports the use of bridging treatment when the expected time lapse between chemotherapy and alloSCT is long. There were more secondary AML patients in the no consolidation group, but the type of AML did not affect the RFS or OS (Table 3). A previous study from Ciftciler *et al.*[21] suggested two cycles of consolidation chemotherapy with high dose cytarabine before alloSCT with RIC conditioning. However, due to the small number of patients and changes in AML treatment over the course of the study period, we could not determine the optimal bridging consolidation cycles and dose.

Another concern regarding the bridging consolidation chemotherapy is the toxicity. Fortunately, however, there was no case of consolidation chemotherapy related mortality, thus the argument that consolidation chemotherapy may come with significant unnecessary morbidity and mortality does not apply here. Consolidation chemotherapy did not seem to exert negative effects on neutrophil and platelet engraftment, infection rates, or acute GVHD incidence. On the other hand, patients undergoing consolidation chemotherapy showed trends towards a more severe degree of chronic GVHD (Table 2). Whether this is due to pre-transplant tissue damage and inflammation caused by higher dose of chemotherapy or due to transplant-related factors such as donors and conditioning cannot be determined. However, more vigilant monitoring is recommended based on our results.

One of the most obvious limitations of this study is the retrospective nature. There is the innate selection bias as patients who experienced early relapse or treatment related mortality prior to a planned alloSCT were excluded. Another major pitfall is the lack of standardized MRD information. Neither of the centers routinely perform MRD using multiparameter flow cytometry, thus MRD information was limited to those with genetic mutations trackable by real-time quantitative PCR. There were nine patients harboring *FLT3-ITD* mutation but since all but two of them underwent consolidation chemotherapy prior to

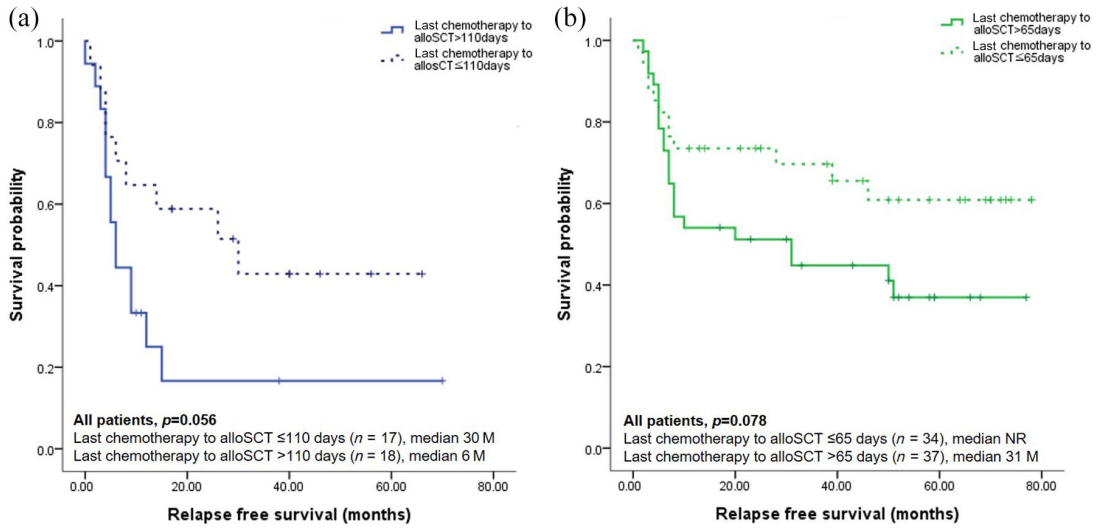

Figure 2. (a) No consolidation group, relapse free survival between patients undergoing allogeneic stem cell transplantation (alloSCT) within 110 days of last chemotherapy *versus* those undergoing alloSCT after 100 days. (b) Consolidation group, relapse free survival between patients undergoing alloSCT within 65 days of last chemotherapy *versus* those undergoing alloSCT after 65 days.
M, months; NR, not reached.

alloSCT, comparative analysis was not possible. All of them were *FLT3-ITD* negative at the time of alloSCT. There were seven patients harboring *NPM1* mutation, but since all but one of them underwent consolidation chemotherapy prior to alloSCT, survival comparison could not be made. There were 15 patients harboring *RUNX1-RUNX1T1*, six in no consolidation group *versus* nine in the consolidation group. There were no differences between the two groups with regard to RFS (median not reached in both groups, $p=0.520$) or OS (median not reached in both groups, $p=0.274$). The role of MRD remains an important issue, thus it should be addressed in future studies.

Conclusions

The exposure to consolidation chemotherapy in CR1 prior to alloSCT with RIC conditioning did not negatively impact the outcomes in Korean AML patients, for whom a suitable donor is rarely immediately available. Therefore, post-remission consolidation chemotherapy is a reasonable option if required. This study also shows that AML treatment and outcomes are influenced by regional health regulation and ethnic disparities in real-world practice outside of the clinical trials setting. With nuclear family becoming the dominant family unit, accessibility to "immediately suitable" donors is becoming more difficult. In the absence of established guidelines, our findings provide further understanding for physicians to infer decision-making nuances regarding an appropriate and realistic AML treatment sequence.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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