TRANSFUSION MEDICINE

Original article

A pilot randomized study for optimal red cell transfusion in acute myeloid leukemia patients with intensive chemotherapy

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Background - Although blood transfusion is fundamental throughout the course of hematologic malignancies, acute myeloid leukemia (AML) patients requiring intensive chemotherapy are left at the edges of patient blood management programs because current guidelines do not have established recommendations for red blood cell (RBC) transfusion threshold in patients treated for hematological disorders with anemia and accompanied severe thrombocytopenia. To provide answers for the trigger and doses of ideal RBC transfusion in such situation, we conducted this prospective randomized trial.

Materials and methods - Newly diagnosed non-acute promyelocytic AML patients undergoing chemotherapy were considered eligible for enrollment. Patients were randomized into 4 groups using a 2 by 2 factorial design, according to the RBC transfusion trigger (hemoglobin [Hb], 7 *vs* 8 g/dL) and the number of units per transfusion episode (quantity, single *vs* double-unit).

Results - Initially 91 patients were randomized into 4 groups, but the protocol adherence rate was 90.1%. Hb trigger did not affect the amount of RBC transfusion required during treatment. Patients receiving RBC transfusion at Hb <7 g/dL used a median of 4 units of RBC (range 0-12), and those receiving transfusion at Hb <8 g/dL also used a median of 4 units of RBC (range 0-24) (p=0.305). The number of RBC units per transfusion did not affect the total amount of RBC transfusion required during treatment. AML treatment outcomes and bleeding events did not differ across the 4 groups.

Discussion - This study demonstrated the feasibility for restrictive RBC transfusion (Hb <7 g/dL, RBC 1 unit) in AML patients undergoing chemotherapy, regardless of chemotherapy intensity.

Keywords: *red blood cell, transfusion, acute myeloid leukemia, chemotherapy.*

INTRODUCTION

Red blood cell (RBC) transfusions are widely used to treat anemia or bleeding in diverse medical circumstances. Despite cumulating scientific evidence and guidelines that favor restrictive RBC transfusion strategies[1-9], transfusion practices still vary across the globe with an increasing number of centers implementing patient blood management (PBM) for optimal blood use. In the past 2 years, PBM programs gained more attention with the

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spread of COVID-19. This unprecedented situation has impacted the community, hospitals, transfusion services and blood collection facilities. To mitigate the risk of blood inventory shortages, many institutions lowered the hemoglobin (Hb) threshold of RBC transfusion to 7 g/dL[10,11].

Although blood transfusion is fundamental throughout the course of hematologic malignancy management and cellular blood components are dominantly used for these patients in high-income countries[12], evidence is too limited for a solid consensus[13-15]. Specifically, in the Cochrane analysis[15] looking at the differences between liberal versus conservative RBC triggers in myelodysplastic syndrome, aplastic anemia, and bone marrow failure syndromes, little could be concluded. More recent randomized pilot study[13] in acute leukemias showed that fatigue and bleeding of any grade were similar between conservative versus liberal RBC transfusion arms, but this study alone was not enough to provide concrete answers for the trigger and doses of ideal RBC transfusion. Already left at the edges of recommendations as such, the agonizing battle with blood products scarcity during COVID-19 pandemic hit patients with hematologic malignancy especially hard. Acute myeloid leukemia (AML) patients requiring intensive chemotherapy epitomize such precarious situation, especially because these patients usually deal with both anemia and thrombocytopenia, but the AABB does not have specific recommendations for a transfusion threshold in patients treated for hematological disorders nor for those with severe thrombocytopenia who are at risk of bleeding[5]. Since red blood cells increase platelet responsiveness[16,17], some physicians have been advocating higher Hb thresholds in AML patients with thrombocytopenia who are at risk of bleeding. On the other hand, others prefer stringent use of blood products because of alloimmunization risk and its possible toll on subsequent bone marrow transplant outcomes[18].

To close the gaps in inconsistencies of RBC transfusion care, we conducted this pilot randomized prospective trial focusing on newly diagnosed AML patients undergoing intensive chemotherapy.

MATERIALS AND METHODS

Design overview

This was a randomized prospective trial of newly diagnosed AML patients diagnosed and treated at a single center between September 2018 and February 2022. **Figure 1** outlines the study design. Patients were randomized into 4 groups using a 2 by 2 factorial design, according to the RBC transfusion trigger (i.e, Hb trigger

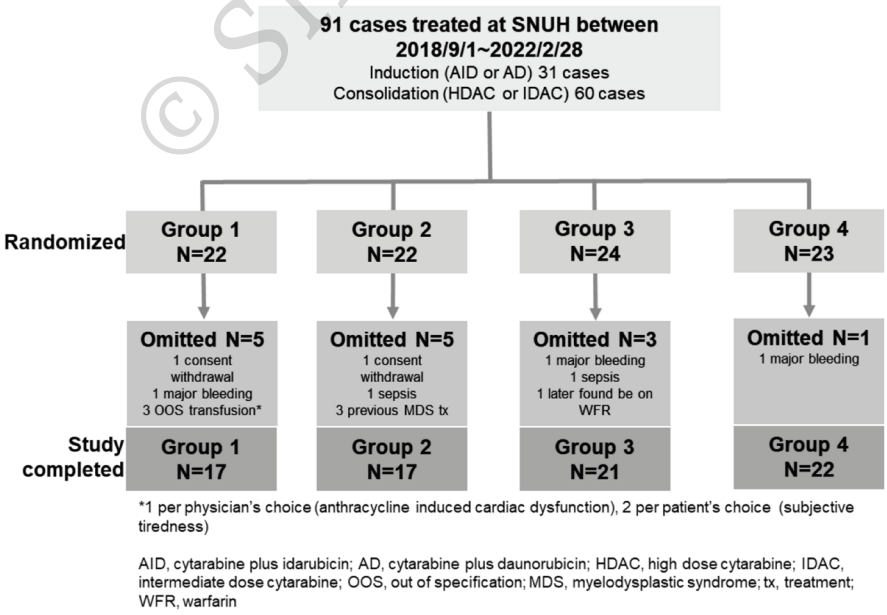

Figure 1 - CONSORT diagram

7 *vs* 8 g/dL) and the number of units per transfusion episode (i.e, quantity, single *vs* double-unit). In case patients became hemodynamically unstable due to major bleeding, severe infection, ischemic heart disease, stroke or any other compromising conditions, liberal RBC transfusion was allowed regardless of the grouping to ensure the patients' safety. Platelet transfusion was done liberally to avoid bleeding symptom with trigger platelet count of 10 to 20×10^9/L.

Study population

Newly diagnosed non-acute promyelocytic leukemia AML patients aged between 19 to 70 years old, undergoing cytarabine ± anthracycline chemotherapy were considered eligible for enrollment. The diagnosis of AML was made according to the WHO Classification of Hematopoietic Neoplasms[19,20]. For induction therapy, either idarubicin 12 mg/m^2 for 3 days plus cytarabine 100 mg/m^2 for 7 days or daunorubicin 60 to 90 mg/m^2 for 3 days plus cytarabine 100 mg/m^2 for 7 days were used. For FMS-related tyrosine kinase 3 (*FLT3*) positive patients, midostaurin use was allowed. For consolidation therapy, high dose cytarabine (HDAC, 3 g/m^2 twice daily over 3 days) or intermediate dose cytarabine (IDAC, 2 g/m^2 twice daily over 3 days), were used. Patients were stratified according to chemotherapy (i.e., induction versus HDAC versus IDAC).

Patients with biphenotypic leukemias, relapsed/refractory disease or treatment history for previous hematologic disease were excluded. Those (1) with history of transfusion related adverse events, (2) on anticoagulation or antiplatelet therapy, (3) active bleeding, (4) with history of major bleeding events according to International Society on Thrombosis and Hemostasis (ISTH)[21] and (4) with a cardio-pulmonary disease requiring higher Hb target levels per attending physician's decision, were also excluded. For newly diagnosed AML patients presenting with Hb <7 g/dL, anemia correction with transfusion to reach Hb ≥8 g/dL was allowed before enrollment. For patients undergoing consolidation, only those with baseline Hb ≥ 8 g/dL were enrolled.

Blood products

Blood components were manufactured and supplied by the Korean Red Cross. Only prestorage leukocyte reduced RBCs were used for transfusion in this study. In brief, 400 mL of whole blood was collected into quadruple blood bags containing citrate phosphate dextrose (CPD) anticoagulant and saline, adenine, glucose, mannitol (SAG-M) additive solution. After a light-spin, RBCs in CPD anticoagulant were separated from platelet-rich plasma, mixed with SAG-M, and then passed through the leukocyte reduction filter. The volume of the final product was 300±30 mL, and the hematocrit was 60±10%. All RBCs used for this study were irradiated by a standard blood bank gamma irradiator before being issued to the patients. Single donor apheresis platelets containing over 3.0×10^{11} platelets per unit were mainly used as the standard therapeutic dose for adults, but a set of 6 random donor platelets were alternatively used according to the supply availability. All platelet components were leukoreduced and irradiated.

Study endpoints

The primary objective of this study was to compare the differences in the number of RBC units per case across the groups. For patients undergoing induction, the RBC units were counted from the chemotherapy start date to first response evaluation date, regardless of remission achievement. For patients undergoing consolidation, the RBC units were counted from the chemotherapy start date to discharge date. Secondary outcomes included newly developed major bleeding and clinical relevant non-major bleeding (CRNM) during treatment according to the ISTH[21], AML treatment outcomes according to the International Working Group[22,23], platelet transfusion, RBC transfusion adherence rates (events of out of specification transfusion), transfusion related adverse events (AE)[24], and infection complications according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Neutrophil recovery was defined as an absolute neutrophil count (ANC) >0.5×10^9/L on 3 consecutive measurements. Platelet recovery was defined as 3 consecutive measurements of 20.0×10^9/L without transfusion.

Statistical analysis

Because the current study is an exploratory, pilot study to draw evidence of optimal RBC transfusion in patients with hematologic malignancy for future larger scale study, there was no calculated and designed sample size. Ninety to 100 patients were planned to be 1:1:1:1 randomized to each group. Fisher's exact test was used for nominal variables, and Mann-Whitney *U* test was used for continuous variables. For all statistical analyses of

effective variables, two-tailed tests were performed. P values of <0.05 were considered statistically significant. All data were analyzed using the Statistical Package for the Social Sciences software (IBM® SPSS® Statistics, version 25.0).

RESULTS

Patient enrollment

As shown in **Figure 1**, initially 91 patients were randomized into 4 groups. In group 1, 22 patients were randomized but five patients did not complete the study because one withdrew consent after randomization, one experienced major bleeding (gastrointestinal tract), two requested additional transfusion due to subjective tiredness, and one experienced anthracycline induced cardiac dysfunction thus Hb target was raised by the attending physician. In group 2, 22 patients were also randomized but five dropped out of the study because 1 withdrew consent after randomization, one suffered from vancomycin resistant enterococcus (VRE) pneumonia and *Enterococcus faecium* bacteremia with septic shock, and three were later found to have received chemotherapy for antecedent myelodysplastic syndrome from other hospitals. In group 3, 24 patients were initially randomized but three patients did not complete the study because one had major bleeding (gastrointestinal tract), one had *Acinetobacter junii* bacteremia with septic shock, and one was later found to be on warfarin treatment from another hospital for abdominal aortic aneurysm. Likewise, 23 patients were randomized to group 4 but one was omitted for major bleeding (gluteus muscle hematoma requiring embolization). At the end, 17 patients in group 1, 17 patients in group 2, 21 patients in group 3 and 22 patients in group 4 were able to complete the study. The baseline characteristics of all 91 randomized patients are presented in *Online Content*, **Table SI**.

The protocol adherence rate was calculated for patients who received transfusion according to the protocol regardless of study completion. Overall, the protocol adherence rate was 90.1% as shown in *Online Content*, **Table SII**.

Baseline characteristics

The baseline characteristics of the 77 patients who were able to complete the study are shown in **Table I**. There were no significant differences across the 4 groups with regards to the age at study enrollment, sex, AML type, line of therapy and baseline laboratory findings. However, group 3 contained the highest percentage of patients undergoing induction, and accordingly associated with higher baseline WBC count.

The patients were then grouped according to Hb trigger (Hb 7 *vs* 8 g/dL; p_1-values) and quantity (RBC single *vs* double-unit; p_2-values) and compared. Again, no differences were noted between the groups.

Table I - *Baseline characteristics of patients who completed the study*

No. (%)	Total	Group 1 Hb <7 g/dL RBC 1 unit	Group 2 Hb <7 g/dL RBC 2 units	Group 3 Hb <8 g/dL RBC 1 unit	Group 4 Hb <8 g/dL RBC 2 units	p_0 Grp 1 *vs* 2 *vs* 3 *vs* 4	$p_{1\,(Hb)}$ Grp 1+2 *vs* Grp 3+4	$p_{2\,(RBC)}$ Grp 1+3 *vs* Grp 2+4
Total No. of patients	77	17	17	21	22	NA	NA	NA
Age, years, median (range)	56 (23-69)	57 (37-66)	59 (28-66)	50 (23-68)	56 (24-69)	0.293	0.370	0.380
Sex, male	47 (61.0)	9 (52.9)	10 (58.8)	13 (61.9)	15 (68.2)	0.806	0.409	0.577
AML type						0.947	0.847	0.861
de novo	72 (93.5)	16 (94.1)	16 (94.1)	20 (95.2)	20 (90.9)			
Secondary	5 (6.5)	1 (5.9)	1 (5.9)	1 (4.8)	2 (9.1)			
Treatment						0.964	0.827	0.665
Induction	24 (31.2)	4 (23.5)	5 (29.4)	8 (38.1)	7 (31.8)			
Consolidation #1	31 (40.3)	8 (47.1)	7 (41.2)	7 (33.3)	9 (40.9)			
Consolidation #2	12 (15.6)	2 (11.8)	4 (23.5)	3 (14.3)	3 (13.6)			
Consolidation #3	10 (13.0)	3 (17.6)	1 (5.9)	3 (14.3)	3 (13.6)			
Baseline lab findings*								
WBC, 10^3/µL	9.6±12.9	8.0±9.2	7.1±8.0	16.0±19.5	6.5±8.1	0.058	0.224	0.055
Hemoglobin, g/dL	10.4±1.7	10.7±1.7	9.9±1.4	10.7±1.6	10.4±1.8	0.505	0.523	0.211
Platelet, 10^3/µL	126.7±74.7	123.2±82.1	117.2±66.4	128.5±78.5	135.1±75.2	0.899	0.497	0.947

*Data presented as mean ± standard deviation. Hb: hemoglobin; RBC: red blood cell; NA: not applicable; Grp: group; AML: acute myeloid leukemia; lab: laboratory; SD: standard deviation; WBC: white blood cell.

Transfusion outcomes

Transfusion outcomes of the 77 patients who completed the study are shown in **Table II-IV**. As a whole, patients received a median (Q_1-Q_3) of 4 (2-6) units of RBCs. Although not statistically significant, the median (Q_1-Q_3) of RBC units used for transfusion during treatment was the lowest in group 1. Among 257 RBC transfusion episodes, AE occurred in 15 (5.8%) episodes for 13 (16.9%) patients. There were no incidents or near misses, and all the AE were adverse reactions. There were 14 events of allergic reactions, and another event of allergic reaction accompanied by febrile non hemolytic transfusion reaction. There were no cases of fatal adverse reactions such as anaphylaxis, acute hemolysis, or transfusion-associated acute lung injury.

Hb trigger did not affect the amount of RBC transfusion required during treatment (**Table III**). Patients receiving RBC transfusion at Hb <7 g/dL (groups 1+2) used a median (Q_1-Q_3) of 4 (2-6) units of RBC, and those receiving transfusion at Hb <8 g/dL (groups 3+4) also used a median

Table II - *Transfusion outcomes of the patients who completed the study*

	Total	Group 1 Hb <7 g/dL RBC 1 unit	Group 2 Hb <7 g/dL RBC 2 units	Group 3 Hb <8 g/dL RBC 1 unit	Group 4 Hb <8 g/dL RBC 2 units	P_0 Grp 1 *vs* 2 *vs* 3 *vs* 4
Total No. of patients	77	17	17	21	22	NA
RBC transfusion, mL Median (range) Mean (standard deviation)	 1,600 (0-9,600) 1,843 (1,450)	 1,200 (0-2,800) 1,202 (883)	 1,600 (0-4,800) 2118 (314)	 1,600 (0-4,800) 1,821 (1,202)	 1,600 (400-9,600) 2,145 (1,969)	0.181
RBC transfusion, units Median (range) IQR (Q1, Q3) Mean (standard deviation)	 4 (0-24) 4 (2, 6) 4.6 (3.6)	 3 (0-7) 4 (1, 3) 3 (2.2)	 4 (0-12) 4 (3.5, 7.5) 5.3 (3.2)	 4 (0-12) 4 (2.5, 6.5) 4.6 (3.0)	 4 (1-24) 4.25 (2, 6.25) 5.4 (4.9)	0.180
RBC transfusion, episodes, median (range)	3 (0-12)	3 (0-7)	2 (0-6)	4 (0-12)	2 (1-12)	0.064
RBC transfusion related AE, any, No. (%)	13 (16.9)	3 (17.6)	1 (5.9)	3 (14.3)	6 (27.3)	0.352
Plt transfusion, mL Median (range) Mean (standard deviation)	 2,910 (250-20,380) 3,734 (3,685)	 2,820 (500-9,200) 3,014 (2,657)	 3,900 (750-203,80) 5,559 (1,201)	 2,670 (250-8,550) 3,258 (2,263)	 2,210 (500-18,960) 3,335 (4084)	0.142
Plt transfusion, episodes, median (range)	5 (1-25)	6 (2-10)	7 (2-21)	5 (1-13)	4.5 (2-25)	0.268

NA: not applicable; Hb: hemoglobin; RBC: red blood cell; Grp: group; IQR: interquartile range; Q1: first quartile (25th percentile); Q3: third quartile (75th percentile); AE: adverse events; Plt: platelet.

Table III - *Transfusion outcomes of the patients who completed the study, per hemoglobin trigger*

	Total No.=77	Group 1 + 2 Hb <7 g/dL No.=34	Group 3+ 4 Hb <8 g/dL No.=43	p_1 Grp 1+2 *vs* Grp 3+4
RBC transfusion, mL Median (range) Mean (standard deviation)	 1,600 (0-9,600) 1,843 (1,450)	 1,600 (0-4,800) 1,660 (1,186)	 1,600 (0-9,600) 1,987 (1629)	0.312
RBC transfusion, units Median (range) IQR (Q1, Q3) Mean (standard deviation)	 4 (0-24) 4 (2, 6) 4.6 (3.6)	 4 (0-12) 4 (2, 6) 4.1 (3.0)	 4 (0-24) 4 (2,6) 5.0 (4.0)	0.305
RBC transfusion, episodes, median (range)	3 (0-12)	2.5 (0-7)	3 (0-12)	0.171
RBC transfusion related AE, any, No. (%)	13 (16.9)	4 (11.8)	9 (20.9)	0.286
Plt transfusion, mL Median (range) Mean (standard deviation)	 2,910 (250-20,380) 3,734 (3,685)	 3,460 (500-20,380) 4,287 (4123)	 2,670 (250-18,960) 3,297 (3,283)	0.258
Plt transfusion, episodes, median (range)	5 (1-25)	6 (2-21)	5 (1-25)	0.256

Hb: hemoglobin; RBC: red blood cell ; Grp: group; IQR: interquartile range; Q1: first quartile (25th percentile); Q3: third quartile (75th percentile); AE: adverse events; Plt: platelet.

(Q_1-Q_3) of 4 (2-6) units of RBC (p_1=0.305). The AE rates associated with RBC transfusion were similar between the two groups (p_1=0.286). As for platelet transfusion, there were no differences regarding transfusion frequency (p_1=0.256) or amount (p_1=0.258) between the 2 groups as shown in **Table III**. These findings were replicated in the cohort of all randomized patients (*Online Content*, **Table SIII**).

Although not statistically significant (p_2=0.076), the median (Q_1-Q_3) of RBC units for patients receiving 1 unit of RBC per transfusion episode (groups 1+3; 3.25 [2-5.25]) was lower than that of patients receiving 2 units of RBCs (groups 2+4; 5 [2-7]) (**Table IV**). Patients receiving 1 RBC unit per transfusion episode required transfusion more frequently (p_2=0.045). There were no differences in platelet transfusion frequency (p_2=0.370) or amount (p_2=0.170) between the two groups. These trends were also noted in the cohort of all randomized patients (*Online Content*, **Table SIV**).

AML treatment outcomes

AML treatment outcomes are shown in **Tables V** and *Online Content*, **Table SV**. Overall, treatment outcomes did not differ across the 4 groups. Group 3 had the lowest treatment success rate at 85.7% (18/21) and group 1 showed the best response rate, but the difference did not show statistical significance. The median time to neutrophil recovery was 14.5 days (range 0-86) and to platelet recovery was 23 days (12-127 days). There were 30 cases (39.0%) of documented infection, 2 of which were fungal origin.

Table IV - *Transfusion outcomes of the patients who completed the study, per transfused RBC quantity*

	Total No.=77	Group 1+3 RBC 1 unit No.=38	Group 2+4 RBC 2 units No.=39	P_2 Grp 1+3 *vs* Grp 2+4
RBC transfusion, mL				0.074
Median (range)	1,600 (0-9,600)	1,225 (0-4,800)	1,600 (0-9,600)	
Mean (standard deviation)	1,843 (1,450)	1,544 (1,102)	2,133 (1,688)	
RBC transfusion, units				0.076
Median (range)	4 (0-24)	3 (0-12)	4 (0-24)	
IQR (Q1, Q3)	4 (2, 6)	3.25 (2, 5.25)	5 (2, 7)	
Mean (standard deviation)	4.6 (3.6)	3.9 (2.8)	5.3 (4.2)	
RBC transfusion, episodes, median (range)	3 (0-12)	3.5 (0-12)	2 (0-12)	0.045
RBC transfusion related AE, any, No. (%)	13 (16.9)	6 (15.8)	7 (17.9)	0.800
Plt transfusion, mL				0.170
Median (range)	2,910 (250-20,380)	2,745 (250-9,200)	3,000 (500-20,380)	
Mean (standard deviation)	3,734 (3,685)	3,149 (2,416)	4,305 (4,561)	
Plt transfusion, episodes, median (range)	5 (1-25)	5 (1-13)	5 (2-25)	0.370

Hb: hemoglobin; RBC: red blood cell; Grp: group; IQR: interquartile range; Q1: first quartile (25th percentile); Q3: third quartile (75th percentile); AE: adverse events; Plt: platelet .

Table V - *AML treatment outcomes of the patients who completed the study*

	Total	Group 1 Hb <7 g/dL RBC 1 unit	Group 2 Hb <7 g/dL RBC 2 units	Group 3 Hb <8 g/dL RBC 1 unit	Group 4 Hb <8 g/dL RBC 2 units	p_0 Grp 1 *vs* 2 *vs* 3 *vs* 4	p_1 Grp 1+2 *vs* Grp 3+4	p_2 Grp 1+3 *vs* Grp 2+4
Achieved treatment goal	68 (88.3)	16 (94.1)	15 (88.2)	18 (85.7)	19 (86.4)	0.856	0.487	0.754
Length of inpatient stay, days	26 (16-105)	25 (16-42)	27 (17-105)	26 (20-42)	27 (18-44)	0.245	0.393	0.169
Time to neutrophil recovery, days	14.5 (0-86)	14 (2-72)	15 (2-84)	16 (0-86)	12 (2-66)	0.929	0.925	0.717
Time to platelet recovery, days	23 (12-127)	26 (17-48)	31 (16-127)	22 (15-98)	21 (12-37)	0.067	0.140	0.870
Documented infection	30 (39.0)	7 (41.2)	6 (35.3)	6 (28.6)	11 (50.0)	0.277	0.908	0.399
Febrile neutropenia	59 (76.6)	13 (76.5)	14 (82.4)	14 (66.7)	18 (81.8)	0.078	0.607	0.254

*Data are reported as frequency (%) or median (range). AML: acute myeloid leukemia; Hb: hemoglobin; RBC: red blood cell; Grp: group.

As mentioned above, there were 3 cases of major bleeding: 2 cases of gastrointestinal bleeding and 1 case of muscle hematoma, all requiring interventions (*Online Content*, **Table SVI**). There was 1 case of CRNM: the patient had grade 1 epistaxis that did not require intervention. There were 4 deaths during the follow-up: 2 due to uncontrolled AML and 2 due to infection. Three out of the 4 patients demised during induction.

DISCUSSION

Through this study, we sought to obtain evidence for the establishment of an optimal RBC transfusion strategy in patients treated for hematological disorder. The importance of this trial lies in that 1) we conducted a randomized prospective trial for patients who are left outside the current guidelines, and performed it successfully with a protocol adherence rate of >90%; 2) we showed lower Hb trigger (Hb <7 g/dL) is judicious even in hematologic malignancy patients undergoing chemotherapy; 3) we also showed single unit transfusion is not inferior to double unit transfusion; and 4) we demonstrated that strict use of RBC products is not associated with increased platelet transfusion requirements nor increased risk of bleeding in patients with marked thrombocytopenia.

Restrictive versus liberal transfusion has been a longstanding enigma for patients with cardiac disease. This problem was eloquently addressed in Mazer *et al.*'s[9] open-label trial, which showed that a restrictive strategy regarding RBC transfusion was non-inferior to a liberal strategy with respect to the composite outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis, with less blood transfused for patients undergoing cardiac surgery. Encouraged by such results, Tay *et al.*[25] carried out a randomized trial to shed light on optimal PBM in the hematologic malignancies setting, as patients with hematologic malignancies constitute another pillar of the optimal transfusion conundrum. In this study, patients undergoing hematopoietic stem cell transplantation (HSCT) for hematologic malignancies were randomly assigned to restrictive transfusion (Hb trigger <7 g/dL) versus liberal transfusion (Hb trigger <9 g/dL) groups. Clinical outcomes were similar between the 2 groups, but patients in the liberal group ended up using more RBC units (p=0.0004).

Conducted among slightly different but more uniform set of population, our study resonates Tay *et al.*'s[14, 25] study and consolidates Hb <7 g/dL as the adequate trigger for RBC transfusion. In our study, we chose to compare Hb <7 *vs* <8 g/dL because we sought to investigate the feasibility and safety of implementing relatively low Hb triggers even in patients with significant thrombocytopenia. From our results, it is quite evident that Hb triggers of <7 g/dL and 8 <g/dL can both be similarly used without compromising treatment outcomes. On the other hand, we saw that the patients receiving double-unit transfusion had a tendency to use more RBC products (p_2=0.076). This latter finding advocates the use of single-unit RBC transfusion, as in the absence of obvious benefits, more exposure to blood products only leads to potentially higher chances of alloimmunization and other adverse transfusion reactions. Moreover, although the median number of RBC units used in each group was 4, group 1 showed the lowest values of Q_1 and Q_3 (**Table II**), indicating that the lowest number of RBC transfusion can be achieved by combining Hb trigger of 7 g/dL and single-unit RBC transfusion.

Also, chemotherapy intensity did not affect the RBC transfusion requirement. We stratified the patients undergoing consolidation according to the intensity of the chemotherapy (i.e., HDAC versus IDAC). As shown in *Online Content* **Table SIV**, the patients were randomized evenly as expected. There were no differences between the 2 groups with regards to RBC transfusion quantity and frequency. The platelet transfusion quantity and frequency also did not differ between the 2 groups.

It is interesting to note that there were 2 patients in group 1 (Hb <7 g/dL, RBC 1 unit) who "wanted" additional RBC transfusion for subjective "tiredness" (*Online Content*, **Table SII**). This was an open-label trial, thus these patients were aware of their randomization results along with their daily CBC. Since it is difficult to objectify one's degree of fatigue, we cannot say if additional RBC transfusion (therefore protocol violation) was a "medical" decision. Furthermore, both of the patients were enrolled during consolidation: they were used to being transfused previously when Hb <8 g/dL during induction chemotherapy, so it is possible that their prior experience led to prejudice and anxiety regarding to changes in the transfusion policy. We do not think that this particular finding threatens

Hb <7 g/dL as the legitimate trigger to initiate RBC transfusion in AML patients undergoing chemotherapy. Nevertheless, because this kind of clinical situation was only observed in group 1, it is important that patients should be closely followed up for adjustments when adopting restrictive transfusion policies.

Limitation of this study is the relatively small number of patients enrolled. Results of this study need to be validated in larger scale, more definitive transfusion trials in the future. Notwithstanding, we believe as our data are closely representative of the real-world situations, our results can be easily translated and implemented into clinics to guide through nuanced treatment decisions.

CONCLUSIONS

In conclusion, this study demonstrated the feasibility for restrictive RBC transfusion in AML patients undergoing chemotherapy. For stable patients without significant medical history, RBC transfusion can be safely initiated when Hb <7 g/dL and 1 unit per episode is adequate regardless of chemotherapy intensity. Since infection and bleeding complications occur more often during the induction, these patients should be more closely followed-up for additional RBC transfusion requirements.

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ETHICAL CONSIDERATION

The study was conducted ethically, with all study procedures being in accordance with the requirements of the World Medical Association's Declaration of Helsinki. This study was reviewed and approved by the Institutional Review Board at Seoul National University Hospital (H-1807-168-962). Written informed consent was obtained from all patients before participating in any study-related procedure. This trial was registered at the Clinical Research Information Service Identifier (KCT00007596) found at http://cris.nih.go.kr.

AUTHORS' CONTRIBUTIONS

JH and HK created the concept and design; all Authors provided the study materials or patients; JMB and JH collected and assembled the data; and all Authors contributed to the writing and the final approval of the manuscript.

The Authors declare no conflicts of interest.

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