Medical Science and Discovery
ISSN: 2148-6832

FLAMSA vs BU-FLU in patients undergoing allogeneic stem cell transplantation for acute leukemia and myelodysplastic syndrome

Ahmet Sarıcı[1], Mehmet Ali Erkurt[1]*, İrfan Kuku[1], Selim Gök[2], Ömer Faruk Bahçecioğlu[2], Soykan Biçim[1], İlhami Berber[1], Emin Kaya[1], Mustafa Özgül[1]

1 Dept. of Adult Hematology, Inonu University, Turgut Özal Medical Center, Malatya, TR
2 Dept. of Clinical Pharmacy, Inonu University, Faculty of Pharmacy, Malatya, TR

*** Corresponding Author:** Mehmet Ali Erkurt **E-mail:** erkurtali@hotmail.com

ABSTRACT

Objective: Similar to other regimens, the specific role of fludarabine-amsacrine-cytarabine (FLAMSA) regimen before allogeneic transplantation is still unclear. We compared the results of patients who received either the FLAMSA regimen or the busulfan-fludarabine (BuFlu) regimen prior to allogeneic transplantation.

Materials and Methods: Patients who underwent allogeneic transplantation and who administered reduced-intensity conditioning (RIC) regimens before transplantation were included in to the this study. Patients were divided into two groups (BuFlu and FLAMSA) according to the applied RIC regimens.

Results: A total of 37 allogeneic transplant patients (13 FLAMSA, 24 BuFlu patients) were included in this study. The time between diagnosis and transplantation was shorter in the patients in the FLAMSA group compared to the patients in the BuFlu group ($p<0.001$). Although platelet engraftment time was shorter in the FLAMSA group than in the busulfan-fludarabine group ($p=0.048$), the neutrophil engraftment time and adverse events were similar in the two groups (all $p>0.05$). The estimated median disease-free survival of the patients in the FLAMSA group was 7.2 months, while it was 3.7 months in the busulfan-fludarabine group ($p=0.778$). Similarly, the estimated median overall survival of the patients in the FLAMSA group was 7.2 months, while 7 months in the BuFlu group ($p=0.815$).

Conclusion: BuFlu and FLAMSA are two alternative conditioning regimen options that provide similar efficacy, toxicity profile and survival as regimens used in allogeneic transplantation. The FLAMSA regimen may be an alternative to Bu-Flu as a priming regimen for allogeneic stem cell transplantation. Meta-analyzes should be performed to evaluate with more patients.

Keywords: Allogeneic stem cell transplantation; Busulfan; Flamsa; Acute leukemia; Myelodysplastic syndrome

Research Article

Received 04-05-2021

Accepted 27-05-2021

Available Online: 12-06-2021

Published 30-06-2021

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only potentially curative treatment for several hematological diseases. Reduced-intensity conditioning (RIC) regimens were created to decrease the adverse events related to the myeloablative conditioning (MAC) regimen, particularly in elderly and fragile patients (1). However, subsequent studies revealed that RIC regimens were remarkably associated with the risk of relapse (2). Although non-relapse mortality (NRM) appears to be lower with RIC regimens as compared to MAC regimens, since AML includes a group of chemosensitive diseases, increasing concerns that RIC preparative regimens may have a negative impact on the risk of relapse (3). The archetype RIC protocol comprises reduced-dose busulfan-fludarabine (BuFlu). Requested outcomes were obtained using a busulfan-based reduced conditioning regimen in myelodysplastic syndromes (MDS) or secondary acute myeloid leukemia (sAML) (4, 5). Afterward, the efficacy of different dose intensities of busulfan in the combination of fludarabine has also been compared in the trials (6, 7).

http://dx.doi.org/10.36472/msd.v8i6.545

In the early 2000s, alternative conditioning regimens have been developed (8). In the beginning, the combination of fludarabine, amsacrine, and cytarabine (FLAMSA) was adopted for high-risk MDS and AML patients to unite advanced anti-leukemic effect with the usefulnesses of RIC regimen (9, 10). Recently, in a study of 265 patients with intermediate or poor-risk AML patients using FLAMSA-RIC as a conditioning regimen before HSCT, promising outcomes with 2-year disease-free survival (DFS) of 52.8% and overall survival (OS) 56.1 were obtained (11). There are limited trials that comparing FLAMSA-RIC with other frequently utilised RIC regimens (12, 13). For this reason, we compared the results of AML-MDS and acute lymphoblastic leukaemia (ALL) patients who received either the FLAMSA regimen or the BuFlu regimen before transplantation.

MATERIAL and METHODS

Patients who underwent allogeneic HSCT between 01.01.2014 and 31.12.2020 due to the diagnosis of AML, ALL or MDS and who administered RIC regimens before transplantation were included in this study. RIC regimens were applied to the patients because of advanced age, presence of comorbidity or poor performance status. Patients were divided into two groups (BuFlu and FLAMSA) according to the applied RIC regimens. Information such as age, gender, diagnosis, donor types, used conditioning regimens, and lifespan of the patients were retrospectively analysed from electronic patient records. In addition, neutrophil engraftment (the first day when the neutrophil count was over 500/mm^3 for three consecutive days) and platelet engraftment times (the first day when the platelet count was around 20000/mm^3 for three consecutive days) of patients were calculated. Graft-versus-host disease (GVHD) and sinusoidal obstruction syndrome (SOS) diagnoses were made according to determined international criteria (14, 15). Adverse events due to BuFlu or FLAMSA conditioning regimens were defined and classified according to the Common Terminology Criteria for Adverse Events version 5.0.

The scheme of administration of the BuFlu regimen is as follows: fludarabine 30 mg/m2 intravenously daily between days -6 and -2, and busulfan 3.2 mg/kg intravenously daily on day -3 and -2.

The administration of the FLAMSA regimen is as follows: fludarabine 30 mg/m2 daily, cytarabine 2 g/m2 daily, amsacrine 100 mg/m2 daily. All drugs were administered intravenously for 4 days between -10 and -7 days. All patients were infused with peripheral blood-derived stem cells obtained from donors via G-CSF on day 0.

Our study was conducted under the ethical standards, and approval was obtained from the Inonu University Health Sciences non-interventional ethics committee before starting the study (decision no: 2021/1815).

Statistical analysis

Normality analysis of quantitative data such as age, the time between diagnosis and transplantation, and engraftment times was performed using the Shapiro-Wilk test. Independent samples t-test was used to compare the mean age between the BuFlu and FLAMSA groups, and the Mann-Whitney U test was used to compare other quantitative data. Chi-square test was used to compare categorical data such as gender, diagnosis, comorbidity and adverse event incidences between BuFlu and FLAMSA groups. A Log-rank test was performed to compare DFS and OS of patients who received BuFlu or FLAMSA as a regimen.

RESULTS

A total of 37 allogeneic transplant patients (13 FLAMSA, 24 BuFlu patients) were included in this study. The initial patient characteristics before transplantation are summarised in Table 1. All patients had a complete response to the treatments before allogeneic transplantation. The time between diagnosis and transplantation was shorter in the patients in the FLAMSA group compared to the patients in the BuFlu group ($p<0.001$).

Table 1. Initial characteristics of two groups who underwent allogeneic transplantation

	Busulfan-fludarabine (n=24)	FLAMSA (n=13)	p value
Age, mean±SD	58.1±7.4	54.6±8.5	0.199
Gender			
Male, n	19 (79.2%)	8 (61.5%)	0.275
Female, n	5 (20.8%)	5 (38.5%)	
Disease			
AML, n	17 (70.8%)	12 (92.3%)	0.272
ALL, n	3 (12.5%)	0 (0%)	0.637
MDS, n	4 (16.7%)	1 (7.7%)	0.631
Comorbidity			
Present, n	17 (70.8%)	5 (38.5%)	0.118
Absent, n	7 (29.2%)	8 (61.5%)	
ECOG performance scale			
1, n	3 (12.5%)	1 (7.6%)	1
2, n	17 (70.8%)	6 (46.2%)	0.261
3, n	4 (16.7%)	6 (46.2%)	0.123
Donor type			
MRD, n	19 (79.2%)	12 (92.3%)	0.394
MUD, n	5 (20.8%)	1 (7.7%)	
Time between diagnosis and transplantation, median (day)	40 (27-62)	41 (22-85)	0.345
Number of CD34+ cells given before transplantation, median	7.29x10^6/kg (5.11x10^6/kg-12.15x10^6/kg)	7.93x10^6/kg (4.6x10^6/kg-11.7x10^6/kg)	0.681

http://dx.doi.org/10.36472/msd.v8i6.545

The neutrophil engraftment times, platelet engraftment times, acute and chronic GVHD rates of the two groups, and adverse events in the early period after transplantation are given in table 2. None of the patients developed pulmonary or central nervous system toxicity. Although platelet engraftment time was shorter in the FLAMSA group than in the busulfan-fludarabine group (p=0.048), the neutrophil engraftment time, GVHD and SOS rates, and adverse events were similar in the two groups (all p>0.05).

Fifteen (62.5%) of the patients in the BuFlu group died after a median follow-up of 5.5 (1-48.8) months. Eight (61.5%) of the patients in the FLAMSA group died after a median follow-up of 7.2 (1-37.9) months. Although the median follow-up times of the two groups were different, no statistically significant difference was observed between the groups (p=0.448).

Of the patients in the BuFlu group, 5 (33.3%) died from infection, 3 (20%) from relapse, 6 (40%) from organ failure due to GVHD, and 1 (6.7%) from organ failure due to SOS. Of the patients in the FLAMSA group, 5 (62.5%) died from infection, 1 (12.5%)from GVHD-related organ failure and 2 (25%) from SOS-related organ failure.

The estimated median DFS of the patients in the FLAMSA group was 7.2 months, while it was 3.7 months in the busulfan-fludarabine group, but no statistically significant difference was observed between the groups (p=0.778) (Figure 1). Similarly, the estimated median OS of the patients in the FLAMSA group was 7.2 months, while it was 7 months in the BuFlu group, but no statistically significant difference was observed between the groups (p=0.815) (Figure 2).

Table 2: Comparison of the clinical outcomes and adverse events of the two groups

	Busulfan-fludarabine (n=24)	FLAMSA (n=13)	p value
Neutrophil engraftment time, median (day)	16 (11-21)	16 (11-20)	0.732
Platelet engraftment time, median (day)	15.5 (10-28)	13 (13-15)	0.048
Febrile neutropenia, n	17 (70.8%)	10 (76.9%)	1
CMV reactivation, n	14 (58.3%)	7 (53.8%)	1
BK virus reactivation, n	7 (29.2%)	5 (38.5%)	0.716
Creatinine elevation, n	3 (12.5%)	2 (15.4%)	1
Liver enzyme elevation, n	5 (20.8%)	3 (18.8%)	1
Arrhythmia, n	1 (4.2%)	0 (0%)	1
SOS, n	11 (45.8%)	6 (37.5%)	0.747
Acute GVHD, n	5 (20.8%)	1 (7.7%)	0.394
Chronic GVHD, n	3 (12.5%)	3 (23.1%)	0.643

CMV: Cytomegalovirus, **SOS:** Sinusoidal obstruction syndrome, **GVHD:** Graft versus host disease

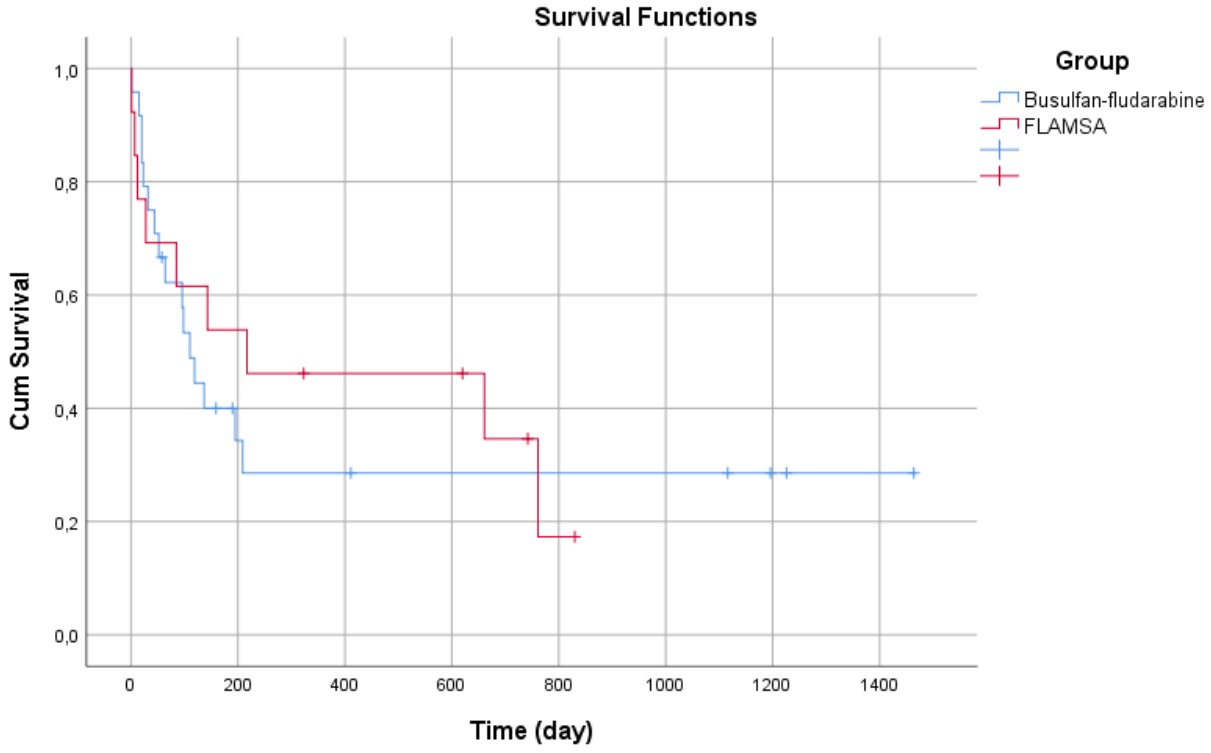

Figure 1: Disease-free survival of two groups

http://dx.doi.org/10.36472/msd.v8i6.545

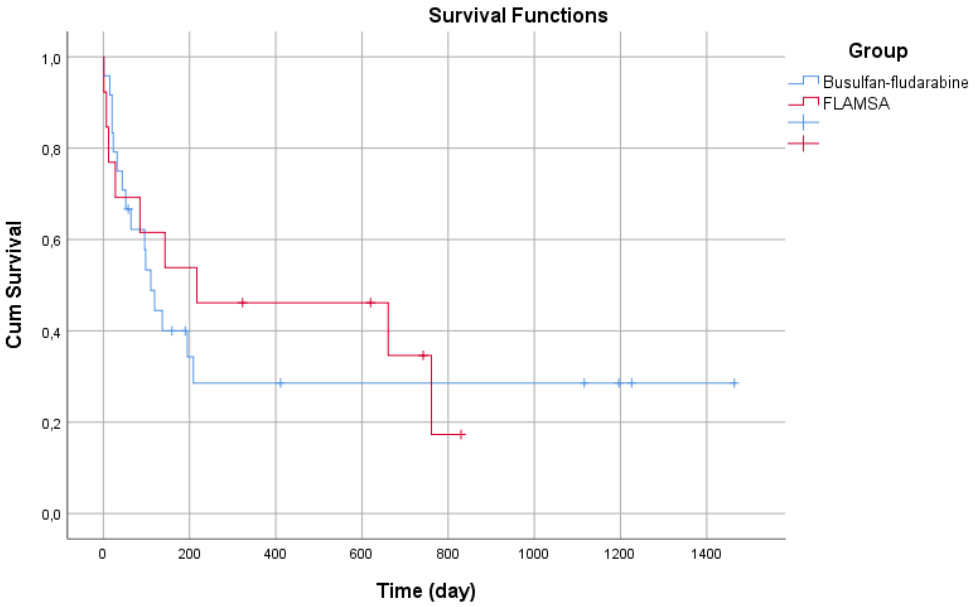

Figure 2. Overall survival of two groups

DISCUSSION

Data on the option of the conditioning regimen for patients who underwent allogeneic HSCT is limited (13). We compared the consequences of two frequently utilised conditioning regimens, namely BuFlu and FLAMSA regimen, in this study. No remarkable difference could be noticed in regard of DFS, OS, GVHD and SOS. When looking at engraftment times, the time to platelet engraftment was shorter in the FLAMSA group than in the busulfan-fludarabine group (p=0.048). However, there was no difference between the groups regarding the time to neutrophil engraftment (p=0.732). RIC protocols were emerged to decreasing adverse effects and making HSCT suitable for fragile patients. However, RIC protocols may not be sufficiently effective for patients with high-risk characteristics (**16**). FLAMSA-RIC was introduced in 2005 to overcome this restriction (**8**). There is increasing evidence from studies that non-relapse mortality is lower after RIC regimens than after MAC regimen (**17**). However, Scott et al. demonstrated that RIC regimens had been associated with a higher relapse rate (51% vs. 15.9%, respectively) compared with MAC regimens. Also, OS was remarkably better with MAC rather than RIC (**18**). The RIC conditioning regimen BuFlu has appropriate tolerability, and Rambaldi et al. demonstrated that even the BuFlu MAC regimen (Busulfan total dose: 12.8 mg/kg) associated with lower 1-year nonrelapse mortality rather than busulfan/cyclophosphamide (17.2% vs. 7.9%) According to the results of this trial, the BuFlu regimen can be selected when potent antileukemic activity is desired in groups for which consideration of adverse effects related to the treatment regimen is a priority (fragile and/or older patients) (**19**).

Chen et al. compared two different busulfan doses-BuFlu regimens (3.2 mg/kg vs 6.4 mg/kg) in AML and MDS patients. Two-year DFS and OS were also similar between both regimens. Two-year NRM rates were identical for both regimens (**6**). Shimoni et al. compared BuFlu MAC regimen (FB4, total busulfan dose 12.8 mg/kg) and BuFlu RIC regimen (FB2, total busulfan dose 6.4 mg/kg) in patients with AML and MDS. Shimoni et al. found that NRM and OS rates were similar in both conditioning regimens (**7**).

Heinicke et al. found that FLAMSA-TBI resulted in decreased relapse incidence, rather than BuFlu conditioning regimen, according to multivariate analysis (p=0.04). Also, a better DFS rate was observed FLAMSA-TBI regimen group compared with BuFlu group. In univariate analysis, NRM was 16.1%, 16.4%, and 26.7%, in the BuFlu, FLAMSA-Total body irradiation (FLAMSA-TBI), and FLAMSA-Bu groups, respectively (p<0.01). However, no statistically significant result was demonstrated between the groups regarding 2-year OS. The incidence of grade II-IV acute GVHD is higher in the BuFlu group than in the FLAMSA-TBI group (21.1% vs 26.9%, p<0.001). However, there was no difference between the groups in terms of the incidence of chronic GVHD (**12**).

In a study, treosulfan-based regimen compared to BuFlu plus thiotepa or FLAMSA-RIC as conditioning regimen for AML patients no difference was observed with regards to NRM, DFS, OS rates. Likewise, GVHD rates similar between all groups (**13**). These results contradict the argument that the development of chronic GVHD is associated with busulfan-induced prolonged dysfunction of anti-infectious immunity (**20**).

The limitations of this trial are related to the retrospective nature of the study. At the same time, the limited number of patients included in this trial is among the limitations of our research.

CONCLUSIONS

BuFlu and FLAMSA are two alternative conditioning regimen options that provide similar efficacy, toxicity profile and survival as regimens used in allogeneic transplantation. Conflicting results were obtained in trials comparing the endpoints (OS, PFS, NRM) of BuFlu and FLAMSA-RIC. Meta-analyzes should be performed to evaluate with more patients.

Author Contributions: AS, MAE, İK, SG, ÖFB, SB, İB, EK, MÖ: Study design and Data collection, Statistical Analyzes, **MAE:** Article writing and revisions.

Financial & competing interest's disclosure: The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee.

Conflict of interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Slavin S, Nagler A, Naparstek E, Kapelushnik Y, Aker M, Cividalli G, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Blood, The Journal of the American Society of Hematology. 1998;91(3):756-63.

2. Shimoni A, Nagler A. Allogeneic hematopoietic stem-cell transplantation in patients with acute myeloid leukemia in first complete remission: new answers for an old question. Leukemia. 2005;19(6):891-3.

3. Blaise D, Vey N, Faucher C, Mohty M. Current status of reduced intensity conditioning allogeneic stem cell transplantation for acute myeloid leukemia. Haematologica. 2007;92(4):533-41.

4. Ho AY, Pagliuca A, Kenyon M, Parker JE, Mijovic A, Devereux S, et al. Reduced-intensity allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome and acute myeloid leukemia with multilineage dysplasia using fludarabine, busulphan, and alemtuzumab (FBC) conditioning. Blood. 2004;104(6):1616-23.

5. Parker JE, Shafi T, Pagliuca A, Mijovic A, Devereux S, Potter M, et al. Allogeneic stem cell transplantation in the myelodysplastic syndromes: interim results of outcome following reduced-intensity conditioning compared with standard preparative regimens. British journal of haematology. 2002;119(1):144-54.

6. Chen Y-B, Coughlin E, Kennedy KF, Alyea EP, Armand P, Attar EC, et al. Busulfan dose intensity and outcomes in reduced-intensity allogeneic peripheral blood stem cell transplantation for myelodysplastic syndrome or acute myeloid leukemia. Biology of Blood and Marrow Transplantation. 2013;19(6):981-7.

7. Shimoni A, Hardan I, Shem-Tov N, Yeshurun M, Yerushalmi R, Avigdor A, et al. Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative versus reduced-intensity conditioning: the role of dose intensity. Leukemia. 2006;20(2):322-8.

8. Schmid C, Schleuning M, Ledderose G, Tischer J, Kolb H-J. Sequential regimen of chemotherapy, reduced-intensity conditioning for allogeneic stem-cell transplantation, and prophylactic donor lymphocyte transfusion in high-risk acute myeloid leukemia and myelodysplastic syndrome. Journal of Clinical Oncology. 2005;23(24):5675-87.

9. Schmid C, Schleuning M, Schwerdtfeger R, Hertenstein B, Mischak-Weissinger E, Bunjes D, et al. Long-term survival in refractory acute myeloid leukemia after sequential treatment with chemotherapy and reduced-intensity conditioning for allogeneic stem cell transplantation. Blood. 2006;108(3):1092-9.

10. Schmid C, Schleuning M, Hentrich M, Markl G, Gerbitz A, Tischer J, et al. High antileukemic efficacy of an intermediate intensity conditioning regimen for allogeneic stem cell transplantation in patients with high-risk acute myeloid leukemia in first complete remission. Bone marrow transplantation. 2008;41(8):721-7.

11. Malard F, Labopin M, Stuhler G, Bittenbring J, Ganser A, Tischer J, et al. Sequential intensified conditioning regimen allogeneic hematopoietic stem cell transplantation in adult patients with intermediate-or high-risk acute myeloid leukemia in complete remission: a study from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Biology of Blood and Marrow Transplantation. 2017;23(2):278-84.

12. Heinicke T, Labopin M, Schmid C, Polge E, Socié G, Blaise D, et al. Reduced Relapse Incidence with FLAMSA–RIC Compared with Busulfan/Fludarabine for Acute Myelogenous Leukemia Patients in First or Second Complete Remission: A Study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Biology of Blood and Marrow Transplantation. 2018;24(11):2224-32.

13. Saraceni F, Labopin M, Brecht A, Kröger N, Eder M, Tischer J, et al. Fludarabine-treosulfan compared to thiotepa-busulfan-fludarabine or FLAMSA as conditioning regimen for patients with primary refractory or relapsed acute myeloid leukemia: a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). Journal of hematology & oncology. 2019;12(1):1-10.

14. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biology of blood and marrow transplantation. 2005;11(12):945-56.

15. Mohty M, Malard F, Abecassis M, Aerts E, Alaskar A, Aljurf M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. Bone marrow transplantation. 2016;51(7):906-12.

16. Owattanapanich W, Ungprasert P, Wais V, Kungwankiattichai S, Bunjes D, Kuchenbauer F. FLAMSA-RIC for Stem Cell Transplantation in Patients with Acute Myeloid Leukemia and Myelodysplastic Syndromes: A Systematic Review and Meta-Analysis. Journal of clinical medicine. 2019;8(9):1437.

17. Diaconescu R, Flowers CR, Storer B, Sorror ML, Maris MB, Maloney DG, et al. Morbidity and mortality with nonmyeloablative compared with myeloablative conditioning before hematopoietic cell transplantation from HLA-matched related donors. Blood. 2004;104(5):1550-8.

18. Scott BL, Pasquini MC, Logan BR, Wu J, Devine SM, Porter DL, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. Journal of Clinical Oncology. 2017;35(11):1154.

19. Rambaldi A, Grassi A, Masciulli A, Boschini C, Micò MC, Busca A, et al. Busulfan plus cyclophosphamide versus busulfan plus fludarabine as a preparative regimen for allogeneic haemopoietic stem-cell transplantation in patients with acute myeloid leukaemia: an open-label, multicentre, randomised, phase 3 trial. The lancet oncology. 2015;16(15):1525-36.

20. Beelen DW, Trenschel R, Stelljes M, Groth C, Masszi T, Reményi P, et al. Treosulfan or busulfan plus fludarabine as conditioning treatment before allogeneic haemopoietic stem cell transplantation for older patients with acute myeloid leukaemia or myelodysplastic syndrome (MC-FludT. 14/L): a randomised, non-inferiority, phase 3 trial. The Lancet Haematology. 2020;7(1):e28-e39.