IJHOSCR

Original Article

International Journal of Hematology-Oncology and Stem Cell Research

Conditioning Regimens in Allogeneic Hematopoietic Stem Cell Transplantation Do Not Fit All: Adjusting BuCy2 in Mexico to Improve Outcomes in Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS)

Eucario León-Rodríguez, Monica M. Rivera-Franco

Hematopoietic Cell Transplantation Program, Department of Hematology and Oncology, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico

Corresponding Author: Eucario León-Rodríguez, Hematopoietic Cell Transplantation Program, Department of Hematology and Oncology, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico
Email: eucarios@hotmail.com

Received: 03, Sep, 2020
Accepted: 29, Oct, 2020

ABSTRACT

Background: Conditioning regimens are critical for allogeneic hematopoietic cell transplantation (allo-HCT). After unfavorable results using BuCy2 at the beginning of our HCT Program, a restructuring was made with the consequent development of a modified HCT method including a reduced conditioning regimen. The objective of this study was to describe the outcomes using Reduced BuCy2 (rBuCy2) in allo-HCT**.**

Materials and Methods: Data from 38 consecutive patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) who underwent allo-HCT conditioned with rBuCy2 in a 21-year period were retrospectively analyzed.

Results: Most patients were males (53%) and the median age was 35 years. The most common disease was myelodysplastic syndrome (55%). Toxicity grades III-IV were observed in 44%; and acute and chronic graft-versus-host disease were observed in 26% and 34%, respectively; the median follow-up was 26 months; 30-day non-relapse mortality (NRM) was 3%, and 1 and 2-year NRM were 8%. Ten-year overall survival (OS) was 60%, and 86%, for AML and MDS, respectively.

Conclusion: Our rBuCy2 maintains a myeloablative effect, along with immunosuppression for fast engraftment and more importantly, this regimen reduces grades III-IV acute GVHD and NRM in allo-HCT and improves the OS and it appears to be an option for low and middle-income countries.

Keywords: Hematopoietic cell transplantation; Conditioning regimen; Non-relapse mortality; Developing country

INTRODUCTION

Conditioning regimens are critical for allogeneic hematopoietic cell transplantation (allo-HCT). The aims of these regimens include the prevention of the graft rejection secondary to the infusion of the HSCs and the reduction of the underlying disease burden[1]. There are three main types of conditioning regimens: myeloablative (MAC), reduced-intensity (RIC)[2], and non-myeloablative (NMA). The former includes high-dose chemotherapy (busulfan (Bu) >8 mg/kg) or

total body irradiation ≥5 Gy in a single dose, causing prolonged pancytopenia [3]. Young patients with good performance status are usually candidates for MAC regimens in the context of an allo-HCT. NMA and RIC regimens could be administered in patients with a controlled underlying disease, who are not candidates for MAC regimens. The most common MAC regimens include BuCy4 [4] (busulfan 16 mg/kg and cyclophosphamide (Cy) 200 mg/kg) and more recently, BuCy2 (busulfan 10-12 mg/kg with cyclophosphamide 120 mg/kg)[5,6]. Moreover, a number of variations on these MAC such as dose escalation or modifications have been employed at centers worldwide. For instance, Lucarelli et al. reduced the doses of Bu and Cy according to the HLA class antibodies in patients with thalassemia [7].

On the other hand, non-relapse mortality (NRM) still represents a risk in allo-HCT caused by toxicity to conditioning regimens, infections, or graft-versus-host disease (GVHD). Our institutional HCT Program was established in 1986, performing 33 transplantations throughout the following decade, obtaining an overall survival (OS) of 28% and a high non-relapse mortality (NRM) of 61% in allo-HCT. According to these unfavorable results, in 1998 our program was formally restructured with the consequent development of a modified HCT method and a reduced conditioning regimen (Reduced BuCy 2: rBuCy2) adapting to our limited resources with the objective of decreasing the NRM and improving the OS.

The purpose of this study was to describe the outcomes of adult patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) undergoing allo-HCT using rBuCy2 as the conditioning regimen at a referral center in Mexico.

MATERIALS AND METHODS

Patients and data

Since 1998, our program has performed 397 HCT in 356 patients. Most of those transplantations have been autologous (60%). Further, most of our allo-HCT have been performed in aplastic anemia and other non-malignant diseases. Haploidentical HCT were excluded. Therefore, this study includes data from 38 consecutive patients with AML and MDS who underwent allo-HCT, conditioned with rBuCy2 from May 1999 to May 2020. The dataset used for this study derived from the prospectively collected database of the HCT Program, containing all the information regarding the overall HCT procedure collected during the hospital stay and outcomes such as infections, graft-versus-host disease, relapse, last follow-up, and death. Moreover, electronic medical records were reviewed.

Hematopoietic stem cells (HSCs) harvest and conditioning regimen

PBSC was the preferred source for high-risk malignancies, but G-CSF-primed bone marrow (G-BM) was mostly used in myelodysplastic syndromes when bone marrow collection containers were out of stock. Both G-BM and steady-state bone marrow (SS-BM) were used when GVHD was a potential complication according to clinical characteristics of the recipient and donor. BM harvests were conducted using the same protocol over the 18-year period without variation. For SS-BM and G-BM, HSCs were collected from donors by multiple aspirations of the iliac crests, in an operating room, under spinal anesthesia, G-CSF (10μg/kg/day) was administered 3 days (every 8 hours) prior the procedure for the latter. The volume of harvest was adapted to the recipients' body weight (BW) (maximum 15 ml/kg donors' BW). Mid-harvest CD34+ counts were not obtained. For PBSC, HSCs were collected by apheresis with prior administration of G-CSF for 3 days.

Reduced BuCy2 conditioning regimen consisted of: Busulfan 12mg/kg, divided in 4 days (3mg/kg/day, ORAL, during days -7, -6, -5, and -4), and Cyclophosphamide, IV, 80mg/kg, divided in 2 days (40mg/kg/day, during days -3, and -2). Therapeutic busulfan monitoring was not available at our Institution, thus, it was not performed.

GVHD and Antimicrobial Prophylaxis

Cyclosporine A (CsA) and Methotrexate (MTX) were given for GVHD prophylaxis. MTX was administered IV, 15mg/m^2 day +3, and 10mg/m^2 during days +6 and +11[8]. CsA was administered IV, 1.5mg/kg/12 hours, during day -1 and adjusting according to serum levels (200-300 ng/μl) until 2005. Afterwards, CsA was administered orally either by capsules or

solution (IV presentation was taken off the market), 10 mg/kg during day -1, and 5 mg/kg starting day 0, adjusting according to the therapeutic monitoring. CsA was maintained for 4 months post-transplant, and was subsequently reduced weekly (10%) until suspended, unless the development of GVHD. NIH criteria was used to diagnose and evaluate severity of acute and chronic GVHD [9,10].

Ciprofloxacin (500 mg/12 hours, ORAL) and acyclovir (250 mg/8 hours, IV) were administered starting the conditioning regimen. Antifungal prophylaxis for allo-HCT patients included amphotericin B (0.2mg/kg daily, IV), which was started in aplasia usually with an absolute neutrophil count (ANC) of ≤ 500/uL, but was replaced for caspofungin in 2015 (50 mg/daily, IV, after an initial loading dose of 70 mg, IV, on day 1). Trimethoprim-sulfamethoxazole (given as prophylaxis for pneumocystis jirovecii pneumonia) was started with an ANC of 1,000/uL and suspended one month after immunosuppressive therapy was deferred. Patients were discharged when engraftment occurred in the absence of infections or complications and were followed in the outpatient clinic.

Endpoints and definitions

Disease Risk Index (DRI) was classified as low, intermediate or high using standard definitions[11], and the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) [12] score was assigned to each patient. Morbidity post-transplant was analyzed through the toxicity evaluation according to the NCI CTCAE v4.0. Non-relapse mortality (NRM) was defined as death related to the conditioning regimen, infections during aplasia or under immunosuppressive treatment, or associated with the development of GVHD, without relapse and excluding all causes directly associated with the underlying disease. Disease-free survival (DFS) was established as the length of time from transplantation until relapse of the underlying disease. OS was defined as time from transplantation until death from any cause.

Statistical analysis

Categorical variables were described by frequencies and percentiles. Continuous variables were described by the median and interquartile range using the frequency analysis. Overall survival for all patients was calculated using the Kaplan-Meier estimator. Cumulative incidence estimates were calculated for other endpoints (NRM, relapse, GVHD) to account for competing risks. SPSS v.21 (IBM, Chicago, IL) was used.

RESULTS

Demographics: A total of 38 consecutive patients with AML or MDS who received an allo-HCT using rBuCy2 regimen were included. Most patients were males (53%), and the median age was 35 years (range, 16-58). Most MDS patients (n=21, 55%) eventually progressed to AML (n=17, 45%). The disease risk index (DRI) was mostly intermediate (n=32, 84%). Comorbidities prior HCT were calculated by the HCT-CI, and most patients had a low index (n=26, 76%). Overall demographics and clinical characteristics are shown in Table 1.

HCT*:* The most frequently used HSC source was G-BM (n=21, 55%), followed by SS-BM (n=8, 21%). Most patients had an HLA-matched sibling donor (n=36, 95%). Gender disparity was observed in 47% (n=18). The median infused CD34+ cells was 2.2 x 10^6/kg (range, 0.90-8.26). Initial engraftment was observed in all patients. Median days of neutrophil and platelet engraftment were 19 (range, 12-39) and 15 days (range, 7-78), respectively. Median duration of hospitalization were 36 days (range, 19-128).

Toxicity, infections, and GVHD: These data are summarized in Table 2. Conditioning-related toxicity was observed in 62 patients (87%; 48% grades III-IV). The most common adverse event was oral mucositis (n=30, 88%) being grades III-IV in 13 patients. Nausea was present in 14 patients (35%), and none of the patients developed grade III-IV GVHD. Nine patients (26%) developed hepatic toxicity, of whom 3 developed grade III-IV GVHD. Five patients (15%) presented renal toxicity, none of the patients developed grade III-IV GVHD. Neurologic toxicity as tonic-clonic epileptic seizures was observed in one patient. None of the patients developed veno-occlusive disease (VOD).

Thirty-one patients (82%) developed 44 infections during the in-patient stay with a median onset of 7 days (range, 0-36). The most common infections were: neutropenic fever (46%), followed by soft tissue (14%), gastrointestinal infections (9%), and pneumonia (9%). One patient (3%) developed Clostridium difficile diarrhea. With a median onset of 17 days (range, 12-103), 10 patients developed acute GVHD (26%), 60% grades I-II. Thirteen patients (34%) developed chronic GVHD: 69% limited and 31% extensive. Seven (54%) evolved from an acute GVHD.

Table 1. Patient demographics and clinical characteristics (N=38)

Characteristic	n (%)
Patient gender	
Male	20 (53)
Female	18 (47)
Median age (range)	35 (16-58)
Underlying disease	
AML	17 (45)
1° CR	7
≥2° CR	10
MDS	21 (55)
Hypoplastic	11
Refractory anemia	4
Multilineage dysplasia	5
CMML	1
Disease Risk Index [11]	
Intermediate	32 (84)
High	6 (16)
HCT-CI [12]	
Low	29 (76)
Intermediate	8 (21)
High	1 (3)
HSC	
G-BM	21 (55)
SS-BM	8 (21)
PBSC	8 (21)
CBSC	1 (3)
HLA matched donor	
Related	36 (95)
Unrelated (8/8 matched)	2 (5)
Median infused CD34+ cells x 10^6/kg (range)	2.2 (0.90-8.26)
Gender disparity	
Yes	18 (47)
No	20 (53)
Median days of neutrophil engraftment (range)	19 (12-39)
Median days of platelet engraftment (range)	15 (7-78)
Median days of hospitalization (range)	36 (19-128)

Abbreviations: AML: Acute myeloid leukemia; CBSC: Cord blood stem cells; CMML: Chronic myelomonocytic leukemia; CR: Complete remission; G-BM: G-CSF-primed bone marrow; MDS: Myelodysplastic syndrome; PBSC: Peripheral blood stem cells; SS-BM: Steady-state bone marrow.

Table 2. Post HCT complications (N=38)

Complication	n (%)
Overall toxicity to conditioning regimen	34 (89)
Grade I-II	19 (56)
Grade III-IV	15 (44)
Types of toxicities and grading*	
Oral mucositis	30 (88)
Grades III-IV	13 (43)
Nausea	14 (40)
Grades III-IV	0
Hepatic	9 (26)
Grades III-IV	3 (33)
Renal	5 (15)
Grades III-IV	0
Neurotoxicity	1 (3)
VOD	0
Patients with infections	31 (82)
Total infections*	44
Neutropenic fever	20 (46)
Soft tissue	6 (14)
Gastrointestinal	4 (9)
Pneumonia	4 (9)
Urinary tract	3 (7)
Upper respiratory tract	3 (7)
Catheter	2 (5)
Clostridium difficile diarrhea	1 (2)
Other	1 (2)
Acute GVHD	10 (26)
Grades I-II	6 (60)
Grades III-IV	4 (40)
Chronic GVHD	13 (34)
Limited	9 (69)
Extensive	4 (31)
Secondary graft failure	6 (16)
Treatment	
High-dose MP + IA	4 (66)
Recoveries	3 (75)
DLI	1 (17)
Recoveries	1 (100)
Second HCT	1 (17)
Recoveries	0

Abbreviations: DLI: Donor lymphocyte infusion; GVHD: Graft-versus-host disease; HCT: Hematopoietic cell transplantation; IA: Immunosuppression adjustment; MP: Methylprednisolone; VOD: Veno-occlusive disease.
*Some patients presented more than 1 type of toxicity and more than 1 infection.

Relapse and survival: Although primary graft failure (GF) was not observed, secondary GF was observed in six patients (16%). Four patients (66%) received high-dose methylprednisolone and adjustment of immunosuppression, of whom 3 engrafted. One patient (17%) received donor lymphocyte infusion with full recovery of the engraftment, and one patient (17%) underwent a second HCT without recovery. At the last follow-up, with a median of 26 months (range, 0-152), relapse after allo-HCT was documented in 5 patients (13%), mostly AML (n=4, 80%). Also, 30 patients (79%) were alive after this median follow-up. Relapse was the cause of death in four patients (50%), followed by infections (38%) and GVHD (12%).Thirty and 100-day NRM were 3% and 8%, respectively. One and 2-year NRM was 8%.

Figure 1 depicts the 5-year DFS: 65% in AML and 94% in MDS. Figure 2 shows the 5-year OS: 60% in AML and 86% in MDS.

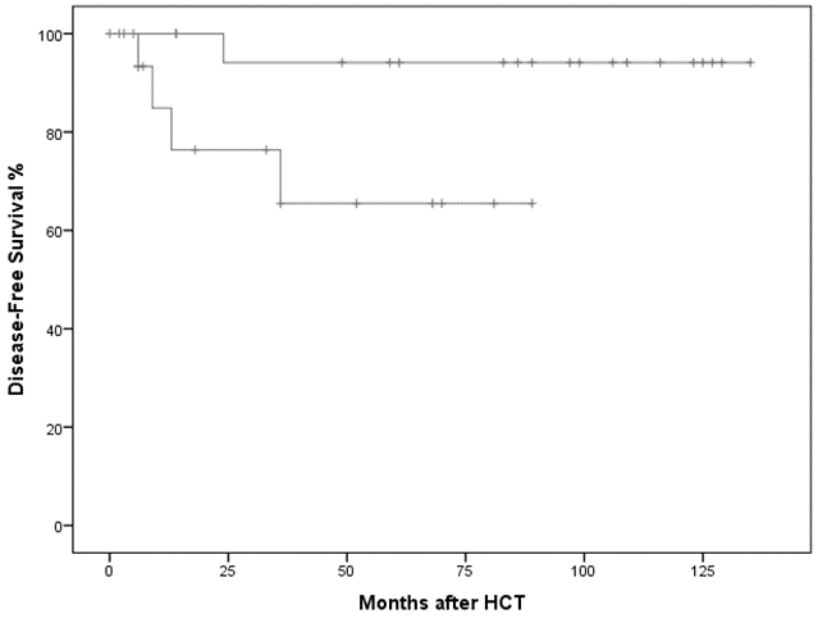

Figure 1. Five-year DFS: 65% in AML and 94% in MDS

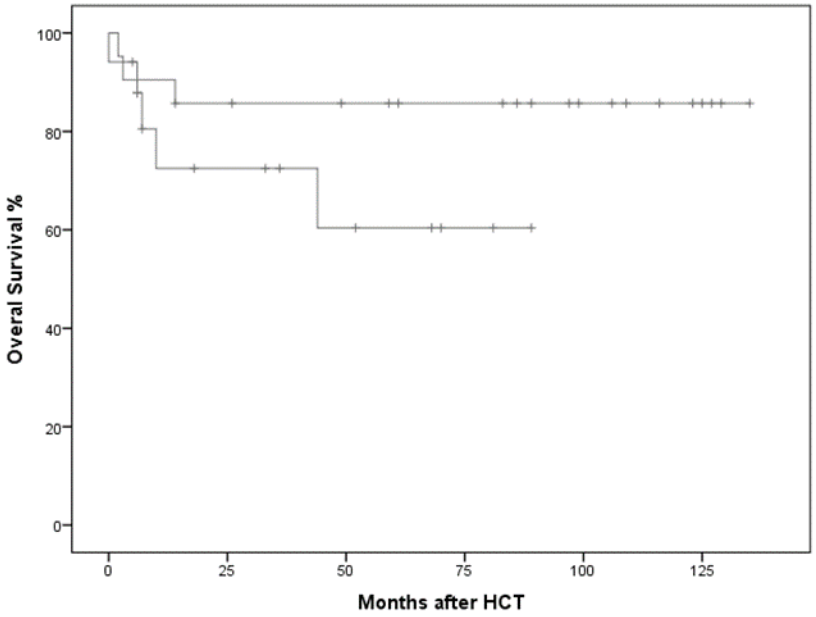

Figure 2. Five-year OS: 60% in AML and 86% in MDS

DISCUSSION

Choosing a standard conditioning regimen for HCT might represent a challenge as clinical practice varies across institutions and regions. Thus, the decision for selecting a conditioning regimen is usually based upon clinical judgement, taking into account the recipient comorbidities, underlying condition, the status of the disease, type of donor, and HSC source. Busulfan has been widely used in high-dose chemotherapy based regimens as a substitution of total body irradiation (TBI), either to avoid the associated short- and long- term toxicities[13] or due to unavailability in some countries. In the context of the latter, we decided to continue using BuCy (with the substantial dosage reduction) because although Bu in combination of Melphalan (Mel) has been used in the HCT setting, few data have been available on the use of this conditioning regimen in allo-HCT. There is even paucity of experience using this regimen among our patients undergoing autologous HCT, and more importantly, intravenous Mel is not widely available in Mexico as it must be imported from another country.

On the other hand, although it was reported that the substantial variability in plasma levels of patients using oral busulfan was associated with graft rejection or regimen-related toxicity such as VOD[14], and despite a lower frequency of those plasma variations using intravenous busulfan, the early regimen-related toxicity remained a concern with both presentations. Thus, a regimen using high-dose busulfan (16 mg/kg total dose) and cyclophosphamide (200 mg/kg total dose) was developed[4], but it was posteriorly modified decreasing the total dose of cyclophosphamide to 120 mg/kg [6], and ever since, it has been widely used in patients undergoing autologous and allogeneic HCT. Nonetheless, intravenous busulfan is substantially more expensive compared to the oral formulation making it unaffordable in limited-resource scenarios. Our rBuCy2 regimen consists of reducing conventional BuCy2 (Bu 12 mg/kg (oral) and Cy 80 mg/kg; < 25% of Bu, and < 33% Cy, respectively), considering a reduced tissue injury but preserving a myeloablative potential and therefore lower systemic toxicity and lower incidence of GVHD.

Further, the reduction of NRM remains of interest in the allogeneic HCT scenario. It is known that RIC regimens have decreased NRM in allo-HCT[15]; however, the risk of developing acute and chronic GVHD still remains high (up to 29% and 55%, respectively) [16,17]. Using rBuCy2, we have observed a low overall NRM among our cohort (2-year NRM of 8%), contrasting with the 2-year NRM using reduced intensity regimens and standard treatments (20-33%) [16-19]. NRM did not show variations over time, which demonstrates that the low percentage described in this study was associated with the dose reduction and not as a result of changes in supportive care or HCT safety. Among our patients, oral mucositis was observed in 89% which was similar to the results of a recently published meta-analysis[20] reporting 86.5% using myeloablative regimens, respectively. Further, in our study, 44% had grade III-IV which is lower than the results of the meta-analysis using MAC (56.4%) [19]. 26% of patients developed acute GVHD, while chronic GVHD was present in 34% of patients, which was limited in 69%. It might seem that the low incidence of acute GVHD was conditioned by the reduction in Bu and Cy dosages, as tissue damage (potentially lower due to these reductions) is a well-known factor for the development of this complication.

Although acknowledging that the replacement of Cy with Fludarabine in combination with Bu (BuFlu) associates with higher DFS and OS [21], unfortunately, intravenous Flu is not available in our country. Nonetheless, the 1-year NRM using rBuCy2 was comparable to BuFlu (8% versus 10%). In the scenario of GVHD, among our cohort, both acute and chronic GVHD were lower compared to BuFlu (40% versus 26% and 44% versus 34%).

Moreover, according to the underlying disease, 5-year OS was 60% and 86%, in AML and MDS, respectively, which is similar to studies using standard BuCy2 or BuCy4.

Additionally, we acknowledge the high secondary GF among our cohort (16%) which was higher than reports using unrelated donors (5-10%) or matched sibling donors (2%) [22]. This phenomenon could be potentially explained as follows: 1) RIC usually has a higher incidence of graft rejection due to residual host cytotoxic T cells and natural killer cells [23], 2)

regimens including Bu and Cy have been associated with a relatively higher GF rate compared to other regimens [24], 3) most patients received CD34 + stem cell dose < 3×10^6/kg, 4) cord blood was used in one patient with AML, and 5) myelodysplastic syndrome was the most common diagnosis among these patients.

It is important to highlight that the median age of the patients undergoing allo-HCT during the first decade of our HCT Program (n=33) and those transplanted using rBuCy2 was similar, and the high NRM due to toxicities in the former despite their young age could be potentially explained by pharmacoethnicity. Although to date, there are no specific studies reporting higher toxicities associated with conditioning regimens in Hispanic patients, and the data on this topic are limited when it comes to this ethnic group, there are studies including patients with solid tumors, reporting that being Hispanic is a predictor of acute-chemotherapy associated toxicity[25-27]. This could be exemplified by 44% of toxicities grade III-IV observed among cohort despite receiving rBuCy2. Further research in the HCT field is required.

CONCLUSION

In conclusion, our rBuCy2 maintains a myeloablative effect, along with immunosuppression for fast engraftment. More importantly, this regimen reduces grades III-IV acute GVHD and NRM in allo-HCT, which appears to be a feasible option for low and middle-income countries.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Gyurkocza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not fit all. Blood. 2014; 124(3): 344-53.

2. Giralt S, Ballen K, Rizzo D, et al. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. Biol Blood Marrow Transplant 2009; 15(3):367-9.

3. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant. 2009; 15(12):1628–33.

4. Santos GW, Tutschka PJ, Brookmeyer R, et al. Marrow transplantation for acute nonlymphocytic leukemia after treatment with busulfan and cyclophosphamide. N Engl J Med. 1983; 309(22):1347–53.

5. Gratwohl A, Carreras E. Principles of Conditioning. In: ESH-EBMT Handbook on Haematopoietic Stem Cell Transplantation 2012, 6th edition, Apperley J, Carreras E, Gluckman E, Masszi T (Eds), European School of Haematology, Paris 2012. p.126.

6. Tutschka PJ, Copelan EA, Klein JP. Bone marrow transplantation for leukemia following a new busulfan and cyclophosphamide regimen. Blood. 1987; 70(5):1382–8.

7. Lucarelli G, Clift RA, Galimberti M, et al. Bone Marrow Transplantation in Adult Thalassemic Patients. Blood. 1999; 93 (4): 1164-7.

8. Leon Rodriguez E, Rivera Franco MM, Campos Castro A. Is Day +1 Omission of Methotrexate associated with higher incidence of Acute Graft-Versus-Host-Disease in Hematopoietic Stem Transplantation? Bone Marrow Transplant. 2017; 52(5):772-774.

9. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant. 2015; 21(3): 389–401.e1.

10. Vigorito A, Campregher P, Storer B, et al. Evaluation of NIH consensus criteria for classification of late acute and chronic GVDH. Blood. 2009; 114 (3): 702-8.

11. Armand P, Kim HT, Logan BR, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. Blood. 2014; 123(23):3664-71.

12. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005; 106(8):2912-19.

13. Clift RA, Buckner CD, Thomas ED, et al. Marrow transplantation for chronic myeloid leukemia: a randomized study comparing cyclophosphamide and total body irradiation with busulfan and cyclophosphamide. Blood. 1994; 84(6):2036-43.

14. Grochow LB. Busulfan disposition: the role of therapeutic monitoring in bone marrow transplantation induction regimens. Semin Oncol. 1993; 20(4 Suppl 4):18-25; quiz 26.

15. Tanaka Y, Kurosawa S, Tajima K, et al. Analysis of non-relapse mortality and causes of death over 15 years following allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2016; 51(4): 553-9.

16. Rubio MT, Labopin M, Blaise D, et al. The Impact Of Graft-*Versus*-Host Disease Prophylaxis In Reduced-

Intensity Conditioning Allogeneic Stem Cell Transplant In Acute Myeloid Leukemia: A Study From The Acute Leukemia Working Party Of The European Group For Blood And Marrow Transplantation. Haematologica. 2015; 100(5): 683-9.
17. Malard F, Chevallier P, Guillaume T, et al. Continuous reduced nonrelapse mortality after allogenei c hematopoietic stem cell transplantation: a single-institution's three-decade experience. Biol Blood Marrow Transplant. 2014; 20(8):1217-23.
18. Kurosawa S, Yakushijin K, Yamaguchi T, et al. Recent decrease in non-relapse mortality due to GVHD and infection after allogeneic hematopoietic cell transplantation in non-remission acute leukemia. Bone Marrow Transplant. 2013; 48(9): 1198–204.
19. Kurosawa S, Yakushijin K, Yamaguchi T, et al. Changes in incidence and causes of non-relapse mortality after allogeneic hematopoietic cell transplantation in patients with acute leukemia/myelodysplastic syndrome: an analysis of the Japan Transplant Outcome Registry. Bone Marrow Transplant. 2013; 48(4): 529–36.
20. Chaudhry HM, Bruce AJ, Wolf RC, et al. The Incidence and Severity of Oral Mucositis among Allog eneic Hematopoietic Stem CellTransplantation Patients: A Systematic Review. Biol Blood Marrow Transplant. 2016; 22(4):605-616.
21. Chae YS, Sohn SK, Kim JG, et al. New myeloablative conditioning regimen with fludarabine and busulfan for allogeneic stem cell transplantation: comparison with BuCy2. Bone Marrow Transplantat. 2007; 40(6): 541-7.
22. Ottinger HD, Ferencik S, Beelen DW, et al. Hematopoietic stem cell transplantation: contrasting the outcome of transplantations from HLA-identical siblings, partially HLA mismatched related donors, and HLA-matched unrelated donors. Blood. 2003; 102(3): 1131-7.
23. Masouridi-Levrat S, Simonetta F, Chalandon Y. Immunological Basis of Bone Marrow Failure after Allogeneic Hematopoietic Stem Cell Transplantation. Front Immunol. 2016; 7:362.
24. Ozdemir ZN, Civriz Bozdağ S. Graft failure after allogeneic hematopoietic stem cell transplantation. Transfus Apher Sci. 2018; 57(2):163-167.
25. Han HS, Reis IM, Zhao W, et al. Racial differences in acute toxicities of neoadjuvant or adjuvant chemotherapy in patients with early-stage breast cancer. Eur J Cancer. 2011; 47(17): 2537-45.
26. Sharib JM, Cyrus J, Horvai A, et al. Predictors of acute chemotherapy-associated toxicity in patients with Ewing sarcoma. Pediatr Blood Cancer. 2012; 59(4):611-6.
27. Bandera EV, Lee VS, Rodriguez-Rodriguez L, et al. Racial/Ethnic Disparities in Ovarian Cancer Treatment and Survival. Clin Cancer Res. 2016; 22(23):5909-5914.