Int J Clin Exp Med 2014;7(11):4357-4368
www.ijcem.com /ISSN:1940-5901/IJCEM0002323

Original Article

Reduced-intensity and myeloablative conditioning allogeneic hematopoietic stem cell transplantation in patients with acute myeloid leukemia and myelodysplastic syndrome: a meta-analysis and systematic review

Wen Zeng[1], Lifang Huang[1], Fankai Meng[1], Zeming Liu[2], Jianfeng Zhou[1], Hanying Sun[1]

[1]*Department of Hematology, Tongji hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095# Jiefang Avenue, Wuhan 430030, China;* [2]*Department of General surgery, Union hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277# Jiefang Avenue, Wuhan 430022, China*

Received September 4, 2014; Accepted October 23, 2014; Epub November 15, 2014; Published November 30, 2014

Abstract: Background: We performed a systematic review and meta-analysis to compare the clinical outcomes and toxicity of reduced-intensity conditioning (RIC) and myeloablative conditioning (MAC) allogeneic hematopoietic stem cell transplantation (alloHSCT) in patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). Evidence acquisition: A comprehensive PubMed and Embase search was performed using the following keywords: "reduced-intensity", "myeloablative", "AML", and "MDS". The primary endpoints were overall survival (OS) and event-free survival (EFS), and the secondary endpoints were relapse incidence (RI), non-relapse mortality (NRM), grade II-IV acute graft-versus-host disease (aGVHD), and chronic GVHD (cGVHD). Results: Eight studies (2 prospective and 6 retrospective) involving 6464 patients who received RIC (n = 1571) or MAC (n = 4893) alloHSCT were included in the analysis. Median age and the number of patients with low hematopoietic cell transplantation-specific comorbidity index scores and who received *ex vivo* or *in vivo* T cell depletion were higher in the RIC arm than in the MAC arm. Significant heterogeneity was not found among the studies for any of the endpoints except for grade II-IV aGVHD. OS (odds ratio [OR], 0.96; 95% confidence interval [CI], 0.84-1.08; p = 0.47) and EFS (OR, 0.88; 95% CI, 0.77-1.00; p = 0.05) were similar in the RIC and MAC arms, whereas RI (OR, 1.41; 95% CI, 1.24-1.59; p < 0.00001) was higher in the RIC arm than in the MAC arm. The incidence of grade II-IV aGVHD (OR, 0.59; 95% CI, 0.36-0.96; p = 0.03) was lower in the RIC arm than in the MAC arm; however, NRM (OR, 0.99; 95% CI, 0.87-1.13; p = 0.85), total cGVHD (OR, 1.10; 95% CI, 0.88-1.38; p = 0.38), and extensive cGVHD (OR, 1.01; 95% CI, 0.75-1.37; p = 0.95) were not significantly different between the two arms. Conclusion: RIC alloHSCT may be an effective treatment strategy for AML/MDS patients who are not suitable candidates for MAC alloHSCT. However, heterogeneity in baseline patient characteristics and treatment protocols may have influenced the outcomes of RIC alloHSCT in our analysis. Future randomized controlled trials are needed to confirm our findings.

Keywords: Reduced-intensity conditioning, myeloablative conditioning, allogeneic hematopoietic stem cell transplantation, acute myeloid leukemia, myelodysplastic syndrome, meta-analysis, systematic review

Introduction

Currently, allogeneic hematopoietic stem cell transplantation (alloHSCT) is the only potentially curative approach for acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS) treatment [1, 2]. However, procedure-related toxicities restrict the use of myeloablative conditioning (MAC) alloHSCT to AML patients younger than 50 years with a good performance status and who are usually in first complete remission (CR1). Reduced-intensity conditioning (RIC) alloHSCT has been shown to reduce procedure-related toxicities with acceptable relapse incidence (RI). Thus, RIC has extended the application of alloHSCT in AML/MDS to

include patients who are not eligible candidates for standard alloHSCT because of advanced age or comorbidities [3-6]. Furthermore, RIC alloHSCT can provide adequate immunosuppression and allow successful donor hematopoietic engraftment to eradicate malignant clonal cells through a graft versus malignancy effect, independent of chemoradiotherapy [7, 8].

Despite the wide use of RIC alloHSCT for the treatment of AML/MDS, few randomized clinical trials have compared the clinical outcomes between RIC and MAC alloHSCT in AML/MDS. Furthermore, retrospective studies comparing the clinical outcomes of RIC and MAC alloHSCT in AML/MDS patients have produced conflicting results. Therefore, we performed a comprehensive systematic review and meta-analysis to compare the clinical outcomes and toxicity of RIC and MAC alloHSCT in patients with AML/MDS.

Materials and methods

Data sources

PubMed and Embase were searched for English-language articles published between January 1995 and May 2014. The National Institutes of Health Clinical Trials Registry (http://clinicaltrials.gov/) and Current Controlled Trials in the metaRegister of Controlled Trials (http://www.controlled-trials.com/) were also searched for related articles. Online abstracts from the following annual meetings were also reviewed: American Society of Hematology, European Hematology Association, Center for International Blood & Marrow Transplant Research (CIBMTR), European Society for Blood and Marrow Transplantation (EBMT), and American Society for Blood and Marrow Transplantation. Keywords used in the search were "reduced-intensity", "myeloablative conditioning", "AML", and "MDS". Eligible studies included clinical trials comparing RIC alloHSCT and MAC alloHSCT in adult AML or MDS patients (16 years or older). Clinical trials involving AML patients with relapsed, refractory, or advanced disease, MDS patients with progressive disease, or subjects undergoing umbilical cord blood transplantation were ineligible for analysis. Studies comparing the outcomes between non-myeloablative (NMA) conditioning and MAC regimens were also ineligible for analysis. RIC was defined as follows [9-11]: (1) ≤ 500 Gy for single-fraction total body irradiation (TBI) or ≤ 800 Gy for fractionated TBI; (2) ≤ 9 mg/kg oral or intravenous busulfan; (3) ≤ 140 mg/m^2 melphalan; (4) < 10 mg/kg thiotepa; or (5) BEAM (carmustine, etoposide, cytarabine, and melphalan) pretreatment. NMA was defined as follows: (1) 200-Gy fractionated TBI; (2) TBI (200 Gy) plus fludarabine (Flu); or (3) Flu plus cyclophosphamide [8, 12-14].

Study selection

Published articles were carefully screened, and only the most current articles with the longest follow-ups were included in the analysis in cases of overlapping information between publications. Preclinical studies, case reports, and reviews were excluded from the analysis.

Clinical endpoints

Study data including patient characteristics, treatment protocol, endpoint definitions, results, and follow-up information were extracted by two independent reviewers (ZW and HLF). In cases of discrepancies between the reviewers, the data were re-extracted until a consensus was reached. The primary endpoints of the analysis were overall survival (OS) and event-free survival (EFS), and the secondary endpoints were RI, non-relapse mortality (NRM), grade II-IV acute graft-versus-host disease (aGVHD), and chronic GVHD (cGVHD). OS was defined as the time from transplantation to the time of death from any cause or last follow-up. EFS was defined as the time from transplantation to the time of relapse or death from any cause. NRM was defined as the incidence of death not related to relapse.

Statistical analyses

Statistical analyses were performed using RevMan 5.0 software. Publication bias was calculated using Comprehensive Meta-Analysis (Biostat, Englewood, NJ, USA) and analyzed using Begg's and Egger's tests. Data regarding OS, RI, NRM, EFS, grade II-IV aGVHD, and cGVHD were directly extracted from the studies. Two-tailed P values < 0.05 were considered statistically significant. Before the meta-analysis, Cochrane's Q and I^2 statistics were used to evaluate heterogeneity among the studies. The random effects model was used to calculate pooled effects.

Table 1. Characteristics of the eligible trials included in the meta-analysis

Reference	Disease	Study type	Centers
Bornhäuser 2012 [15]	AML	prospective	multicenters
Hiramoto 2014 [16]	MDS/AML-MLD	retrospective	single
Khabori 2011 [17]	AML/MDS	retrospective	single
Lioure 2012 [18]	AML	prospective	multicenters
Luger 2012 [14]	AML/MDS	retrospective	multicenters
Martino 2012 [12]	AML/MDS	retrospective	multicenters
Philipp 2010 [19]	AML	retrospective	single
Shimoni 2012 [20]	AML/MDS	retrospective	single

Note: AML, acute myeloid leukemia; AML-MLD: acute myeloid leukemia with multilineage dysplasia; MDS myelodysplastic syndrome.

Results

Study characteristics

Eight studies involving 6464 AML/MDS patients were included in the analysis [12, 14-20]. Of the 6464 AML/MDS patients, 1571 patients received RIC alloHSCT and 4893 patients received MAC alloHSCT. Patient and treatment characteristics and clinical outcomes of the eligible studies are listed in **Tables 1**-**4**, respectively.

The distribution of baseline patient characteristics was heterogeneous. Factors contributing to the baseline heterogeneity included median age, hematopoietic cell transplantation-specific comorbidity index (HCT-CI) score, and the bone marrow (BM) blast count at HSCT. Median age was significantly higher in the RIC arm than in the MAC arm, with over half of the patients in the RIC arm being over 51 years of age. Four studies [15, 17, 19, 20] evaluated HCT-CI scores. The proportion of patients with low HCT-CI scores was greater in the RIC arm than in the MAC-HSCT arm (25.6% [72/281] vs. 13.7% [41/299]; p = 0.04). The proportion of patients with < 5% BM blasts at alloHSCT was 77% (1034/1344) in the RIC arm and 79% (3191/4024) in the MAC arm (p = 0.01). Twenty-two percent (345/1537) of patients in the RIC arm and 18% (852/4837) of patients in the MAC arm had unfavorable/high-risk cytogenetics (p = 0.05). The Karnofsky score at alloHSCT was not significantly different between the RIC and MAC arms (p = 0.70).

Thirty-seven percent (677/1816) and 31% (403/1283) of patients in the RIC arm and 53% (2530/4803) and 27% (1080/3968) of patients in the MAC arm received human leukocyte antigen (HLA)-identical sibling (MRD) alloHSCT and matched unrelated donor (MUD) alloHSCT (p = 0.05 for both), respectively. In total, 72% (1103/1537) of patients in the RIC arm and 74% (3599/4837) of patients in the MAC arm received HLA-matched alloHSCT (p = 0.12). Peripheral blood stem cells (PBSC) were used as the stem cell source in 63% (1134/1814) of patients in the RIC arm and in 49% (2387/4847) of patients in the MAC arm (p = 0.06). In the remaining patients, BM was used as the stem cell source. T cell depletion (TCD) including *ex vivo* TCD and *in vivo* TCD with anti-thymocyte globulin or alemtuzumab, were performed in 44% (653/1470) of patients in the RIC arm and in 19% (896/4814) of patients in the MAC arm (p = 0.001).

Comparison of OS and EFS between RIC and MAC alloHSCT

Eight [12, 14-20] and six trials [12, 14, 15, 17-19] were available for OS and EFS analysis, respectively. Heterogeneity among the studies in terms of OS (I^2 = 0%; p = 0.97) and EFS (I^2 = 0%; p = 0.87) was not significant. The pooled effect showed no significant difference in OS (OR, 0.96; 95% CI, 0.84-1.08; p = 0.47) or EFS (OR, 0.88; 95% CI, 0.77-1.00; p = 0.05) between the RIC and MAC arms.

Comparison of RI and NRM between RIC and MAC alloHSCT

All studies were available for NRM and RI analysis. Heterogeneity among the studies in this regard was not significant (NRM: I^2 = 0%, p = 0.59; RI: I^2 = 0%, p = 0.91). RI was lower in the MAC arm (OR, 1.41; 95% CI, 1.24-1.59; p < 0.00001). NRM was not significantly different between the two arms (OR, 0.99; 95% CI, 0.87-1.13; p = 0.85).

Comparison of grade II-IV aGVHD and cGVHD between RIC and MAC alloHSCT

Seven [12, 14, 16-20] and six [12, 15-19] studies were available for total (n = 6189) and extensive (n = 1501) cGVHD analysis, respectively. Heterogeneity among the studies was

Table 2. Patient's characteristics of the eligible trials included in the meta-analysis

Reference	Conditioning regimen	No. of pts	Meidan Age at HCT (range)	Male, no. (%)	Cytogenetic risk, unfavorable/ poor, no. (%)	Karnofsky score at HCT, no. (%)	HCT-CI score, ≥ 3 (high), no. (%)	Disease status at HCT, no. (%)	BM blast < 5% at HCT, no. (%)	MRD, no. (%)	MUD, no. (%)	Donor Related, no. (%)	HLA match, no. (%)
Bornhäuser 2012 [15]	RIC	99	44 (18-60)	43 (43)	22 (22)	NA	15 (15)	CR1, 99 (100)	99 (100)	59 (60)	28 (28)	59 (60)	87 (88)
	MAC	96	45 (18-60)	47 (49)	26 (27)	NA	17 (18)	CR1, 96 (100)	96 (100)	58 (60)	24 (25)	58 (60)	82 (85)
Hiramoto 2014 [16]	RIC	81	57 (19-68)	58 (72)	33 (41)	< 90%, 14 (17)	NA	CR, 42 (52)	42 (52)	NA	NA	43 (53)	70 (86)
	MAC	34	46 (23-57)	24 (71)	7 (21)	< 90%, 5 (15)	NA	CR, 18 (53)	18 (53)	NA	NA	12 (35)	31 (91)
Khabori 2011 [17]	RIC	39	53 (42-60)	19 (49)	NA	median, 90%	11 (28)	CR, 39 (100)	39 (100)	NA	NA	18 (46)	NA
	MAC	62	50 (40-59)	32 (52)	NA	median, 90%	7 (11)	CR, 62 (100)	62 (100)	NA	NA	42 (68)	NA
Lioure 2012 [18]	RIC	47	54 (34-60)	17 (36)	10 (21)	NA	NA	CR, 47 (100)	47 (100)	47 (100)	0	47 (100)	47 (100)
	MAC	117	39 (17-50)	67 (57)	14 (12)	NA	NA	CR, 117 (100)	117 (100)	115 (98)	0	117 (100)	115 (98)
Luger 2012 [14]	RIC	1041	55 (18-70)	604 (58)	227 (22)	< 90%, 322 (31)	NA	CR, 408 (39); MDS untreated 123 (40)	770 (74)	376 (36)	307 (29)	376 (36)	683 (66)
	MAC	3731	42 (18-68)	1991 (53)	691 (17)	< 90%, 1190 (32)	NA	CR, 1754 (47); MDS untreated, 110 (12)	2842 (76)	1560 (42)	999 (27)	1560 (42)	2559 (69)
Martino 2012 [12]	RIC	126	54 (19-70)	64 (51)	14 (21)	< 80%, 5 (4)	NA	CR+PR, 126 (100)	< 10%, 126 (100)	126 (100)	NA	126 (100)	126 (100)
	MAC	718	39 (18-63)	367 (51)	86 (12)	< 80%, 17 (2.4)	NA	CR+PR, 718 (100)	< 10%, 718 (100)	718 (100)	NA	718 (100)	718 (100)
Philipp 2010 [19]	RIC	37	51 (19-68)	15 (41)	13 (35)	NA	18 (49)	CR1, 37(100)	37 (100)	22 (60)	13 (35)	22 (60)	35 (95)
	MAC	56	34 (17-66)	24 (43)	15 (27)	NA	7 (13)	CR1, 56 (100)	56 (100)	37 (66)	16 (29)	37 (66)	53 (95)
Shimoni 2012 [20]	RIC	106	60 (29-75)	61 (58)	26 (29) for AML	NA	28 (26)	CR1 or MDS with BM Blast < 10%, 54 (51)	NA	47 (44)	55 (52)	47 (44)	55 (52)
	MAC	85	49 (18-66)	48 (56)	13 (19) for AML	NA	10 (12)	CR1 or MDS with BM Blast < 10%, 34 (40)	NA	42 (49)	41 (48)	42 (49)	41 (48)

Note: BM, bone marrow; CR, complete remission; HCT, hematopoietic cell transplantation; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; HLA, human leukocyte antigen; MAC, myeloablative conditioning; MRD, human leukocyte antigen-identical sibling; MUD, matched unrelated donor; NA, not available; PR, partial remission; RIC, reduced-intensity conditioning.

Table 3. Treatment characteristics of the eligible trials included in the meta-analysis

	MAC	62	54 (87)	Ale, in unrelated donor transplants, 20 (32)	Ref [17]*	CsA/MMF or CsA/MTX in related donor HCT, Ale/CsA in unrelated donor HCT
Lioure 2012 [18]	RIC	47	47 (100)	ATG, 47 (100)	Orally 4 mg/kg Bu daily for 2 d plus 30 mg/m² Flu daily for 4 d (100)	CSA (100)
	MAC	117	0	None	Six dose of 2 Gy TBI for 3 d plus 60 mg/kg CY daily for 2 d (100)	CSA + MTX (100)
Luger 2012 [14]	RIC	1041	768 (74)	ATG, 438 (30)	Ref [14]*	CNI + MTX ± other (44), CNI ± other (56)
	MAC	3731	1720 (46)	ATG, 631 (17)	Ref [14]*	CNI + MTX ± other (88), CNI ± other (12)
Martino 2012 [12]	RIC	126	115 (91)	Ex vivo TCD, 2 (2); Ale, 12 (9); ATG, 42 (33)	Ref [12]*	CsA, CsA/MTX, CsA/others
	MAC	718	465 (65)	Ex vivo TCD, 130 (18); Ale, 52 (7.2); ATG, 36 (5)	Ref [12]*	CsA, CsA/MTX, CsA/others
Philipp 2010 [19]	RIC	37	36 (97.3)	ATG, 37 (100)	Orally 4 mg/kg Bu daily for 2 d plus 30 mg/m² Flu daily for 6 d (100)	CsA/MMF (100)
	MAC	56	47 (83.9)	ATG, 3 (5.4)	Six dose of 2 Gy TBI for 3 d plus 60 mg/kg CY daily for 2 d (100)	CsA/MTX (100)
Shimoni 2012 [20]	RIC	106	NA	ATG, in unrelated or mismatched donor and patients with no prior chemotherapy	I.v. 3.2 mg/kg Bu daily for 2 d plus 30 mg/m² Flu daily for 5 d (100)	CsA/MTX (100)
	MAC	85	NA	ATG, in unrelated or mismatched donor and patients with no prior chemotherapy	I.v. 3.2 mg/kg Bu daily for 4 d plus 40 mg/m² Flu daily for 4 d (100)	CsA/MTX (100)

Note: *, multiple regimens are used in this study with details in the reference; 2-CdA, cladribine; Ale, Alemtuzumab; ATG, antithymocyte globulin; Bu, busulfan; CNI, calcineurin inhibitor; CsA, cyclosporine; CY, cyclophosphamide; Flu, fludarabine; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; MAC, myeloablative conditioning; MMF, mycophenolate mofetil; MTX, methotrexate; PBSC, peripheral blood stem cells; RIC, reduced-intensity conditioning; TBI, total body irradiation; TCD, T cell depletion.

Table 4. Transplantation outcomes of the eligible trials included in the meta-analysis

Reference	Conditioning regimen	No. of pts	Median follow-up in survivors, months (range)	Grade II-IV aGVHD, no. (%)	Extensive cGVHD, no. (%)	Total cGVHD, no. (%)	OS, %	EFS, %	NRM, %	RI, %
Bornhäuser 2012 [15]	RIC	94	27 (4-81)	17 (17)	22 (22)	NA	3-yr, 61	3-yr, 58	3-yr, 13	3-yr, 28
	MAC	90	27 (4-81)	23 (24)	16 (17)	NA	3-yr, 58	3-yr, 56	3-yr, 18	3-yr, 26
Hiramoto 2014 [16]	RIC	81	47 (4-125)	36 (44)	37 (50)	43 (58)	4-yr, 42	NA	4-yr, 33	4-y, 25
	MAC	34	40 (4-130)	12 (35)	11 (39)	15 (53)	4-yr, 47	NA	4-yr, 29	4-y, 26
Khabori 2011 [17]	RIC	39	34.3 (3.3-76.4)	24 (62)	18 (46)	22 (56)	3-yr, 50	3-yr, 45	3-yr, 25	3-yr, 31
	MAC	62	34.3 (3.3-76.4)	40 (65)	37 (60)	40 (65)	3-yr, 49	3-yr, 47	3-yr, 31	3-yr, 22
Lioure 2012 [18]	RIC	47	88 (16-119)	5 (11)	5 (11)	16 (34)	5-yr, 70; 9-yr, 69	9-yr, 66	3-yr, 4.2; 5-yr, 4.4; 9-yr, 6.5	3-yr, 21; 5-yr, 28; 9-yr, 29
	MAC	117	88 (30-119)	61 (52)	20 (17)	34 (29)	5-yr, 70; 9-yr, 68	9-yr, 63	3-yr, 13; 5-yr, 13; 9-yr, 16	3-yr, 19; 5-yr, 19; 9-yr, 22
Luger 2012 [14]	RIC	1041	41 (3-124)	451 (44)	NA	427 (42)	5-yr, 33	5-yr, 30	5-yr, 35	5-yr, 40
	MAC	3731	58 (3-128)	1720 (49)	NA	1466 (40)	5-yr, 34	5-yr, 33	5-yr, 34	5-yr, 32
Martino 2012 [12]	RIC	126	76 (42-135)	NA	32 (25)	65 (52)	7-yr, 53	7-yr, 48*	7-yr, 18	7-yr, 34
	MAC	718	82 (27-149)	NA	184 (26)	312 (44)	7-yr, 56	7-yr, 54*	7-yr, 23	7-yr, 23
Philipp 2010 [19]	RIC	37	NA	6 (16)	15 (41)	21 (57)	5-yr, 61	5-yr, 53	5-yr, 16	5-yr, 36
	MAC	56	NA	24 (43)	22 (39)	25 (45)	5-yr, 56	5-yr, 54	5-yr, 20	5-yr, 32
Shimoni 2012 [20]	RIC	106	48 (1-122)#	27 (25)	NA	50 (47)	5-yr, 44	NA	5-yr, 20	5-yr, 47
	MAC	85	29 (4-89)#	31 (37)	NA	51 (60)	5-yr, 50	NA	5-yr, 18	5-yr, 40

Note: *, progression-free survival instead of EFS is evaluated in this study; #, the median follow-up time is for all patients instead of survivors in this study; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; EFS, event-free survival; MAC, myeloablative conditioning; NA, not available; NRM, non-relapse mortality; OS, overall survival; RI, relapse incidence; RIC, reduced-intensity conditioning; yr, year.

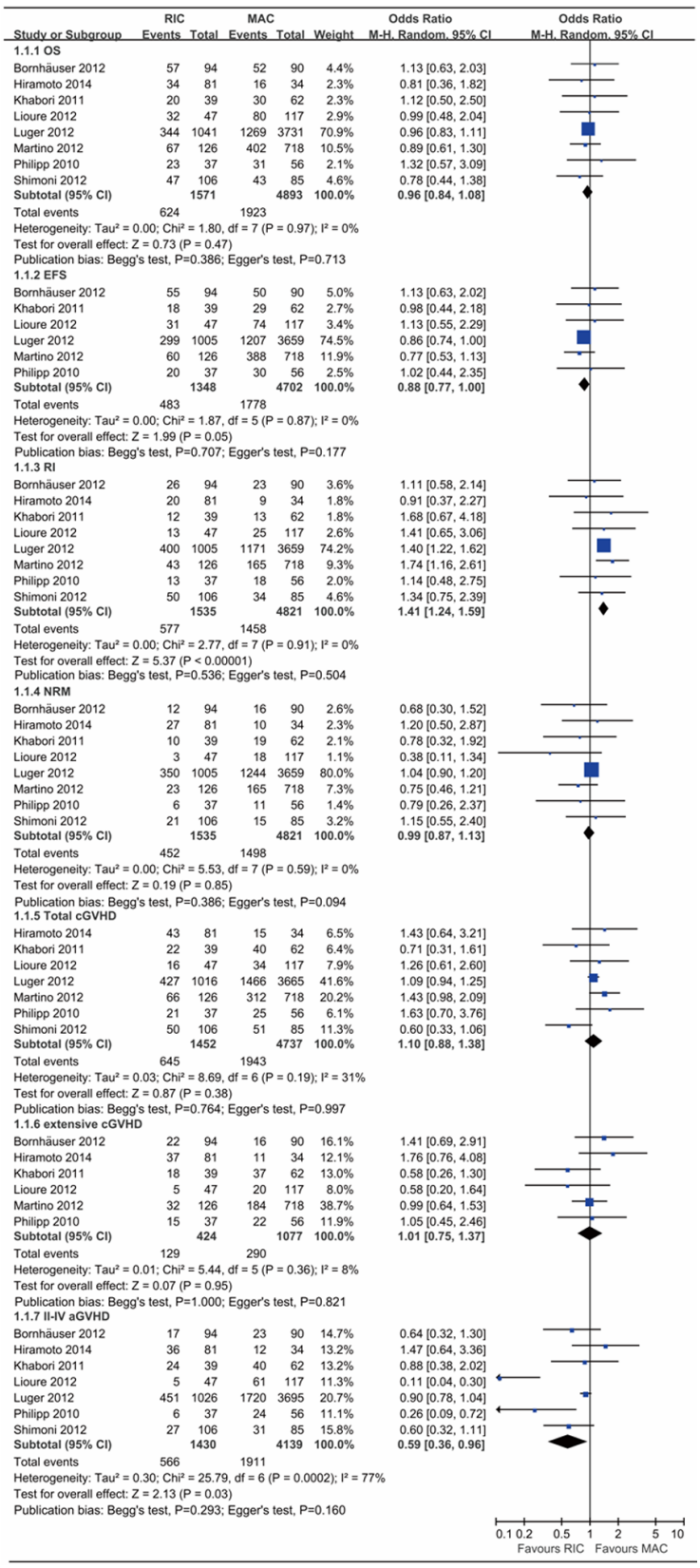

Figure 1. Forest plots from a meta-analysis of transplantation outcomes for RIC compared to MAC arm.

not significant for total (I^2 = 31%; p = 0.19) or extensive (I^2 = 8%; p = 0.36) cGVHD. Total cGVHD (OR, 1.10; 95% CI, 0.88-1.38; p = 0.38) and extensive cGVHD (OR, 1.01; 95% CI, 0.75-1.37; p = 0.95) were similar in the RIC and MAC arms. Seven [14-20] studies including 5563 AML/MDS patients were available for grade II-IV aGVHD analysis, and heterogeneity among the studies was significant (I^2 = 77%; p = 0.0002). The pooled effect showed a significantly lower incidence of grade II-IV aGVHD in the RIC arm than in the MAC arm (OR, 0.59; 95% CI, 0.36-0.96; p = 0.03).

Publication bias

The results of the Begg's and Egger's tests showed no significant indication of publication bias (**Figure 1**). Therefore, it is unlikely that publication bias had a major influence on the pooled effects.

Discussion

AlloHSCT represents a potentially curative therapeutic strategy for AML/MDS treatment [1, 2, 21]. For many years, MAC regimens were given at the maximum tolerable dose with the aim to eliminate tumor burden, clear host hematopoietic cells from the BM, and provide sufficient immunosuppression to allow successful donor cell engraftment before HSCT. However, these high-dose regimens result in considerable toxicity and GVHD, the two leading causes of death in recipients of alloHSCT. Given that GVHD contributes to the toxicity of preparative regimens [7, 22], RIC regimens were proposed. The relatively low toxicity and lower incidence and severity of GVHD of RIC regimens allows their application to patients who are not suitable candidates for MAC alloHSCT because of advanced age or comorbidities [23].

The main finding of our study was that RIC and MAC yield similar outcomes (OS and EFS), even though patients in the RIC arm were elderly and thus, in worse general condition. In a retrospective study from the Gruppo Italiano Trapianto Di Midollo Osseo (GITMO), the conditioning regimen for alloHSCT (RIC vs. MAC) was found not to be significantly associated with 3-year OS in AML patients with active disease in both the univariate and multivariate analyses [24]. The EBMT reported that OS and leukemia-free survival (LFS) were not significantly different between RIC and MAC MRD alloHSCT in AML [25] and MDS [26] patients. Furthermore, updated data from this study are consistent with the original findings [12]. The EBMT reported that RIC and MAC MUD alloHSCT were associated with similar adjusted 2-year LFS rates in AML patients [27]. The CIBMTR suggested that MAC and RIC yield similar 5-year OS and disease-free survival (DFS) rates [14]. In the subgroup analysis, the adjusted 5-year DFS rate was 43% in the MAC arm, 37% in the RIC BM arm, and 33% in the RIC PBSC arm for AML patients in CR1 and MDS patients with < 5% BM blasts who were 40-60 years of age and had Karnofsky scores ≥ 90%. Although the adjusted 5-year DFS rate was higher in the MAC arm, this difference was not significant (vs. RIC BM, p = 0.46; vs. RIC PBSC, p = 0.06). Lioure [18] and Bornhäuser [15] conducted prospective randomized trials in 2012 to compare the outcomes between RIC and MAC alloHSCT in AML. In the Bornhäuser 2012 study, patients were well matched in terms of age, cytogenetic risk, induction therapy, and donor type, and the 3-year OS and DFS rates were similar in the RIC and MAC arms. In the Lioure 2012 study, patients were well matched in terms of baseline characteristics, complete remission rate, and donor type but not in terms of gender distribution (higher proportion of male patients in the MAC arm) and age (older age in the RIC arm). Nine-year OS and EFS rates were not significantly different between the MAC and RIC arms in this study (68% vs. 65.8% and 63.4% vs. 69.3%, respectively).

Disease relapse is the major cause of treatment failure after alloHSCT in patients with AML/MDS and is profoundly influenced by cytogenetics [28-30], disease status at HSCT [29, 31], and treatment procedure [32, 33]. RIC was associated with a worse RI than MAC, which was associated with the lower efficacy of RIC in eradicating malignant clonal cells [14, 26]. Predictors of relapse risk after MAC alloHSCT in AML/MDS patients have been identified [34-40]. The association of these factors with relapse risk after RIC alloHSCT should be investigated as relapse risk factors may differ according to conditioning regimen. Manjappa et al. [40] recently reported that cytomegalovirus (CMV) reactivation after MRD alloHSCT with TCD was associated with a significantly lower risk of relapse for AML patients in the MAC, but not in the RIC, arm. This indicates that the risk profile might differ to some extent between these two arms.

Interestingly, the results of our analysis suggest that NRM was similar for RIC and MAC alloHSCT. The integrated score, which was developed by Versluis et al. [41], contains the most dominant parameters from the HCT-CI [42] and EBMT [43] scores and is useful in predicting NRM for AML patients in CR1 proceeding to RIC HSCT. In this new scoring system, the parameters associated with NRM include age at alloHSCT, patient and donor CMV status, unrelated donor, time interval to alloHSCT, and various comorbidities, whereas disease stage and donor-recipient sex combination, which are included in the EBMT score, are irrelevant. The CIBMTR reported that, although early NRM was less frequent for RIC than for MAC, the 3-year and 5-year NRM rates were similar for the two regimens [14]. The Bornhäuser 2012 study [15] reported that the 12-month cumulative incidence of NRM was 8% for RIC and 17% for MAC (p = 0.048). NRM at 3 years increased by 5% in the RIC arm and by 1% in the MAC arm; thus, similar rates of NRM in the two arms were reached at 3 years after transplantation (13% for RIC and 18% for MAC). The adjusted hazard ratio (HR) for the 3-year NRM rate was not significantly different between RIC and MAC in this study (HR, 0.62; 95% CI, 0.30-1.31; p = 0.22). It is possible that RIC is more advantageous than MAC in preventing early, but not late, NRM. Scoring systems such as the HCT-CI score [42], EBMT score [43], and integrated score [41] could be used to identify parameters predictive of early and late NRM in patients receiving RIC and MAC alloHSCT. The results of these studies and our analysis suggest that NRM is not favorable with RIC. However, RIC may still have a positive effect on NRM as most patients in

these studies were not matched in terms of age or comorbidities. Thus, patients in the RIC arm may have been at a higher risk of NRM.

Various factors have been shown to increase the risk of aGVHD, including HLA mismatch, unrelated donor, older donor age, and sex mismatch [44-48]. Treatment-related procedures such as GVHD prophylaxis and TCD can also impact the incidence of aGHVD [49-51]. The CIBMTR reported that, for MRD alloHSCT, the incidence of grade II-IV aGVHD was significantly lower in the RIC PBSC arm than in the MAC PBSC with TBI arm (OR, 0.70; 95% CI, 0.56-0.88; p = 0.002), whereas the incidence was similar in the MAC PBSC with TBI and RIC BM arms (OR, 0.90; 95% CI, 0.54-1.49; p = 0.67) [52]. However, for MUD alloHSCT, both RIC PBSC (OR, 0.75; 95% CI, 0.57-1.00; p = 0.05) and RIC BM (OR, 0.47; 95% CI, 0.29-0.76; p = 0.002) were found to significantly lower the incidence of grade II-IV aGVHD compared with MAC PBSC with TBI. Risk profiles of cGVHD and aGHVD were similar; however, some notable differences were observed [13, 47, 53]. The EBMT reported that the stem cell source (PBSC vs. BM) does not influence cGVHD in AML patients in complete remission receiving MRD RIC alloHSCT (HR, 1.15; 95% CI, 0.78-1.69; p = 0.48) [13]. Arora et al., on behalf of the CIBMTR, developed a cGVHD risk score by analyzing the patient and transplantation characteristics of 5343 AML, acute lymphoblastic leukemia, chronic myeloid leukemia, and MDS patients receiving alloHSCT. Ten specific risk factors were validated; however, conditioning intensity before alloHSCT was found not to be a significant risk factor for cGVHD [53].

Our study has several limitations. First, the majority of eligible studies were retrospective in nature, which might have introduced some bias into our findings. Second, baseline patient characteristics (age, HCT-CI score, and disease status at HSCT) and treatment protocols (TCD) might have influenced survival outcomes, RI, and GVHD incidence in our analysis.

Conclusion

The results of our analysis suggest that RIC alloHSCT is an effective treatment strategy for AML/MDS patients who are not suitable candidates for MAC alloHSCT because of advanced age or comorbidities. However, heterogeneity in the baseline patient characteristics and treatment protocols may influence the outcomes of RIC alloHSCT in our analysis. Future randomized clinical trials are needed to further evaluate the efficacy of RIC alloHSCT in AML/MDS.

Acknowledgements

This study was supported by the Hubei Natural Science Foundation (grant number 2013CFB098).

Disclosure of conflict of interest

None.

Address correspondence to: Hanying Sun, Department of Hematology, Tongji hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095# Jiefang Avenue, Wuhan 430030, China. Tel: +86-13807165617; Fax: +86-027-83663625; E-mail: hanying.sun@hotmail.com

References

[1] Liu H, Zhai X, Song Z, Sun J, Xiao Y, Nie D, Zhang Y, Huang F, Zhou H, Fan Z, Tu S, Li Y, Guo X, Yu G and Liu Q. Busulfan plus fludarabine as a myeloablative conditioning regimen compared with busulfan plus cyclophosphamide for acute myeloid leukemia in first complete remission undergoing allogeneic hematopoietic stem cell transplantation: a prospective and multicenter study. J Hematol Oncol 2013; 6: 15.

[2] Kanate AS, Pasquini MC, Hari PN and Hamadani M. Allogeneic hematopoietic cell transplant for acute myeloid leukemia: Current state in 2013 and future directions. World J Stem Cells 2014; 6: 69-81.

[3] Wahid SF. Indications and outcomes of reduced-toxicity hematopoietic stem cell transplantation in adult patients with hematological malignancies. Int J Hematol 2013; 97: 581-598.

[4] Cornelissen JJ, Gratwohl A, Schlenk RF, Sierra J, Bornhauser M, Juliusson G, Racil Z, Rowe JM, Russell N, Mohty M, Lowenberg B, Socie G, Niederwieser D and Ossenkoppele GJ. The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach. Nat Rev Clin Oncol 2012; 9: 579-590.

[5] Horwitz ME. Reduced intensity versus myeloablative allogeneic stem cell transplantation for the treatment of acute myeloid leukemia, myelodysplastic syndrome and acute lymphoid leukemia. Curr Opin Oncol 2011; 23: 197-202.

[6] Pidala J, Kim J, Anasetti C, Kharfan-Dabaja MA, Nishihori T, Field T, Perkins J, Perez L and Fernandez HF. Pharmacokinetic targeting of intravenous busulfan reduces conditioning regimen related toxicity following allogeneic hematopoietic cell transplantation for acute myelogenous leukemia. J Hematol Oncol 2010; 3: 36.

[7] Schanz U. Allogeneic haematopoietic stem cell transplantation with reduced intensity conditioning regimens ("minitransplants"). Swiss Med Wkly 2001; 131: 59-64.

[8] Blaise D, Vey N, Faucher C and Mohty M. Current status of reduced-intensity-conditioning allogeneic stem cell transplantation for acute myeloid leukemia. Haematologica 2007; 92: 533-541.

[9] Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, Apperley J, Slavin S, Pasquini M, Sandmaier BM, Barrett J, Blaise D, Lowski R and Horowitz M. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant 2009; 15: 1628-1633.

[10] Giralt S, Ballen K, Rizzo D, Bacigalupo A, Horowitz M, Pasquini M and Sandmaier B. 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: 367-369.

[11] Hamadani M, Mohty M and Kharfan-Dabaja MA. Reduced-intensity conditioning allogeneic hematopoietic cell transplantation in adults with acute myeloid leukemia. Cancer Control 2011; 18: 237-245.

[12] Martino R, de Wreede L, Fiocco M, van Biezen A, von dem Borne PA, Hamladji RM, Volin L, Bornhauser M, Robin M, Rocha V, de Witte T, Kroger N and Mohty M. Comparison of conditioning regimens of various intensities for allogeneic hematopoietic SCT using HLA-identical sibling donors in AML and MDS with < 10% BM blasts: a report from EBMT. Bone Marrow Transplant 2013; 48: 761-770.

[13] Nagler A, Labopin M, Shimoni A, Mufti GJ, Cornelissen JJ, Blaise D, Janssen JJ, Milpied N, Vindelov L, Petersen E, Gribben J, Bacigalupo A, Malm C, Niederwieser D, Socie GJ, Arnold R, Brown P, Goker H, Rocha V and Mohty M. Mobilized peripheral blood stem cells compared with bone marrow from HLA-identical siblings for reduced-intensity conditioning transplantation in acute myeloid leukemia in complete remission: a retrospective analysis from the Acute Leukemia Working Party of EBMT. Eur J Haematol 2012; 89: 206-213.

[14] Luger SM, Ringden O, Zhang MJ, Perez WS, Bishop MR, Bornhauser M, Bredeson CN, Cairo MS, Copelan EA, Gale RP, Giralt SA, Gulbas Z, Gupta V, Hale GA, Lazarus HM, Lewis VA, Lill MC, McCarthy PL, Weisdorf DJ and Pulsipher MA. Similar outcomes using myeloablative vs reduced-intensity allogeneic transplant preparative regimens for AML or MDS. Bone Marrow Transplant 2012; 47: 203-211.

[15] Bornhauser M, Kienast J, Trenschel R, Burchert A, Hegenbart U, Stadler M, Baurmann H, Schafer-Eckart K, Holler E, Kroger N, Schmid C, Einsele H, Kiehl MG, Hiddemann W, Schwerdtfeger R, Buchholz S, Dreger P, Neubauer A, Berdel WE, Ehninger G, Beelen DW, Schetelig J and Stelljes M. Reduced-intensity conditioning versus standard conditioning before allogeneic haemopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: a prospective, open-label randomised phase 3 trial. Lancet Oncol 2012; 13: 1035-1044.

[16] Hiramoto N, Kurosawa S, Tajima K, Okinaka K, Tada K, Kobayashi Y, Shinohara A, Inoue Y, Ueda R, Tanaka T, Kim SW, Yamashita T, Heike Y and Fukuda T. Positive impact of chronic graft-versus-host disease on the outcome of patients with de novo myelodysplastic syndrome after allogeneic hematopoietic cell transplantation: a single-center analysis of 115 patients. Eur J Haematol 2014; 92: 137-146.

[17] Khabori MA, El-Emary M, Xu W, Guyatt G, Galal A, Kuruvilla J, Lipton J, Messner H and Gupta V. Impact of intensity of conditioning therapy in patients aged 40-60 years with AML/myelodysplastic syndrome undergoing allogeneic transplantation. Bone Marrow Transplant 2011; 46: 516-522.

[18] Lioure B, Bene MC, Pigneux A, Huynh A, Chevallier P, Fegueux N, Blaise D, Witz B, Delain M, Cornillon J, Luquet I, Blanchet O, Cornillet-Lefebvre P, Carre M, Hunault M, Larosa F, Lamy T, Randriamalala E, Ojeda-Uribe M, Berthou C, Fornecker L, Harousseau JL, Bouscary D, Ifrah N and Cahn JY. Early matched sibling hematopoietic cell transplantation for adult AML in first remission using an age-adapted strategy: long-term results of a prospective GOELAMS study. Blood 2012; 119: 2943-2948.

[19] Hemmati PG, Terwey TH, Massenkeil G, le Coutre P, Vuong LG, Neuburger S, Dorken B and Arnold R. Reduced intensity conditioning prior to allogeneic stem cell transplantation in first complete remission is effective in patients with acute myeloid leukemia and an intermediate-risk karyotype. Int J Hematol 2010; 91: 436-445.

[20] Shimoni A, Shem-Tov N, Volchek Y, Danylesko I, Yerushalmi R and Nagler A. Allo-SCT for AML and MDS with treosulfan compared with BU-based regimens: reduced toxicity vs reduced intensity. Bone Marrow Transplant 2012; 47: 1274-1282.

[21] Lv M and Huang XJ. Allogeneic hematopoietic stem cell transplantation in China: where we are and where to go. J Hematol Oncol 2012; 5: 10.

[22] Hill GR, Crawford JM, Cooke KR, Brinson YS, Pan L and Ferrara JL. Total body irradiation and acute graft-versus-host disease: the role of gastrointestinal damage and inflammatory cytokines. Blood 1997; 90: 3204-3213.

[23] Bacigalupo A. Hematopoietic stem cell transplants after reduced intensity conditioning regimen (RI-HSCT): report of a workshop of the European group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant 2000; 25: 803-805.

[24] Todisco E, Ciceri F, Oldani E, Boschini C, Mico C, Vanlint MT, Donnini I, Patriarca F, Alessandrino PE, Bonifazi F, Arcese W, Barberi W, Marenco P, Terruzzi E, Cortelazzo S, Santarone S, Proia A, Corradini P, Tagliaferri E, Falcioni S, Irrera G, Dallanegra L, Castagna L, Santoro A, Camboni A, Sacchi N, Bosi A, Bacigalupo A and Rambaldi A. The CIBMTR score predicts survival of AML patients undergoing allogeneic transplantation with active disease after a myeloablative or reduced intensity conditioning: a retrospective analysis of the Gruppo Italiano Trapianto Di Midollo Osseo. Leukemia 2013; 27: 2086-2091.

[25] Aoudjhane M, Labopin M, Gorin NC, Shimoni A, Ruutu T, Kolb HJ, Frassoni F, Boiron JM, Yin JL, Finke J, Shouten H, Blaise D, Falda M, Fauser AA, Esteve J, Polge E, Slavin S, Niederwieser D, Nagler A and Rocha V. Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT). Leukemia 2005; 19: 2304-2312.

[26] Martino R, Iacobelli S, Brand R, Jansen T, van Biezen A, Finke J, Bacigalupo A, Beelen D, Reiffers J, Devergie A, Alessandrino E, Mufti GJ, Barge R, Sierra J, Ruutu T, Boogaerts M, Falda M, Jouet JP, Niederwieser D and de Witte T. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. Blood 2006; 108: 836-846.

[27] Ringden O, Labopin M, Ehninger G, Niederwieser D, Olsson R, Basara N, Finke J, Schwerdtfeger R, Eder M, Bunjes D, Gorin NC, Mohty M and Rocha V. Reduced intensity conditioning compared with myeloablative conditioning using unrelated donor transplants in patients with acute myeloid leukemia. J Clin Oncol 2009; 27: 4570-4577.

[28] Nevill TJ, Shepherd JD, Sutherland HJ, Abou Mourad YR, Lavoie JC, Barnett MJ, Nantel SH, Toze CL, Hogge DE, Forrest DL, Song KW, Power MM, Nitta JY, Dai Y and Smith CA. IPSS poor-risk karyotype as a predictor of outcome for patients with myelodysplastic syndrome following myeloablative stem cell transplantation. Biol Blood Marrow Transplant 2009; 15: 205-213.

[29] Deeg HJ, Scott BL, Fang M, Shulman HM, Gyurkocza B, Myerson D, Pagel JM, Platzbecker U, Ramakrishnan A, Radich JP, Sandmaier BM, Sorror M, Stirewalt DL, Wilson WA, Storb R, Appelbaum FR and Gooley T. Five-group cytogenetic risk classification, monosomal karyotype, and outcome after hematopoietic cell transplantation for MDS or acute leukemia evolving from MDS. Blood 2012; 120: 1398-1408.

[30] Armand P, Kim HT, Zhang MJ, Perez WS, Dal Cin PS, Klumpp TR, Waller EK, Litzow MR, Liesveld JL, Lazarus HM, Artz AS, Gupta V, Savani BN, McCarthy PL, Cahn JY, Schouten HC, Finke J, Ball ED, Aljurf MD, Cutler CS, Rowe JM, Antin JH, Isola LM, Di Bartolomeo P, Camitta BM, Miller AM, Cairo MS, Stockerl-Goldstein K, Sierra J, Savoie ML, Halter J, Stiff PJ, Nabhan C, Jakubowski AA, Bunjes DW, Petersdorf EW, Devine SM, Maziarz RT, Bornhauser M, Lewis VA, Marks DI, Bredeson CN, Soiffer RJ and Weisdorf DJ. Classifying cytogenetics in patients with acute myelogenous leukemia in complete remission undergoing allogeneic transplantation: a Center for International Blood and Marrow Transplant Research study. Biol Blood Marrow Transplant 2012; 18: 280-288.

[31] Oran B, Kongtim P, Popat U, de Lima M, Jabbour E, Lu X, Chen J, Rondon G, Kebriaei P, Ahmed S, Andersson B, Alousi A, Ciurea S, Shpall E and Champlin RE. Cytogenetics, Donor Type, and Use of Hypomethylating Agents in Myelodysplastic Syndrome with Allogeneic Stem Cell Transplantation. Biol Blood Marrow Transplant 2014; 20: 1618-25.

[32] Remberger M, Mattsson J, Svahn BM and Ringden O. Using reduced intensity conditioning and HLA-identical sibling donors, antithymocyte globulin increases the risk of relapse,

which can be overcome by a high stem cell dose. Bone Marrow Transplant 2008; 42: 769-771.

[33] Jurado M, Deeg HJ, Storer B, Anasetti C, Anderson JE, Bryant E, Chauncey T, Doney K, Flowers ME, Hansen J, Martin PJ, Nash RA, Petersdorf E, Radich J, Sale G, Sandmaier BM, Storb R, Wade J, Witherspoon R and Appelhaum FR. Hematopoietic stem cell transplantation for advanced myelodysplastic syndrome after conditioning with busulfan and fractionated total body irradiation is associated with low relapse rate but considerable nonrelapse mortality. Biol Blood Marrow Transplant 2002; 8: 161-169.

[34] Weisdorf D, Zhang MJ, Arora M, Horowitz MM, Rizzo JD and Eapen M. Graft-versus-host disease induced graft-versus-leukemia effect: greater impact on relapse and disease-free survival after reduced intensity conditioning. Biol Blood Marrow Transplant 2012; 18: 1727-1733.

[35] Koreth J, Kim HT, Nikiforow S, Milford EL, Armand P, Cutler C, Glotzbecker B, Ho VT, Antin JH, Soiffer RJ, Ritz J and Alyea EP 3rd. Donor Chimerism Early after Reduced-Intensity Conditioning Hematopoietic Stem Cell Transplantation Predicts Relapse and Survival. Biol Blood Marrow Transplant 2014; 20: 1516-21.

[36] Reshef R, Hexner EO, Loren AW, Frey NV, Stadtmauer EA, Luger SM, Mangan JK, Gill SI, Vassilev P, Lafferty KA, Smith J, Van Deerlin VM, Mick R and Porter DL. Early Donor Chimerism Levels Predict Relapse and Survival after Allogeneic Stem Cell Transplantation with Reduced-Intensity Conditioning. Biol Blood Marrow Transplant 2014; 20: 1758-66.

[37] Elmaagacli AH, Steckel NK, Koldehoff M, Hegerfeldt Y, Trenschel R, Ditschkowski M, Christoph S, Gromke T, Kordelas L, Ottinger HD, Ross RS, Horn PA, Schnittger S and Beelen DW. Early human cytomegalovirus replication after transplantation is associated with a decreased relapse risk: evidence for a putative virus-versus-leukemia effect in acute myeloid leukemia patients. Blood 2011; 118: 1402-1412.

[38] Green ML, Leisenring WM, Xie H, Walter RB, Mielcarek M, Sandmaier BM, Riddell SR and Boeckh M. CMV reactivation after allogeneic HCT and relapse risk: evidence for early protection in acute myeloid leukemia. Blood 2013; 122: 1316-1324.

[39] Nikolousis E, Robinson S, Nagra S, Brookes C, Kinsella F, Tauro S, Jeffries S, Griffiths M, Mahendra P, Cook M, Paneesha S, Lovell R, Kishore B, Chaganti S, Malladi R, Raghavan M, Moss P, Milligan D and Craddock C. Post-transplant T cell chimerism predicts graft versus host disease but not disease relapse in patients undergoing an alemtuzumab based reduced intensity conditioned allogeneic transplant. Leuk Res 2013; 37: 561-565.

[40] Manjappa S, Bhamidipati PK, Stokerl-Goldstein KE, DiPersio JF, Uy GL, Westervelt P, Liu J, Schroeder MA, Vij R, Abboud CN, Fehniger TA, Cashen AF, Pusic I, Jacoby M, Meera SJ and Romee R. Protective effect of cytomegalovirus reactivation on relapse after allogeneic hematopoietic cell transplantation in acute myeloid leukemia patients is influenced by conditioning regimen. Biol Blood Marrow Transplant 2014; 20: 46-52.

[41] Versluis J, Labopin M, Niederwieser D, Socie G, Schlenk RF, Milpied N, Nagler A, Blaise D, Rocha V, Cornelissen JJ and Mohty M. Prediction of non-relapse mortality in recipients of reduced intensity conditioning allogeneic stem cell transplantation with AML in first complete remission. Leukemia 2014; [Epub ahead of print].

[42] Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG and Storer B. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 2005; 106: 2912-2919.

[43] Gratwohl A. The EBMT risk score. Bone Marrow Transplant 2012; 47: 749-756.

[44] Eapen M, Logan BR, Confer DL, Haagenson M, Wagner JE, Weisdorf DJ, Wingard JR, Rowley SD, Stroncek D, Gee AP, Horowitz MM and Anasetti C. Peripheral blood grafts from unrelated donors are associated with increased acute and chronic graft-versus-host disease without improved survival. Biol Blood Marrow Transplant 2007; 13: 1461-1468.

[45] Carlens S, Ringden O, Remberger M, Lonnqvist B, Hagglund H, Klaesson S, Mattsson J, Svahn BM, Winiarski J, Ljungman P and Aschan J. Risk factors for chronic graft-versus-host disease after bone marrow transplantation: a retrospective single centre analysis. Bone Marrow Transplant 1998; 22: 755-761.

[46] Loiseau P, Busson M, Balere ML, Dormoy A, Bignon JD, Gagne K, Gebuhrer L, Dubois V, Jollet I, Bois M, Perrier P, Masson D, Moine A, Absi L, Reviron D, Lepage V, Tamouza R, Toubert A, Marry E, Chir Z, Jouet JP, Blaise D, Charron D and Raffoux C. HLA Association with hematopoietic stem cell transplantation outcome: the number of mismatches at HLA-A, -B, -C, -DRB1, or -DQB1 is strongly associated with overall survival. Biol Blood Marrow Transplant 2007; 13: 965-974.

[47] Flowers ME, Inamoto Y, Carpenter PA, Lee SJ, Kiem HP, Petersdorf EW, Pereira SE, Nash RA, Mielcarek M, Fero ML, Warren EH, Sanders JE,

Storb RF, Appelbaum FR, Storer BE and Martin PJ. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. Blood 2011; 117: 3214-3219.

[48] McGuirk J, Hao G, Hou W, Abhyankar S, Williams C, Yan W, Yuan J, Guan X, Belt R, Dejarnette S, Wieman J and Yan Y. Serum proteomic profiling and haptoglobin polymorphisms in patients with GVHD after allogeneic hematopoietic cell transplantation. J Hematol Oncol 2009; 2: 17.

[49] Al-Kadhimi Z, Gul Z, Chen W, Smith D, Abidi M, Deol A, Ayash L, Lum L, Waller EK, Ratanatharathorn V and Uberti J. High incidence of severe acute graft-versus-host disease with tacrolimus and mycophenolate mofetil in a large cohort of related and unrelated allogeneic transplantation patients. Biol Blood Marrow Transplant 2014; 20: 979-985.

[50] Dulery R, Mohty M, Duhamel A, Robin M, Beguin Y, Michallet M, Vigouroux S, Lioure B, Garnier A, El Cheikh J, Bulabois CE, Huynh A, Bay JO, Daguindau E, Ceballos P, Clement L, Dauriac C, Maillard N, Legrand F, Cornillon J, Guillerm G, Francois S, Lapusan S, Chevallier P, Damaj G and Yakoub-Agha I. Antithymocyte globulin before allogeneic stem cell transplantation for progressive myelodysplastic syndrome: a study from the French Society of Bone Marrow Transplantation and Cellular Therapy. Biol Blood Marrow Transplant 2014; 20: 646-654.

[51] Soiffer RJ, Lerademacher J, Ho V, Kan F, Artz A, Champlin RE, Devine S, Isola L, Lazarus HM, Marks DI, Porter DL, Waller EK, Horowitz MM and Eapen M. Impact of immune modulation with anti-T-cell antibodies on the outcome of reduced-intensity allogeneic hematopoietic stem cell transplantation for hematologic malignancies. Blood 2011; 117: 6963-6970.

[52] Jagasia M, Arora M, Flowers ME, Chao NJ, McCarthy PL, Cutler CS, Urbano-Ispizua A, Pavletic SZ, Haagenson MD, Zhang MJ, Antin JH, Bolwell BJ, Bredeson C, Cahn JY, Cairo M, Gale RP, Gupta V, Lee SJ, Litzow M, Weisdorf DJ, Horowitz MM and Hahn T. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. Blood 2012; 119: 296-307.

[53] Arora M, Klein JP, Weisdorf DJ, Hassebroek A, Flowers ME, Cutler CS, Urbano-Ispizua A, Antin JH, Bolwell BJ, Boyiadzis M, Cahn JY, Cairo MS, Isola L, Jacobsohn DA, Jagasia M, Klumpp TR, Lee SJ, Petersdorf EW, Santarone S, Gale RP, Schouten HC, Spellman S, Wingard JR, Horowitz MM and Pavletic SZ. Chronic GVHD risk score: a Center for International Blood and Marrow Transplant Research analysis. Blood 2011; 117: 6714-6720.