Biol Blood Marrow Transplant 25 (2019) 2398–2407

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Comparison of High Doses of Total Body Irradiation in Myeloablative Conditioning before Hematopoietic Cell Transplantation

Mitchell Sabloff[1], Saurabh Chhabra[2,3,*], Tao Wang[2,4], Caitrin Fretham[5], Natasha Kekre[6], Allistair Abraham[7], Kehinde Adekola[8], Jeffery J. Auletta[9], Christopher Barker[10], Amer M. Beitinjaneh[11], Christopher Bredeson[6], Jean-Yves Cahn[12], Miguel Angel Diaz[13], Cesar Freytes[14], Robert Peter Gale[15], Siddhartha Ganguly[16], Usama Gergis[17], Eva Guinan[18], Betty K. Hamilton[19], Shahrukh Hashmi[20,21], Peiman Hematti[22], Gerhard Hildebrandt[23], Leona Holmberg[24], Sanghee Hong[25], Hillard M. Lazarus[26], Rodrigo Martino[27], Lori Muffly[28], Taiga Nishihori[29], Miguel-Angel Perales[30], Jean Yared[31], Shin Mineishi[32], Edward A. Stadtmauer[33], Marcelo C. Pasquini[2], Alison W. Loren[34]

[1] *Division of Hematology, Department of Medicine, University of Ottawa and Ottawa Hospital Research Institute, Ottawa, Canada*
[2] *Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin*
[3] *Division of Hematology/Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin*
[4] *Division of Biostatistics, Institute of Health and Equity, Medical College of Wisconsin, Milwaukee, Wisconsin*
[5] *Center for International Blood and Marrow Transplant Research, National Marrow Donor Program/Be the Match, Minneapolis, Minnesota*
[6] *The Ottawa Hospital Blood and Marrow Transplant Program and the Ottawa Hospital Research Institute, Ottawa, Ontario, Canada*
[7] *Division of Blood and Marrow Transplantation, Center for Cancer and Blood Disorders, Children's National Medical Center, Washington, DC*
[8] *Division of Hematology/Oncology, Department of Medicine and Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, Illinois*
[9] *Blood and Marrow Transplant Program and Host Defense Program, Divisions of Hematology/Oncology/Bone Marrow Transplant and Infectious Diseases, Nationwide Children's Hospital, Columbus, Ohio*
[10] *Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York*
[11] *Division of Hematology/Oncology, University of Miami, Miami, Florida*
[12] *Department of Hematology, CHU Grenoble Alpes, Grenoble, France*
[13] *Department of Hematology/Oncology, Hospital Infantil Universitario Nino Jesus, Madrid, Spain*
[14] *Adult Blood & Marrow Transplant Program, Texas Transplant Institute, San Antonio, Texas*
[15] *Hematology Research Centre, Division of Experimental Medicine, Department of Medicine, Imperial College London, London, United Kingdom*
[16] *Division of Hematological Malignancy and Cellular Therapeutics, University of Kansas Health System, Kansas City, Kansas*
[17] *Hematolgic Malignancies & Bone Marrow Transplant, Department of Medical Oncology, New York Presbyterian Hospital/Weill Cornell Medical Center, New York, New York*
[18] *Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts*
[19] *Blood & Marrow Transplant Program, Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio*
[20] *Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota*
[21] *Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia*
[22] *Division of Hematology/Oncology/Bone Marrow Transplantation, Department of Medicine, University of Wisconsin, Madison, Wisconsin*
[23] *Markey Cancer Center, University of Kentucky, Lexington, Kentucky*
[24] *Division of Medical Oncology, Fred Hutchinson Cancer Research Center, Seattle, Washington*
[25] *Department of Medicine, Cleveland Clinic Taussig Cancer Center, Cleveland Ohio*
[26] *Case Western Reserve University, Cleveland, Ohio*
[27] *Divison of Clinical Hematology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*
[28] *Division of Blood and Marrow Transplantation, Stanford University, Stanford, California*
[29] *Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida*
[30] *Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York*
[31] *Blood & Marrow Transplantation Program, Division of Hematology/Oncology, Department of Medicine, Greenebaum Comprehensive Cancer Center, University of Maryland, Baltimore, Maryland*
[32] *Division of Hematology and Oncology, Department of Medicine, Penn State Hershey Medical Center, Hershey, Pennsylvania*
[33] *Division of Hematology/Oncology, Department of Medicine, Abramson Cancer Center, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania*
[34] *Division of Hematology/Oncology, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania*

Financial disclosure: See Acknowledgments on page 2406.
* Correspondence and reprint requests: Saurabh Chhabra, MD, MS, Division of Hematology/Oncology, Department of Medicine, Medical College of Wisconsin, 9200 W Wisconsin Avenue, Milwaukee, WI 53226
E-mail address: schhabra@mcw.edu (S. Chhabra).

https://doi.org/10.1016/j.bbmt.2019.08.012

Article history:
Received 24 May 2019
Accepted 14 August 2019

Keywords:
Total body irradiation
Allogeneic hematopoietic cell transplantation
Myeloablative conditioning
Hematologic malignancies

A B S T R A C T

Malignancy relapse is the most common cause of treatment failure among recipients of hematopoietic cell transplantation (HCT). Conditioning dose intensity can reduce disease relapse but is offset by toxicities. Improvements in radiotherapy techniques and supportive care may translate to better outcomes with higher irradiation doses in the modern era. This study compares outcomes of recipients of increasing doses of high-dose total body irradiation (TBI) divided into intermediate high dose (IH; 13-13.75 Gy) and high dose (HD; 14 Gy) with standard dose (SD; 12 Gy) with cyclophosphamide. A total of 2721 patients ages 18 to 60 years with hematologic malignancies receiving HCT from 2001 to 2013 were included. Cumulative incidences of nonrelapse mortality (NRM) at 5 years were 28% (95% confidence interval [CI], 25% to 30%), 32% (95% CI, 29% to 36%), and 34% (95% CI, 28% to 39%) for SD, IH, and HD, respectively (P = .02). Patients receiving IH-TBI had a 25% higher risk of NRM compared with those receiving SD-TBI (12 Gy) (P = .007). Corresponding cumulative incidences of relapse were 36% (95% CI, 34% to 38%), 32% (95% CI, 29% to 36%), and 26% (95% CI, 21% to 31%; P = .001). Hazard ratios for mortality compared with SD were 1.06 (95% CI, .94 to 1.19; P = .36) for IH and .89 (95% CI, .76 to 1.05; P = .17) for HD. The study demonstrates that despite improvements in supportive care, myeloablative conditioning using higher doses of TBI (with cyclophosphamide) leads to worse NRM and offers no survival benefit over SD, despite reducing disease relapse.

INTRODUCTION

Relapse of underlying disease is the most frequent cause of treatment failure after allogeneic hematopoietic cell transplant (HCT) for hematologic malignancies [1]. Nonrelapse mortality (NRM) accounts for the bulk of the remainder of deaths (20% to 30%) [2-5]. One strategy to reduce relapse risk is to intensify the pretransplant conditioning regimen. Several studies have demonstrated that increasing the intensity of the conditioning regimen can reduce relapse risk [6-9]. Indeed, a prospective randomized trial of myeloablative conditioning (MAC) versus reduced-intensity conditioning for adults with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) in first remission confirmed that greater conditioning intensity resulted in significantly lower relapse risk and improved relapse-free survival [10]. The outcomes after MAC regimens of cyclophosphamide (Cy) with total body irradiation (Cy/TBI) and busulfan/Cy after allogeneic HCT for acute and chronic leukemia were compared in a prospective study [11] and demonstrated that the adjusted 3-year overall survival (OS) was higher with Cy/TBI (versus busulfan/Cy with oral busulfan), although there was no difference in relapse-free survival between the cohorts. More recently, however, a few observational studies have reported that busulfan/Cy (using intravenous busulfan) may offer a survival advantage over Cy/TBI in patients with AML [12-14], whereas for acute lymphoblastic leukemia (ALL) patients, TBI was associated with a lower relapse rate and favorable event-free survival, compared with oral busulfan when combined with Cy [15]. Attempts to further optimize conditioning regimens have not improved outcomes except in small, single-center studies [16-20].

Radiation is highly lethal to leukemic cells in a dose-dependent fashion [21,22]. This observation led investigators, over 3 decades ago, to attempt to escalate radiation doses given as conditioning before transplant. The use of higher doses of TBI (>12 Gy), in combination with chemotherapy, has been reported in small, single-institution studies [23-26]. The upper limit of TBI dose of 16 Gy was established in combination with Cy and of 14.4 Gy when used in combination with etoposide. A study comparing 12 Gy with 15.75 Gy established that the maximum tolerable dose of TBI with Cy was fractionated TBI at a dose of 12 Gy [27]. Although higher doses of radiation were indeed associated with lower relapse risk, this benefit was negated by increased NRM, and there was no difference in OS. However, in the last 2 decades advances in the delivery of radiation therapy and substantial improvements in supportive care raise the question of whether, in the current era, higher doses of TBI (>12 Gy) result in improved NRM and lower relapse rate and therefore improved OS outcomes after allogeneic HCT, respectively [28-30]. We queried the Center for International Blood and Marrow Transplant Research (CIBMTR) registry to understand whether high-dose TBI would translate into improved survival outcomes. We hypothesized that advances in supportive care and radiation delivery would reduce toxicity and NRM, thus yielding an OS advantage to higher doses of TBI.

METHODS

Data Source

The CIBMTR is a research collaboration between the Medical College of Wisconsin and the National Marrow Donor Program. The CIBMTR comprises a network of more than 450 transplant centers worldwide that contribute data on allogeneic and autologous HCTs to a centralized statistical center for observational studies [31]. Health information is collected and maintained in the CIBMTR's capacity as a public health authority under the Health Insurance Portability and Accountability Act privacy rules.

Patients

The study included 2721 adults with AML, ALL, MDS, and chronic myeloid leukemia (CML) receiving Cy/TBI, with TBI at varying doses, as conditioning in anticipation of a first allogeneic HCT from a well-matched sibling or unrelated donor between 2001 and 2013. Either matched siblings or well-matched or partially matched (7/8) unrelated donors were included. Patients with inherited syndromes predisposing to acute leukemia, those with central nervous system involvement with disease, and those who received prior radiation for any reason were excluded. We defined 3 TBI dose groups: patients receiving standard dose (12 Gy, SD-TBI), intermediate high dose (13-13.75 Gy, IH-TBI), and high dose (14 Gy, HD-TBI).

Study Endpoints

The primary endpoint of the study was NRM, defined as death from any cause in continuous remission or death within the first 28 days of transplant from any cause and was summarized by cumulative incidence estimate with relapse as competing risk. Secondary endpoints included OS, defined as time from transplant to death from any cause, with surviving patients censored at time of last contact, and disease-free survival (DFS), in which events were defined as death or relapse. Relapse was summarized by cumulative incidence estimate with NRM as the competing risk. We also sought to evaluate the incidence of other forms of toxicity and morbidity after allogeneic HCT including acute and chronic graft-versus-host disease (GVHD), veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) of the liver [32,33], and idiopathic pneumonia syndrome (IPS) [34], all diagnosed on the basis of established criteria. Grading of acute and chronic GVHD was based on previously defined consensus criteria [35,36].

Statistical Analysis

Patient-, disease-, and transplant-related characteristics were compared among the TBI dose groups using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Outcomes of 3 TBI dose groups were compared using log-rank and Gray's test. NRM was described using the cumulative incidence function, with relapse as a competing risk,

according to the method of Fine and Gray [37]. Cumulative incidences of GVHD, VOD/SOS, and IPS were evaluated by Fine and Gray's method of competing risks as well, with death as competing risk. Disease relapse was also reported using the cumulative incidence function, with NRM as the competing risk. Survival probabilities of OS and DFS were calculated using the Kaplan-Meier estimator and compared using the log-rank test. Multivariate analysis was performed using Cox proportional hazards regression models for OS, DFS, acute GVHD, chronic GVHD, VOD/SOS, and IPS, whereas Fine and Gray subdistribution hazards models [37] were used for relapse and NRM.

The following variables were included in the analysis: recipient age, disease, disease status at HCT, donor type, in vivo T cell depletion, GVHD prophylaxis, Karnofsky performance score (KPS), donor-recipient sex match, and year of transplant. All clinical variables were tested first for the affirmation of the proportional hazards assumption. Factors violating the proportional hazards assumption were adjusted through stratification. Then, a stepwise, forward-backward procedure was performed to select the adjusted clinical variables (with a threshold of .05 for both entry and stay in the model) and to build the multivariate models. To account for multiple comparisons, $P < .01$ was used as the significance level for the main effect. Analysis was also conducted to evaluate center effect. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient and Transplant Characteristics

Patient characteristics across the 3 TBI groups in the study cohort (N = 2721) are shown in Table 1. Patients in the 3 groups received TBI doses of 12 Gy (SD-TBI; n = 1745), 13 to 13.75 Gy (IH-TBI; n = 648), and 14 Gy (HD-TBI; n = 328). The completeness index at 5 years after allogeneic HCT was excellent (92% to 96%). The HD-TBI group was older and had lower KPSs. AML was the most common indication for allogeneic HCT across the cohort and was a more frequent indication in the HD-TBI group compared with the SD-TBI group (60% versus 48%, respectively). ALL, in contrast, was less common in the HD-TBI group versus SD-TBI group (15% versus 37%, respectively). HD-TBI–based HCTs were reported from 13 centers, compared with SD-TBI recipients from 155 centers and IH-TBI recipients from 49 centers. Median follow-up of survivors was similar across the groups at 67 to 73 months after allogeneic HCT.

Transplant characteristics are presented in Table 2. Fractionated TBI was administered to patients in all 3 groups. The IH-TBI group received a median of 8 fractions with a median dose of 165 cGy per fraction, compared with a median of 6 and 7 fractions (with median doses of 200 cGy per fraction) in the SD-TBI and HD-TBI groups, respectively ($P < .001$). The HD-TBI group received a lower dose of Cy (median 90 mg/kg versus 120 mg/kg in the other 2 groups, $P < .001$). The SD-TBI group had a higher proportion of patients with a matched sibling donor (43% versus 33% in the other 2 groups, $P < .001$). Approximately 17% of patients in all 3 groups received allogeneic HCT using a 7/8-matched unrelated donor. With respect to GVHD prophylaxis, most patients (>98%) received a calcineurin inhibitor, and most did not receive in vivo T cell depletion. Peripheral blood grafts were used more commonly in the HD-TBI group (76%) compared with both the SD-TBI (71%) and IH-TBI (65%) groups.

Impact of Conditioning TBI Dose on Post-Transplant Outcomes

Nonrelapse mortality

Univariate analysis revealed that at 5 years post-HCT, NRM was 28% (95% confidence interval [CI], 25% to 30%) for the SD-TBI group, 32% (95% CI, 29% to 36%) for the IH-TBI group, and 34% (95% CI, 28% to 39%) for the HD-TBI group ($P = .02$) (Table 3). Multivariate modeling using Fine and Gray's method accounting for competing risks confirmed that TBI dose was statistically significantly associated with NRM ($P = .009$) (Table 4, Figure 1). Patients receiving IH-TBI (13 to 13.75 Gy) had a 25% higher risk of NRM compared with those receiving SD-TBI (12 Gy) ($P = .007$). The HD-TBI group (14 Gy), however, did not have a significantly increased NRM risk compared with the SD-TBI ($P = .03$) or IH-TBI ($P = .96$) groups. Multivariate analysis also showed older patients (>30 years versus <20 years), those with MDS and ALL (versus AML), those with unrelated donor (versus matched sibling donor), and those who received calcineurin inhibitor/mycophenolate mofetil (versus calcineurin inhibitor/methotrexate) had a higher NRM risk (Supplemental Table S1). In addition, NRM risk improved with each time period (2011 to 2013 versus 2001 to 2003; hazard ratio [HR], .46; $P < .0001$) over the years.

Overall survival

OS after allogeneic HCT was similar across the 3 TBI dose groups on univariate analysis: 5-year OS was 42% (95% CI, 39% to 44%), 40% (95% CI, 36% to 44%), and 45% (95% CI, 39% to 50%)

Table 1
Patient Characteristics in the Observational Study of Allogeneic Transplant Patients Receiving MAC Regimen of Cy and TBI with Different Doses of TBI Between 2001 and 2013

Characteristics	12 Gy (n = 1745)	13-13.75 Gy (n = 648)	14 Gy (n = 328)	*P*
No. of centers	155	49	13	
Age, yr, median (range)	39 (18-60)	39 (18-60)	43 (18-60)	<**.001**
Male sex	959 (55)	344 (53)	169 (52)	.436
KPS 90%-100%	1197 (69)	405 (63)	190 (58)	<**.001**
Disease				<**.001**
AML	836 (48)	352 (54)	198 (60)	
ALL	647 (37)	175 (27)	49 (15)	
CML	202 (12)	89 (14)	50 (15)	
MDS	60 (3)	32 (5)	31 (9)	
Disease status before transplant				.50
Early	912 (52)	331 (51)	157 (48)	
Intermediate	421 (24)	164 (25)	78 (24)	
Advanced	407 (23)	153 (24)	90 (27)	
Not reported	5 (<1)	0	3 (<1)	
BMI, kg/m^2, median (range)	25 (16-49)	24 (17-49)	27 (17-49)	<**.001**

Values are n (%) unless otherwise defined.
Bold P-values denote statistical significance.

Table 2
Transplant Characteristics in The Observational Study of Allogeneic Transplant Patients Receiving MAC Regimen of Cy and TBI at Different Doses Between 2001 and 2013

Characteristics	12 Gy (n = 1745)	13-13.75 Gy (n = 648)	14 Gy (n = 328)	*P*
Time from diagnosis to transplant, mo, median (range)	7 (1-252)	7 (2-310)	6 (1-222)	.44
Number of fractions, median (range)	6 (2-12)	8 (3-12)	7 (2-8)	**<.001**
TBI dose per fraction, cGy, median (range)	200 (100-600)	165 (108-440)	200 (175-700)	**<.001**
Cy dose, mg/kg, median (range)	120 (34-240)	120 (36-239)	90 (33-206)	**<.001**
Donor type				**<.001**
HLA-identical sibling	746 (43)	216 (33)	109 (33)	
Matched unrelated (8/8)	694 (40)	313 (48)	164 (50)	
Partially matched unrelated (7/8)	305 (17)	119 (18)	55 (17)	
Graft source				**<.001**
Bone marrow	504 (29)	228 (35)	79 (24)	
Peripheral blood	1241 (71)	420 (65)	249 (76)	
Donor–recipient sex match				.37
Male–male	606 (35)	218 (34)	114 (35)	
Male–female	446 (26)	176 (27)	78 (24)	
Female–male	347 (20)	125 (19)	55 (17)	
Female–female	338 (19)	128 (20)	81 (25)	
Not reported	8 (<1)	1 (<1)	0	
Donor–recipient cytomegalovirus status				.02
-/-	510 (29)	157 (24)	99 (30)	
-/+	429 (25)	183 (28)	96 (29)	
+/-	193 (11)	63 (10)	38 (12)	
+/+	527 (30)	207 (32)	76 (23)	
Not reported	86 (5)	38 (6)	19 (6)	
Unrelated donor age, yr, median (range)	33 (19-61)	33 (18-58)	32 (19-60)	.95
Year of transplant				**.005**
2001-2005	809 (46)	267 (41)	149 (45)	
2006-2010	749 (43)	308 (48)	161 (49)	
2011-2013	187 (11)	73 (11)	18 (5)	
Inpatient days, median (range)	29 (<1-123)	32 (<1-175)	26 (<1-100)	
Follow-up of survivors, mo, median (range)	72 (3-167)	67 (4-148)	72 (5-144)	

Values are n (%) unless otherwise defined.
Bold P-values denote statistical significance.

in the SD-TBI, IH-TBI, and HD-TBI groups, respectively ($P = .39$) (Table 3). The multivariate analysis also showed no significant association between the TBI dose and OS ($P = .18$) (Table 4, Figure 2). The analysis also demonstrated that younger patients (<20 years versus >40 years), those with CML (versus AML), those with matched sibling donor (versus unrelated donor), those receiving calcineurin inhibitor/methotrexate (versus calcineurin inhibitor/mycophenolate mofetil), and those with KPS ≥ 90 (versus <90) had significantly improved OS (Supplemental Table S2). OS also improved significantly with each time interval (eg, 2011 to 2013 versus 2001 to 2003; HR, .6; $P < .0001$)

Disease-free survival

Univariate analysis demonstrated that the 5-year probability of DFS did not differ significantly among TBI dose groups and was 37% (95% CI, 34% to 39%), 35% (95% CI, 32% to 39%), and 40% (95% CI, 35% to 46%) in the SD-TBI, IH-TBI, and HD-TBI groups, respectively ($P = .36$) (Table 3). There was no significant difference in DFS among the 3 TBI dose groups on multivariate analysis (Table 4, Figure 3).

Relapse

The risk of disease relapse post-HCT differed significantly among the TBI dose groups on univariate analysis. The 5-year cumulative incidences of relapse were 36% (95% CI, 34% to 38%) in the SD-TBI group, 32% (95% CI, 29% to 36%) in the IH-TBI group, and 26% (95% CI, 21% to 31%) in the HD-TBI group ($P < .001$) (Table 3). Multivariate analysis showed that HD-TBI recipients had a significantly lower relapse risk compared with SD-TBI recipients (HR, .69; $P = .002$) (Table 4, Figure 4). Patients with MDS (versus AML) and early (versus intermediate or advanced) disease and with matched sibling donor (versus unrelated) had a lower risk of relapse (Supplemental Table S3).

Acute GVHD

Univariate analysis revealed 1-year cumulative incidence of grades II to IV acute GVHD in the IH-TBI group was 49% (95% CI, 45% to 53%) compared with 43% in the SD-TBI group (95% CI, 40% to 45%) and 42% in the HD-TBI group (95% CI, 37% to 47%; $P = .02$) (Table 3). On multivariate analysis, TBI dose was not associated with grades II to IV acute GVHD ($P = .01$) or grades III to IV acute GVHD ($P = .21$) (Table 4).

Chronic GVHD

On univariate analysis, 5-year cumulative incidence of chronic GVHD was not significantly different among the three groups: 52% (95% CI, 49% to 54%) in the SD-TBI group, 50% (95% CI, 46% to 54%) in the IH-TBI group, and 53% (95% CI, 48% to 59%) in the HD-TBI group ($P = .68$) (Table 3). However,

Table 3
Unadjusted Clinical Outcomes after MAC Allogeneic Transplant Using Matched Sibling and Unrelated Donor by TBI Dose (2001-2013)

Outcomes	12 Gy (n = 1745)	13-13.75 Gy (n = 648) Probability (95% CI)	14 Gy (n = 328) Probability (95% CI)	*P*
VOD/SOS				
100-day	5 (4-6)	6 (4-7)	9 (6-12)	.09
IPS				
2-year	8 (6-9)	8 (6-11)	9 (6-13)	.57
Grade II-IV acute GVHD				
1-year	43 (40-45)	49 (45-53)	42 (37-47)	.02
Grade III-IV acute GVHD				
1-year	19 (17-21)	23 (20-26)	20 (16-25)	.10
Chronic GVHD				
5-year	52 (49-54)	50 (46-54)	53 (48-59)	.68
Relapse				
1-year	27 (25-29)	25 (22-28)	20 (16-24)	.01
5-year	36 (34-38)	32 (29-36)	26 (21-31)	**<.001***
NRM				
5-year	28 (25-30)	32 (29-36)	34 (28-39)	.02
DFS				
5-year	37 (34-39)	35 (32-39)	40 (35-46)	.29
OS				
5-year	42 (39-44)	40 (36-44)	45 (39-50)	.39

Values are probability in percents (95% CI).
Bold P-values denote statistical significance.
* Significant at $P < .01$ level.

multivariate analysis suggested that the risk of chronic GVHD among the 3 cohorts was time dependent. TBI was significantly associated with chronic GVHD in the first 8 months post-HCT ($P = .0001$) but not beyond 8 months after HCT ($P = .02$) (Table 4). HD-TBI conferred a lower risk of chronic GVHD compared with SD-TBI (HR, .64; $P = .0001$) early on after allogeneic HCT.

TBI-associated post-transplant organ dysfunction

On univariate analysis, the 100-day cumulative incidences of VOD/SOS after allogeneic HCT were 5% (95% CI, 4% to 6%), 6% (95% CI, 4% to 7%), and 9% (95% CI, 6% to 12%) in the SD-TBI, IH-TBI, and HD-TBI groups, respectively (Table 3). Multivariate analysis showed TBI dose was not significantly associated with risk of VOD/SOS ($P = .03$) (Table 4). TBI dose also had no significant association with IPS after allogeneic HCT, which carried a 2-year cumulative incidence of 8% to 9% in the 3 cohorts (Tables 3-4).

Causes of Death

Relapse of primary disease was the most common cause of death in all 3 groups (Table 5). However, there were more relapse-related deaths with SD-TBI (55%) compared with the other 2 groups (47% in the IH-TBI group and 40% in the HD-TBI group). The proportion of deaths due to organ failure increased with higher doses of TBI (19% in the HD-TBI group and 9% in the SD-TBI group). Respiratory and multiorgan failure were most common, followed by heart failure and hepatic dysfunction (Table 6).

DISCUSSION

This contemporary observational study compared MAC regimens containing Cy combined with 3 TBI dose groups in allogeneic HCT recipients with AML, ALL, CML, and MDS. The HD-TBI group had a more frequent use of peripheral blood graft and unrelated donors, had fewer patients with KPS > 90, and had a higher median age: All variables were included in multivariate modeling to account for the baseline differences. Compared with 12 Gy TBI, we observed increased NRM with an intermediate TBI dose of 13 to 13.75 Gy and lower relapse with a high TBI dose (14 Gy). Although the analysis showed significant difference in NRM risk between the SD-TBI and IH-TBI groups, there was no significant difference in the risk of NRM between the HD-TBI and the other 2 groups. However, the impact on NRM seemed to be equal once the TBI dose increased beyond SD-TBI: Comparing the NRM risk between the HD-TBI and SD-TBI groups in the multivariate model showed the HR for death was 1.25 (the same as the HR with the IH-TBI compared with the SD-TBI group). It is likely that the statistical significance was not reached given the small sample size of the HD-TBI group, hindering the power to detect a difference; a larger population may have shown significant results. With regards to the relapse model, there is a linear relationship with increments on the TBI dose: HR (for death) of 1.0 for the SD-TBI group, .92 for the IH-TBI group, and .69 for the HD-TBI group (not statistically significant). With the potentially opposing effects of TBI dose on relapse and NRM, there was no significant difference observed in OS and DFS among the TBI dose groups in the study.

There was no statistically significant difference in the risk of grades II to IV or III to IV acute GVHD. Furthermore, no association of TBI dose with the risk of IPS was found. The risk of chronic GVHD (in the early post-HCT period) was lower in patients receiving HD-TBI, an unexpected finding, particularly given the absence of significant difference in acute GVHD risk. Although there is no good explanation for having an increased risk of chronic GVHD after SD-TBI compared with higher doses, one possibility is that SD-TBI patients received early interventions to prevent or treat relapse, such as withdrawal of immunosuppression or donor leukocyte infusions, which would then be expected to result in increased risk of early-onset chronic GVHD. However, we did not have access to the post-transplant data to support this hypothesis. There is also a possibility of residual confounding by other variables that were not included in the analysis such as post-transplant therapeutic interventions. The

Table 4
TBI Dose in Multivariate Models of Treatment with Cy plus TBI as MAC Regimen for Allogeneic Transplant Using Matched Sibling and Unrelated Donor (2001-2013)

Outcome	n	Events	HR	Upper	Lower	*P*
OS						
TBI dose						.18
12 Gy	1732	1024	1.0			
13-13.75 Gy	647	394	1.06	.94	1.19	.36
14 Gy	325	190	.89	.76	1.05	.17
14 Gy vs. TBI 13-13.75 Gy (Ref.)			.85	.71	1.01	.06
DFS						
TBI dose						.04
12 Gy	1727	1098	1.0			
13-13.75 Gy	644	423	1.01	.90	1.13	.90
14 Gy	323	199	.83	.71	.97	.02
14 Gy vs. TBI 13-13.75 Gy (Ref.)			.82	.69	.97	.02
NRM						
TBI dose						**.009**[*]
12 Gy	1734	486	1.0			
13-13.75 Gy	645	215	1.25	1.06	1.48	**.007**
14 Gy	326	117	1.25	1.02	1.53	.03
14 Gy vs. TBI 13-13.75 Gy (Ref.)			.99	.79	1.25	.96
Relapse						
TBI dose						**.008**[*]
12 Gy	1737	618	1.0			
13-13.75 Gy	646	209	.92	.78	1.08	.29
14 Gy	323	84	.69	.55	.88	**.002**[*]
14 Gy vs. TBI 13-13.75 Gy (Ref.)			.76	.59	.98	.03
Acute GVHD grades II-IV						
TBI dose[†]	.	.	.	.	.	.01
12 Gy	1724	739	1.0	.	.	.
13-13.75 Gy	640	313	1.15	1.00	1.31	.05
14 Gy	326	137	.85	.71	1.03	.09
14 Gy vs. TBI 13-13.75 Gy (Ref.)			.74	.61	.91	.004
Acute GVHD grades III-IV						
TBI dose						.21
12 Gy	1728	329	1.0			
13-13.75 Gy	641	148	1.18	.97	1.44	.10
14 Gy	324	66	.96	.73	1.27	.79
14 Gy vs. TBI 13-13.75 Gy (Ref.)			.82	.61	1.10	.18
Chronic GVHD						
TBI dose (≤8 months)						**.0001**[‡]
12 Gy	1127	622	1.0			
13-13.75 Gy	401	205	.83	.71	.97	.02
14 Gy	193	96	.64	.52	.80	**.0001**[*]
14 Gy vs. TBI 13-13.75 Gy (Ref.)			.78	.61	1.00	.05
TBI dose (>8 months)						.02
12 Gy	588	217	1.0			
13-13.75 Gy	239	102	1.10	.98	1.24	.12
14 Gy	133	75	1.00	.62	1.62	.99
14 Gy vs. TBI 13-13.75 Gy (Ref.)			.91	.51	1.63	.75
VOD/SOS						
TBI dose						.03
12 Gy	1737	88	1.0			
13-13.75 Gy	648	36	1.16	.78	1.71	.46
14 Gy	322	30	1.77	1.17	2.69	.007
14 Gy vs. TBI 13-13.75 Gy (Ref.)			1.53	.94	2.49	.08
IPS						
TBI dose						.80
12 Gy	1715	131	1.0			
13-13.75 Gy	634	53	1.08	.78	1.49	.63

(*continued*)

Table 4 (*Continued*)

Outcome	n	Events	HR	Upper	Lower	*P*
14 Gy	318	30	1.12	.75	1.67	.57
14 Gy vs. TBI 13-13.75 Gy (Ref.)			1.04	.66	1.63	.87

Bold P-values denote statistical significance.
* Significant at $P < .01$ level.
† All patients received Cy with TBI.
‡ Significant at $P < .01$ level.

study demonstrated no significant association between the TBI dose and the risk of IPS after allogeneic HCT. Although the incidence of VOD/SOS of the liver was higher with higher doses of TBI, this observation did not meet statistical significance.

Radiation is a potent antitumor therapy that is not dependent on cell cycle, growth, or metabolism and is not affected by common methods of chemotherapy resistance such as P-glycoprotein pumps [38-40], and so chemotherapy-resistant clones may still be radiosensitive [41]. Furthermore, radiation is directly toxic to hematopoietic stem cells [21,22] and can reach potential sanctuary sites such as testis and brain [41], making TBI an important component of the conditioning regimens before allogeneic HCT for treatment of hematologic malignancies. TBI has traditionally been a part of MAC regimens with the objective of eradicating malignant cells and also providing the immunosuppression needed to prevent rejection of donor hematopoietic cells [41]. Dose escalation of TBI in MAC has been investigated and demonstrated to be feasible with acceptable NRM in several single-center studies [23,24,26]. Myeloablative TBI dose cohorts have been compared in a few studies and have shown reduced relapse risk of AML [27,42], CML [43], and ALL [44] with higher dose TBI in the conditioning. A randomized study by Clift et al. [42] published in 1990s evaluated a conditioning regimen of Cy 120 mg/kg in combination with TBI 15.75 Gy with 7 consecutive daily fractions of 2.25 Gy (n = 37) and demonstrated a lower relapse risk compared with TBI 12 Gy with 6 consecutive daily fractions of 2 Gy (n = 34) in patients with AML in first complete remission. The 3-year probabilities of relapse were 35% for the 12-Gy group and 12% for the 15.75-Gy group ($P = .06$). However, the 3-year NRM was 12% and 32% for the 2 respective groups ($P = .04$). In essence, the increased dose of TBI significantly reduced the probability of relapse but did not improve OS because of increased NRM.

Baseline demographics show the HD-TBI recipients were older, with poorer KPS: This suggests the possibility of selection bias by clinicians to target a higher risk patient population with increased TBI dose. However, multivariate analysis should account for these differences. Similarly, the analysis accounted for the higher proportion of AML patients in the HD-TBI group. The analysis demonstrated significantly better OS in CML patients (versus AML; HR, .8; $P = .006$); MDS patients experienced higher NRM (versus AML; HR, 1.82; $P = .0001$) and lower relapse risk (versus AML; HR, .45; $P < .0001$) on multivariate analysis. With regards to donor–recipient HLA matching, because the proportion of 7/8-matched unrelated donors was similar across all 3 groups and our multivariate analysis adjusted for degree of HLA matching, this small group of patients is unlikely to have altered our results. It is worth noting that we tested for interaction between the TBI dose and disease type, disease risk, and all other variables for each endpoint and found none. The study covered a period of 14 years, and, as expected, patients receiving allogeneic HCT in more recent years experienced significantly less NRM (36% better in 2008 to 2010 and 54% improvement in 2011 to 2013 as compared with 2001 to 2003, respectively) and OS (23% and 40% improvement over 2001 to 2003, respectively) (Supplemental Tables S1 and S2). The lack of significant interaction between the TBI dose and the categorical variable of year of HCT indicates that the improvement in NRM over time has been observed in all TBI-based MAC allogeneic HCTs regardless of the TBI dose. Stated differently, the results suggest that despite the improvement in supportive care over the years, which may allow for a higher dose of TBI, NRM continues to be higher with HD-TBI.

This study has many limitations, including those inherent with the retrospective nature of the study arising from nonrandom assignment to the TBI groups, institutional variability in TBI dosing and fractionation, and variation in Cy dosing (the HD-TBI group had a lower median Cy dose to allow a higher TBI dose) (Table 2). It is important to point out that the reason for selecting the doses of TBI is not known; the TBI doses were

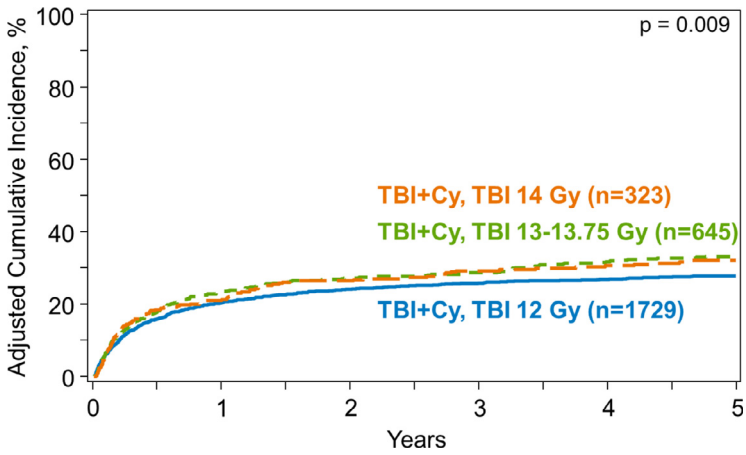

Figure 1. Cumulative incidence function of NRM by dose of TBI.

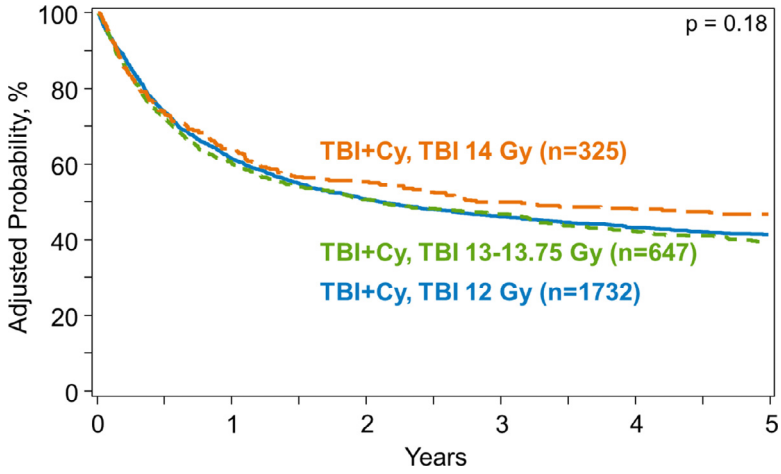

Figure 2. Kaplan-Meier curve of OS by dose of TBI.

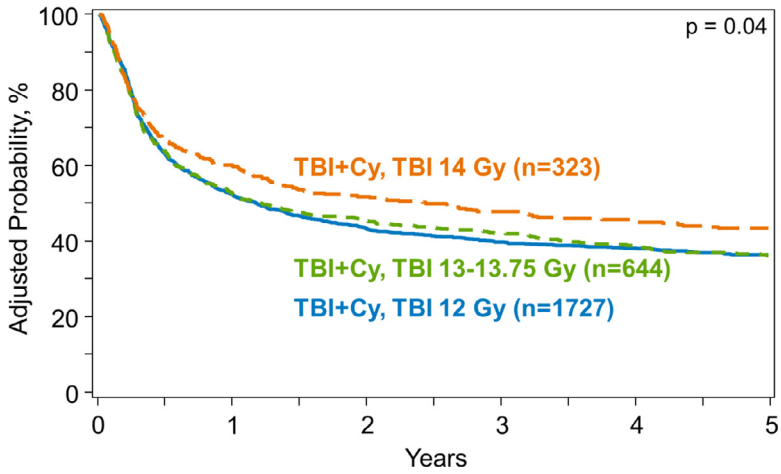

Figure 3. Kaplan-Meier curves of DFS by dose of TBI.

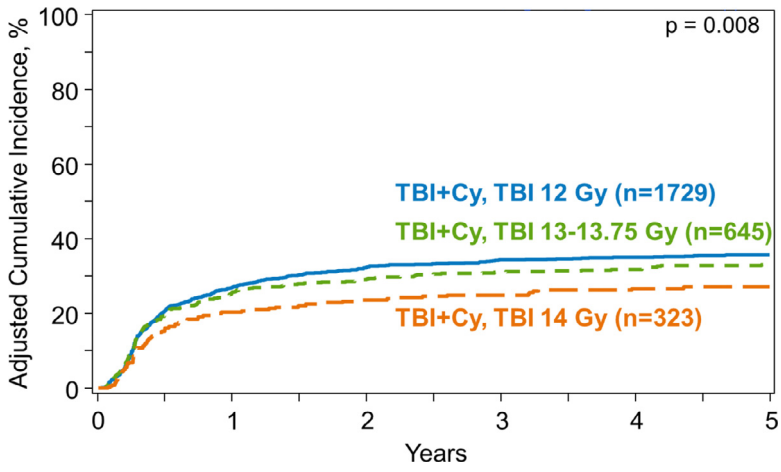

Figure 4. Cumulative incidence function of relapse by dose of TBI.

most likely decided by the institutions as a matter of preference and were likely not based on the disease risk category, as evident from Table 1. Nonetheless, we cannot exclude potential selection bias in the higher dose TBI groups and residual confounding that could not be addressed by the analysis. The much smaller number of HD-TBI conditioned transplant in the recent time periods (6% in 2011 to 2013 versus 12% in 2001 to 2005 versus 13% in 2006 to 2010) may indicate that this bias is present (Table 1). From a radiobiologic perspective, a major shortcoming of this analysis is anchoring the analysis on total

Table 5
Causes of Death after MAC Allogeneic Transplant Using Cy and TBI as Conditioning by TBI Dose (2001-2013)

Cause of Death	12 Gy (n = 1034)	13-13.75 Gy (n = 395)	14 Gy (n = 192)
Primary disease	564 (55)	184 (47)	77 (40)
New malignancy	9 (1)	4 (1)	3 (2)
GVHD	112 (11)	63 (16)	24 (13)
Interstitial pneumonitis	52 (5)	15 (4)	9 (5)
Infection	131 (13)	47 (12)	27 (14)
Organ failure	96 (9)	46 (12)	37 (19)
Other cause	62 (6)	29 (7)	13 (7)
Not reported	8 (1)	7 (2)	2 (1)

Values are n (%).

Table 6
Organ Failure as Cause of Death after MAC Allogeneic Transplant Using Cy and TBI as Conditioning by TBI Dose (2001-2013)

Organ	12 Gy	13-13.75 Gy	14 Gy
Liver (n = 21)	10	7	4
VOD/SOS (n = 14)	4	4	6
Cardiac (n = 28)	17	8	3
Pulmonary (n = 61)	36	10	15
Central nervous system (n = 5)	3	2	0
Renal (n = 6)	4	0	2
Multiple organ (n = 39)	20	13	6
Other (n = 4)	1	2	1

TBI dose; we were unable to incorporate dose rate and/or protractionation. These fundamental variables are known to be associated with the biologic consequences of ionizing radiation exposure, and interpreting the data in the absence of these variables can be difficult. This variability in clinical practice with regards to the use of TBI among centers is exemplified by the study by European Society for Blood and Marrow Transplantation that surveyed 56 centers from 23 countries and demonstrated significant differences in the treatment technique, dose per fraction, in the organs shielded and the maximum accepted total delivered dose to those organs [45]. Furthermore, we did not evaluate TBI dose in combination with chemotherapy agents other than Cy such as etoposide, melphalan, or fludarabine, and this limits the generalizability of the study findings. The question of optimal TBI dose for other types of allogeneic transplant, such as umbilical cord blood and haploidentical transplants in the myeloablative setting, remains unanswered.

In conclusion, TBI dose of over 12 Gy was demonstrated to reduce relapse risk, but this advantage was hampered by the increase in NRM, which likely translated into no significant impact on OS. The study results suggest that Cy/TBI 12 Gy therefore should be considered the optimal conditioning regimen for patients with AML, ALL, MDS, and CML undergoing MAC allogeneic HCT. Higher TBI dosing may be associated with greater morbidity, as evidenced by the higher incidence of organ failure as the cause of death (Table 5). We can speculate that young adults (<40 years) with robust performance status (KPS $\geq$ 90), advanced disease (myeloid malignancy), and a matched sibling donor may derive greater survival benefit from HD-TBI (compared with <14 Gy TBI; Supplemental Tables S2 and S4). Future research should focus on novel strategies to protect patients against the adverse effects of high-dose TBI. Its potency in disease control is clear; reducing TBI's toxicity and NRM may therefore help overcome relapse, the most significant barrier to long-term survival after allogeneic HCT. Developing safer methods to deliver radiation, and sparing sensitive organs, continues to be an important area of research to maximize the effectiveness of high-dose TBI in allogeneic HCT recipients.

ACKNOWLEDGMENTS

The authors thank Jennifer Motl for editorial support in accordance with Good Publication Practice guidelines (http://www.ismpp.org/gpp3).

Financial disclosure: The CIBMTR is supported primarily by Public Health Service Grant/Cooperative Agreement 5U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases; a grant/cooperative agreement (1U24HL138660) from the NHLBI and NCI; a contract (HHSH250201700006C) with Health Resources and Services Administration; grants N00014–17–1–2388, N00014–17–1–2850, and N00014–18–1–2045 from the Office of Naval Research (HHSH250201700006C); and grants from Adaptive Biotechnologies; *Amgen, Inc.; Anonymous donation to the Medical College of Wisconsin; Astellas Pharma US; Atara Biotherapeutics, Inc.; Be the Match Foundation; *bluebird bio, Inc.; *Bristol Myers Squibb Oncology; *Celgene Corporation; *Chimerix, Inc.; *CytoSen Therapeutics, Inc.; Fred Hutchinson Cancer Research Center; Gamida Cell Ltd.; Gilead Sciences, Inc.; HistoGenetics, Inc.; Immucor; *Incyte Corporation; Janssen Scientific Affairs, LLC; *Jazz Pharmaceuticals, Inc.; Karius, Inc.; Karyopharm Therapeutics, Inc.; *Kite Pharma, Inc.; Medac, GmbH; *Mediware; The Medical College of Wisconsin; *Merck & Co, Inc.; *Mesoblast; MesoScale Diagnostics, Inc.; Millennium, the Takeda Oncology Co.; *Miltenyi Biotec, Inc.; Mundipharma EDO; National Marrow Donor Program; Novartis Pharmaceuticals Corporation; PCORI; *Pfizer, Inc; *Pharmacyclics, LLC; PIRCHE AG; *Sanofi Genzyme; *Seattle Genetics; Shire; Spectrum Pharmaceuticals, Inc.; St. Baldrick's Foundation; Swedish Orphan Biovitrum, Inc.; *Takeda Oncology; and University of Minnesota. The views expressed in this article do not reflect the official policy or position of the National Institutes of Health, the Department of the Navy, the Department of Defense, Health Resources and Services Administration, or any other agency of the US Government.

Asterisk indicates corporate members.

Conflict of interest statement: There are no conflicts of interest to report.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2019.08.012.

REFERENCES

1. Barrett AJ, Battiwalla M. Relapse after allogeneic stem cell transplantation. *Expert Rev Hematol*. 2010;3:429–441.
2. Majhail NS, Chitphakdithai P, Logan B, et al. Significant improvement in survival after unrelated donor hematopoietic cell transplantation in the recent era. *Biol Blood Marrow Transplant*. 2015;21:142–150.
3. Horan JT, Logan BR, Agovi-Johnson M-A, et al. Reducing the risk for transplantation-related mortality after allogeneic hematopoietic cell transplantation: how much progress has been made? *J Clin Oncol*. 2011;29:805–813.
4. Hahn T, M Jr. PL, Hassebroek A, et al. Significant improvement in survival after allogeneic hematopoietic cell transplantation during a period of significantly increased use, older recipient age, and use of unrelated donors. *J Clin Oncol*. 2013;31:2437–2449.
5. Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2010;363:2091–2101.
6. Chhabra S, Ahn KW, Hu Z-H, et al. Myeloablative vs reduced-intensity conditioning allogeneic hematopoietic cell transplantation for chronic myeloid leukemia. *Blood Adv*. 2018;2:2922–2936.

7. Ringdén O, Labopin M, Ehninger G, et al. Reduced intensity conditioning compared with myeloablative conditioning using unrelated donor transplants in patients with acute myeloid leukemia. *J Clin Oncol*. 2009;27:4570–4577.
8. Bornhäuser M, Kienast J, Trenschel R, et al. 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.
9. Aoudjhane M, Labopin M, Gorin NC, et al. 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.
10. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2017;35:1154–1161.
11. Ringden O, Ruutu T, Remberger M, et al. A randomized trial comparing busulfan with total body irradiation as conditioning in allogeneic marrow transplant recipients with leukemia: a report from the Nordic Bone Marrow Transplantation Group. *Blood*. 1994;83:2723–2730.
12. Nagler A, Rocha V, Labopin M, et al. Allogeneic hematopoietic stem-cell transplantation for acute myeloid leukemia in remission: comparison of intravenous busulfan plus cyclophosphamide (Cy) versus total-body irradiation plus Cy as conditioning regimen—a report from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2013;31:3549–3556.
13. Copelan EA, Hamilton BK, Avalos B, et al. Better leukemia-free and overall survival in AML in first remission following cyclophosphamide in combination with busulfan compared with TBI. *Blood*. 2013;122:3863–3870.
14. Bredeson C, LeRademacher J, Kato K, et al. Prospective cohort study comparing intravenous busulfan to total body irradiation in hematopoietic cell transplantation. *Blood*. 2013;122:3871–3878.
15. Granados E, de La Camara R, Madero L, et al. Hematopoietic cell transplantation in acute lymphoblastic leukemia: better long term event-free survival with conditioning regimens containing total body irradiation. *Haematologica*. 2000;85:1060–1067.
16. Wu Q, Zhang R, Wang H, et al. Comparison of outcomes of idarubicin intensified TBI-CY and traditional TBI-CY conditioning regimen for high-risk acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplantation: A single center experience. *Leuk Res*. 2015;39:1192–1200.
17. Tachibana T, Tanaka M, Hagihara M, et al. Clinical significance of the administration of cytarabine or thiotepa in addition to total body irradiation and cyclophosphamide for allogeneic hematopoietic cell transplantation in patients with acute leukemia. *Int J Hematol*. 2015;102:451–459.
18. Stein AS, O'Donnell MR, Synold TW, et al. Phase-2 trial of an intensified conditioning regimen for allogeneic hematopoietic cell transplant for poor-risk leukemia. *Bone Marrow Transplant*. 2010;46:1256.
19. Mengarelli A, Iori A, Guglielmi C, et al. Standard versus alternative myeloablative conditioning regimens in allogeneic hematopoietic stem cell transplantation for high-risk acute leukemia. *Haematologica*. 2002;87:52–58.
20. Li Q-b, Li L, You Y, et al. A comparative study of outcomes of idarubicin- and etoposide-intensified conditioning regimens for allogeneic peripheral blood stem cell transplantation in patients with high-risk acute leukemia. *Acta Pharmacol Sin*. 2009;30:1471.
21. Lijian S, Yi L, Daohong Z. Hematopoietic stem cell injury induced by ionizing radiation. *Antiox Redox Signal*. 2014;20:1447–1462.
22. Guo C-Y, Luo L, Urata Y, et al. Sensitivity and dose dependency of radiation-induced injury in hematopoietic stem/progenitor cells in mice. *Sci Rep*. 2015;5:8055.. -8055.
23. Sobecks RM, Daugherty CK, Hallahan DE, et al. A dose escalation study of total body irradiation followed by high-dose etoposide and allogeneic blood stem cell transplantation for the treatment of advanced hematologic malignancies. *Bone Marrow Transplant*. 2000;25:807.
24. Petersen FB, Deeg HJ, Buckner CD, et al. Marrow transplantation following escalating doses of fractionated total body irradiation and cyclophosphamide—a phase I trial. *Int J Radiat Oncol Biol Physi*. 1992;23:1027–1032.
25. Girinsky T, Benhamou E, Bourhis J-H, et al. Prospective randomized comparison of single-dose versus hyperfractionated total-body irradiation in patients with hematologic malignancies. *J Clin Oncol*. 2000;18:981.
26. Alyea E, Neuberg D, Mauch P, et al. Effect of total body irradiation dose escalation on outcome following T-cell-depleted allogeneic bone marrow transplantation. *Biol Blood Marrow Transplant*. 2002;8:139–144.
27. Clift RA, Buckner CD, Appelbaum FR, et al. Long-term follow-up of a randomized trial of two irradiation regimens for patients receiving allogeneic marrow transplants during first remission of acute myeloid leukemia. *Blood*. 1998;92:1455–1456.
28. Wong JYC, Rosenthal J, Liu A, et al. Image-guided total-marrow irradiation using helical tomotherapy in patients with multiple myeloma and acute leukemia undergoing hematopoietic cell transplantation. *Int J Radiat Oncol Biol Phys*. 2009;73:273–279.
29. Wong JYC, Forman S, Somlo G, et al. Dose escalation of total marrow irradiation with concurrent chemotherapy in patients with advanced acute leukemia undergoing allogeneic hematopoietic cell transplantation. *Int J Radiat Oncol Biol Phys*. 2013;85:148–156.
30. Stein A, Palmer J, Tsai N-C, et al. Phase I trial of total marrow and lymphoid irradiation transplantation conditioning in patients with relapsed/refractory acute leukemia. *Biol Blood Marrow Transplant*. 2017;23:618–624.
31. Horowitz MM. The role of registries in facilitating clinical research in BMT: examples from the Center for International Blood and Marrow Transplant Research. *Bone Marrow Transplant*. 2008;42:S1.
32. Jones RJ, Lee KSK, Beschorner WE, et al. enoocclusive disease of the liver following bone marrow transplantation. *Transplantation*. 1987;44:778–783.
33. Mcdonald GB, Sharma P, Matthews DE, et al. Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. *Hepatology*. 1984;4:116–122.
34. Clark JG, Hansen JA, Hertz MI, et al. Idiopathic pneumonia syndrome after bone marrow transplantation. *Am Rev Respir Dis*. 1993;147:1601–1606.
35. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus conference on acute GVHD grading. *Bone Marrow Transplant*. 1995;15:825–828.
36. Filipovich AH, Weisdorf D, Pavletic S, 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. *Biol Blood Marrow Transplant*. 2005;11:945–956.
37. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.
38. Juliano RL, Ling V. A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. *Biochim Biophys Acta*. 1976;55:152–162.
39. Shareef MM, Brown B, Shajahan S, et al. Lack of P-glycoprotein expression by low-dose fractionated radiation results from loss of nuclear factor-κB and NF-Y activation in oral carcinoma cells. *Mol Cancer Res*. 2008;6:89–98.
40. Ruth AC, Roninson IB. Effects of the multidrug transporter P-glycoprotein on cellular responses to ionizing radiation. *Cancer Res*. 2000;60:2576–2578.
41. Wong JYC, Filippi AR, Dabaja BS, et al. Total body irradiation: guidelines from the International Lymphoma Radiation Oncology Group (ILROG). *Int J Radiat Oncol Biol Phys*. 2018;101:521–529.
42. Clift R, Buckner C, Appelbaum F, et al. Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission: a randomized trial of two irradiation regimens [see comments]. *Blood*. 1990;76:1867–1871.
43. Scarpati D, Frassoni F, Vitale V, et al. Total body irradiation in acute myeloid leukemia and chronic myelogenous leukemia: influence of dose and dose-rate on leukemia relapse. *Int J Radiat Oncol Biol Phys*. 1989;17:547–552.
44. Marks DI, Forman SJ, Blume KG, et al. A comparison of cyclophosphamide and total body irradiation with etoposide and total body irradiation as conditioning regimens for patients undergoing sibling allografting for acute lymphoblastic leukemia in first or second complete remission. *Biol Blood Marrow Transplant*. 2006;12:438–453.
45. Giebel S, Miszczyk L, Slosarek K, et al. Extreme heterogeneity of myeloablative total body irradiation techniques in clinical practice: a survey of the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Cancer*. 2014;120:2760–2765.