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ORIGINAL REPORT

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Risk Factors for Acute Graft-Versus-Host Disease After Human Leukocyte Antigen–Identical Sibling Transplants for Adults With Leukemia

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ABSTRACT

Purpose
Acute graft-versus-host disease (GVHD) causes substantial morbidity and mortality after human leukocyte antigen (HLA)-identical sibling transplants. No large registry studies of acute GVHD risk factors have been reported in two decades. Risk factors may have changed in this interval as transplant-related techniques have evolved.

Patients and Methods
Acute GVHD risk factors were analyzed in 1,960 adults after HLA-identical sibling myeloablative transplant for acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), or chronic myeloid leukemia (CML) reported by 226 centers worldwide to the Center for International Blood and Marrow Transplant Research from 1995 to 2002. Outcome was measured as time from transplant to onset of grade 2 to 4 acute GVHD, with death without acute GVHD as a competing risk.

Results
Cumulative incidence of grade 2 to 4 acute GVHD was 35% (95% CI, 33% to 37%). In multivariable analyses, factors significantly associated with grade 2 to 4 acute GVHD were cyclophosphamide + total-body irradiation versus busulfan + cyclophosphamide (relative risk [RR] = 1.4; $P < .0001$), blood cell versus bone marrow grafts in patients age 18 to 39 years (RR = 1.43; $P = .0023$), recipient age 40 and older versus age 18 to 39 years receiving bone marrow grafts (RR = 1.44; $P = .0005$), CML versus AML/ALL (RR = 1.35; $P = .0003$), white/Black versus Asian/Hispanic race (RR = 1.54; $P = .0003$), Karnofsky performance score less than 90 versus 90 to 100 (RR = 1.27; $P = .014$), and recipient/donor cytomegalovirus-seronegative versus either positive (RR = 1.20; $P = .04$). Stratification by disease showed the same significant predictors of grade 2 to 4 acute GVHD for CML; however, KPS and cytomegalovirus serostatus were not significant predictors for AML/ALL.

Conclusion
This analysis confirmed several previously reported risk factors for grade 2 to 4 acute GVHD. However, several new factors were identified whereas others are no longer significant. These new data may facilitate individualized risk estimates and raise several interesting biologic questions.

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INTRODUCTION

Acute graft-versus-host disease (GVHD) is a substantial cause of morbidity and mortality after allogeneic hematopoietic stem-cell transplantation (HSCT). Diverse acute GVHD risk factors have been described over the last three decades, including human leukocyte antigen (HLA) disparity, donor and recipient age, donor parity, donor and recipient sex, increased dose of total-body irradiation (TBI), conditioning regimen intensity, acute GVHD prophylaxis, lack of protective environments, splenectomy, immunoglobulin use, underlying disease, ABO compatibility, prior exposure to herpes viruses, donor transfusions, performance score, antibiotic gut decontamination, and post-transplant transfusions.[1-13]

Many of these risk factors were identified in small studies from single centers, concerned bone marrow transplants only, or used older methods of acute GVHD prevention. The last International Bone Marrow Transplant Registry (IBMTR) analysis of acute GVHD risk factors in patients with leukemia and aplastic anemia was published in 1987, before the general use of cyclosporine or tacrolimus

combined with methotrexate and/or methylprednisolone for acute GVHD prevention, before the use of blood cell grafts and before the introduction of hematopoietic growth factors and other supportive care post-HSCT.[12] The current study was designed to determine whether risk factors for and incidence of acute GVHD have changed since the last IBMTR study. Understanding these risk factors may facilitate individualized approaches to acute GVHD prevention and donor selection.

PATIENTS AND METHODS

The Center for International Blood and Marrow Transplant Research

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a research affiliation of the IBMTR, Autologous Blood and Marrow Transplant Registry (ABMTR), and the National Marrow Donor Program (NMDP) that comprises a voluntary working group of more than 450 transplantation centers worldwide contributing detailed data on consecutive allogeneic and autologous hematopoietic stem-cell transplants to a statistical center at the Department of Population Health of the Medical College of Wisconsin in Milwaukee (WI) or the NMDP Coordinating Center in Minneapolis (MN). Participating centers are required to report all transplants consecutively; compliance is monitored by on-site audits. Patients are followed longitudinally, with yearly follow-up. Computerized checks for errors, physicians' review of submitted data and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed with a waiver of informed consent and in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations as determined by the Institutional Review Board and the Privacy Officer of the Medical College of Wisconsin.

Study Design

This is a retrospective study to analyze the incidence and risk factors for acute GVHD after HLA-identical, sibling, myeloablative, non–T-cell depleted HSCT in 1,960 adults (age $\geq$ 18 years at HSCT) treated for acute myeloid leukemia (AML; n = 761), acute lymphoblastic leukemia (ALL; n = 303), or chronic myeloid leukemia (CML; n = 896) from 1995 to 2002 and reported to the CIBMTR by 226 HSCT centers worldwide. Patients who died less than 14 days post-HSCT were not included in the cohort. To reduce heterogeneity in the study population, the data set was restricted to patients who received busulfan + cyclophosphamide (BU+CY $\pm$ other, 64%) or cyclophosphamide + TBI (CY+TBI $\pm$ other, 36%) as conditioning, cyclosporine and methotrexate (CSA+MTX) alone (85%) or combination with other agents (15%) for acute GVHD prophylaxis, and white, Black, Hispanic or Asian race. Patients with "other" race (n = 73) and Native Americans (n = 11) were excluded because of their low frequency. Patients with missing/unknown data on any one of the following factors were excluded: performance status (n = 37), cytomegalovirus (CMV) status (n = 47), and donor pregnancy (n = 244).

Total doses of MTX are not collected on registry forms, and too few patients were treated with tacrolimus-based GVHD prophylaxis regimens (n = 136); therefore, these two factors could not be analyzed. "Early disease" was defined using standard CIBMTR criteria as acute leukemia patients in first complete remission or CML patients in first chronic phase. "Intermediate disease" was defined as acute leukemia in second or later complete remission and CML in accelerated phase or second or later chronic phase. All other patients were defined as having "advanced disease."

Statistical Methods

Acute GVHD was defined as grade 2 to 4 acute GVHD using standard criteria,[14] with a date of onset before day +100 post-HSCT and was analyzed as time to event, with death without GVHD as a competing event. The day +100 landmark was chosen as the end of observation time in accordance with the standard criteria during the study period and in consideration of the possibility that early-onset (preday +100) and late-onset (postday +100) acute GVHD risk factors may differ. Granulocyte colony-stimulating factor (G-CSF) usage post-HSCT was analyzed as a time-dependent covariate; at a given study time, the patient was coded as receiving G-CSF only if its administration started before the given study time. Interactions were tested for age by all potential predictors of acute GVHD. A significant interaction existed between age and graft type (blood cells *v* bone marrow); therefore age, graft type, and the interaction term were included in all model building. Multivariable analyses used the Cox proportional hazards model with backward stepwise selection with $P > .05$ to remove each factor from the model. The proportionality assumption was tested and was met. Factors that were tested in the multivariable analyses were recipient age, graft type, interaction term for age $\times$ graft type, recipient-donor sex match, recipient race/ethnicity, disease, disease status at HSCT, time from diagnosis to HSCT, year of transplant, conditioning regimen, Karnofsky performance score (KPS) at HSCT, recipient/donor CMV serostatus, donor pregnancies, ABO compatibility, and time to G-CSF usage post-HSCT. A two-sided $P < .05$ was considered statistically significant for all analyses. After determination of the final multivariable model for grade 2 to 4 acute GVHD in all patients, the significant risk factors were tested for validity in the following groups: grade 3 to 4 acute GVHD in all patients, grade 2 to 4 acute GVHD in AML and ALL patients, grade 3 to 4 acute GVHD in AML and ALL patients, grade 2 to 4 acute GVHD in CML patients, and grade 3 to 4 acute GVHD in CML patients. One author (M.J.Z.) performed all statistical analyses.

RESULTS

Acute GVHD incidence by Patient Cohort

Recipient and donor characteristics are outlined in Table 1. The study population was divided into two cohorts, "early" (1995 to 1998) and "late" (1999 to 2002), to determine whether recipient or donor characteristics and incidence of acute GVHD had changed over time. Factors that changed significantly over time were fewer transplants for CML ($P = .0279$), fewer transplants for recipients with early disease ($P = .0127$), increased use of blood cell grafts ($P < .0001$), and increased number of CMV-positive recipients ($P = .0393$). The day +100 cumulative incidence of grade 2 to 4 acute GVHD was 35% (95% CI, 33% to 37%) and did not significantly change over time (early cohort, 35%; 95% CI, 32% to 37%; late cohort, 32%; 95% CI, 29% to 35%; Appendix Fig A1, online only). After stratifying by disease, the day +100 cumulative incidence of grade II to IV acute GvHD did not significantly change over time for acute leukemia (early cohort, 27%; 95% CI, 24% to 30%; late cohort, 27%; 95% CI, 22% to 31%) but significantly decreased for CML (early cohort, 39%; 95% CI, 36% to 42%; late cohort, 30%; 95% CI, 25% to 36%; $P = .0058$; Fig 1).

Multivariable Risk Factors for Acute GVHD

Table 2 summarizes the results of the multivariable analysis of time to onset of grade 2 to 4 acute GVHD. Because there was a significant interaction of age and graft type with time to onset of grade 2 to 4 acute GVHD, these factors were forced into the model and the results are shown for both interactions. In addition, all factors that were statistically significant in the univariate analysis were tested in the multivariable analysis. Blood cell grafts conferred an increased risk of grade 2 to 4 acute GVHD in the younger (18 to 39 years) age group and did not influence risk in the older (40+ years) age group (Fig 2). Conversely, the older (40+ years) age group had a significantly increased risk of grade 2 to 4 acute GVHD among those who received bone marrow grafts. Age was not an independent risk factor in those who received blood cells for transplantation.

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Table 1. Recipient-, Donor-, and Transplant-Related Variables for 1960 HLA-Identical Sibling Transplants for Leukemia (AML, ALL, CML), Between 1995 and 2002 and Reported to the Center for International Blood and Marrow Transplant Research by 226 Teams Worldwide

Variable	1995-1998			1999-2002			*P*
	No. Assessable	No.	%	No. Assessable	No.	%	
Recipient age, years	1,298			662			.7235
Median		37			37		
Range		18-69			18-67		
18-39		749	58		377	57	.7490
≥ 40		549	42		285	43	
Donor age, years	1,284			657			.6068
Median		36			36		
Range		< 1-73			< 1-72		
0-9		9	1		12	2	.2063
10-19		103	8		56	9	
20-29		259	20		138	21	
30-39		406	31		185	28	
40-49		320	25		167	25	
≥ 50		187	14		99	15	
Donor-recipient sex match	1,298			662			.1075
Male → Male		448	35		230	35	
Male → Female		363	28		160	24	
Female → Male		252	19		156	24	
Female → Female		235	18		116	18	
Karnofsky performance score	1,298			662			.1650
0-80		282	22		126	19	
90-100		1016	78		536	81	
Leukemia type	1,298			662			.0279
Acute myeloid leukemia		493	38		268	40	
Acute lymphoblastic leukemia		186	14		117	18	
Chronic myeloid leukemia		619	48		277	42	
Leukemia status prior to HSCT	1,298			662			.0127
Early		973	75		455	69	
Intermediate		182	14		119	18	
Advanced		143	11		88	13	
Race	1,298			662			.4911
White		1022	79		526	79	
Black		33	3		10	2	
Asian		168	13		84	13	
Hispanic		75	6		42	6	
Recipient-donor cytomegalovirus status	1,298			662			.0393
Recipient–/donor–		376	29		158	24	
Recipient+/donor–		175	13		105	16	
Recipient–/donor+		134	10		59	9	
Recipient+/donor+		613	47		340	51	
Donor pregnancy	1,298			662			.3079
Female, No		178	14		100	15	
Female, Yes		309	24		172	26	
Male		811	62		390	59	
Graft type	1,298			662			< .0001
Bone marrow		963	74		314	47	
Peripheral blood		335	26		348	53	
Time from diagnosis to HSCT, months	1,298			662			.1555
Median		7			7		
Range		1-655			< 1-207		

Abbreviations: HLA, human leukocyte antigen; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; HSCT, hematopoietic stem-cell transplantation.

Because white and Black race both conferred an increased risk of acute GVHD that was not significantly different between them, they were modeled as white/Black. Similarly, Asian and Hispanic race both conferred a decreased risk of acute GVHD that was not significantly different between them and were combined as Asian/Hispanic. White/Black race conferred a significantly increased risk of grade 2 to 4 acute GVHD.

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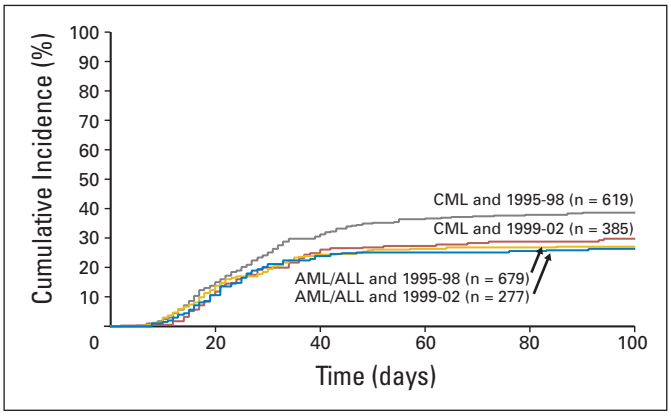

Fig 1. Cumulative incidence of grade 2 to 4 acute graft-versus-host disease, comparing patients who underwent transplantation in 1995 to 1998 versus 1999 to 2002 by disease. AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia.

Because there was no significant difference in acute GVHD risk between AML and ALL, they were analyzed as acute leukemia. Additional statistically significant predictors of an increased risk for grade 2 to 4 acute GVHD included the nonmodifiable risk factors of CML versus acute leukemia and the potentially modifiable risk factors of poor performance score (KPS $<$ 90), CMV serologic status (recipient and donor negative) and conditioning regimen (CY+TBI $\pm$ other). Of note, there was a higher early mortality rate in the CMV-positive group (recipient and/or donor positive) compared with the group with both recipient and donor CMV negative (23% *v* 19%) that yielded a higher rate of grade 2 to 4 acute GVHD in the group with recipient and donor CMV negative. G-CSF usage post-HSCT was added as a time-dependent covariate to the final multivariable model and did not significantly alter the final model.

Validation of the Final Multivariable Model in Grade 3-4 Acute GVHD

The statistically significant risk factors for grade 2 to 4 acute GVHD were tested for validity in severe grade 3 to 4 acute GVHD (Table 3). The interaction of age with stem-cell source was maintained in severe acute GVHD; in addition CML, poor performance score, and CMV negativity conveyed a significantly increased risk. However, white/Black race and CY+TBI $\pm$ other were not associated with grade 3 to 4 acute GVHD.

Validation of the Final Multivariable Model in the Acute Leukemia Subgroup

Appendix Table A1 (online only) shows the results for grade 2 to 4 and grade 3 to 4 acute GVHD risk factors in AML and ALL patients. White/Black race, CY+TBI $\pm$ other, and blood cell grafts in patients age 18 to 39 years significantly increased risk of grade 2 to 4 acute GVHD. In addition, blood cell grafts, regardless of age group, significantly increased risk of grade 3 to 4 acute GVHD. Poor performance score and age 40+ years demonstrated a nonsignificant increased risk of grade 3 to 4 acute GVHD.

Table 2. Multivariable Analysis of Risk Factors for Grade 2-4 Acute Graft-Versus-Host Disease

Variable	RR	95% CI	*P*
For recipients age 18-39 years			
Bone marrow graft	1.0		
Peripheral blood stem-cell graft	1.43	1.14 to 1.79	.0023
For recipients age 40+ years			
Bone marrow graft	1.0		
Peripheral blood stem-cell graft	0.98	0.78 to 1.23	.8528
Age for recipients of bone marrow transplants, years			
18-39	1.0		
40+	1.44	1.17 to 1.77	.0005
Age for recipients of peripheral-blood stem-cell transplants, years			
18-39	1.0		
40+	0.99	0.77 to 1.27	.9273
Race			
Asian/Hispanic	1.0		
White/Black	1.54	1.22 to 1.94	.0003
Leukemia type			
Acute myeloid or lymphoblastic leukemia	1.0		
Chronic myeloid leukemia	1.35	1.15 to 1.59	.0003
Karnofsky performance score at transplant			
90-100	1.0		
0-80	1.27	1.05 to 1.53	.0144
Conditioning regimen			
BuCy $\pm$ other	1.0		
CyTBI $\pm$ other	1.40	1.19 to 1.66	$<$ .0001
Recipient-donor cytomegalovirus status			
$\geq$ 1 positive	1.0		
Both negative	1.20	1.01 to 1.42	.0415

Abbreviations: RR, relative risk; BuCy $\pm$ other, busulfan and cyclophosphamide with or without additional agents; CyTBI $\pm$ other, cyclophosphamide and total body irradiation with or without additional agents.

Validation of the Final Multivariable Model in the CML Subgroup

Appendix Table A2 (online only) shows the results for grade 2 to 4 and grade 3 to 4 acute GVHD risk factors for CML patients. Age 40+

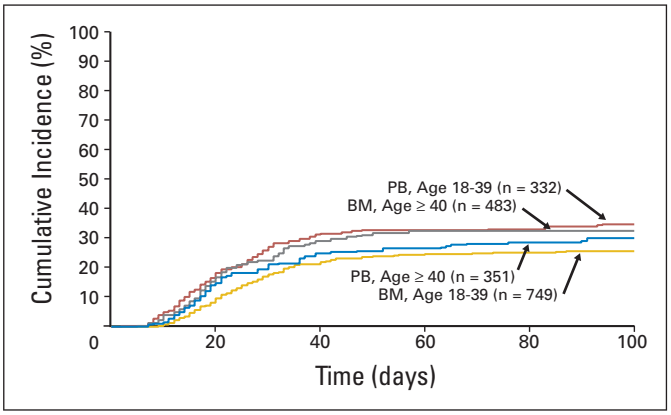

Fig 2. Cumulative incidence of grade 2 to 4 acute graft-versus-host disease, demonstrating the interaction between age and graft type. PB, peripheral blood; BM, bone marrow.

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Table 3. Validation of Final Multivariable Model for Grade 3-4 Acute Graft-Versus-Host Disease

Variable	RR	95% CI	*P*
For recipients age 18-39 years			
Bone marrow graft	1.0		
Peripheral blood stem-cell graft	1.51	1.07 to 2.14	.0201
For recipients age 40+ years			
Bone marrow graft	1.0		
Peripheral blood stem-cell graft	1.31	0.94 to 1.83	.1091
Age for recipients of bone marrow transplants, years			
18-39	1.0		
40+	1.43	1.04 to 1.96	.0280
Age for recipients of peripheral-blood stem-cell transplants, years			
18-39	1.0		
40+	1.24	0.86 to 1.79	.2492
Race			
Asian/Hispanic	1.0		
White/Black	1.03	0.75 to 1.41	.8736
Leukemia type			
Acute myeloid or lymphoblastic leukemia	1.0		
Chronic myeloid leukemia	1.32	1.03 to 1.69	.0261
Karnofsky performance score at transplant			
90-100	1.0		
0-80	1.47	1.12 to 1.93	.0063
Conditioning regimen			
BuCy ± other	1.0		
CyTBI ± other	0.99	0.77 to 1.27	.9127
Recipient-donor cytomegalovirus status			
≥ 1 positive	1.0		
Both negative	1.33	1.03 to 1.71	.0308

Abbreviations: RR, relative risk; BuCy ± other, busulfan and cyclophosphamide with or without additional agents; CyTBI ± other, cyclophosphamide and total body irradiation with or without additional agents.

years in bone marrow grafts, poor performance score, CY+TBI ± other and CMV negativity significantly increased risk of grade 2 to 4 acute GVHD. In addition, blood cell grafts in patients age 18 to 39 years and white/Black race demonstrated a nonsignificant increased risk of grade 2 to 4 acute GVHD. For grade 3 to 4 acute GVHD, only poor performance score and CMV negativity significantly increased risk.

Comparison of the Multivariable Models

Table 4 summarizes the risk factors for the main model and the validation models. All significant risk factors for grade 2 to 4 acute GVHD were valid in the CML subgroup, whereas performance score and CMV serostatus were not valid in the AML/ALL subgroup. Of note, the interaction between age and stem-cell source was maintained in both leukemia subgroups. For grade 3 to 4 acute GVHD, neither race nor conditioning regimen were valid risk factors in any group. Poor performance score was a consistent risk factor across all leukemia groups; however, CMV serostatus was again only valid in the CML group and blood stem cells increased risk in the AML/ALL group, regardless of recipient age. When we examined regimen intensity by disease, a significantly higher proportion of acute leukemia patients received CY+TBI ± other compared with CML patients (46% *v* 25%; $P < .0001$).

DISCUSSION

A prior IBMTR study found these risk factors for acute GVHD: female donor/male recipient, female donor with prior pregnancies or transfusions, no acute GVHD prophylaxis, and older recipient age.[12] In the current study, only older age remained significant. The reason for this difference is unclear, but new transplant techniques (graft type, multidrug GVHD prevention, differences in conditioning regimens, and improved supportive care) may explain these differences. Also, neither study recorded the offspring sex of parous female donors, which may influence GVHD risk in male recipients.

Although increased acute GVHD risk in older recipients[12] and in white race[15] has been reported, several risk factors we describe are in contrast to prior reports. A smaller CIBMTR/EBMT study of peripheral blood (n = 249) versus bone marrow transplant (n = 490) in adults with HLA-identical sibling donors found no significantly increased risk of grade 2 to 4 acute GVHD.[16] However, this study included conditioning regimens in addition to CY+TBI ± other or

Table 4. Summary of Validation of Significant Risk Factors for Acute GVHD in Multiple Subgroups

Risk Factor	Grade 2-4 Acute GVHD	Grade 2-4 Acute GVHD AML+ALL Only	Grade 2-4 Acute GVHD CML Only	Grade 3-4 Acute GVHD	Grade 3-4 Acute GVHD AML+ALL Only	Grade 3-4 Acute GVHD CML Only
PBSCT in patients age 18-39 years	+	+	+	+	+	–
PBSCT in patients age 40+ years	–	–	–	–	+	–
BMT in patients age 40+ years	+	+*	+	+	+*	–
White/Black race	+	+	+	–	–	–
Chronic myeloid leukemia	+	NA	NA	+	NA	NA
< 90 Karnofsky performance score	+	–	+	+	+*	+
CyTBI ± other	+	+	+	–	–	–
R/D CMV negative	+	–	+	+	–	+

NOTE. (±) indicates whether or not the risk factor was significant for the outcome listed in the column heading
Abbreviations: GVHD, graft-versus-host disease; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; PBSCT, peripheral blood stem cell transplant; BMT, bone marrow transplant; NA, not applicable; CyTBI, cyclophosphamide + total body irradiation; R/D, recipient/donor; CMV, cytomegalovirus.
*$P > .05$ and $\leq .10$.

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BU+CY ± other and included GVHD prophylaxis regimens in addition to CSA+MTX ± other. A report from the Stem Cell Trialists' Collaborative Group demonstrated an increased risk for blood cell transplants of grade 3 to 4, but not grade 2 to 4, acute GVHD in a meta-analysis of individual patient data of 1,111 HLA-identical sibling transplant patients from nine randomized clinical trials.[17] However, the clinical trials included in this meta-analysis were heterogeneous hematologic malignancies in patients age 7 to 65 years, and the meta-analysis did not evaluate incidence of acute GVHD by competing-risks analysis.

The interaction we report between age and graft type on acute GVHD risk was not assessed in either of the aforementioned studies.[16-17] When we examined grade 3 to 4 acute GVHD, age and stem-cell source were risk factors in the acute leukemia group but not in CML patients. A similar interaction has been reported with HLA mismatching and age where HLA-mismatching conveys a higher risk of grade 3 to 4 acute GVHD only in patients older than 20 years.[2] Also, there is a strong correlation between donor and recipient age in sibling transplants. Consequently, younger recipients may receive a higher number of or functionally different T cells in blood cell grafts than older recipients. Our study did not analyze graft T-cell dose as a risk for acute GVHD because these data were unavailable to us. It is unclear why older age showed a significantly increased risk of acute GVHD in recipients of bone marrow grafts. These age-related disparities may offer an important clue to human immune development.

Four randomized trials of BU+CY versus CY+TBI are reported,[18-21] but only one found a significantly increased risk of grade 2 to 4 acute GVHD with CY+TBI.[21] However, all studies had fewer than 170 participants, all included recipients of bone marrow grafts, two studies accrued only CML patients, and all four studies were not powered to detect differences in risk of grade 2 to 4 acute GVHD. Our study found an increased risk of grade 2 to 4, but not grade 3 to 4, acute GVHD for CY+TBI ± other that was seen in both acute leukemia and CML patients. TBI-containing regimens may cause release of more inflammatory cytokines than regimens without radiation, resulting in increased endothelial cell damage that may precipitate the cytokine storm associated with acute GVHD.[22-23] An alternative explanation is that regimen-related toxicity associated with TBI-containing regimens may be misclassified as grade 2 acute GVHD.

Acute GVHD was analyzed as a time-dependent competing event (death without GVHD); hence, more patients were at risk for acute GVHD in the CMV-negative group because of a differential early mortality rate. Therefore, the early mortality experienced by the CMV-positive group precluded the development of grade 2 to 4 acute GVHD and may have resulted in informative censoring. Another recent study also reported a significantly higher treatment-related mortality in CMV-positive recipients and a significantly increased risk of grade 2 to 4 acute GVHD in CMV-negative recipients.[24]

The incidence of grade 2 to 4 acute GVHD did not change during the study period for acute leukemia but declined for CML. We confirm that CML is associated with increased risk of both grade 2 to 4 and grade 3 to 4 acute GVHD.[24-25] CML is associated with higher tumor necrosis factor (TNF) α serum levels pretransplant than acute leukemia, which may precipitate the "cytokine storm" of acute GVHD.[26] Significant increases in TNFα post-transplant have been associated with acute GVHD.[26] Also, CML patients underwent transplant in the late 1990s to early 2000s with little or no prior cytotoxic therapy compared with acute leukemia patients, and thus may have had more, and better functioning, antigen-presenting cells to generate acute GVHD. The tyrosine kinase inhibitor imatinib mesylate was first approved by the US Food and Drug Administration in May 2001; therefore, most patients in this study were not exposed pretransplant. It is unknown how pretransplant imatinib or transplant in CML patients after imatinib-failure will influence acute GVHD risk; however, a recent CIBMTR study suggests that pretransplant imatinib therapy may improve transplant outcomes.[27]

The differential effect of leukemia type reinforces the contribution of underlying disease on risk of acute GVHD. The higher mortality associated with grade 3 to 4 acute GVHD makes the distinction in risk factors for grade 2 versus 3 acute GVHD important. Knowing that blood stem cells confer increased GVHD risk in acute leukemia but not CML can affect the choice of stem-cell source for future transplant patients in the former group but not the latter. Similarly, conditioning with TBI may increase risk of moderate, but not severe, acute GVHD, regardless of leukemia type. This study emphasizes that risk factors for acute GVHD differ by disease, and necessitate distinct risk models for each disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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