Plenary Paper

TRANSPLANTATION

Prospective cohort study comparing intravenous busulfan to total body irradiation in hematopoietic cell transplantation

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Key Points

- Compared with TBI, IV-BU resulted in superior survival with no increased risk for relapse or TRM.
- The results support the use of myeloablative IV-BU vs TBI-based conditioning regimens for treatment of myeloid malignancies.

We conducted a prospective cohort study testing the noninferiority of survival of ablative intravenous busulfan (IV-BU) vs ablative total body irradiation (TBI)-based regimens in myeloid malignancies. A total of 1483 patients undergoing transplantation for myeloid malignancies (IV-BU, N = 1025; TBI, N = 458) were enrolled. Cohorts were similar with respect to age, gender, race, performance score, disease, and disease stage at transplantation. Most patients had acute myeloid leukemia (68% IV-BU, 78% TBI). Grafts were primarily peripheral blood (77%) from HLA-matched siblings (40%) or well-matched unrelated donors (48%). Two-year probabilities of survival (95% confidence interval [CI]), were 56% (95% CI, 53%-60%) and 48% (95% CI, 43%-54%, P = .019) for IV-BU (relative risk, 0.82; 95% CI, 0.68-0.98, P = .03) and TBI, respectively. Corresponding incidences of transplant-related mortality (TRM) were 18% (95% CI, 16%-21%) and 19% (95% CI, 15%-23%, P = .75) and disease progression were 34% (95% CI, 31%-37%) and 39% (95% CI, 34%-44%, P = .08). The incidence of hepatic veno-occlusive disease (VOD) was 5% for IV-BU and 1% with TBI (P < .001). There were no differences in progression-free survival and graft-versus-host disease. Compared with TBI, IV-BU resulted in superior survival with no increased risk for relapse or TRM. These results support the use of myeloablative IV-BU vs TBI-based conditioning regimens for treatment of myeloid malignancies. (*Blood*. 2013;122(24):3871-3878)

Introduction

Cyclophosphamide (CY) combined with ablative doses of total body irradiation (TBI) or the oral alkylating agent busulfan (BU), have been the main conditioning regimens for allogeneic hematopoietic cell transplantation (HCT) for patients with myeloid malignancies.[1,2] Limited randomized trials in the 1990s suggested that in some settings such as sibling donor transplants for acute myeloid leukemia (AML) in adults, TBI was superior with lower relapse rates and less nonrelapse mortality risks.[3,4] For chronic myelogenous leukemia (CML) in the chronic phase, though, the 2 regimens provided similar outcomes.[5]

In the last decade, intravenous busulfan (IV-BU) has increasingly replaced oral BU in conditioning regimens for allogeneic HCT. IV-BU is associated with more predictable pharmacokinetics (PK) and, in some studies, has improved the tolerability of myeloablative BU/CY.[6-8] The substitution of fludarabine (FLU) for CY has led to the development of the "reduced-toxicity" myeloablative FLU/BU-conditioning regimen. Other advances during the last several decades have also contributed to generally superior outcomes after allogeneic transplants.[9] Despite its increasing use, no prospective studies have been performed comparing IV-BU vs TBI-based myeloablative HCT. We performed a large prospective cohort study to test the hypothesis that survival of patients receiving myeloablative IV-BU–based conditioning regimens before a related or volunteer unrelated donor allogeneic HCT for AML, myelodysplastic syndrome (MDS), or CML is not inferior to the recipients of ablative TBI-based regimens.

Methods

Study design

This study was a prospective multicenter cohort study comparing myeloablative IV-BU with TBI-based regimens in patients with myeloid malignancies

undergoing matched related or unrelated donor blood or bone marrow transplants. Patients were prospectively enrolled through the Center for International Blood and Marrow Transplant Research (CIBMTR) data collection mechanism. The CIBMTR is a collaborative working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive HCT to a statistical center at the Medical College of Wisconsin in Milwaukee and the National Donor Program Coordinating Centers in Minneapolis, Minnesota.[10] Observational studies conducted by the CIBMTR are performed in compliance with the Privacy Rule (HIPAA) as a Public Health Authority, and in compliance with all applicable federal regulations pertaining to the protection of human research participants as determined by continuous review of the Institutional Review Boards of the National Marrow Donor Program and the Medical College of Wisconsin since 1985.

CIBMTR transplantation centers from North and South America were invited to participate. Enrollment started March 2009, and data reporting from participating centers were screened for eligibility to enter the study cohort. Eligible patients were selected for comprehensive CIBMTR data reporting track plus additional study-specific data collection of practices related to IV-BU administration. Data reporting and enrollment were monitored monthly during the study period, and compliance with forms reported was greater than 95%.

Eligibility

Patients eligible for enrollment met the following criteria: i) age ≤60 years; ii) undergoing first allogeneic blood or bone marrow HCT; iii) HLA-matched related or volunteer unrelated donor; iv) diagnosis of AML, MDS, CML; v) graft-versus-host disease (GVHD) prophylaxis that included a calcineurin inhibitor (CNI); vi) consensus criteria ablative pretransplant conditioning regimen that was based either on IV-BU (>9 mg/kg) plus CY (≥60mg/kg) or FLU (≥80 mg/m^2) or was based on TBI (≥500 cGY single fraction or ≥800 cGY fractionated) plus CY (≥60 mg/kg) or etoposide (≥30 mg/kg).[11] Informed consent was obtained in accordance with the Declaration of Helsinki.

Study end points and definitions

The primary outcome was survival duration. Other outcomes included neutrophil and platelet recovery, progression-free survival (PFS), treatment-related mortality (TRM), relapse or progression, incidence of veno-occlusive disease/ sinusoidal obstruction syndrome (VOD/SOS), incidence and severity of acute GVHD (aGVHD), incidence of chronic GVHD (cGVHD), incidence of interstitial pneumonitis (IPN), and incidence of severe renal toxicity requiring dialysis and cause of death.

Neutrophil recovery was defined as the first of 3 consecutive laboratory values obtained on different days with an absolute neutrophil count ≥0.5 × 10^9/L without growth factor support. Platelet recovery was defined as the first of 3 consecutive laboratory values obtained on different days with platelets ≥ 20 × 10^9/L without platelet transfusions for 7 days immediately preceding this date. TRM was defined as death from any cause without evidence of relapsed disease. Relapse was defined as reoccurrence of disease after a complete response. Among patients who presented with active disease at the time of transplant (advanced disease) if no complete remission was documented after HCT, the date of disease progression was input as day +1 posttransplant. For patients with leukemia in remission at the time of transplant, relapse was determined whether the disease was morphologically evident or if the treating physician elected to initiate treatment in the setting of cytogenetic or molecular relapse. For the purposes of the analysis, disease progression and relapse were considered as the same event. For PFS, patients were considered to experience failures at the time of relapse, progression, or death from any cause. For survival, the event was death from any cause. For unrelated donors, "well-matched" was defined as no known disparity between donor and recipient at HLA-A, B, C, and DRB1 (8/8), partially matched as 1 known or 1 likely disparity and mismatched as ≥2 disparities.[12] Disease status was classified as early (patients in first complete remission or first chronic-phase CML, refractory anemia with or without ringed sideroblasts); intermediate (patients in second complete remission or higher, second chronic phase); and advanced (patients with active leukemia [relapse or primary

induction failure], accelerated-phase or blast-crisis CML, or refractory anemia with excess blasts).

Statistical analysis

The primary objective of this cohort study was to test the noninferiority of survival between IV-BU and TBI-based myeloablative regimens. The targeted accrual was 1460 patients at an accrual rate of 730 patients per year. This sample size provided 80% power to detect a noninferiority threshold comparing overall mortality after IV-BU with TBI-based regimens on a hazard ratio (HR) scale of 1.26.

Patient, disease, and treatment characteristics were summarized by a conditioning regimen with continuous variables described by median and range and categorical variables described by frequency and percentage. Probabilities of survival and PFS were calculated using the Kaplan-Meier estimator.[13] Probabilities of neutrophil and platelet recovery, aGVHD, cGVHD, TRM, and relapse were calculated using the cumulative incidence function to accommodate competing risks.[13] For neutrophil and platelet recovery, aGVHD, and cGVHD, death without the event was considered the competing risk. For TRM, relapse was the competing event, and for relapse, TRM was the competing event. In all analyses, patients without an event were censored at last follow-up.

In multivariate analysis, the risk for overall morality (inverse of survival), treatment failure (inverse of relapse-free survival [RFS]), TRM, relapse, grade 3 to 4 acute GVHD, and cGVHD were compared between conditioning regimens using the Cox models.[13] The proportional-hazard assumption was evaluated for all variables. The final models were stratified on disease type, donor type, and performance score that did not meet the proportionality assumption. Adjusted survival and RFS curves were generated based on the final Cox model using the method of Zhang et al.[14] Multivariate Cox models were built using stepwise selection procedures with the conditioning regimen included in all steps of model building. All variables with a P value ≤.05 were included in the final models. Variables considered in the analysis include age (≤19 vs 20 – 49 vs ≥50), gender, race (Caucasian vs not Caucasian), performance score (<90 vs 90-100), comorbidity index (≤3 vs >3), disease status (AML early vs AML intermediate vs AML advanced vs CML early vs CML intermediate vs CML advanced vs MDS early vs MDS advanced), graft type (bone marrow vs peripheral blood), donor type (HLA-id sib vs matched unrelated vs partially matched unrelated), donor-recipient gender match (F-M vs M-F vs M-M vs F-F), donor-recipient cytomegalovirus (CMV) status ($^{+/+}$, $^{+/-}$, $^{-/+}$, $^{-/-}$), (GVHD prophylaxis (CNI + methotrexate [MTX] vs CNI + MTX + other vs CNI + mycophenolate mofetil (MMF) ± other vs CNI ± other (no MTX, MMF)), and antithymocyte globulin (ATG)/Campath (yes vs no). Interactions between the conditioning regimen and other covariates were tested for in all models. None was found to be statistically significant. All treatment effects were stated as HR with a 95% confidence interval (CI).

Post hoc comparison of 2-year survival probabilities between IV-BU and TBI-based regimens by disease and disease status was performed. An additional subset analysis within the IV-BU cohort comparing survival, RFS, TRM, and relapse between BU/CY vs FLU/BU was conducted using the Cox models. Patient, disease, and transplant characteristics were also compared across these 2 IV-BU–containing regimens. Analyses were done using SAS software version 9.1 (SAS, Cary, NC).

Results

Accrual

From March 2009 to February 2011, a total of 1483 eligible patients were enrolled from 120 transplantation centers (IV-BU, N = 1025 and TBI, N = 458).

Patient characteristics

Patient, donor, disease, and treatment characteristics are shown in Table 1. The IV-BU and TBI groups were well balanced with

Table 1. Demographic characteristics by conditioning regimen among patients with myeloid malignancies who received HCT with myeloablative conditioning from 2009 to 2011

Characteristics of patients	IV-BU N = 1025 (%)	TBI N = 458 (%)
Number of centers	104	79
Geographic region		
North America	1020 (99)	444 (97)
South America	5 (<1)	14 (3)
Age, median (range), years	46 (<1-60)	43 (1-60)
Gender		
Male	510 (50)	238 (52)
Patient ethnicity		
White	906 (88)	404 (88)
African American	54 (5)	19 (4)
Asian	29 (3)	12 (3)
Other	36 (4)	23 (5)
Performance score		
Karnofsky: 90%-100%	598 (66)	277 (65)
Lansky: 90%-100%	106 (91)	29 (88)
HCI-CI		
0	400 (39)	209 (46)
1-2	302 (29)	112 (24)
≥3	323 (32)	137 (30)
Disease and disease status		
AML early	415 (40)	182 (40)
AML intermediate	143 (14)	82 (18)
AML advanced	143 (14)	95 (21)
CML early	59 (6)	24 (5)
CML intermediate	21 (2)	24 (5)
CML advanced	28 (3)	6 (1)
MDS early	62 (6)	11 (2)
MDS advanced	151 (15)	33 (7)
MDS NOS	3 (<1)	1 (<1)
Prior autologous transplant	21 (2)	11 (2)
Graft type		
Bone marrow	238 (23)	110 (24)
Peripheral blood	787 (77)	348 (76)
Donor type		
HLA-identical sibling	417 (41)	180 (39)
Well-matched unrelated	479 (47)	231 (50)
Partially matched unrelated	115 (11)	43 (9)
Mismatched	2 (<1)	2 (<1)
HLA match information missing unrelated	12 (1)	2 (<1)
D-R sex match		
F-M	194 (19)	91 (20)
F-F	204 (20)	88 (19)
M-M	316 (31)	147 (32)
M-F	311 (30)	132 (29)
D-R CMV status		
−/−	301 (29)	136 (30)
+/+	267 (26)	117 (26)
+/−	135 (13)	58 (13)
−/+	321 (31)	146 (32)
Missing	1 (<1)	1 (<1)
Conditioning regimen		
FLU + BU	289 (28)	0
FLU + BU + ATG/Campath	135 (13)	0
BU + CY $^{+/−}$ others	500 (49)	0
BU + CY $^{+/−}$ OTHERS + ATG/Campath	101 (10)	0
CY + TBI $^{+/−}$ others	0	396 (86)
CY + TBI $^{+/−}$ others + ATG/Campath	0	47 (10)
Etoposide + TBI (No Cy)	0	15 (3)
Total BU dose for patients who received IV BU, median (range), mg/kg	13 (10-28)	—

Table 1. (continued)

Characteristics of patients	IV-BU N = 1025 (%)	TBI N = 458 (%)
BU schedule		—
Every 6 h	586 (57)	—
Daily	427 (42)	—
Twice daily	7 (<1)	—
Other schedule	5 (<1)	—
PKs vs non-PKs		—
No	447 (44)	—
Yes	578 (56)	—
BU dose-adjusted based on PK with a plan		—
No	122 (22)	—
Yes	443 (78)	—
Fractionated TBI		
No	—	21 (5)
Yes	—	437 (95)
TBI dose median (range) cGy		
Unfractionated	—	550 (550-900)
Fractionated	—	1200 (990-1440)
BU dose if no PK, median (range), mg/kg*	13 (10-17)	—
BU dose if PK, median (range), mg/kg†	14 (10-27)	
GVHD prophylaxis		
Tacro+MTX $^{+/−}$ other	645 (63)	322 (70)
Tacro+MMF $^{+/−}$ other	133 (13)	20 (4)
CSA+MTX $^{+/−}$ other	146 (14)	74 (16)
CSA+MMF $^{+/−}$ other	30 (3)	9 (2)
CSA or Tacro $^{+/−}$ other	71 (7)	33 (7)
ATG/Campath		
CNI-based +ATG/Campath	297 (29)	65 (14)
Median follow-up of survivors, range, months	22 (3-36)	23 (8-37)

ALL, acute lymphoblastic leukemia; CSA, cyclosporine A; Tacro, tacrolimus.
*Higher doses were in pediatric patients.
†Higher doses were in a dose-escalated trial at a single center.

respect to age (median age, 45 years), gender (50% women), race (88% Caucasian), performance status (68% in more than 90 patients), and comorbidities. Most patients had AML (68% BU and 78% TBI). The disease status was early (51%), intermediate (18%), and advanced (31%) and was similar in the cohorts. Transplants were performed primarily with peripheral blood grafts (77%) from either related (40%) or well-matched unrelated (48%) donors. Donor age, gender-matching, and donor-recipient CMV status were similar between the cohorts. For GVHD prophylaxis, the CNI was most commonly combined with short-course MTX (79%).

IV-BU was most commonly given in combination with CY (59%). Dosing of BU was more often 4 times a day with CY (82%) and more commonly once a day with FLU (78%). ATG or Campath was used as part of the conditioning regimen or GVHD prophylaxis in 33% of patients in the IV-BU group and in 17% of patients in the TBI group. BU PK was performed in 56% of patients; in 78%, PK resulted in dose adjustment. PK testing was most commonly performed with a BU dosing of 4 times per day (63%). Of 103 centers that used IV-BU regimens, 54 centers performed PK in all patients, 26 centers performed PK in selected patients, and 23 centers never performed PK.

Survival duration

The 2-year probabilities of survival were 56% (95% CI, 53%-60%) and 48% (95% CI, 43%-54%) for IV-BU and TBI-based regimens, respectively ($P = .019$) (Figure 1A). Survival curves according to
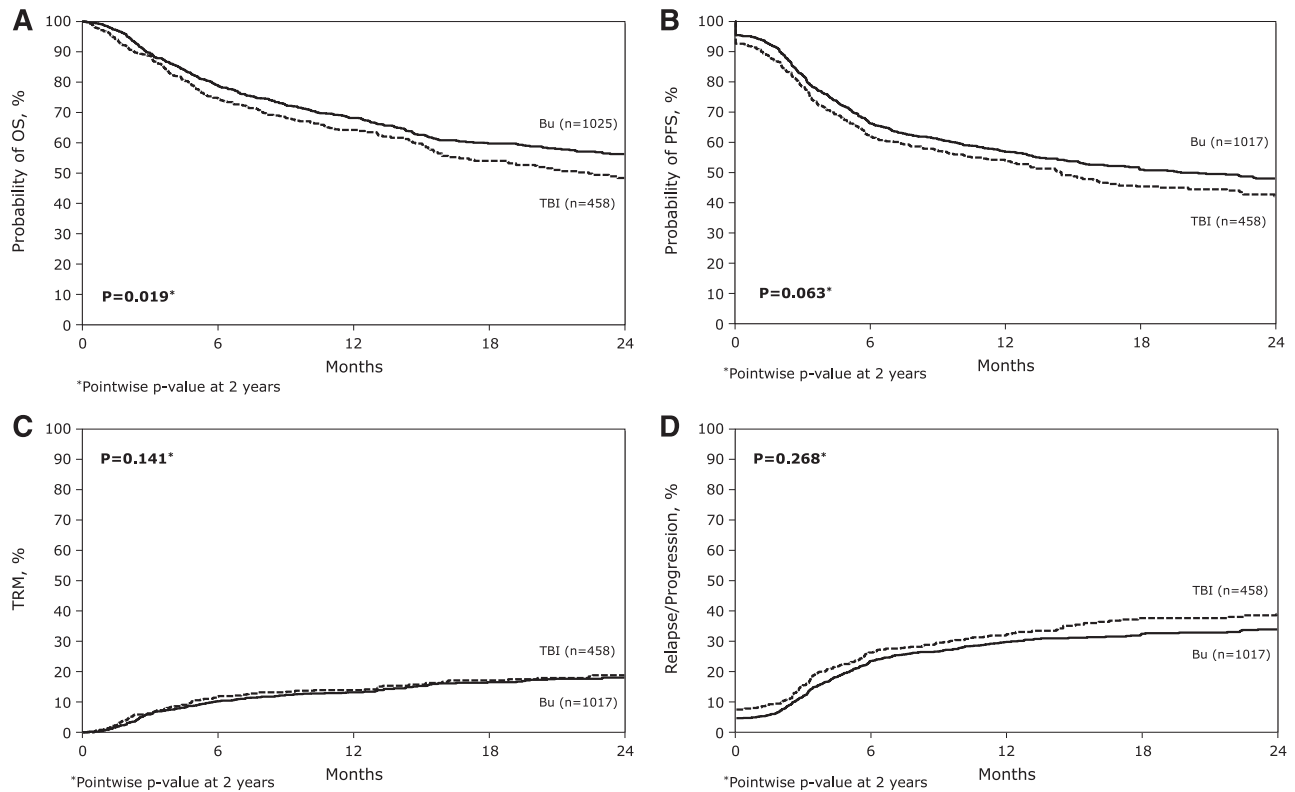
Figure 1. Outcomes of allogeneic HCT with IV-BU or TBI conditioning regimens. (A) Survival by conditioning regimens. (B) Progression free survival by conditioning regimens. (C) Cumulative incidence of TRM by conditioning regimens. (D) Cumulative incidence of disease relapse by conditioning regimens.

diagnosis and disease status are shown in Figure 2A-B, respectively. For patients with AML patients, the 2-year survival rate was 57% (95% CI, 53%-61%) and 46% (95% CI, 40%-52%) in the IV-BU and TBI-based regimens, respectively ($P = .003$). Two-year survival duration was not different for patients with MDS or CML based on conditioning. For patients with early disease, the 2-year survival rate was 64% (95% CI, 59%-69%) and 51% (95% CI, 42%-59%) for IV-BU and TBI-based regimens, respectively ($P = .006$). Survival duration was not different for patients with intermediate or advanced disease based on conditioning regimen. In multivariate analysis, IV-BU–based conditioning was associated with a decreased risk for death (HR, 0.82; 95% CI, 0.68-0.98; $P = .03$) compared with TBI-based conditioning. In addition to conditioning, other factors associated with an increased risk for death included older age, race other than Caucasian, and a HCT comorbidity index score >3 (Table 2).

PFS

Two-year probabilities of PFS were 48% (95% CI, 45%-51%) and 42% (95% CI, 37-47) for IV-BU and TBI-based regimens, respectively ($P = .063$) (Figure 1B).

In multivariate analysis of treatment failure, IV-BU was equivalent to the TBI-based regimen (Table 2).

Engraftment

The cumulative incidence of neutrophil recovery at day 28 were 96% (95% CI, 95%-97%) and 93% (95% CI, 90%-95%) for IV-BU and TBI-based regimens, respectively ($P = .01$). Corresponding cumulative incidences for platelet recovery at day 28 were 76% (95% CI, 74%-79%) and 73% (95% CI, 69%-77%), respectively ($P = .147$).

Toxicities and TRM

The 100-day cumulative incidences for VOD/SOS were 5% (95% CI, 4%-6%) and 1% (95% CI, 0%-3%; $P < .001$); for IPN, 4% (95% CI, 2%-5%) and 6% (95% CI, 4%-8%; $P = .055$); and for renal failure requiring dialysis, 6% (95% CI, 4%-7%) and 7% (95% CI, 5%-10%; $P = .243$) for IV-BU and TBI-based regimens, respectively.

Corresponding 2-year cumulative incidences of TRM were 18% (95% CI, 16%-21%) and 19% (95% CI, 15%-23%; $P = .75$), respectively (Figure 1C).

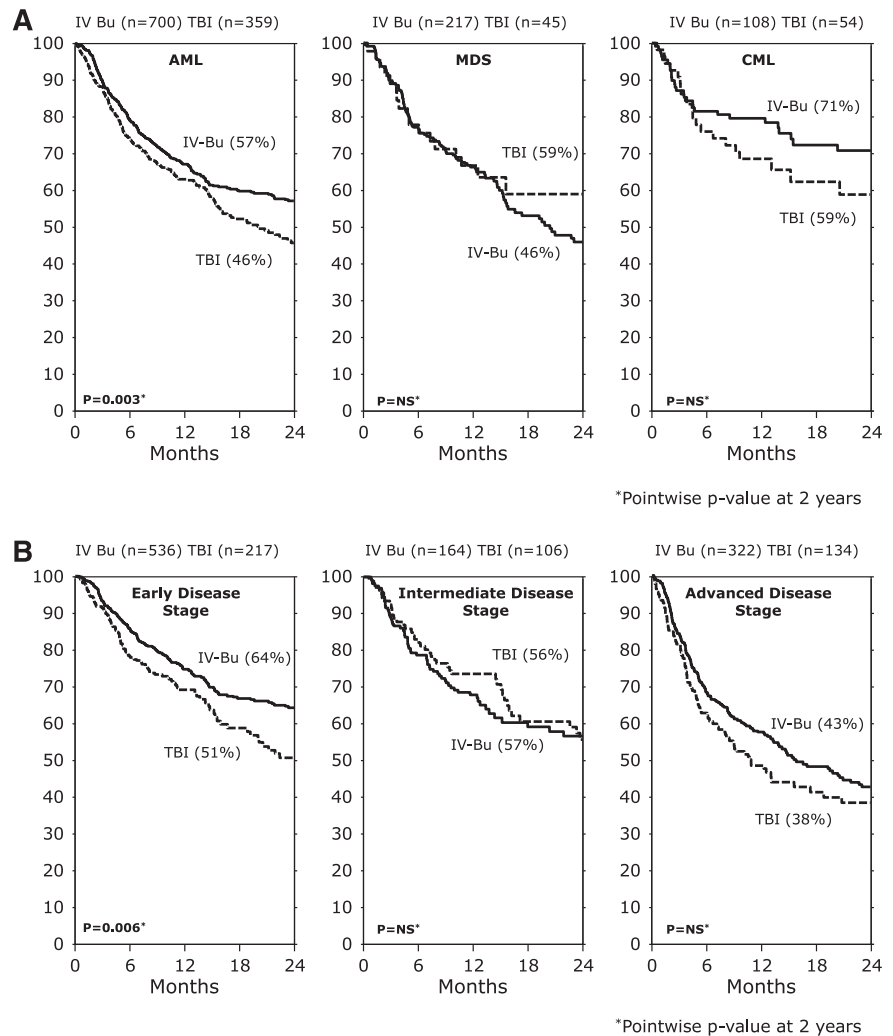In multivariate analysis for TRM, IV-BU was similar to TBI-based regimens (Table 2).

GVHD

The 100-day cumulative incidences of grades 2 to 4 acute GVHD were 46% (95% CI, 43%-49%) and 51% (95% CI, 46%-55%; $P = .128$), and grades 3 to 4 acute GVHD were 18% (95% CI, 16%-21%) and 23% (95% CI, 19%-27%; $P = .052$) for IV-BU and TBI-based regimens, respectively. Corresponding 1-year cumulative incidences of cGVHD were 44% (95% CI, 41%-47%) and 42% (95% CI, 37%-46%; $P = .397$), respectively. Multivariate analysis shows no treatment effect on grade 3 to 4 acute GVHD (0.81; 95% CI, 0.63-1.05; $P = .11$) and no treatment effect on cGVHD (HR, 1.07; 95% CI, 0.90-1.29; $P = .44$). Additional variables associated with GVHD outcomes are shown in supplemental Tables 1 and 2.

Disease relapse/progression

The 2-year cumulative incidences of disease relapse/progression were 34% (95% CI, 31%-37%) and 39% (95% CI, 34%-44%; $P = .084$) for IV-BU and TBI-based regimens, respectively (Figure 1D).

Figure 2. Survival after allogeneic HCT with IV-BU or TBI conditioning stratified on diagnosis and disease status. (A) Survival by diagnosis and conditioning regimens. (B) Survival by disease status and conditioning regimens

In multivariate analysis for disease relapse, IV-BU was equivalent to the TBI-based regimen (Table 2).

Causes of death

Causes of death as reported by the transplant center were similar in the 2 cohorts and are outlined in Table 3.

BU/CY vs FLU/BU

There were some differences between the patients conditioned with BU/CY and FLU/BU. Patients receiving BU/CY were younger, with 22% of these patients being younger than 20 years vs 6% for patients receiving FLU/BU. Patients undergoing BU/CY also had a greater proportion with a performance score of 90 to 100 and an HCT comorbidity index score of 0 to 3. Patients receiving BU/CY more commonly received a bone marrow graft. IV-BU was administered every 6 hours in 82% of recipients of BU/CY vs daily in 78% of recipients of FLU/BU (supplemental Table 3). Despite these differences, in multivariate analysis, study outcomes did not differ between patients receiving BU/CY-based vs FLU/BU-based conditioning, including overall mortality (HR, 0.95; $P = .63$), treatment failure (HR, 1.02; $P = .81$), relapse (HR, 0.96; $P = .75$), and TRM (HR, 1.14; $P = .44$). In addition, the incidence of VOD was not different between the BU/CY and FLU/BU cohorts (5% vs 4%; $P = .53$)

Discussion

The practice of HCT is in continual evolution as new therapies are developed, evaluated, and reported in the literature. Although it is not feasible to test every development in prospective trials, it is problematic to apply results of outdated studies to current practice. The last randomized trial comparing CYTBI with BU/CY was reported more than 15 years ago. Since then, numerous changes have been introduced and general transplant results have improved for almost all patient groups.[9,10,15] More has also been learned regarding the late effects of transplant conditioning.[16-18] A gradual decrease in ablative TBI-based transplants and an increase in IV-BU–based transplants have occurred without supportive prospective data comparing the approaches.

Although a randomized controlled trial is the reference standard for comparing treatments, such a trial was considered unlikely to accrue based on physician bias and competition for limited resources. Instead, using the data collection capabilities of the CIBMTR, we conducted a large prospective cohort study with strict eligibility and reporting requirements and adjusted for differences between the groups using standard multivariable statistical methods.

Our study was designed to test, in the modern era, the non-inferiority of IV-BU–based vs TBI-based myeloablative conditioning

Table 2. Multivariate analysis comparing intravenous formulation busulfan to TBI-based myeloablative conditioning regimens before HCT for myeloid malignancies

Overall mortality*	Level	N	HR (95% CI)	P value
Conditioning regimen	TBI	446	1	
	IV-BU	993	0.819 (0.683-0.981)	.0302
Patient age (y)	≤19	199	1	.0008†
	20-49	704	1.347 (0.989-1.836)	.0592
	≥50	536	1.727 (1.258-2.371)	.0007
Race	White	1278	1	
	Other	161	1.409 (1.084-1.831)	.0104
HCT CI	≤3	1186	1	
	>3	253	1.417 (1.153-1.743)	.0009
TRM*				
Conditioning regimen	TBI	446	1	
	IV-BU	988	0.800 (0.596-1.075)	.1395
Patient age, years	≤19	198	1	.0167†
	20-49	701	1.309 (0.810-2.114)	.2710
	≥50	532	1.829 (1.123-2.979)	.0153
Race	White	1271	1	
	Other	160	1.719 (1.158-2.551)	.0072
Disease relapse*				
Conditioning regimen	TBI	446	1	
	IV-BU	988	0.933 (0.766-1.137)	.4940
HCT CI	≤3	1179	1	
	>3	252	1.329 (1.050-1.683)	.0180
Treatment failure*‡				
Conditioning regimen	TBI	446	1	
	IV-BU	985	0.894 (0.759-1.053)	.1795
HCT CI	≤3	1179	1	
	>3	252	1.354 (1.119-1.638)	.0018

*Model stratified by disease status (AML early vs AML intermediate vs AML advanced vs CML early vs CML intermediate vs CML advanced vs MDS early vs MDS advanced), donor type (HLA-id sib vs well-matched unrelated vs partially matched unrelated), and performance score (<90% vs ≥90%).

†Overall P value.

‡Treatment failure is 1/relapse-free survival; events are death or disease relapse.

for allogeneic transplantation. We included several common BU-based and TBI-based regimens in the 2 cohorts; of note, there were not significant outcome differences between the regimens in each group. Specifically, our hypothesis was that IV-BU–based conditioning does not lead to inferior survival compared with TBI-based conditioning for patients with AML, MDS, and CML receiving related or volunteer unrelated donor grafts. The results strongly support this hypothesis. The data actually suggest a possible advantage to using IV-BU in this patient population. This advantage was most evident in patients with early-stage disease and AML.

Among IV-BU–containing regimens, some studies suggest that FLU/BU results in lower regimen-related toxicity compared with BU/CY.[19-22] Results from a recently reported prospective randomized trial found similar nonrelapse mortality rates but improved survival outcomes with BU/CY compared with FLU/BU.[23] The current study demonstrated that FLU/BU most commonly used IV-BU once daily, and it was administered to older patients and a higher proportion of patients with a lower performance score or a higher HCT comorbidity index. Despite these differences in the populations, the outcomes between FLU/BU and BU/CY were similar. Thus, this subset analysis supports that the 2 most commonly used non-TBI regimens are equivalent, despite differences in practices on when they are generally selected.

Adverse outcomes were similar with IV-BU–based and TBI-based approaches with slightly lower rates of TRM and relapse with

IV-BU, although they did not reach statistical significance. There was a higher incidence of VOD/SOS with IV-BU. Other toxicities including IPN, the need for dialysis by 1 year posttransplant, cGVHD, and causes of death were remarkably similar in the 2 cohorts. The multivariate analyses on severe acute GVHD (grades 3-4) and cGVHD showed no benefit for IV-BU.

ATG/Campath was more commonly included with the FLU/BU regimens as developed by Russell et al.[20] The use of ATG/Campath did not significantly affect survival or relapse outcomes. However, in the GVHD multivariate models, the use of ATG/Campath was associated with lower rates of acute and cGVHD (supplemental Tables 1 and 2). Unfortunately, we do not have the details of IV-BU dose adjustments for patients undergoing PK testing. Toxicity and TRM are known to be increased in patients with high levels of BU, whereas relapse and graft rejection increase with low levels.[24-26]

Prospective cohort studies are capable of accruing large number of patients and of measuring outcomes of contemporary transplant practices. Approximately 80% of patients undergoing transplantation in the United States who met eligibility criteria for the study during the accrual period were enrolled on this trial, providing an evaluation of these treatment approaches in the real world. In addition, data completeness approaching 100% through active monitoring outlines a novel and robust application of the CIBMTR infrastructure and outcomes database to address transplantation questions. These feature of a prospective cohort study address some of the pitfalls often assailed against retrospective cohort studies, particularly retrospective eligibility determination, data accuracy, and completeness. Although the issue of treatment assignment vs random selection will always remain for cohort studies, in this study, the similarities between the treatment groups and the ability to perform a robust statistical analysis because of the large sample size mitigate these concerns. Furthermore, it is unlikely that a randomized controlled trial of TBI-based vs IV-BU–based conditioning will ever be performed; we must work with the tools at hand.

For patients meeting the eligibility and practice approach of this study, IV-BU–based conditioning was not inferior to TBI-based conditioning. This information is helpful to clinicians for choosing conditioning regimens and counseling patients. The results went further to suggest that IV-BU resulted in a small but significant improvement in survival duration. The role of BU PK as part of such an approach requires further study. Future studies are required to understand the mechanism by which IV-BU–based regimens resulted in superior survival outcomes for patients with early-stage disease and AML in our study.

Table 3. Causes of death by conditioning regimens

	IV-BU	TBI
Description	N = 400 (%)	N = 207 (%)
Primary disease	197 (49)	107 (52)
GVHD	56 (14)	22 (11)
Infection	62 (16)	27 (13)
Organ failure		
Lung (IPS/ARDS)	23 (6)	18 (9)
Liver	4 (1)	0
Renal	4 (1)	2 (<1)
Other/multiple	18 (5)	11 (5)
Thromboembolic/hemorrhage	2 (<1)	2 (<1)
Graft failure	5 (1)	3 (1)
Second primary malignancy	1 (<1)	1 (<1)
Other causes	28 (8)	14 (6)

ARDS, adult respiratory distress syndrome; IPS, idiopathic pneumonia syndrome.

Authorship

Contribution: C.B., K.K, and M.C.P. designed the study, analyzed results, and wrote the manuscript; J.L. and X.Z. provided the statistical support; and J.F.D., E.A., S.M.D., F.R.A., M.R.T., G.G.L., P.L.M., V.T.H., K.R.C., E.A., A.S., J.D.R., and J.M.B. interpreted data and critically reviewed the manuscript. All authors approved the final manuscript.

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References

1. Thomas ED, Buckner CD, Clift RA, et al. Marrow transplantation for acute nonlymphoblastic leukemia in first remission. *N Engl J Med.* 1979; 301(11):597-599.

2. Tutschka PJ, Copelan EA, Kapoor N. Replacing total body irradiation with busulfan as conditioning of patients with leukemia for allogeneic marrow transplantation. *Transplant Proc.* 1989;21(1 Pt 3): 2952-2954.

3. Blaise D, Maraninchi D, Archimbaud E, et al. Allogeneic bone marrow transplantation for acute myeloid leukemia in first remission: a randomized trial of a busulfan-Cytoxan versus Cytoxan-total body irradiation as preparative regimen: a report from the Group d'Etudes de la Greffe de Moelle Osseuse. *Blood.* 1992;79(10):2578-2582.

4. Ringdén 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(9):2723-2730.

5. Clift RA, Buckner CD, Thomas ED, et al. Marrow transplantation for chronic myeloid leukemia: a randomized study comparing cyclophosphamide and total body irradiation with busulfan and cyclophosphamide. *Blood.* 1994; 84(6):2036-2043.

6. Andersson BS, Kashyap A, Gian V, et al. Conditioning therapy with intravenous busulfan and cyclophosphamide (IV BuCy2) for hematologic malignancies prior to allogeneic stem cell transplantation: a phase II study. *Biol Blood Marrow Transplant.* 2002;8(3):145-154.

7. Thall PF, Champlin RE, Andersson BS. Comparison of 100-day mortality rates associated with i.v. busulfan and cyclophosphamide vs other preparative regimens in allogeneic bone marrow transplantation for chronic myelogenous leukemia: Bayesian sensitivity analyses of confounded treatment and center effects. *Bone Marrow Transplant.* 2004;33(12):1191-1199.

8. Kashyap A, Wingard J, Cagnoni P, et al. Intravenous versus oral busulfan as part of a busulfan/cyclophosphamide preparative regimen for allogeneic hematopoietic stem cell transplantation: decreased incidence of hepatic venoocclusive disease (HVOD), HVOD-related mortality, and overall 100-day mortality. *Biol Blood Marrow Transplant.* 2002;8(9):493-500.

9. Horan JT, Logan BR, Agovi-Johnson MA, 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(7):805-813.

10. Pasquini MC, Wang Z, Horowitz MM, Gale RP. 2010 report from the Center for International Blood and Marrow Transplant Research (CIBMTR): current uses and outcomes of hematopoietic cell transplants for blood and bone marrow disorders. *Clin Transpl.* 2010;87-105.

11. Giralt S, Ballen K, Rizzo D, et al. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant.* 2009;15(3):367-369.

12. Weisdorf D, Spellman S, Haagenson M, et al. Classification of HLA-matching for retrospective analysis of unrelated donor transplantation: revised definitions to predict survival. *Biol Blood Marrow Transplant.* 2008;14(7):748-758.

13. Klein J, Moeschberger ML. *Survival Analysis: Statistical Methods for Censored and Truncated Data,* 2nd ed. New York, NY: Springer-Verlag; 2003.

14. Zhang X, Loberiza FR, Klein JP, Zhang MJ. A SAS macro for estimation of direct adjusted survival curves based on a stratified Cox regression model. *Comput Methods Programs Biomed.* 2007;88(2):95-101.

15. Socié G, Clift RA, Blaise D, et al. Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow-up of 4 randomized studies. *Blood.* 2001; 98(13):3569-3574.

16. Pulsipher MA, Skinner R, McDonald GB, et al. National Cancer Institute, National Heart, Lung and Blood Institute/Pediatric Blood and Marrow Transplantation Consortium First International Consensus Conference on late effects after pediatric hematopoietic cell transplantation: the need for pediatric-specific long-term follow-up guidelines. *Biol Blood Marrow Transplant.* 2012;18(3):334-347.

17. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Rev Bras Hematol Hemoter.* 2012;34(2):109-133.

18. Andersson BS, de Lima M, Thall PF, et al. Once daily i.v. busulfan and fludarabine (i.v. Bu-Flu) compares favorably with i.v. busulfan and cyclophosphamide (i.v. BuCy2) as pretransplant conditioning therapy in AML/MDS. *Biol Blood Marrow Transplant.* 2008;14(6):672-684.

19. Bredeson CN, Zhang MJ, Agovi MA, et al. Outcomes following HSCT using fludarabine, busulfan, and thymoglobulin: a matched comparison to allogeneic transplants conditioned with busulfan and cyclophosphamide. *Biol Blood Marrow Transplant.* 2008;14(9):993-1003.

20. Russell JA, Tran HT, Quinlan D, et al. Once-daily intravenous busulfan given with fludarabine as conditioning for allogeneic stem cell transplantation: study of pharmacokinetics and early clinical outcomes. *Biol Blood Marrow Transplant.* 2002;8(9):468-476.

21. McCune JS, Gooley T, Gibbs JP, et al. Busulfan concentration and graft rejection in pediatric patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2002; 30(3):167-173.

22. Liu H, Zhai X, Song Z, et al. 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):15.

23. Lee JH, Joo YD, Kim H, et al. Randomized trial of myeloablative conditioning regimens: busulfan plus cyclophosphamide versus busulfan plus fludarabine. *J Clin Oncol.* 2013;31(6): 701-709.

24. Bolinger AM, Zangwill AB, Slattery JT, et al. An evaluation of engraftment, toxicity and busulfan concentration in children receiving bone marrow transplantation for leukemia or genetic disease. *Bone Marrow Transplant.* 2000;25(9):925-930.

25. Slattery JT, Sanders JE, Buckner CD, et al. Graft-rejection and toxicity following bone marrow transplantation in relation to busulfan

pharmacokinetics. *Bone Marrow Transplant.* 1995;16(1):31-42.

26. Geddes M, Kangarloo SB, Naveed F, et al. High busulfan exposure is associated with worse outcomes in a daily i.v. busulfan and fludarabine allogeneic transplant regimen. *Biol Blood Marrow Transplant.* 2008;14(2): 220-228.