REGULAR ARTICLE

blood advances

Hematopoietic cell transplant for acute myeloid leukemia and myelodysplastic syndrome: conditioning regimen intensity

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Key Points

- Bu4/Cy, Flu/Bu4, and Flu/Mel are optimal regimens for patients with AML in clinical remission or those with MDS.
- Flu/Mel, considered a less-intense regimen, is ideal for less fit patients.

In this study, we sought to identify specific individual high-intensity or reduced-intensity conditioning regimens with the best relapse-free survival (RFS) rather than the global high- vs reduced-intensity regimen comparison. Patients (median age, 58 years) with acute myeloid leukemia (AML; n = 1258), who were in first or subsequent remission, or with MDS (n = 951) who had refractory anemia with unilineage or multilineage dysplasia, 5q− syndrome, or refractory anemia with excess blasts received nonirradiation-containing regimens and were transplanted between 2009 and 2014 in the United States. Three-year RFS with high-intensity busulfan/cyclophosphamide (Bu4/Cy; 44%) was comparable to conditioning with high-intensity fludarabine/busulfan (Flu/Bu4; 44%), reduced-intensity fludarabine/melphalan (Flu/Mel; 52%; $P = .53$), and Flu/Mel + anti-thymocyte globulin (ATG; 44%; $P = .38$). RFS was lower with reduced-intensity Flu/Bu2 + ATG (31%; $P = .0006$). RFS was also lower with high-intensity Flu/Bu4 + ATG (38%; $P = .05$) and reduced-intensity Flu/Bu2 (38%; $P = .02$), although the difference did not reach the level of significance set for these analysis. RFS with Flu/Mel was superior to RFS with Flu/Bu2 ($P = .01$) and Flu/Bu2 + ATG ($P = .0006$). The 3-year incidence of relapse was 22% with Flu/Mel compared with 46% with Flu/Bu2 and 56% with Flu/Bu2 + ATG. With only a modest reduction in nonrelapse mortality with the Flu/Bu2 regimens, the higher relapse incidence resulted in lower RFS. The data support optimal RFS with Bu4/Cy, Flu/Bu4, and Flu/Mel regimens for AML in remission or MDS. The low relapse rate with reduced-intensity Flu/Mel resulted in RFS comparable to that after the higher-intensity regimens.

Introduction

Hematopoietic cell transplantation (HCT) from suitably HLA-matched related or unrelated donors is the treatment option with the highest chance for prolonged survival with disease control for many patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). The frequency of HCT has increased progressively, in part related to wider donor availability and the introduction of reduced-intensity transplant conditioning (RIC) regimens intended for older and less fit patients. Several retrospective studies report a higher risk for relapse and lower nonrelapse mortality (NRM), but similar overall survival, with RIC compared with high-intensity myeloablative conditioning (MAC) regimens in adults with AML or MDS.[1-7] Because of the lower rates of toxicity associated with RIC, these regimens are increasingly being offered to young and fit adults with AML or MDS.

Three recent prospective randomized trials comparing MAC vs RIC for AML and MDS yielded mixed results.[8-10] One trial randomized patients with AML in first remission to total body irradiation (TBI)-containing MAC (TBI 12 Gy and cyclophosphamide) or RIC (TBI 8 Gy and fludarabine) and found no significant difference in NRM, relapse incidence, or survival.[8] The second trial randomized adults with AML in clinical remission or with MDS and <5% blasts to RIC or MAC regimens.[9] The RIC regimens included fludarabine and busulfan (Flu/Bu2) or

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Table 1. Patient, disease, and transplant characteristics

	Flu/Bu4	Flu/Bu4 + ATG	Bu4/Cy	Flu/Bu2	Flu/Bu2 + ATG	Flu/Mel	Flu/Mel + ATG
Patients, n	477	276	518	405	263	198	72
Median age, y	56	56	51	63	63	63	64
Age, y							
18-39	72 (15)	54 (20)	113 (22)	14 (4)	13 (5)	6 (3)	6 (8)
40-59	255 (54)	130 (47)	355 (68)	112 (27)	78 (30)	52 (26)	17 (24)
≥60	150 (31)	92 (33)	50 (10)	279 (69)	172 (65)	140 (71)	49 (68)
Sex, male	264 (55)	156 (57)	266 (51)	257 (63)	115 (58)	157 (60)	43 (60)
CMV serostatus							
Negative	179 (37)	100 (36)	211 (41)	169 (42)	53 (27)	87 (33)	17 (24)
Positive	290 (61)	173 (63)	303 (58)	234 (58)	144 (73)	176 (67)	55 (76)
Not reported	8 (2)	3 (1)	4 (<1)	2 (<1)	1 (<1)	—	—
Performance score							
90-100	297 (62)	181 (66)	340 (66)	193 (48)	142 (54)	95 (48)	43 (60)
≤80	169 (36)	88 (32)	178 (34)	207 (51)	120 (46)	101 (51)	29 (40)
Not reported	11 (2)	7 (2)	—	5 (1)	1 (<1)	2 (1)	—
HCT-CI							
0-2	248 (52)	148 (54)	269 (52)	180 (44)	100 (38)	92 (46)	35 (49)
≥3	229 (48)	128 (46)	247 (48)	225 (56)	160 (61)	103 (52)	37 (51)
Not reported	—	—	2 (<1)	—	3 (1)	3 (2)	—
Disease							
AML	285 (60)	161 (58)	362 (70)	178 (44)	142 (54)	96 (48)	34 (47)
MDS	192 (40)	115 (42)	156 (30)	227 (56)	121 (46)	102 (52)	38 (53)
Disease status*							
CR1	220 (46)	113 (41)	264 (51)	146 (36)	111 (42)	78 (39)	25 (35)
CR2	65 (13)	48 (17)	98 (19)	32 (7)	31 (11)	18 (9)	9 (13)
RA/RARS	14 (3)	6 (1)	18 (3)	15 (3)	11 (5)	11 (6)	5 (7)
RCMD	51 (11)	29 (11)	26 (5)	62 (15)	33 (13)	19 (10)	5 (7)
5q− syndrome	1 (<1)	1 (<1)	2 (<1)	4 (<1)	—	1 (<1)	—
RAEB-1/RAEB-2	126 (27)	79 (28)	110 (21)	146 (36)	77 (29)	71 (36)	28 (39)
Cytogenetic risk							
Favorable	22 (5)	16 (6)	30 (6)	10 (3)	13 (5)	4 (2)	2 (3)
Intermediate	353 (74)	180 (65)	388 (75)	290 (72)	171 (65)	140 (71)	52 (72)
Unfavorable	87 (18)	71 (26)	75 (14)	83 (20)	64 (24)	44 (22)	15 (21)
Not reported	15 (3)	9 (3)	25 (5)	22 (5)	15 (6)	10 (5)	3 (4)
Disease risk index							
Low	22 (5)	16 (6)	30 (6)	10 (3)	13 (5)	4 (2)	2 (3)
Intermediate	273 (57)	144 (52)	315 (61)	191 (47)	130 (49)	97 (49)	36 (50)
High	166 (35)	106 (38)	146 (28)	178 (44)	105 (40)	86 (44)	31 (43)
Not reported	16 (3)	10 (4)	27 (5)	26 (6)	15 (6)	11 (5)	3 (4)
Donor							
Matched sibling	229 (48)	22 (8)	228 (44)	177 (44)	37 (14)	84 (42)	4 (6)
Unrelated donor: matched	223 (47)	204 (74)	256 (49)	192 (47)	199 (76)	91 (46)	39 (54)
Unrelated donor: mismatched	25 (5)	50 (18)	34 (7)	36 (9)	27 (10)	23 (12)	29 (40)

With the exception of the number of patients and median age, all data are n (%).

—, null; CR, complete remission; CsA, cyclosporine; MMF, mycophenolate; MTX, methotrexate; RAEB, RA with excess blasts; RARS, RA with ringed sideroblast; RCMD, RA with multilineage dysplasia; Tac, tacrolimus.

*World Health Organization 2016 MDS terminology: RA, MDS-SLD (MDS with single lineage dysplasia); RARS, MDS-RS-SLD (MDS with ringed sideroblasts and single lineage dysplasia); RCMD, MDS-MLD (MDS with multilineage dysplasia); RAEB-1/2, MDS-EB1/2 (MDS with excess blasts); 5q− syndrome, MDS with isolated del(5q).

Table 1. (continued)

	Flu/Bu4	Flu/Bu4 + ATG	Bu4/Cy	Flu/Bu2	Flu/Bu2 + ATG	Flu/Mel	Flu/Mel + ATG
Graft							
Bone marrow	50 (10)	49 (18)	83 (16)	8 (2)	17 (6)	25 (13)	21 (29)
Peripheral blood	427 (90)	227 (82)	435 (84)	397 (98)	246 (94)	173 (87)	51 (71)
Donor/recipient sex match							
Female/female	76 (16)	39 (14)	99 (19)	63 (16)	30 (11)	37 (19)	15 (21)
Female/male	88 (18)	48 (18)	96 (18)	75 (18)	29 (11)	36 (18)	11 (15)
Male/female	137 (29)	81 (29)	153 (30)	85 (21)	76 (29)	46 (23)	14 (19)
Male/male	176 (37)	108 (39)	170 (33)	182 (45)	128 (49)	79 (40)	32 (44)
GVHD prophylaxis							
Tac + MMF	106 (22)	61 (22)	40 (8)	49 (12)	119 (45)	42 (21)	13 (18)
Tac + MTX	353 (74)	203 (74)	418 (81)	338 (84)	126 (48)	125 (63)	44 (61)
CsA + MMF	11 (3)	6 (2)	22 (4)	8 (2)	14 (5)	11 (6)	5 (7)
CsA + MMF	7 (1)	6 (2)	38 (7)	10 (2)	4 (2)	20 (10)	10 (14)
Transplant period							
2009-2011	221 (46)	141 (51)	276 (53)	102 (25)	121 (46)	52 (26)	15 (21)
2012-2014	256 (54)	135 (49)	242 (47)	303 (75)	142 (54)	146 (74)	57 (79)

With the exception of the number of patients and median age, all data are n (%).

—, null; CR, complete remission; CsA, cyclosporine; MMF, mycophenolate; MTX, methotrexate; RAEB, RA with excess blasts; RARS, RA with ringed sideroblast; RCMD, RA with multilineage dysplasia; Tac, tacrolimus.

*World Health Organization 2016 MDS terminology: RA, MDS-SLD (MDS with single lineage dysplasia); RARS, MDS-RS-SLD (MDS with ringed sideroblasts and single lineage dysplasia); RCMD, MDS-MLD (MDS with multilineage dysplasia); RAEB-1/2, MDS-EB1/2 (MDS with excess blasts); 5q− syndrome, MDS with isolated del(5q).

fludarabine and melphalan (Flu/Mel); the MAC regimens included Flu/Bu4, busulfan and cyclophosphamide (Bu4/Cy), and TBI (12-14 Gy) and cyclophosphamide. In this trial, relapse-free survival (RFS) and overall survival were higher with MAC, although the difference in survival did not reach statistical significance.[9] The third trial randomized patients with MDS or secondary AML to Flu/Bu2 or Bu4/Cy and showed that RFS and overall survival were similar.[10]

Randomization provides unbiased allocation to treatment arms; ensures that even if the groups are not identical with respect to relevant prognostic factors, such differences will be due to chance, allowing statistical theory based on random sampling to calculate confidence intervals (CIs); and offers the highest quality data that may lead to modification of clinical practice.[11-13] However, there are limitations to participating in clinical trials, which may include eligibility criteria and access to the trial. Further, the randomized trials that asked the fundamental question of whether to select a MAC or a RIC regimen allowed for multiple MAC and RIC regimens, and differences among the trials may be attributed to the specific regimen examined.

Therefore, using data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), the current analyses, including >2000 recipients of HCT in the United States, compared HCT outcomes with commonly used individual MAC and RIC regimens in adults with AML in clinical remission or MDS. We sought to identify the regimen(s) associated with the best RFS.

Patients and methods

Patients

The CIBMTR collects data prospectively on consecutively transplanted patients from >400 transplant centers and follows patients until death or loss to follow-up. Included in the present analysis were transplants performed in the United States between 2009 and 2014. Eligible patients were aged 18 years or older and had AML in clinical remission (bone marrow blasts <5%, with normal maturation of all cellular components in the bone marrow, no blasts with Auer rods, no extramedullary disease, absolute neutrophil count $>1 \times 10^9$/L, platelets $>100 \times 10^9$/L, and red blood cell transfusion independence) or MDS (refractory anemia [RA], refractory cytopenia, RA with ring sideroblasts, del(5q) syndrome, or RA with excess blasts). In 9% of AML patients and 23% of MDS patients, the disease was treatment related. Conditioning regimens included commonly used non-TBI MAC regimens, including Flu/Bu4 with or without anti-thymocyte globulin (ATG) or Bu4/Cy (Bu4 dose, 10-13 mg/kg IV or 16-18 mg oral), and RIC regimens, including Flu/Bu2 with or without ATG (Bu2 dose, 4-7 mg/kg IV or 5-8 mg/kg oral) or Flu/Mel with or without ATG (melphalan dose, 100 or 140 mg/m^2 IV). Pharmacokinetics (busulfan) was performed for 53% of busulfan-containing myeloablative regimens and 5% of reduced-intensity regimens. Only 48 of 270 recipients of melphalan received 100 mg/m^2. All patients received calcineurin inhibitor–containing graft-versus-host disease (GVHD) prophylaxis. Patients provided written informed consent for research. The Institutional Review Board of the National Marrow Donor Program approved this study. Complete follow-up to the closing date for analyses was available for >90% patients; median follow-up of survivors was 3 years (range, 0.5-7 years).

End points

The primary end point was RFS. Relapse and death from any cause were considered events (treatment failure). Grades II-IV acute GVHD and chronic GVHD were based on reports from each transplant center using standard criteria.[14,15] Primary and secondary graft failure were considered a single outcome. Primary graft failure was defined as failure to achieve an absolute neutrophil count $\geq 0.5 \times 10^9$/L for 3

consecutive days or donor chimerism <5%. Secondary graft failure was defined as initial donor engraftment followed by graft loss, as evidenced by a persistent decline in the absolute neutrophil count ($<0.5 \times 10^9$/L), donor chimerism <5%, or second transplant in patients with documented clinical remission. Relapse was defined as disease recurrence (morphologic, cytogenetic, or molecular). NRM was defined as death in remission. Overall mortality was defined as death from any cause. Surviving patients were censored at last follow-up.

Statistical methods

The cumulative incidences of graft failure and acute and chronic GVHD were calculated using the cumulative incidence estimator to accommodate competing risks.[16] Multivariate models were built to examine the effect of transplant conditioning regimen on treatment failure, overall mortality, NRM, relapse, and acute and chronic GVHD using Cox regression models.[17] The probabilities of RFS, overall survival, NRM, and relapse adjusted for other risk factors were calculated from the final Cox regression models.

The variable for conditioning regimen (Table 1) was held in all steps of model building. Other variables tested included patient age, sex, cytomegalovirus (CMV) serostatus, HCT comorbidity index (HCT-CI), performance score, diagnosis, disease risk index (composite of diagnosis, disease status, and cytogenetic risk), donor type, graft type, and transplant period (Table 1). All variables tested met the assumptions for proportionality, and there were no first-order interactions between the variable for conditioning regimen and other variables held in the final multivariate model. Variables that attained $P \leq .01$ were included in the final multivariate model. The effect of transplant center on survival was tested using the frailty model.[18] All P values are 2-sided, and analyses were done using SAS version 9.4 (Cary, NC).

Results

The characteristics of the study population by conditioning regimen are shown in Table 1. Compared with recipients of MAC, recipients of RIC regimens were older and were more likely to be CMV seropositive, to have HCT-CI scores ≥ 3, to have performance scores ≤ 80%, to have MDS, and to receive 1 HLA locus–mismatched unrelated donor HCT. There were no differences in cytogenetic risk, disease risk index, graft type, or GVHD prophylaxis. Of the 1258 patients with AML, FLT3 mutation was not tested in 431 patients (34%). FLT3 mutation was absent in 827 of 1258 patients (49%) and present in 205 of 1258 patients (16%). The distribution of $FLT3^+$ patients ranged between 12% and 19% across treatment groups. NPM1 mutational status was collected after 2012. Of the 598 evaluable patients, only 313 were tested; 66 (11%) tested positive, and the distribution across treatment groups ranged between 3% and 8%. In all conditioning regimen groups, unrelated-donor transplantations were more common than HLA-matched sibling transplantations, as was the use of peripheral blood as a source of stem cells. Recipients of unrelated donor transplants were more likely to receive ATG-containing regimens: 8% of matched-sibling transplants compared with 37% of matched-unrelated transplants, and 47% of 1 locus–mismatched unrelated-donor transplants. Rabbit-derived ATG was the most commonly used ATG (88%), with a median dose of 5 mg/kg (interquartile range [IQR], 4-6). The median dose of equine ATG was 40 mg/kg (IQR, 30-60). The most common GVHD prophylaxis was tacrolimus + methotrexate. The follow-up of the study population was 0.5 to 7 (median 3) years.

Table 2. Risk factors associated with acute and chronic GVHD

Conditioning regimen	Hazard ratio (95% CI)	*P*
Grade II-IV acute GVHD*		
Risks compared with Bu4/Cy		
Bu4/Cy	1.00	
Flu/Bu4	0.79 (0.66-0.94)	.01
Flu/Bu4/ATG	0.61 (0.48-0.76)	<.001
Flu/Bu2	0.55 (0.44-0.67)	<.001
Flu/Bu2/ATG	0.58 (0.46-0.73)	<.001
Flu/Mel	0.69 (0.54-0.89)	.004
Flu/Mel/ATG	0.86 (0.60-1.22)	.39
Risks compared with Flu/Mel		
Flu/Mel	1.00	
Flu/Bu2	0.79 (0.61-1.03)	.08
Flu/Bu2/ATG	0.84 (0.63-1.11)	.22
Flu/Mel/ATG	1.24 (0.83-1.83)	.29
Grade III-IV acute GVHD†		
Risks compared with Bu4/Cy		
Bu4/Cy	1.00	
Flu/Bu4	0.83 (0.63-1.11)	.21
Flu/Bu4/ATG	0.52 (0.46-0.75)	.001
Flu/Bu2	0.62 (0.45-0.84)	.003
Flu/Bu2/ATG	0.48 (0.32-0.71)	<.001
Flu/Mel	0.77 (0.53-1.13)	.18
Flu/Mel/ATG	0.89 (0.53-1.50)	.67
Risks compared with Flu/Mel		
Flu/Mel	1.00	
Flu/Bu2	0.79 (0.53-1.19)	.27
Flu/Bu2/ATG	0.62 (0.39-0.98)	.04
Flu/Mel/ATG	1.15 (0.65-2.05)	.62
Chronic GVHD‡		
Risks compared with Bu4/Cy		
Bu4/Cy	1.00	
Flu/Bu4	0.98 (0.83-1.15)	.80
Flu/Bu4/ATG	0.49 (0.39-0.61)	<.001
Flu/Bu2	0.65 (0.54-0.78)	<.001
Flu/Bu2/ATG	0.53 (0.43-0.66)	<.001
Flu/Mel	0.81 (0.65-1.01)	.055
Flu/Mel/ATG	0.39 (0.25-0.61)	<.001
Risks compared with Flu/Mel		
Flu/Mel	1.00	
Flu/Bu2	0.80 (0.63-1.01)	.065
Flu/Bu2/ATG	0.66 (0.50-0.86)	.003
Flu/Mel/ATG	0.48 (0.30-0.77)	.003

*Risks were higher in patients with MDS (hazard ratio [HR], 1.30; 95% CI, 1.14-1.48; $P < .0001$), HLA-matched (HR, 1.64; 95% CI, 1.41-1.90; $P < .0001$), and 1 HLA locus–mismatched (HR, 2.01; 95% CI, 1.60-2.52; $P < .0001$) unrelated donor transplants, and transplantation of peripheral blood graft (HR, 1.27; 95% CI, 1.03-1.56; $P = .024$).

†Risks were higher in patients with MDS (HR, 1.47; 95% CI, 1.21-1.80; $P = .0002$), HLA-matched (HR, 1.47; 95% CI, 1.17-1.86; $P = .001$) and 1 HLA locus–mismatched (HR, 2.09; 95% CI, 1.49-2.94; $P < .0001$) unrelated donor transplants, and calcineurin inhibitor with methotrexate GVHD prophylaxis (HR, 1.47; 95% CI, 1.16-1.85; $P = .001$).

‡Risks were higher in patients with MDS (HR, 1.14; 95% CI, 1.01-1.29; $P = .028$), HLA-matched (HR, 1.30; 95% CI, 1.14-1.48; $P < .0001$) and 1 HLA locus–mismatched (HR, 1.74; 95% CI, 1.40-2.16; $P < .0001$) unrelated donor transplants, and transplantation of peripheral blood graft (HR, 1.79; 95% CI, 1.46-2.20; $P < .0001$).

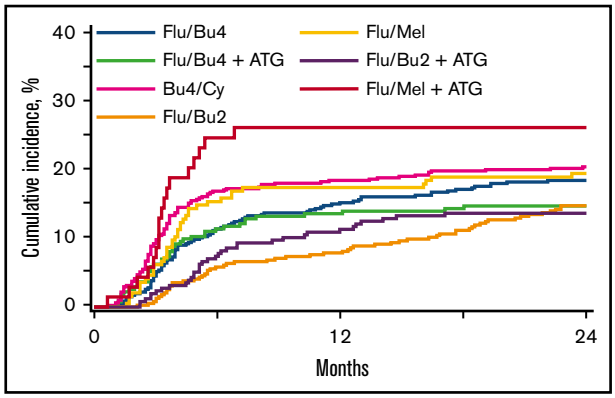

Figure 1. Grade 3-4 acute GVHD by conditioning regimen intensity. The 6-month incidence of grade 3-4 acute GVHD was 21% (95% CI, 17-24) for Bu4/Cy, 19% (95% CI, 16-23) for Flu/Bu4, 15% (95% CI, 11-19) for Flu/Bu4 + ATG, 16% (95% CI, 13-20) for Flu/Bu2, 14% (95% CI, 10-18) for Flu/Bu2 + ATG, 19% (95% CI, 14-25) for Flu/Mel, and 26% (95% CI, 16-37) for Flu/Mel + ATG.

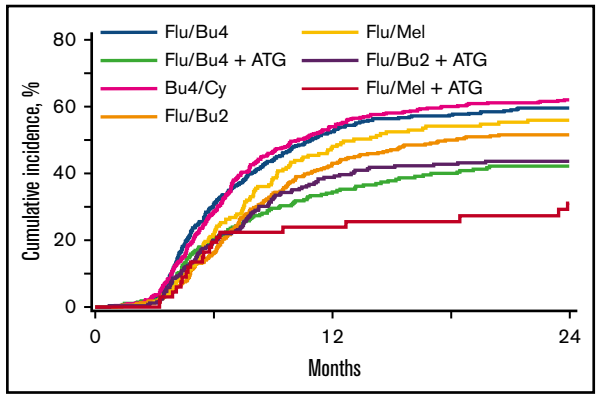

Figure 2. Chronic GVHD by conditioning regimen intensity. The 2-year incidence of chronic GVHD was 62% (95% CI, 58-66) for Bu4/Cy, 60% (95% CI, 55-64) for Flu/Bu4, 42% (95% CI, 36-48) for Flu/Bu4 + ATG, 52% (95% CI, 47-57) for Flu/Bu2, 44% (95% CI, 37-50) for Flu/Bu2 + ATG, 56% (95% CI, 49-63) for Flu/Mel, and 31% (95% CI, 20-43) for Flu/Mel + ATG.

Graft failure

The 1-year incidence of graft failure did not differ among patients conditioned with Bu4/Cy (1%; 95% CI, 0-2), Flu/Bu4 (2%; 95% CI, 1-4), and Flu/Bu4 + ATG (4%; 95% CI, 2-6). Similarly, graft failure did not differ among patients conditioned with Flu/Mel (5%; 95% CI, 2- 9), Flu/Mel + ATG (11%; 95% CI, 4-20), Flu/Bu2 (2%; 95% CI, 1-4), and Flu/Bu2 + ATG (7%; 95% CI, 4-11). However, compared with Bu4/Cy, the graft failure rate was higher after Flu/Mel ($P = .02$), Flu/Mel + ATG ($P = .02$), and Flu/Bu2 + ATG ($P = .003$) but not after Flu/Bu2 ($P = .46$).

GVHD

After adjusting for diagnosis, donor-recipient HLA match, and graft type, the risk for grades II-IV acute GVHD was lower with Flu/Bu4, Flu/Bu4 + ATG, Flu/Bu2, Flu/Bu2 + ATG, and Flu/Mel compared with Bu4/Cy (Table 2). The risk of grades III-IV acute GVHD was also lower with Flu/Bu4 + ATG, Flu/Bu2, and Flu/Bu2 + ATG regimens compared with Bu4/Cy (Table 2; Figure 1). The risk for chronic GVHD was significantly lower with Flu/Bu4 + ATG, Flu/Bu2, Flu/Bu2 + ATG, and Flu/Mel + ATG compared with Bu4/Cy after adjusting for diagnosis, donor-recipient HLA match, and graft type (Table 2; Figure 2). There were no differences in grade II-IV or grade III-IV acute GVHD risks among recipients of the various RIC regimens, but the risk for chronic GVHD was lower with Flu/Bu2 + ATG and Flu/Mel + ATG compared with Flu/Mel. Chronic GVHD severity was graded as mild in 41%, moderate in 34%, and severe in 23% of patients with chronic GVHD. For 2% of patients with chronic GVHD, the severity grade was not reported. Severity of chronic GVHD did not vary among conditioning regimens.

NRM

There were no significant differences in NRM risks between any of the MAC or RIC regimens compared with Bu4/Cy (Table 3). The observed modest difference in NRM with Flu/Bu2 with or without ATG regimens compared with Bu4/Cy did not reach the level of significance set for this study. NRM was lower in patients conditioned with Flu/Bu2 compared with Flu/Mel (Table 3). Figure 3A shows the 3-year probabilities of NRM by conditioning regimen adjusted for age, sex, disease, performance score, HCT-CI, and donor type/donor-recipient HLA match, the other factors potentially associated with NRM risks.

Relapse

Compared with Bu4/Cy, relapse risks were higher with the Flu/Bu4 + ATG and Flu/Bu2 with or without ATG regimens but not with the Flu/Mel with or without ATG regimens (Table 3). Risks were also higher with Flu/Bu2 with or without ATG regimens compared with Flu/Mel. Relapse was detected by molecular methods in 13% of patients who received myeloablative regimens and in 9% of patients who received reduced-intensity regimens. Figure 3B shows the 3-year probabilities of relapse by conditioning regimen adjusted for diagnosis, disease risk index, performance score, HCT-CI, and donor type/donor-recipient HLA match, the other factors potentially associated with relapse risks. One-year GVHD RFS was higher after Flu/Bu4/ATG (41%; 95% CI, 35-47) compared with Flu/Bu4 (27%; 95% CI, 23-31), Bu4/Cy (31%; 95% CI, 27-35), Flu/Bu2 (26%; 95% CI, 22-30), and Flu/Bu2/ATG (33%; 95% CI, 27-39) but not Flu/Mel (36%; 95% CI, 29-43) or Flu/Mel/ATG (39%; 95% CI, 28-51).

Treatment failure

Compared with Bu4/Cy, treatment failure (relapse or death; inverse of RFS) was more frequent with Flu/Bu2 + ATG but not with the Flu/Mel or Flu/Bu4 regimens (Table 3). The risk was also higher with Flu/Bu2 with or without ATG regimens compared with Flu/Mel. Figure 4A shows the 3-year probabilities of RFS by conditioning regimen adjusted for age, performance score, HCT-CI, diagnosis, and disease risk index, the other factors potentially associated with treatment failure.

Overall mortality

There were no significant differences in overall mortality risks between any of the MAC or RIC regimens compared with Bu4/Cy (Table 3). However, there were differences among the RIC regimens, with a higher mortality risk with Flu/Bu2 + ATG compared with Flu/Mel (Table 3). Figure 4B shows the 3-year probabilities of overall survival by conditioning regimen adjusted for

Table 3. Risk factors associated with NRM, relapse, treatment failure, and overall mortality

Conditioning regimen	Hazard ratio (95% CI)	*P*
NRM*		
Risks compared with Bu4/Cy		
Bu4/Cy	1.00	
Flu/Bu4	0.99 (0.75-1.29)	.92
Flu/Bu4/ATG	0.95 (0.69-1.32)	.77
Flu/Bu2	0.71 (0.52-0.98)	.03
Flu/Bu2/ATG	0.72 (0.50-1.02)	.07
Flu/Mel	1.12 (0.80-1.57)	.49
Flu/Mel/ATG	1.17 (0.74-1.84)	.50
Risks compared with Flu/Mel		
Flu/Mel	1.00	
Flu/Bu2	0.63 (0.45-0.88)	.008
Flu/Bu2/ATG	0.64 (0.43-0.94)	.02
Flu/Mel/ATG	1.04 (0.65-1.67)	.87
Relapse†		
Risks compared with Bu4/Cy		
Bu4/Cy	1.00	
Flu/Bu4	1.05 (1.07-1.81)	.64
Flu/Bu4/ATG	1.47 (1.14-1.88)	.003
Flu/Bu2	1.66 (1.34-2.07)	<.0001
Flu/Bu2/ATG	2.09 (1.65-2.64)	<.0001
Flu/Mel	0.71 (0.50-1.00)	.05
Flu/Mel/ATG	0.99 (0.59-1.64)	.96
Risks compared with Flu/Mel		
Flu/Mel	1.00	
Flu/Bu2	2.32 (1.67-3.33)	<.0001
Flu/Bu2/ATG	2.95 (2.07-4.19)	<.0001
Flu/Mel/ATG	1.39 (0.79-2.47)	.26
Treatment failure‡		
Risks compared with Bu4/Cy		
Bu4/Cy	1.00	
Flu/Bu4	1.03 (0.86-1.22)	.75
Flu/Bu4/ATG	1.22 (1.00-1.47)	.05
Flu/Bu2	1.24 (1.03-1.49)	.02
Flu/Bu2/ATG	1.41 (1.16-1.72)	.0006
Flu/Mel	0.93 (0.73-1.17)	.53
Flu/Mel/ATG	1.16 (0.84-1.61)	.37
Risks compared with Flu/Mel		
Flu/Mel	1.00	
Flu/Bu2	1.33 (1.06-1.69)	.01
Flu/Bu2/ATG	1.52 (1.20-1.94)	.0006
Flu/Mel/ATG	1.25 (0.85-1.79)	.22
Overall mortality§		
Risks compared with Bu4/Cy		
Bu4/Cy	1.00	
Flu/Bu4	1.05 (0.88-1.27)	.54
Flu/Bu4/ATG	1.26 (1.03-1.56)	.02
Flu/Bu2	1.14 (0.93-1.38)	.20
Flu/Bu2/ATG	1.28 (1.04-1.58)	.02
Flu/Mel	0.92 (0.72-1.18)	.50
Flu/Mel/ATG	1.36 (0.98-1.91)	.07
Risks compared with Flu/Mel		
Flu/Mel	1.00	
Flu/Bu2	1.23 (0.97-1.56)	.08
Flu/Bu2/ATG	1.40 (1.08-1.80)	.009
Flu/Mel/ATG	1.49 (1.03-2.14)	.03

Other significant factors in multivariate models are listed below.

*Risks were higher in patients aged 45-65 years (hazard ratio [HR], 1.61; 95% CI, 1.19-2.16; $P = .002$) and 65-83 years (HR, 2.30; 95% CI, 1.62-3.28; $P < .0001$) compared with those aged 18-44 years, males (HR, 1.29; 95% CI, 1.07-1.56; $P = .006$), diagnosis of MDS (HR, 1.42; 95% CI, 1.17- 1.71; $P = .0003$), performance score ≤ 80 (HR, 1.29; 95% CI, 1.08-1.55; $P = .006$), HCT-CI score ≥ 3 (HR, 1.36; 95% CI, 1.14-1.63; $P = .0008$), and HLA-matched unrelated (HR, 1.24; 95% CI, 1.01-1.53; $P = .045$) and 1 HLA locus–mismatched unrelated (HR, 1.78; 95% CI, 1.32-2.38; $P = .0001$) donor transplants compared with HLA-matched sibling transplants.

†Risks were higher in patients with performance score ≤ 80 (HR, 1.20; 95% CI, 1.04-1.39; $P = .013$), HCT-CI score ≥ 3 (HR, 1.23; 95% CI, 1.06-1.41; $P = .005$), AML (HR, 1.59; 95% CI, 1.29-1.96; $P < .0001$), and intermediate disease risk (HR, 1.62; 95% CI, 1.08-2.44; $P = .019$) and high disease risk (HR, 2.84; 95% CI, 1.82-4.43; $P < .0001$) compared with low disease risk index. Risks were lower after HLA-matched (HR, 0.77; 95% CI, 0.66-0.90; $P = .001$) and 1 HLA locus–mismatched unrelated (HR, 0.65; 95% CI, 0.49-0.86; $P = .003$) donor transplants compared with HLA-matched sibling transplants.

‡Risks were higher in patients aged 45-64 years (HR, 1.30; 95% CI, 1.10-1.55; $P = .0025$) and ≥65 years (HR, 1.44; 95% CI, 1.16-1.77; $P = 0.0007$) compared with 18-44 years, with AML (HR, 1.20; 95% CI, 1.02-1.43; $P = .03$), performance score ≤ 80 (HR, 1.23; 95% CI, 1.10-1.38; $P = .0003$), HCT-CI score ≥ 3 (HR, 1.27; 95% CI, 1.14-1.42; $P < .0001$), and intermediate (HR, 1.49; 95% CI, 1.07-2.06; $P = .02$) and high (HR, 2.20; 95% CI, 1.54-3.15; $P < .0001$) disease risk index compared with low disease risk index.

§Risks were higher in patients aged 45-64 years (HR, 1.40; 95% CI, 1.16-1.68; $P = .0004$) and ≥65 years (HR, 1.60; 95% CI, 1.28-1.99; $P < .0001$) compared with 18-44 years, performance score ≤ 80 (HR, 1.27; 95% CI, 1.13-1.44; $P < .0001$) and HCT-CI score ≥ 3 (HR, 1.33; 95% CI, 1.18-1.50; $P < .0001$), and intermediate (HR, 1.74; 95% CI, 1.20-2.51; $P = .003$) and high (HR, 2.24; 95% CI, 1.54-3.26; $P < .0001$) disease risk index compared with low disease risk index.

age, performance score, HCT-CI, and disease risk index, the other factors potentially associated with mortality risks. There were no transplant center effects associated with overall survival.

Discussion

The optimum transplant conditioning regimen remains to be determined. In the current study of patients with AML in remission or MDS, we analyzed and compared HCT outcomes with several commonly used non-TBI regimens, categorized as MAC or RIC regimens, by currently used criteria. Findings in this retrospective analysis identified Bu4/Cy, Flu/Bu4, and Flu/Mel as optimal for RFS. Considering the results of a recent prospective trial comparing high-intensity and reduced-intensity regimens, the data from the present retrospective analysis suggest that high-intensity regimens, such as Bu4/Cy and Flu/Bu4, are acceptable for patients with low HCT-CI and good performance scores, regardless of their age.[9] Relapse after a Flu/Mel regimen, considered to provide less-intensive conditioning, was comparable to that after Bu4/Cy and Flu/Bu4; however, 82% of patients received melphalan at a dose (140 mg/m^2) that is considered to be borderline myeloablative. Given the sample size, the study had 60% and 70% power, respectively, to detect a 30% reduction in relapse after Flu/Mel

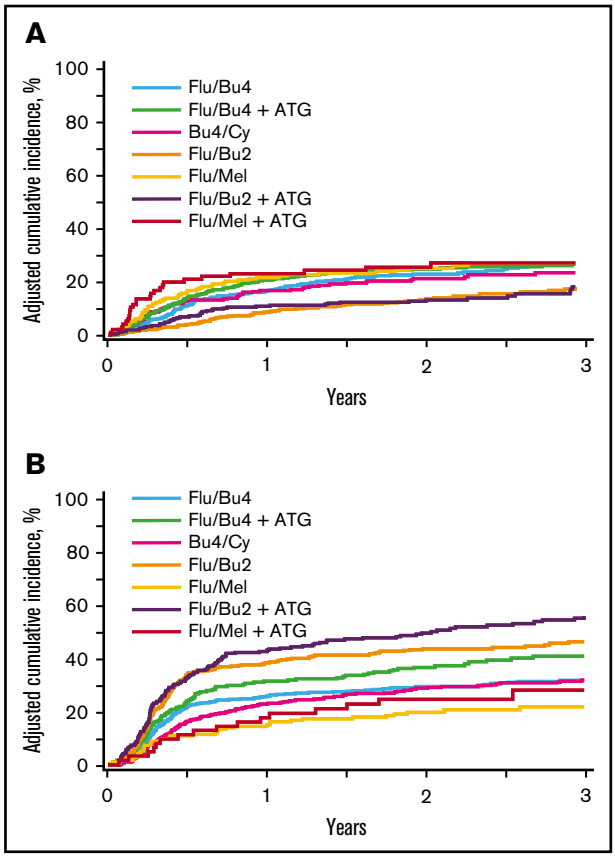

Figure 3. NRM and relapse by conditioning regimen intensity. (A) The 3-year incidence of NRM adjusted for age, sex, performance score, HCT-CI, diagnosis, and donor type/donor-recipient HLA match was 27% (95% CI, 22-31) for Bu4/Cy, 27% (95% CI, 23-32) for Flu/Bu4, 23% (95% CI, 18-29) for Flu/Bu4 + ATG, 18% (95% CI, 14-22) for Flu/Bu2, 18% (95% CI, 18-24) for Flu/Bu2 + ATG, 27% (95% CI, 21-34) for Flu/Mel, and 27% (95% CI, 18-37) for Flu/Mel + ATG. (B) The 3-year incidence of relapse adjusted for performance score, HCT-CI, diagnosis, disease risk index, and donor type/donor-recipient HLA match was 32% (95% CI, 28- 36) for Bu4/Cy, 32% (95% CI, 27-36) for Flu/Bu4, 41% (95% CI, 34-47) for Flu/Bu4 + ATG, 46% (95% CI, 41-51) for Flu/Bu2, 56% (95% CI, 49-62) for Flu/Bu2 + ATG, 22% (95% CI, 16-28) for Flu/Mel, and 28% (95% CI, 17-41) for Flu/Mel + ATG.

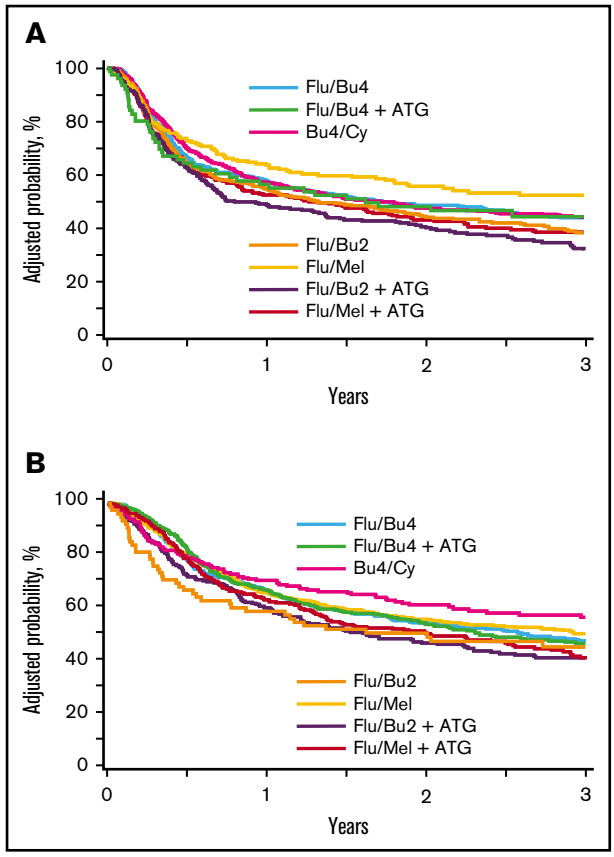

Figure 4. RFS and overall survival by conditioning regimen intensity. (A) The 3-year probability of RFS adjusted for age, performance score, HCT-CI, diagnosis, and disease risk index was 44% (95% CI, 39-48) for Bu4/Cy, 44% (95% CI, 39-48) for Flu/Bu4, 38% (95% CI, 32-44) for Flu/Bu4 + ATG, 38% (95% CI, 33-43) for Flu/Bu2, 31% (95% CI, 26-37) for Flu/Bu2 + ATG, 52% (95% CI, 45-59) for Flu/Mel, and 44% (95% CI, 33-55) for Flu/Mel + ATG. (B) The 3-year probability of survival adjusted for age, performance score, HCT-CI, and disease risk index was 51% (95% CI, 46-56) for Bu4/Cy, 48% (95% CI, 43-53) for Flu/Bu4, 42% (95% CI, 36-48) for Flu/Bu4 + ATG, 47% (95% CI, 42-52) for Flu/Bu2, 41% (95% CI, 35-47) for Flu/Bu2 + ATG, 57% (95% CI, 50-64) for Flu/Mel, and 46% (95% CI, 34-57) for Flu/Mel + ATG.

compared with Bu4/Cy or Flu/Bu4. Prospective confirmation of the effectiveness of the Flu/Mel regimen compared with Bu4/Cy and Flu/Bu4 is desirable before widely adopting Flu/Mel for younger and fit patients. A recent phase 3 randomized trial for AML also confirmed the effectiveness of Bu4/Cy and Flu/Bu4.[19] The Flu/Bu2 regimen accounted for one third of transplants and for 75% of RIC transplants in the current analysis. Although Flu/Bu2 was associated with a low incidence of GVHD and a modest reduction in NRM, this benefit was offset by a higher relapse incidence, resulting in lower RFS than observed with Bu4/Cy, Flu/Bu4, or Flu/Mel conditioning. Despite differences in RFS, a significant difference in overall survival was only observed between the Flu/Mel and Flu/Bu2/ATG regimens and was explained by substantially higher relapse seen with the Flu/Bu2/ATG regimen that was not offset by lower GVHD. The lack of a significant difference in overall survival between the other regimens is attributed to lower relapse risks being offset by higher GVHD risks.

Inclusion of ATG in transplant-conditioning regimens is intended to lower the incidence of chronic GVHD, and its use was common in RIC regimens. The current analysis showed differences in RFS and overall survival between ATG-containing and non-ATG–containing, but otherwise identical, regimens, with data suggesting caution in the use of ATG in nonirradiation MAC or RIC regimens. ATG-containing RIC regimens were also associated with higher graft failure. The deleterious effect of ATG on survival, despite lower chronic GVHD, is consistent with an earlier CIBMTR report in an independent patient population.[20] Although questions have been raised with regard to the dose (and type) of ATG, we hypothesize that the lower antileukemia efficacy of RIC in general, as well as a dampening of the GVHD-associated graft-versus-leukemia effect by ATG, may contribute to the differences in survival between ATG-containing and non-ATG–containing regimens. The 3 recent trials that compared MAC and RIC for patient populations similar to the present cohort were unable to show statistically significant

differences in survival.[8-10] A fundamental difference between those trials and the current analysis was our ability to compare differences between specific individual regimens rather than global MAC vs RIC comparisons, as reported for those trials.

A weakness of our study is the fact that definition of remission pretransplant for AML considered the European Leukemia Net criteria for "complete remission," which does not consider minimal residual disease.[21] In addition to the European Leukemia Net criteria for "complete remission," minimal residual disease, as determined by flow cytometry or polymerase chain reaction–based assays, was considered in defining posttransplant remission.[22] Almost 40% of patients in the current analyses had disease considered high risk for relapse based on disease risk index,[23-25] and the risk for relapse with minimal residual disease is high, particularly with RIC.[26] We have assumed conditioning regimens were chosen based on a number of factors, including tolerability of the regimen, transplant center preference, and/or patient and physician preference, and acknowledge that randomization is ideal when comparing treatment options. A strength of our study is the large number of patients, which allowed for comparison of several commonly used regimens, rather than the broad categories MAC and RIC, as was the case with the randomized trial in the United States,[9] or limited to specific regimens,[8,10,19] as was the case in Europe. The results suggest that adults with acceptable HCT-CI scores, regardless of their age, should be conditioned with Bu4/Cy, Flu/Bu4, or Flu/Mel. If the excellent RFS observed with Flu/Mel can be confirmed in a prospective trial, then younger fit patients with AML in remission and MDS could also benefit from conditioning with this regimen without experiencing an excessive relapse risk.

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Authorship

Contribution: M.E., R.B., W.S.P., M.M.H., and H.J.D. designed the study; R.B., M.H., and W.S.P. prepared the data file and analyzed the data; M.E., R.B., M.H., W.S.P., P.S., M.M.H., and H.J.D. interpreted the data; M.E. prepared the manuscript and R.B., M.H., W.S.P., P.S., M.M.H., and H.J.D. critically reviewed the manuscript; and all authors approved the final version.

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