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Can we move beyond myeloablative conditioning (MAC)? A comparison of MAC versus reduced intensity conditioning (RIC) in patients aged younger than 65 years undergoing allogeneic haematopoietic cell transplantation using ATG-PTCy-CSA for GVHD prophylaxis

Ruah Alyamany^{1,2}  | Ahmed Alnughmush^{1,2}  | Mats Remberger³ | Arjun Datt Law^{1,2}  | Wilson Lam^{1,2} | Dennis (Dong Hwan) Kim^{1,2}  | Fotios V. Michelis^{1,2}  | Ivan Pasic^{1,2} | Igor Novitzky-Basso^{1,2} | Armin Gerbitz^{1,2} | Rajat Kumar^{1,2} | Jonas Mattsson^{1,2} | Auro Viswabandya^{1,2}

¹Hans Messner Allogeneic Blood and Marrow Transplant Program, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada

²Department of Medicine, University of Toronto, Toronto, Ontario, Canada

³KFUE, Uppsala University Hospital, and IMV, Uppsala University, Uppsala, Sweden

Correspondence

Auro Viswabandya, Allogeneic Blood and Marrow Transplantation Program, Hans Messner Allogeneic Blood and Marrow Transplantation Program, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Department of Medicine, University of Toronto, Rm-6-323, OPG Building, 700 University Ave, Toronto, ON, Canada M5G1X6.
 Email: auro.viswabandya@uhn.ca

Summary

Allogeneic haematopoietic cell transplantation (HCT) offers a curative option for numerous haematological disorders; however, its myeloablative conditioning (MAC) regimens are associated with substantial toxicity. Reduced intensity conditioning (RIC) regimens were developed to mitigate transplant-related toxicity and broaden eligibility—particularly for older or medically unfit patients—though their use in younger, fit patients remains debated. In this retrospective study, we compared outcomes between MAC and RIC in patients aged younger than 65 years undergoing allogeneic HCT with a unified graft-versus-host disease (GVHD) prophylaxis regimen comprising anti-thymocyte globulin (ATG), post-transplant cyclophosphamide (PTCy) and ciclosporin (CsA). Propensity score matching was applied to reduce confounding. At 2 years post-transplant, there were no statistically significant differences in overall survival (OS) between the groups (MAC: 68.6% vs. RIC: 65.9%; $p = 0.61$) or in non-relapse mortality (NRM) (MAC: 15.8% vs. RIC: 12.5%; $p = 0.26$). However, relapse incidence was significantly higher in the RIC group (27.0%) than in the MAC group (16.1%; $p = 0.01$). These findings reinforce the continued relevance of MAC in younger patients who are candidates for intensive therapy, as it appears to offer superior disease control without a concomitant increase in NRM. Prospective studies are warranted to further delineate the role of conditioning intensity in the context of contemporary GVHD prophylaxis.

KEY WORDS

conditioning, GVHD prophylaxis, myeloablative, reduced intensity, stem cell transplant

Ruah Alyamany and Ahmed Alnughmush contributed equally.

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INTRODUCTION

Allogeneic haematopoietic cell transplantation (HCT) marked a transformative breakthrough in medicine when the first successful transplantation was performed in 1956.¹ Since then, it has offered new hope as a potential cure for a range of haematological disorders.^{2–4} Yet, it comes with significant risks that, in some cases, proved fatal. To address these challenges, physicians and scientists sought ways to make HCT safer, leading to the development of reduced intensity conditioning (RIC) regimens in the late 1990s.^{5–12}

Initially reserved for patients who were elderly or too frail to tolerate the more intense myeloablative conditioning (MAC), RIC expanded transplant eligibility, enabling even those previously deemed unfit to undergo this life-saving procedure.^{5–9,13,14} This development has driven ongoing research, with many studies seeking to validate RIC's effectiveness against MAC, especially in terms of survival and quality of life.¹⁵

RIC has shown numerous benefits, including reduced non-relapse mortality (NRM), lower rates of graft-versus-host disease (GVHD) and decreased organ toxicity.^{16–20} However, the reduced intensity comes with trade-offs, notably a higher relapse rate.^{17,18,21} Intriguingly, other studies, such as the RICMAC trial and the meta-analysis by Song et al., have found comparable relapse rates between the MAC and RIC groups, suggesting that RIC could be equally effective as MAC while offering a lower NRM.^{22,23}

Despite the advantages demonstrated by RIC, its application in younger and/or fit patients remains controversial, with conflicting findings particularly in the setting of high-risk diseases.^{10,23–33} Many prior studies provided valuable insights but often focused on certain disease groups or specific transplant-related factors, such as donor type, without consistently accounting for confounding variables like a unified GVHD prophylaxis regimen.

In this study, we aimed to bridge these gaps by evaluating the outcomes of RIC versus MAC in a cohort of patients aged younger than 65 years with various haematological disorders. Using a unified GVHD prophylaxis regimen (ATG-PTCy-CSA), widely utilized at our centre for its demonstrated effectiveness in reducing acute and chronic GVHD rates,⁴ and employing propensity score matching, we sought to minimize design-related biases and provide a more comprehensive comparison between the two conditioning approaches.

METHODS

Study design and patient selection criteria

This retrospective study involved data from patients who underwent allogeneic haematopoietic cell transplantation at Princess Margaret Cancer Centre between October 2015 and October 2023. All patients were under 65 years of age and received a uniform GVHD prophylaxis regimen

with anti-thymocyte globulin (ATG), post-transplant cyclophosphamide (PTCy) and ciclosporin (CsA). The study was approved by the University Health Network Research Ethics Board and the Cancer Registry Data Access Committee at Princess Margaret Cancer Centre, Toronto, Canada. The study was conducted in accordance with the Declaration of Helsinki.

Conditioning regimens and GVHD prophylaxis

Conditioning regimens used pretransplantation were categorized as MAC or RIC following internationally accepted definitions, with the majority of patients receiving a combination of fludarabine, busulfan and TBI (Table S1).

The GVHD prophylaxis regimen included ATG (4.5 or 2 mg) and 50 mg/kg/day of PTCy given on days +3 and +4 post-transplant, along with CsA at 2.5 mg/kg/12h from day +5 post-transplant for all patients. It is worth mentioning that the ATG dose started with 4.5 mg regardless of donor type in 2015, but later dropped to 2 mg/kg due to the increased rates of infections, with an exception for haploidentical donors.³⁴

During the study period, it was institutional practice to prescribe FLT3 inhibitors for patients with FLT3-mutated AML and tyrosine kinase inhibitors (TKIs) for patients with chronic myeloid leukaemia as post-transplant maintenance therapy, when clinically indicated and tolerated.

Infectious prophylaxis

Infectious prophylaxis consisted of ciprofloxacin 500 mg orally daily starting on day 6 until neutrophil engraftment, micafungin 50 mg IV daily or caspofungin 70 mg IV loading dose then 50 mg IV daily starting on day +1 until engraftment, valacyclovir 500 mg twice daily starting on day +1 until 1-year post-transplant, Posaconazole 300 mg orally daily starting at engraftment until day +100 and Pneumocystis prophylaxis starting at engraftment or day +28 until 1-year post-transplant. Beginning in January 2020, patients who were considered at high risk for CMV reactivation received letermovir once daily starting on day +21 until day +100.

Statistical methods, end-points and analysis

The main outcomes of interest were overall survival (OS), relapse-free survival (RFS), GVHD-free/RFS (GRFS) and the cumulative incidence of acute GVHD, chronic GVHD, relapse rate and non-relapse mortality (NRM). Acute and chronic GVHD were graded according to the established criteria.^{35,36}

Categorical variables were reported as percentages and counts, while continuous variables were reported as means, medians and ranges. The Kaplan–Meier curve was used to report OS, RFS and GRFS. The log-rank test was used

to determine the statistical significance between the two groups for each outcome. Cumulative incidence curves, taking competing events into consideration, were used to present other variables such as NRM, relapse, incidence of GVHD, bloodstream infections (BSI), CMV and EBV reactivation at 100 days following transplantation.

In our competing risk analyses, relapse was treated as the competing event for NRM, and NRM was the competing event for relapse. For acute GVHD, death within 100 days without acute GVHD was considered the competing risk, and for chronic GVHD, the competing risk was death without prior chronic GVHD.

The Gray's test was used to determine the statistical significance between the two groups for each outcome. Multivariate analysis was performed to identify predictors of outcomes, with a *p*-value of <0.05 considered statistically significant.

Propensity score matching (PSM)

PSM was conducted to balance baseline covariates between the MAC and RIC groups. The matching procedure was performed using Statistica software with the 'extract matched controls' option. Variables included in the propensity score model were age (<40 vs. 40–65 years), HCT-CI (<3 vs. ≥3), ATG dose (2 vs. 4.5 mg/kg), 2017 ELN risk category, disease risk index (DRI) and HLA mismatch. Logistic regression was used to estimate odds ratios for the selection variables.

From the overall cohort, 155 MAC recipients were matched to 155 RIC recipients using a 1:1 ratio and a calliper width of 0.2. No significant difference in total propensity scores was observed between the matched groups (*p*=1.00). In cases where more than one RIC patient matched an MAC patient, the RIC patient closest in age was selected. Standardized mean differences (SMD) were 0 for the matched covariates.

RESULTS

Patients' baseline characteristics

Prior to PSM (i.e. unmatched cohort)

Table 1 summarizes the baseline characteristics of the unmatched cohort. The majority of patients received RIC. Acute myeloid leukaemia (AML) was the most common indication for transplantation, followed by myelodysplastic syndromes (MDS), 50.3% and 12.5% respectively. A statistically significant difference was noted for myelofibrosis (MF), with most MF patients receiving RIC (11.1%), while only 2.9% received MAC (*p*<0.001). Patients in the RIC group were significantly older than those in the MAC group (median age: 57 vs. 45 years, *p*<0.001), had a worse Karnofsky performance status (KPS <90), 20.3% in the RIC group versus 8.7% in the MAC group (*p*<0.001) and had a higher HCT-CI score (RIC 41.7% vs. MAC 20.9%, *p*<0.001).

The most common type of donor for the entire cohort was MUD (51.1%), followed by haploidentical donors (21.9%), with frozen grafts being used more frequently in the RIC group (*p*=0.02).

Propensity-matched cohort

Table 2 summarizes the baseline characteristics of the propensity score-matched cohort. Patients were evenly distributed between the MAC and RIC groups, with acute leukaemias being the most common diagnosis (76.1%), with no significant difference between the groups. The median age in both groups was around 50 years (range 16–64). The RIC group in this cohort also had a worse KPS (<90), 18.1% vs. 9% in the MAC group (*p*<0.001). The mean CD34+ cell dose was significantly higher in the RIC group than in the MAC group (8.1×10^6 cells/kg vs. 7.0×10^6 cells/kg, respectively, *p*<0.001), and the use of frozen grafts was more frequent in the RIC group than in the MAC group (29.7% vs. 18.1%, respectively, *p*=0.02).

Main outcomes

Unmatched cohort

Two-year OS was significantly higher in the MAC group than in the RIC group (70.8% [95% CI, 63.2–77.1] vs. 61.1% [95% CI, 56.2–65.6]; *p*=0.02). Similarly, 2-year RFS favoured the MAC group (66.4% [95% CI, 58.9–72.9]) than the RIC group (54.7% [95% CI, 49.7–59.4]; *p*=0.014). The cumulative incidence of relapse at 2 years was significantly higher in the RIC group (26.7% [95% CI, 22.5–31.1]) than in the MAC group (17.5% [95% CI, 12.2–23.6]; *p*=0.018). GRFS at 2 years was also superior in the MAC group (55.2% [95% CI, 47.6–62.2]) than in RIC group (43.2% [95% CI, 38.4–48.0]; *p*=0.012). There was no statistically significant difference in NRM between the two groups (MAC: 13.9% [95% CI, 9.6–19.1] vs. RIC: 16.8% [95% CI, 13.4–20.5]; *p*=0.54). In total, 234 patients (36.5%) died. Causes of death are detailed in **Table S2**.

Propensity-matched cohort

Figures 1 and **2** summarize the main outcomes of interest. Two-year OS and NRM did not differ significantly between the MAC and RIC groups. Relapse incidence remained significantly higher with RIC (*p*=0.01), while RFS did not show a statistically significant difference (*p*=0.23). There was no statistically significant difference in GRFS between the two groups (*p*=0.08).

When stratified by disease status (CR1, CR2 or not in CR), 2-year OS and NRM remained comparable between MAC and RIC groups. However, a significantly higher relapse incidence was observed among patients in CR2 who received RIC (46.5% vs. 8.1%; *p*=0.009), a difference that was not

TABLE 1 Baseline characteristics for the unmatched cohort.

Characteristics	All patients	RIC	MAC	<i>p</i> -value
No.	640	434	206	
Age	53 (18–64)	57 (18–64)	45 (18–61)	<0.001
Gender				0.53
Male	361	249	112	
Female	279	185	94	
Diagnosis				
AML	322 (50.3)	207 (47.7)	115 (55.8)	0.07
ALL	65 (10.2)	30 (6.9)	35 (17)	<0.001
MPAL	18 (2.8)	9 (2.1)	9 (4.4)	
MDS	80 (12.5)	59 (13.6)	21 (10.2)	
MDS/MPN	10 (1.6)	10 (2.3)	0	
MPN	5 (0.8)	3 (0.7)	2 (1)	
Lymphoma	29 (4.5)	25 (5.8)	4 (1.9)	<0.05
CML/CLL	31 (4.8)	22 (5.1)	9 (4.4)	
CMML	15 (2.3)	13 (3)	2 (1)	
MF	54 (8.4)	48 (11.1)	6 (2.9)	<0.001
Other malignancies	7 (1.1)	4 (0.9)	3 (1.4)	
Non-malignant conditions	4 (0.6)	4 (0.9)	0	
Status				0.87
CR1	354	222	132	
CR2	81	41	40	
Not in CR	61	46	15	
NA	144	125	19	
DRI				0.67
Low	37 (5.9)	28 (6.5)	9 (4.4)	
Intermediate	464 (73.4)	312 (71.9)	152 (73.8)	
High/very high	131 (20.7)	89 (20.5)	42 (20.4)	
KPS < 90	106 (17)	88 (20.3)	18 (8.7)	<0.001
HCT-CI ≥ 3	224 (35.6)	181 (41.7)	43 (20.9)	<0.001
Donor's age	29 (11–73)	29 (11–73)	29 (16–67)	0.38
CD34 dose (×10 ⁶ cells/kg)	7.5 (0.7–25.2)	7.8 (1.8–25.2)	7 (0.7–16.8)	<0.001
Donor type				0.004
MRD	78 (12.2)	72 (16.6)	6 (2.9)	
MUD	327 (51.1)	208 (47.9)	119 (57.8)	
Haploidentical	140 (21.9)	88 (20.3)	52 (25.2)	
MMUD	95 (14.8)	66 (15.2)	29 (14.1)	
Frozen graft	170 (26.2)	128 (29.5)	42 (20.4)	0.02
CMV status				
Recipient				0.66
Positive	493	337	156	
Negative	147	97	50	
Donor				0.79
Positive	329	221	108	
Negative	311	213	98	
ATG dose				<0.001
2 mg/kg	353 (55.2)	205 (47.2)	148 (71.8)	
4.5 mg/kg	286 (44.8)	228 (52.4)	58 (28.2)	
Follow-up (months)	35.9 (0.9–95.6)	54.4 (0.9–91.3)	24.1 (1.2–95.6)	<0.001

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; ATG, anti-thymocyte globulin; CLL, chronic lymphoblastic leukaemia; CML, chronic myeloid leukaemia; CMML, chronic myelomonocytic leukaemia; CMV, cytomegalovirus; CR, complete remission; DRI, disease risk index; HCT-CI, haematopoietic cell transplant comorbidity index; KPS, Karnofsky performance status; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MF, myelofibrosis; MMUD, mismatched unrelated donor; MPAL, mixed-phenotype acute leukaemia; MPN, myeloproliferative neoplasms; MRD, matched related donor; MUD, matched unrelated donor; NA, not available; RIC, reduced intensity conditioning.

TABLE 2 Baseline characteristics for the matched cohort.

Characteristics	All patients	RIC	MAC	<i>p</i> -value
No.	310	155	155	
Age (years)	50 (18–64)	50 (18–64)	50 (18–61)	0.25
Age < 40 years, <i>n</i> (%)	74 (23.9)	37 (23.9)	37 (23.9)	1
Gender				0.82
Male	169	86	83	
Female	141	69	72	
Diagnosis				1.0
Acute Leukaemias	236 (76.1)	118 (76.1)	118 (76.1)	
Chronic Leukaemias ^a	14 (4.5)	7 (4.5)	7 (4.5)	
MDS/MPN ^a	56 (18.1)	28 (18.1)	28 (18.1)	
Lymphoma	4 (1.3)	2 (1.3)	2 (1.2)	
Status				0.19
CR1	190	96	94	
CR2	49	19	30	
Not in CR	21	8	13	
NA	50	32	18	
High DRI	56 (18.1)	27 (17.4)	29 (18.7)	0.88
KPS < 90	42 (13.5)	28 (18.1)	14 (9)	0.03
HCT-CI ≥ 3	68 (21.9)	34 (21.9)	34 (21.9)	1.0
Donor's age	29 (11–67)	29 (11–66)	29 (16–67)	0.84
CD34 dose (×10 ⁶ cells/kg)	7.5 (0.7–17.8)	8.1 (1.8–17.8)	7 (0.7–16.8)	<0.001
Donor type				0.15
MRD	25 (8.1)	5 (3.2)	20 (12.9)	
MUD	160 (51.6)	83 (53.5)	77 (49.7)	
Haploidentical	81 (26.1)	46 (29.7)	35 (22.6)	
MMUD	44 (14.2)	21 (13.5)	23 (14.8)	
Frozen graft	74 (23.9)	46 (29.7)	28 (18.1)	0.02
CMV status				
Recipient				0.59
Positive	241	123	118	
Negative	69	32	37	
Donor				0.49
Positive	165	79	86	
Negative	145	76	69	
ATG dose				1.0
2 mg/kg	202 (65.2)	101 (65.2)	101 (65.2)	
4.5 mg/kg	108 (34.8)	54 (34.8)	54 (34.8)	
Day 30 chimerism				0.12
Full	223	118	105	
Mixed	57	23	34	
Follow-up (months)	32.7 (2.9–95.6)	54 (2.9–89.9)	24.1 (3–95.6)	<0.001

Note: Bold values indicates *p* value of statistical significance.

Abbreviations: ATG, anti-thymocyte globulin; CLL, chronic lymphoblastic leukaemia; CML, chronic myeloid leukaemia; CMML, chronic myelomonocytic leukaemia; CMV, cytomegalovirus; CR, complete remission; DRI, disease risk index; HCT-CI, haematopoietic cell transplant comorbidity index; KPS, Karnofsky performance status; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MF, myelofibrosis; MPN, myeloproliferative neoplasms; NA, not available; RIC, reduced intensity conditioning.

^a'MDS/MPN' category includes patients with MDS, MF, CMML and atypical CML. 'Chronic leukaemia' includes CML and CLL.

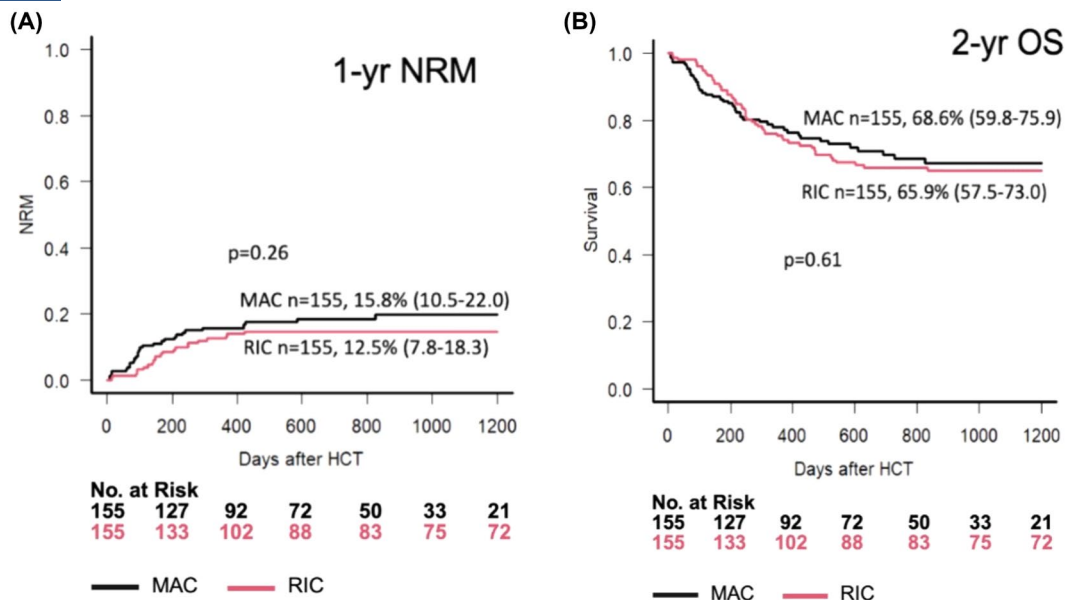


FIGURE 1 Non-relapse mortality and overall survival in the propensity-matched cohort. One-year non-relapse mortality (NRM) and 2-year overall survival (OS) in the propensity-matched cohort. (A) Cumulative incidence of 1-year NRM. (B) 2-year OS.

statistically significant among those in CR1 (21.6% vs. 18.1%; $p=0.35$). These analyses are presented in [Figures S1–S3](#).

Graft-versus-host disease

Unmatched cohort

By day 100, the cumulative incidence of grade II–IV acute GVHD did not differ significantly between the MAC and RIC groups (MAC: 23.3% [17.8–29.3] vs. RIC: 20.0% [16.4–23.9]; $p=0.97$), nor did the incidence of severe (grade III–IV) acute GVHD (MAC: 6.3% [3.5–10.2] vs. RIC: 6.0% [4.0–8.5]; $p=0.74$). At 2 years, the incidence of chronic GVHD was comparable between groups (RIC: 26.2% [21.9–30.8] vs. MAC: 22.6% [16.4–29.5]; $p=0.39$), including rates of moderate-to-severe chronic GVHD (RIC: 15.8% [12.3–19.7] vs. MAC: 13.8% [9.0–19.6]; $p=0.53$).

Propensity-matched cohort

The incidence of acute GVHD by day 100 and chronic GVHD at 2 years, across all grades, did not differ significantly between the MAC and RIC groups, as shown in [Figure 3A–D](#).

Graft failure and post-transplant infections

Unmatched cohort

The incidence of graft failure was significantly higher in the RIC group than in the MAC group (7.4% [5.2–10.2] vs. 2.9% [1.2–5.9]; $p=0.02$). The occurrence of BSI by day 30 did not

differ significantly between groups (RIC: 46.8% [42.0–51.4] vs. MAC: 49.5% [42.5–56.1]; $p=0.90$). CMV reactivation by day 100 was observed more frequently among patients in the RIC group (45.5% [40.7–50.1]) than among those in the MAC group (30.1% [24.0–36.5]; $p<0.001$). In contrast, Epstein-Barr virus (EBV) reactivation at day 100 occurred at comparable rates between the two groups (RIC: 57.3% [52.5–61.8] vs. MAC: 53.9% [46.8–60.4]; $p=0.30$).

Propensity-matched cohort

The graft failure occurred at comparable rates in the RIC and MAC groups (5.8% [2.8–10.3] vs. 3.9% [1.6–7.8]; $p=0.22$). The incidence of BSI by day 30 was also comparable between groups (RIC: 41.3% [33.5–48.9] vs. MAC: 47.7% [39.7–55.4]; $p=0.89$). CMV reactivation by day 100 was significantly more frequent in the RIC group than in the MAC group (47.7% [39.7–55.4] vs. 32.3% [25.0–39.7]; $p=0.007$). EBV reactivation at day 100 was also higher following RIC (62.6% [54.4–69.7]) than MAC (51.6% [43.4–59.2]; $p=0.035$).

DISCUSSION

The results of our study have shown no significant difference in OS and NRM between MAC and RIC groups in allogeneic HCT. However, relapse rates were significantly higher in the RIC group, reinforcing the role of MAC in patients who can tolerate it. This outcome aligns with evidence supporting MAC's irreplaceable role in maintaining disease control.^{10,24,37}

Although previous studies have often linked higher NRM rates with MAC, this association was not observed in our cohort, even after PSM, in agreement with findings from

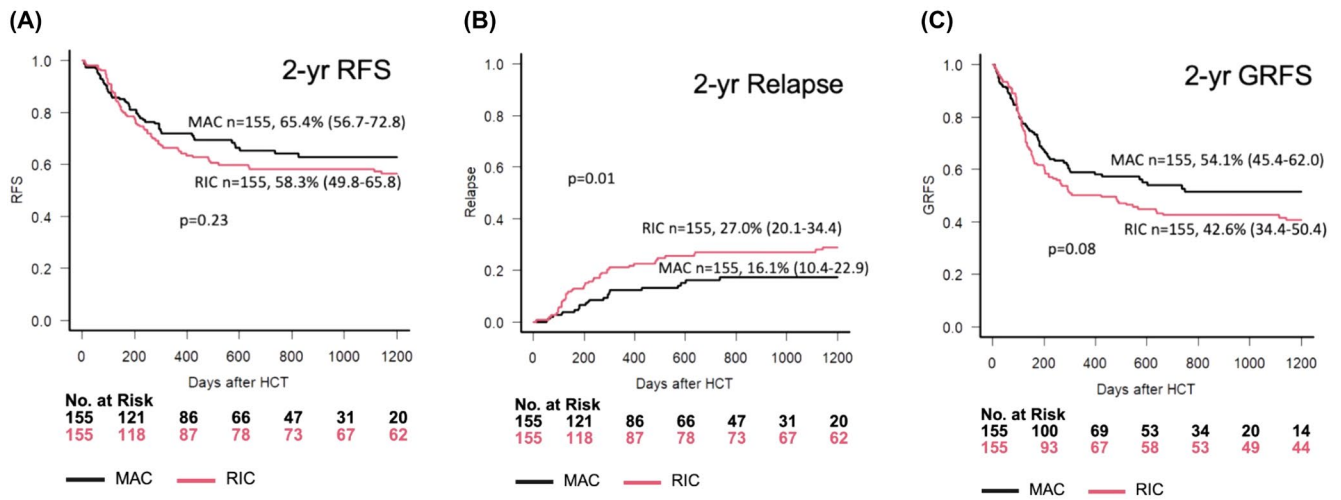


FIGURE 2 Relapse-free survival (RFS), relapse incidence and graft-versus-host disease (GVHD)-free/relapse-free survival (GRFS) in the propensity-matched cohort. Two-year relapse-free survival (RFS), relapse incidence and GVHD-free/relapse-free survival (GRFS) in the propensity-matched cohort. (A) Two-year RFS. (B) Cumulative incidence of relapse at 2 years. (C) Two-year GRFS.

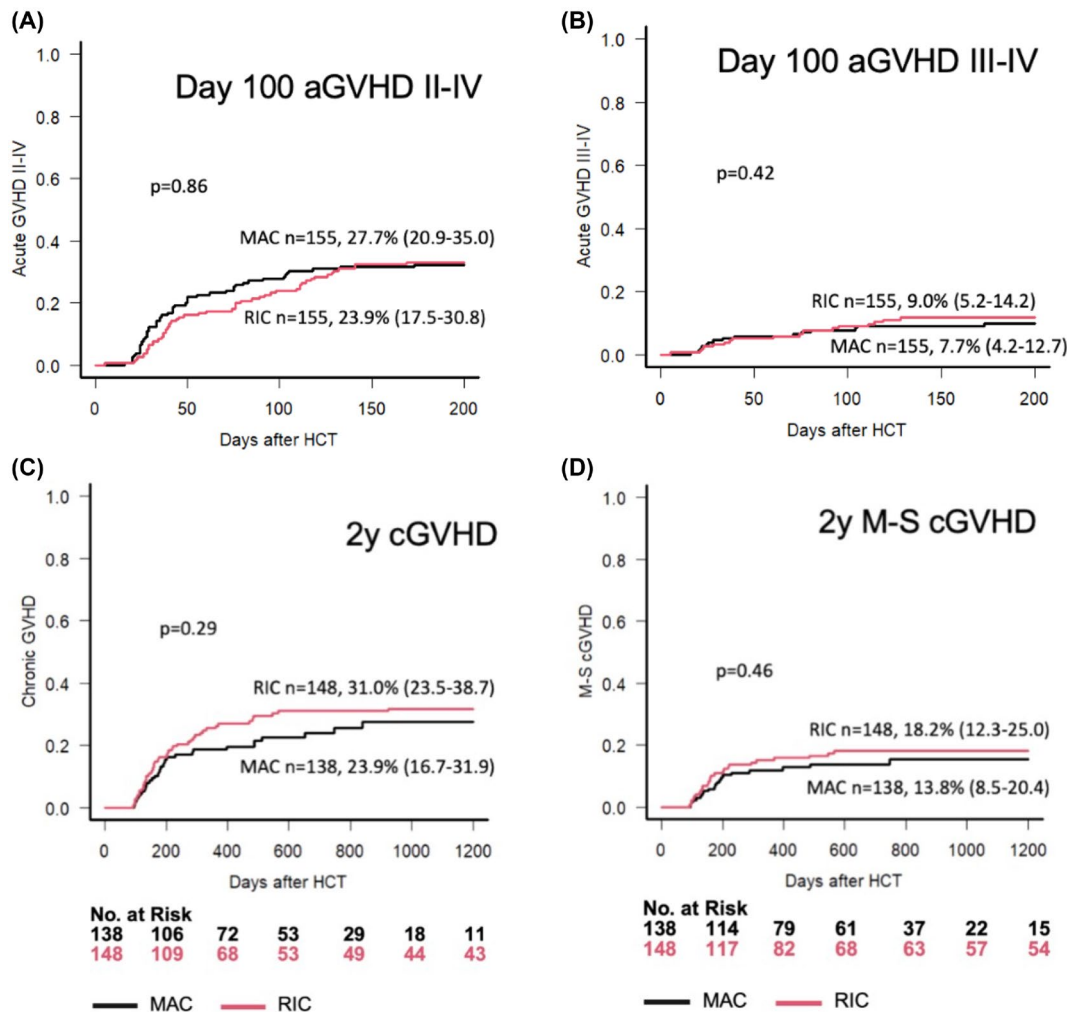


FIGURE 3 Cumulative incidence of graft-versus-host disease (GVHD) in the propensity-matched cohort. (A) Day 100 incidence of grade II-IV acute GVHD (aGVHD). (B) Day 100 incidence of grade III-IV aGVHD. (C) Two-year incidence of chronic GVHD (cGVHD). (D) Two-year incidence of moderate-to-severe cGVHD (M-S cGVHD).

other recent studies.^{23,38,39} While relapse rates were notably elevated in the RIC group for both matched and unmatched cohorts, the 2-year RFS remained similar in the matched cohort. This discrepancy may be attributed to follow-up duration differences, as the MAC cohort had a shorter follow-up due to its increased use starting in 2019, while prior to that, RIC was the standard regimen used in the institution. Given that relapse was the leading cause of mortality in this cohort, these findings underscore MAC's continued importance in minimizing relapse risks.

Regarding GVHD, we found similar rates of both acute and chronic GVHD between the groups after applying the PSM, in contrast to prior studies reporting higher GVHD with MAC.^{16,20} This may reflect the use of a consistent GVHD prophylaxis regimen across all patients, highlighting the conditioning's effect on GVHD rates without the confounding effect of a variable GVHD prophylaxis regimen. Notably, our cohort's rates of moderate-to-severe chronic GVHD at 2-year post-transplantation were lower than previous reports, emphasizing the impact of the use of a dual T-cell depletion strategy with ATG and PTCy on reducing GVHD.^{40,41} Additionally, the lower GVHD rates might have played a role in the lower rates of NRM in the MAC group compared to previous reports.²³ Importantly, this approach did not diminish MAC's benefit in reducing relapse rates, countering previous concerns regarding the potential increased risk of relapse with ATG.^{42,43}

The increased graft failure rate can be partially attributed to the higher reliance on frozen grafts, especially during the COVID-19 pandemic, necessitated by travel restrictions.⁴⁴ Additionally, the greater prevalence of myelofibrosis cases within the RIC group likely contributed to this outcome. RIC was also associated with higher rates of CMV and EBV reactivation, though this may be partly due to coinciding changes in the institution's practice. For instance, the increased use of letermovir after 2019 and the reduced ATG dosing overlapped with the increased use of MAC, potentially lowering CMV and EBV reactivation rates in the MAC group. It is noteworthy that although EBV reactivation rates were higher than previously reported, this did not lead to a high incidence of post-transplant lymphoproliferative disorder (PTLD). Only 17 of 640 patients (2.6%) developed PTLT, a rate consistent with published data.⁴⁵⁻⁴⁹

The retrospective design of our study introduces potential biases and confounding factors; however, PSM helped to control for major confounders. Despite this, some inherent differences remained, such as the greater likelihood of RIC patients being less physically fit and the shorter follow-up duration in the MAC group, which could have influenced the findings. Additionally, data on measurable residual disease (MRD) at the time of transplant and post-transplant maintenance therapy were not consistently captured and therefore not included in the analysis. These factors are important modifiers of relapse risk, and their absence limits the interpretation of relapse-related outcomes.

Limiting our study to patients under 65 may reduce the generalizability of our results, particularly as transplantation

becomes increasingly feasible for older adults. Thus, balancing conditioning intensity with treatment toxicity remains crucial. Another notable limitation is the exclusive use of the ATG-PTCy-CSA regimen for GVHD prevention, which is not widely adopted elsewhere, potentially restricting the generalizability of our findings to settings utilizing different prophylaxis protocols. Future research should consider prospective trials that directly compare MAC and RIC outcomes under a unified GVHD prophylaxis regimen. Such studies could further clarify conditioning intensity's role in transplant outcomes, particularly given the recent advancements in GVHD management.

In conclusion, our findings support the ongoing use of MAC, especially for patients who can tolerate it, as it appears to offer better disease control without increasing NRM.

AUTHOR CONTRIBUTIONS

R.A. and A.A. compiled and summarized the data and wrote the article's first draft. M.R. performed the statistical analysis and contributed to manuscript review and editing. A.V. supervised the project and revised and edited the manuscript. A.L., W.L., D.K., F.M., I.P., I.N., A.G., R.K. and J.M. reviewed and edited the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data are available upon request from the authors at their discretion.

ETHIC APPROVAL STATEMENT

The study was approved by the University Health Network Research Ethics Board and the Cancer Registry Data Access Committee at Princess Margaret Cancer Centre, Toronto, Canada.

PATIENT CONSENT STATEMENT

Informed consent was obtained.

ORCID

Ruah Alyamany  <https://orcid.org/0000-0003-0295-2120>
Ahmed Alnughmush  <https://orcid.org/0000-0001-8489-0642>
Arjun Datt Law  <https://orcid.org/0000-0002-9251-3609>
Dennis (Dong Hwan) Kim  <https://orcid.org/0000-0003-2640-4911>
Fotios V. Michelis  <https://orcid.org/0000-0003-2956-0848>

REFERENCES

1. Thomas ED. Stem cell transplantation: past, present and future. *Arch Immunol Ther Exp*. 1997;45(1):1–5.
2. Gratwohl A, Baldomero H, Aljurf M, Pasquini MC, Bouzas LF, Yoshimi A, et al. Hematopoietic stem cell transplantation; a global perspective. *JAMA*. 2010;303(16):1617–24. <https://doi.org/10.1001/jama.2010.491>
3. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354(17):1813–26. <https://doi.org/10.1056/NEJMra052638>
4. Salas MQ, Prem S, Atenafu EG, Datt Law A, Lam W, al-Shaibani Z, et al. Dual T-cell depletion with ATG and PTCy for peripheral blood reduced intensity conditioning allo-HSCT results in very low rates of GVHD. *Bone Marrow Transplant*. 2020;55(9):1773–83. <https://doi.org/10.1038/s41409-020-0813-9>
5. Solh MM, Solomon SR, Morris LE, Zhang X, Holland HK, Bashey A. The dilemma of conditioning intensity: when does myeloablative conditioning improve outcomes for allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2019;25(3):606–12. <https://doi.org/10.1016/j.bbmt.2018.09.012>
6. Gyurkocza B, Storb R, Storer BE, Chauncey TR, Lange T, Shizuru JA, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia. *J Clin Oncol*. 2010;28(17):2859–67. <https://doi.org/10.1200/JCO.2009.27.1460>
7. McClune BL, Weisdorf DJ, Pedersen TL, da Tunes Silva G, Tallman MS, Sierra J, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. *J Clin Oncol*. 2010;28(11):1878–87. <https://doi.org/10.1200/JCO.2009.25.4821>
8. Lim Z, Brand R, Martino R, van Biezen A, Finke J, Bacigalupo A, et al. Allogeneic hematopoietic stem-cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. *J Clin Oncol*. 2010;28(3):405–11. <https://doi.org/10.1200/JCO.2009.21.8073>
9. Kröger N. Allogeneic stem cell transplantation for elderly patients with myelodysplastic syndrome. *Blood*. 2012;119(24):5632–9. <https://doi.org/10.1182/blood-2011-12-380162>
10. Scott BL, Pasquini MC, Logan BR, Wu J, Devine SM, Porter DL, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2017;35(11):1154–61. <https://doi.org/10.1200/JCO.2016.70.7091>
11. Niederwieser D, Lange T, Cross M, Basara N, Al-Ali H. Reduced intensity conditioning (RIC) haematopoietic cell transplants in elderly patients with AML. *Best Pract Res Clin Haematol*. 2006;19(4):825–38. <https://doi.org/10.1016/j.beha.2006.06.007>
12. Barrett AJ, Savani BN. Stem cell transplantation with reduced-intensity conditioning regimens: a review of ten years experience with new transplant concepts and new therapeutic agents. *Leukemia*. 2006;20(10):1661–72. <https://doi.org/10.1038/sj.leu.2404334>
13. Deeg HJ, Shulman HM, Anderson JE, Bryant EM, Gooley TA, Slattery JT, et al. Allogeneic and syngeneic marrow transplantation for myelodysplastic syndrome in patients 55 to 66 years of age. *Blood*. 2000;95(4):1188–94.
14. Passweg JR, Baldomero H, Bader P, Bonini C, Cesaro S, Dreger P, et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40 000 transplants annually. *Bone Marrow Transplant*. 2016;51(6):786–92. <https://doi.org/10.1038/bmt.2016.20>
15. Salas MQ, Chen S, Lam W, Pasic I, Gerbitz A, Michelis FV, et al. Less is more: superior graft-versus-host disease-free/relapse-free survival with reduced-intensity conditioning and dual T cell depletion in acute myelogenous leukemia. *Biol Blood Marrow Transplant*. 2020;26(8):1511–9. <https://doi.org/10.1016/j.bbmt.2020.04.021>
16. Ma S, Shi W, Li Z, Tang L, Wang H, Xia L, et al. Reduced-intensity versus myeloablative conditioning regimens for younger adults with acute myeloid leukemia and myelodysplastic syndrome: a systematic review and meta-analysis. *J Cancer*. 2020;11(17):5223–35. <https://doi.org/10.7150/jca.46081>
17. Scott BL, Pasquini MC, Fei M, Fraser R, Wu J, Devine SM, et al. Myeloablative versus reduced-intensity conditioning for hematopoietic cell transplantation in acute myelogenous leukemia and myelodysplastic syndromes—long-term follow-up of the BMT CTN 0901 clinical trial. *Transplant Cell Ther*. 2021;27(6):483.e1–483.e6. <https://doi.org/10.1016/j.jtct.2021.02.031>
18. Bejanyan N, Zhang M, Bo-Subait K, Brunstein C, Wang H, Warlick ED, et al. Myeloablative conditioning for allogeneic transplantation results in superior disease-free survival for acute myelogenous leukemia and myelodysplastic syndromes with low/intermediate but not high disease risk index: a Center for International Blood and Marrow Transplant Research Study. *Transplant Cell Ther*. 2021;27(1):68.e1–68.e9. <https://doi.org/10.1016/j.bbmt.2020.09.026>
19. Ringdén O, Erkers T, Aschan J, Garming-Legert K, le Blanc K, Häggglund H, et al. A prospective randomized toxicity study to compare reduced-intensity and myeloablative conditioning in patients with myeloid leukaemia undergoing allogeneic haematopoietic stem cell transplantation. *J Intern Med*. 2013;274(2):153–62. <https://doi.org/10.1111/joim.12056>
20. Yu ZP, Ding JH, Chen BA, Li YF, Ding BH, Qian J. An anti-human thymocyte globulin-based reduced-intensity conditioning regimen is associated with a higher quality of life and lower organ toxicity without affecting lymphocyte reconstitution. *PLoS One*. 2013;8(9):e73755. <https://doi.org/10.1371/journal.pone.0073755>
21. Crawley C, Iacobelli S, Björkstrand B, Apperley JF, Niederwieser D, Gahrton G. Reduced-intensity conditioning for myeloma: lower non-relapse mortality but higher relapse rates compared with myeloablative conditioning. *Blood*. 2007;109(8):3588–94. <https://doi.org/10.1182/blood-2006-07-036848>
22. Song Y, Yin Z, Ding J, Wu T. Reduced intensity conditioning followed by allogeneic hematopoietic stem cell transplantation is a good choice for acute myeloid leukemia and myelodysplastic syndrome: a meta-analysis of randomized controlled trials. *Front Oncol*. 2021;11:708727. <https://doi.org/10.3389/fonc.2021.708727>
23. Kröger N, Iacobelli S, Franke GN, Platzbecker U, Uddin R, Hübel K, et al. Dose-reduced versus standard conditioning followed by allogeneic stem-cell transplantation for patients with myelodysplastic syndrome: a prospective randomized phase III study of the EBMT (RICMAC trial). *J Clin Oncol*. 2017;35:2157–64. <https://doi.org/10.1200/JCO>
24. Kharfan-Dabaja MA, Labopin M, Bazarbachi A, Hamladji RM, Blaise D, Socié G, et al. Comparing i.v. BU dose intensity between two regimens (FB2 vs FB4) for allogeneic HCT for AML in CR1: a report from the Acute Leukemia Working Party of EBMT. *Bone Marrow Transplant*. 2014;49(9):1170–5. <https://doi.org/10.1038/bmt.2014.133>
25. Shimoni A, Hardan I, Shem-Tov N, Yeshurun M, Yerushalmi R, Avigdor A, et al. Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative versus reduced-intensity conditioning: the role of dose intensity. *Leukemia*. 2006;20(2):322–8. <https://doi.org/10.1038/sj.leu.2404037>
26. Scott BL, Pasquini MC, Logan B, Wu J, Devine S, Porter DL, et al. Results of a phase III randomized, multi-center study of allogeneic stem cell transplantation after high versus reduced intensity conditioning in patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML): blood and marrow transplant clinical trials network (BMT CTN) 0901. *Blood*. 2015;126(23):LBA-8. <https://doi.org/10.1182/blood.V126.23.LBA-8.LBA-8>
27. Sibai H, Falcone U, Deotare U, Michelis FV, Uhm J, Gupta V, et al. Myeloablative versus reduced-intensity conditioning in patients with myeloid malignancies: a propensity score-matched analysis. *Biol Blood Marrow Transplant*. 2016;22(12):2270–5. <https://doi.org/10.1016/j.bbmt.2016.08.030>
28. Martino R, Iacobelli S, Brand R, Jansen T, van Biezen A, Finke J, et al. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. *Blood*. 2006;108(3):836–46. <https://doi.org/10.1182/blood-2005-11-4503>

29. Weisdorf DJ. Reduced-intensity versus myeloablative allogeneic transplantation. *Hematol Oncol Stem Cell Ther.* 2017;10(4):321–6. <https://doi.org/10.1016/j.hemonc.2017.05.002>
30. Martino R, de Wreede L, Fiocco M, van Biezen A, von dem Borne PA, Hamladji RM, et al. Comparison of conditioning regimens of various intensities for allogeneic hematopoietic SCT using HLA-identical sibling donors in AML and MDS with <10% BM blasts: a report from EBMT. *Bone Marrow Transplant.* 2013;48(6):761–70. <https://doi.org/10.1038/bmt.2012.236>
31. Luger SM, Ringdén O, Zhang MJ, Pérez WS, Bishop MR, Bornhauser M, et al. Similar outcomes using myeloablative vs reduced-intensity allogeneic transplant preparative regimens for AML or MDS. *Bone Marrow Transplant.* 2012;47(2):203–11. <https://doi.org/10.1038/bmt.2011.69>
32. Pasquini M, Zhu X. Current uses and outcomes of hematopoietic stem cell transplantation: 2014 CIBMTR summary slides. 2014. Available from: <https://www.cibmtr.org/referencecenter/slidesreports/summaryslides/Pages/index.aspx>
33. Hourigan CS, Dillon LW, Gui G, Logan BR, Fei M, Ghannam J, et al. Impact of conditioning intensity of allogeneic transplantation for acute myeloid leukemia with genomic evidence of residual disease. *J Clin Oncol.* 2020;38(12):1273–83. <https://doi.org/10.1200/JCO.19.03011>
34. Salas MQ, Lam W, Al-Shaibani Z, Viswabandya A, Law AD. Dual T cell depletion with anti-thymocyte globulin and post-transplant cyclophosphamide results in low rates of cytokine release syndrome in peripheral blood haplo-hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2019;25(12):e387–e388. <https://doi.org/10.1016/j.bbmt.2019.09.013>
35. Holler E, Greinix H, Zeiser R. Acute graft-versus-host disease. In: Carreras E, Dufour C, Mohty M, Kröger N, editors. *The EBMT handbook: hematopoietic stem cell transplantation and cellular therapies.* 7th ed. Cham: Springer; 2019.
36. Wolff D, Lawitschka A. Chronic graft-versus-host disease. In: Carreras E, Dufour C, Mohty M, Kröger N, editors. *The EBMT handbook: hematopoietic stem cell transplantation and cellular therapies.* 7th ed. Cham: Springer; 2019.
37. Ringdén O, Labopin M, Ehninger G, Niederwieser D, Olsson R, Basara N, et al. Reduced intensity conditioning compared with myeloablative conditioning using unrelated donor transplants in patients with acute myeloid leukemia. *J Clin Oncol.* 2009;27(27):4570–7. <https://doi.org/10.1200/JCO.2008.20.9692>
38. Genadieva-Stavrik S, Boumendil A, Dreger P, Peggs K, Briones J, Corradini P, et al. Myeloablative versus reduced intensity allogeneic stem cell transplantation for relapsed/refractory Hodgkin's lymphoma in recent years: a retrospective analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *Ann Oncol.* 2016;27(12):2251–7. <https://doi.org/10.1093/annonc/mdw421>
39. Alfaro Moya T, Mattsson J, Remberger M, Lipton JH, Kim DD, Viswabandya A, et al. Influence of conditioning regimen intensity on outcomes post-allogeneic hematopoietic cell transplantation for acute myeloid leukemia in complete morphological remission. *Eur J Haematol.* 2023;111(4):553–61. <https://doi.org/10.1111/ejh.14041>
40. Lo Schirico M, Passera R, Gill J, Dellacasa C, Dogliotti I, Giaccone L, et al. Graft-versus-host disease prophylaxis with antithymocyte globulin in patients receiving stem cell transplantation from unrelated donors: an observational retrospective single-center study. *Cancers (Basel).* 2023;15(10):2761. <https://doi.org/10.3390/cancers15102761>
41. Greco R, Lorentino F, Albanese S, Lupo Stanghellini MT, Giglio F, Piemontese S, et al. Posttransplantation cyclophosphamide- and sirolimus-based graft-versus-host-disease prophylaxis in allogeneic stem cell transplant. *Transplant Cell Ther.* 2021;27(9):776.e1–776.e13. <https://doi.org/10.1016/j.jctc.2021.05.023>
42. Soiffer RJ, LeRademacher J, Ho V, Kan F, Artz A, Champlin RE, et al. Impact of immune modulation with anti-T-cell antibodies on the outcome of reduced-intensity allogeneic hematopoietic stem cell transplantation for hematologic malignancies. *Blood.* 2011;117(25):6963–70. <https://doi.org/10.1182/blood-2011-01-332007>
43. Soiffer RJ, Kim HT, McGuirk J, Horwitz ME, Johnston L, Patnaik MM, et al. Prospective, randomized, double-blind, phase III clinical trial of anti-T-lymphocyte globulin to assess impact on chronic graft-versus-host disease-free survival in patients undergoing HLA-matched unrelated myeloablative hematopoietic cell transplantation. *J Clin Oncol.* 2017;35(36):4003–11. <https://doi.org/10.1200/JCO.2017.75.8177>
44. Devine SM, Bo-Subait S, Kuxhausen M, Spellman SR, Bupp C, Ahn KW, et al. Clinical impact of cryopreservation of allogeneic hematopoietic cell grafts during the onset of the COVID-19 pandemic. *Blood Adv.* 2023;7(19):5982–93. <https://doi.org/10.1182/bloodadvances.2023009786>
45. Carpenter B, Haque T, Dimopoulou M, Atkinson C, Roughton M, Grace S, et al. Incidence and dynamics of Epstein-Barr virus reactivation after alemtuzumab-based conditioning for allogeneic hematopoietic stem-cell transplantation. *Transplantation.* 2010;90(5):564–70. <https://doi.org/10.1097/TP.0b013e3181e7a3bf>
46. Dumas PY, Ruggeri A, Robin M, Crotta A, Abraham J, Forcade E, et al. Incidence and risk factors of EBV reactivation after unrelated cord blood transplantation: a Eurocord and Société Française de Greffe de Moelle-Thérapie Cellulaire collaborative study. *Bone Marrow Transplant.* 2013;48(2):253–6. <https://doi.org/10.1038/bmt.2012.117>
47. Curtis RE, Travis LB, Rowlings PA, Socié G, Kingma DW, Banks PM, et al. Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. *Blood.* 1999;94(7):2208–16.
48. Fujimoto A, Hiramoto N, Yamasaki S, Inamoto Y, Uchida N, Maeda T, et al. Risk factors and predictive scoring system for post-transplant lymphoproliferative disorder after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2019;25(7):1441–9. <https://doi.org/10.1016/j.bbmt.2019.02.016>
49. Landgren O, Gilbert ES, Rizzo JD, Socié G, Banks PM, Sobocinski KA, et al. Risk factors for lymphoproliferative disorders after allogeneic hematopoietic cell transplantation. *Blood.* 2009;113(20):4992–5001. <https://doi.org/10.1182/blood-2008-09-178046>

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