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Blood 142 (2023) 236–238

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

723.ALLOGENEIC TRANSPLANTATION: LONG-TERM FOLLOW-UP AND DISEASE RECURRENCE

MMF Is Associated with Worse OS in CMV Seropositive AML Patients Undergoing MUD HCT with Calcineurin-Inhibitor-Based Gvhd Prophylaxis

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Background: Calcineurin-inhibitor (CNI) with mycophenolate mofetil (MMF) or methotrexate (MTX) is commonly used as graft-versus-host disease (GVHD) prophylaxis for HLA-matched hematopoietic cell transplantation (HCT) but MMF, which targets both T- and B-lymphocytes, is associated with higher risk for cytomegalovirus (CMV) reactivation [*Blood Adv.2023;7(8):1394-1403*]. We investigated whether overall survival (OS) differed with MMF- vs MTX-based GVHD prophylaxis according to recipient CMV serostatus and underling HCT disease indication.

Methods: We evaluated 3105 patients with acute myeloid leukemia (AML, n=1572), acute lymphoblastic leukemia (ALL, n=453) or myelodysplastic neoplasms (MDS, n=1080) who underwent HLA-matched unrelated donor (MUD) peripheral blood (PB) HCT from 2008-17 using a publicly available Center for International Blood and Marrow Transplant Research (CIBMTR) dataset. Four groups were compared: MTX/ CMV+ (n=1527), MTX/ CMV- (n=916), MMF/ CMV+ (n=395), and MMF/ CMV- (n=267). All patients also received tacrolimus; none received post-transplant cyclophosphamide (PTCy). Primary outcome was OS.

Results: The median (interquartile range) age was 57 (45-64), 56 (45-64), 62 (54-68), and 61 (50-67) years in the respective 4 groups. Within each group, most patients had AML or MDS. Disease status was mostly early or intermediate (51-63%). About half had HCT-CI > 2. In vivo T cell depletion was used in 41%, 65%, 48% and 52%, respectively. More patients in the MTX groups received myeloablative conditioning (58% and 55%, respectively), while reduced intensity/non-myeloablative conditioning was more common in the MMF groups (73% and 65%, respectively).

In multivariate models stratified by disease, we noted significantly worse OS in CMV+ patients who received MMF, but this effect was restricted to AML. Among AML patients, OS was only 31% (95% confidence interval [CI] 25-37) among the MMF/CMV+ group, but was higher and not significantly different for the MMF/CMV- (54%, 95% CI 45-63) and MTX/CMV+ (51%, 95% CI 48-55) groups compared to the MTX/CMV- group (58%, 95% CI 53-63) [**Figure 1, Table 1**] In ALL, GVHD prophylaxis type/CMV serostatus had no significant association with OS. In MDS, CMV+ patients had worse OS (HR 1.2, 95% CI 1.01-1.4, p=0.03) than CMV- patients irrespective of GVHD prophylaxis (MMF/CMV+ vs MTX/CMV+: HR=1.1, 95% CI 0.8-1.4, p=0.5). Donor CMV serostatus had no impact on these associations. Data on CMV reactivation and causes of death were not available; however, our data suggest that the inferior OS in AML was driven mostly by higher non-relapse mortality and some increase in relapse (data not shown).

To evaluate how the use of PTCy prophylaxis might impact the interaction between MMF and recipient CMV+ serostatus, we next analyzed a separate CIBMTR MUD PB-HCT cohort that received PTCy/CNI/MMF prophylaxis (N=242; AML, n=136, ALL, n=42; MDS, n=64) and assessed the effect of CMV serostatus on OS. A majority (95%) received HCT from 2015-18. Our results showed that CMV+ recipients had a significantly worse OS than CMV- recipients, but only in AML (HR 2.7, 95% CI 1.1-6.4, p=0.03) and not in ALL (HR 0.4, 95% CI 0.1-1.5, p=0.2), or MDS (HR 0.7, 95% CI 0.3-1.5, p=0.3). As all patients in this cohort received PTCy/CNI/MMF, we were unable to assess the independent impact of MMF and CMV serostatus in this setting. Nevertheless, these data suggest similar trends as seen in the CNI cohort (without PTCy), where the inferior OS in the MMF/CMV+ group was noted only in AML patients.

Conclusion: Our data suggest that the use of MMF with CNI-based prophylaxis (without PTCy) should be avoided in AML CMV+ patients. Why this adverse effect of CMV seropositivity and MMF prophylaxis is restricted to AML patients, and not seen in ALL, and whether the same applies to PTCy-prophylaxis with/without MMF, needs further investigation but could be due to CMV-induced expansion of NK cells [*Béziat. Blood. 2013; Foley. Blood. 2012*] which mediates alloreactivity against AML but not ALL [*Ruggeri Blood 1999]* and is suppressed by MMF more than MTX [*Ohata. BBMT. 2011*].

Disclosures Lee: *Amgen, AstraZeneca, Incyte, Kadmon, Pfizer, Syndax:* Research Funding; *Novartis:* Other: Steering Committee member; *Janssen:* Other: Study medication provider; *Equillium, Kadmon, Mallinckrodt:* Consultancy. **Carpenter:** *Incyte, Janssen, AbbVie, and Sanofi:* Research Funding. **Lee:** *Incyte Corp:* Consultancy, Research Funding; *Fresenius Kabi:* Consultancy; *BMS:* Honoraria; *Kite Pharma:* Honoraria, Speakers Bureau; *Sanofi:* Consultancy, Honoraria; *Kadmon:* Honoraria. **Hill:** *Syndax Pharmaceuticals:* Research Funding; *Applied Molecular Transport:* Research Funding; *Cynata Therapeutics:* Consultancy; *Commonwealth Serum Laboratories:* Consultancy; *Heat Biologics:* Research Funding; *Genentech:* Research Funding; *Serplus Technology:* Research Funding; *NapaJen Pharma:* Consultancy; *iTeos Therapeutics:* Consultancy; *Neoleukin Therapeutics:* Consultancy; *Compass Therapeutics:* Research Funding; *Laevoroc Oncology:* Research Funding; *iTeos Therapeutics:* Research Funding; *Generon Corporation:* Consultancy. **Champlin:** *Actinium Pharmaceuticals:* Consultancy; *Omeros:* Consultancy; *Johnson & Johnson/Janssen:* Consultancy; *Arog:* Consultancy; *Orca Bio:* Consultancy; *Kadmon:* Consultancy; *Takeda Corporation:* Patents & Royalties; *Cell Source:* Research Funding. **Rezvani:** *Affimed:* Other: License agreement; *Takeda:* Patents & Royalties. **Shpall:** *NY Blood Center:* Membership on an entity's Board of Directors or advisory committees; *Navan:* Membership on an entity's Board of Directors or advisory committees; *Adaptimmune:* Membership on an entity's Board of Directors or advisory committees; *Affimed:* Other: License agreement; *Takeda:* Other: License agreement; *Fibrobiologics:* Membership on an entity's Board of Directors or advisory committees; *Axio:* Membership on an entity's Board of Directors or advisory committees; *Celaid Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Syena:* Other: License agreement. **Mehta:** *CSL Behring:* Research Funding; *Kadmon:* Research Funding; *Incyte:* Research Funding.

Table 1: Multivariate analysis assessing the association of overall survival with CNI-MMF vs CNI-MTX GVHD prophylaxis and recipient CMV serostatus

	AML N=1572		ALL N=453		MDS N=1080	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Overall Survival						
MTX/ CMV-	1.0		1.0		1.0	
MMF/ CMV-	0.9 (0.7-1.3)	0.6	0.8 (0.4-1.4)	0.4	1.1 (0.8-1.5)	0.4
MTX/ CMV+	1.2 (0.9-1.4)	0.09	0.9 (0.7-1.3)	0.7	1.2 (0.99-1.5)	0.05
MMF/ CMV+	1.8 (1.4-2.3)	<0.001	1.2 (0.7-1.9)	0.5	1.3 (1.0-1.7)	0.04
Donor age >35 years	--		1.5 (1.1-2)	0.004	1.3 (1.1-1.6)	0.004
Age >60 years	1.4 (1.2-1.7)	<0.001	-	-	1.2 (1.05-1.5)	0.01
HCT-CI >2	1.3 (1.1-1.5)	<0.001	1.4 (1.1-1.8)	0.02	1.4 (1.2-1.7)	<0.001
Advanced disease	2.2 (1.9-2.6)	<0.001	1.9 (1.4-2.5)	<0.001	-	-

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; CMV, cytomegalovirus; HCT-CI, Hematopoietic Cell Transplantation-specific Comorbidity Index; HR, Hazard ratio; MDS, myelodysplastic neoplasms.

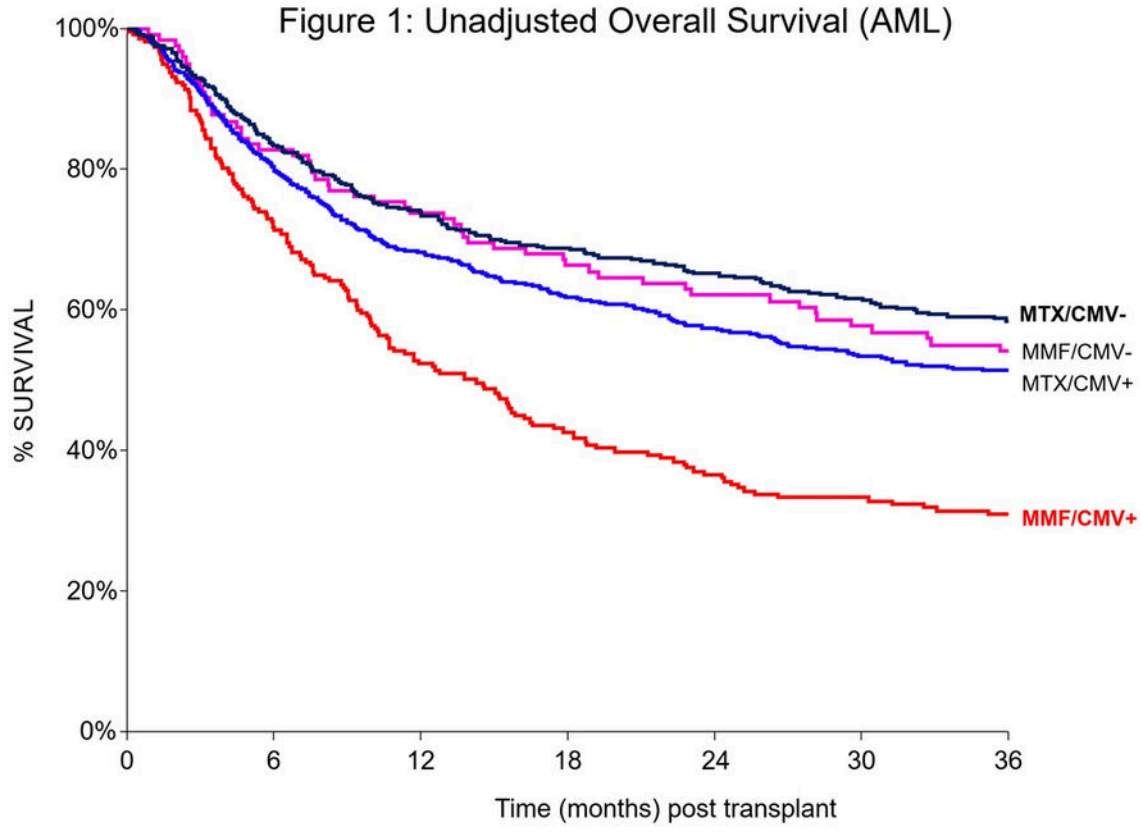

Figure 1

https://doi.org/10.1182/blood-2023-186402