CYTOMEGALOVIRUS REACTIVATION DID NOT IMPACT RELAPSE AFTER HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE: A SINGLE-CENTER EXPERIENCE

Mohammad Tarek[1,2], Abdulrahman Habashy[1,2], Ahmed Samy[1], Hossam Abdeen[1], Omar Emad[1,2], Adham Gamal[1], Mohamed Eissa[1], Hazem Kraitem[1], Nader Abdelaziz[1], Mohamed Fathy[1], Hesham Shaban[1], Ahmed Ismael[1], Khaled Zakareya[1], Essam Khater[1], Omar Abou El-Hasan[1], Islam Elzaeem[1], Islam Abdelwahed[1], Moheb Tharwat[1], Mohamed El-Safty[1], Mohamed Negm[1], Ahmed El-Husseiny[1], Mohamed Elprince[1], Hussein Hammam[1], Ahmed Kasbar[1], Sameh Emara[1], AbdelSalaam Atallah[1], Sherif Mahmoud[1], George Baheig[1], Mohamed Khalaf[1]

[1] Clinical Hematology and Bone Marrow Transplantation Department, Oncology & Hematology Hospital, Maady Military Medical Compound., Cairo, Egypt
[2] Clinical Hematology Department, Armed Forces College of Medicine (AFCM), Cairo, Egypt

Introduction

Haploidentical hematopoietic stem cell transplantation (haplo-HSCT) with post-transplant cyclophosphamide (PTCy) has significantly increased access to transplantation for patients with hematologic malignancies. Cytomegalovirus (CMV) reactivation is a frequent complication in this setting, and its impact on transplant outcomes, particularly malignant relapse, remains a subject of debate with conflicting evidence. This single-center study aimed to evaluate the incidence and clinical impact of CMV reactivation on post-transplant complications, relapse, progression-free survival (PFS), and overall survival (OS) in patients undergoing haplo-HSCT with PTCy.

Methods

This retrospective cohort study included 117 consecutive patients who underwent haplo-HSCT with PTCy at a single center in Cairo, Egypt between January 2022 and June 2024. Patients were stratified into two groups based on the occurrence of CMV reactivation, defined as detection of CMV DNAemia ≥57 copies/mL by quantitative PCR. Baseline patient, donor, and transplant characteristics, as well as post-transplant complications, were compared between the groups using univariate statistical tests (Chi-square or Fisher's exact test for categorical variables, independent samples t-test for continuous variables). Time-to-event outcomes, including cumulative incidence of relapse (analyzed using competing risks with non-relapse mortality as the competing event) and Kaplan-Meier estimates for PFS and OS, were compared between the CMV reactivation groups using the Log-rank test (or Gray's test for cumulative incidence).

Results

CMV reactivation occurred in 72 patients (61.5%). The CMV reactivation group had a higher frequency of recipient (61.1% vs 37.8%, P=0.023) and donor (52.8% vs 28.9%, P=0.019) CMV immunodominant alleles compared to the no reactivation group. Patients with CMV reactivation had already had significantly slower platelet (mean 14.4 vs 9.8 days, P<0.001) and neutrophil (mean 18.2 vs 12.9 days, P<0.001) engraftment, and required more TPO-RA use (88.9% vs 8.9%, P<0.001) likely due to antiviral associated thrombocytopenia. Tocilizumab -for CRS- use (25.0% vs 6.7%, P=0.023) was higher in the reactivation group.

Acute GVHD (aGVHD) was more frequent overall (65.3% vs 37.8%, P=0.007), with higher rates of Grade 3 (20.8% vs 0.0%, P=0.003), Skin (No Skin aGVHD 50.0% vs 75.6%, P=0.011), Stage I-II Liver aGVHD (20.8% vs 4.4%, P=0.029), and steroid-responsive aGVHD (68% vs 65%, P=0.8).

Hemorrhagic cystitis (HC) incidence (48.6% vs 26.7%, P=0.031) and duration (mean 9.69 vs 2.94 days, P=0.008) were significantly higher in the reactivation group. Full donor chimerism was also more frequently observed (98.6% vs 82.2%, P=0.004) in the reactivation group.

Despite these associations with complications, CMV reactivation status did not significantly impact the cumulative incidence of relapse (16.7% vs 15.6% at ~350 days, P=0.9055), PFS (38.9% vs 42.2% at ~350 days, P=0.5226), or OS (51.4% vs 44.4% at ~350 days, P=0.1692). Refined-DRI was a significant predictor of relapse risk (P<0.05), but not OS in unadjusted analysis.

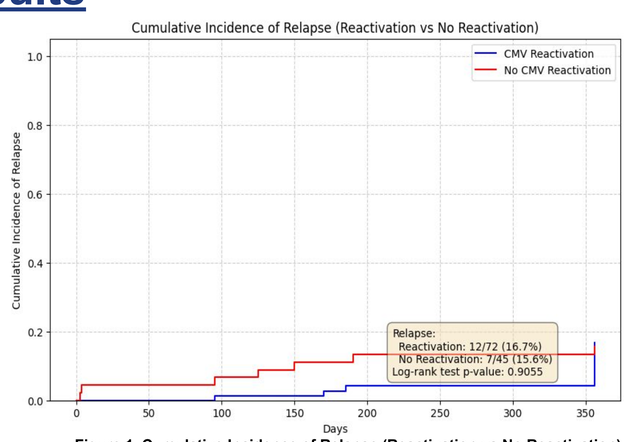

Figure 1. Cumulative Incidence of Relapse (Reactivation vs No Reactivation)

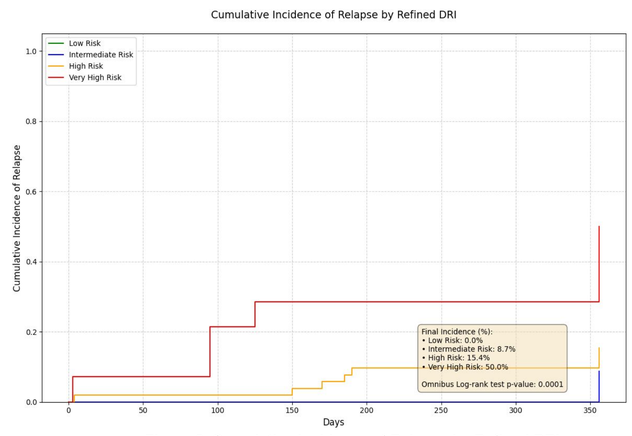

Figure 2. Cumulative Incidence of Relapse by Refined DRI

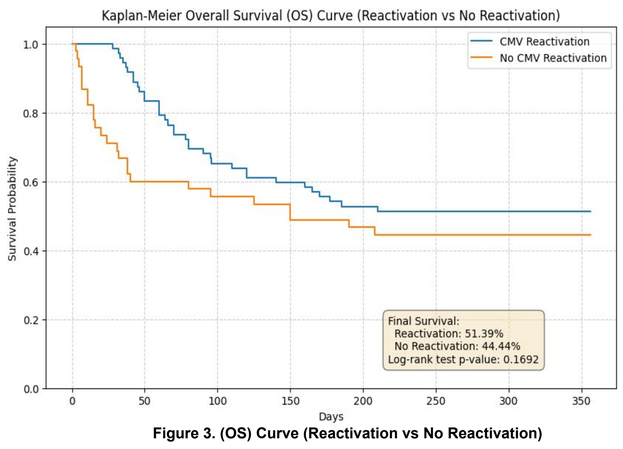

Figure 3. (OS) Curve (Reactivation vs No Reactivation)

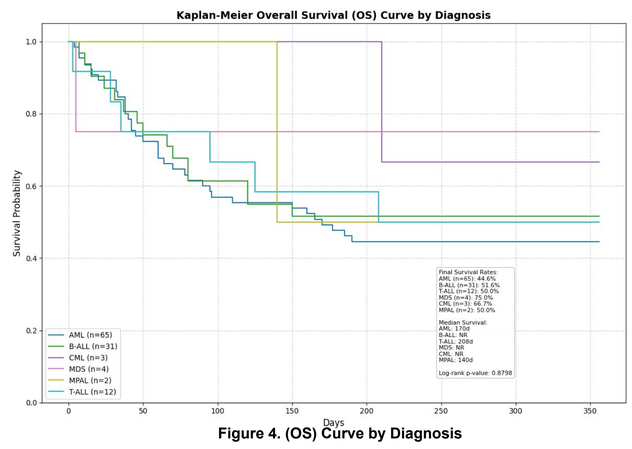

Figure 4. (OS) Curve by Diagnosis

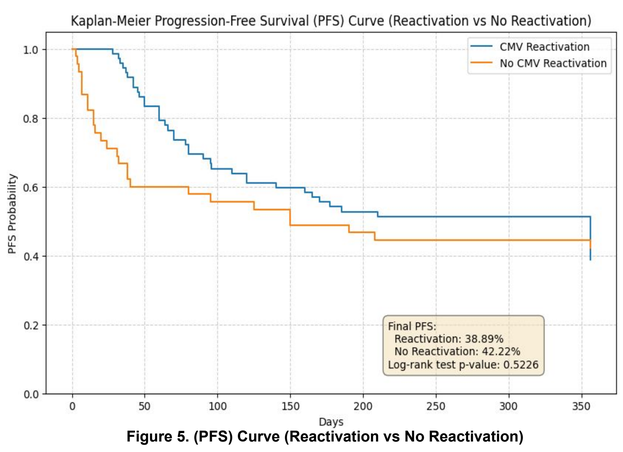

Figure 5. (PFS) Curve (Reactivation vs No Reactivation)

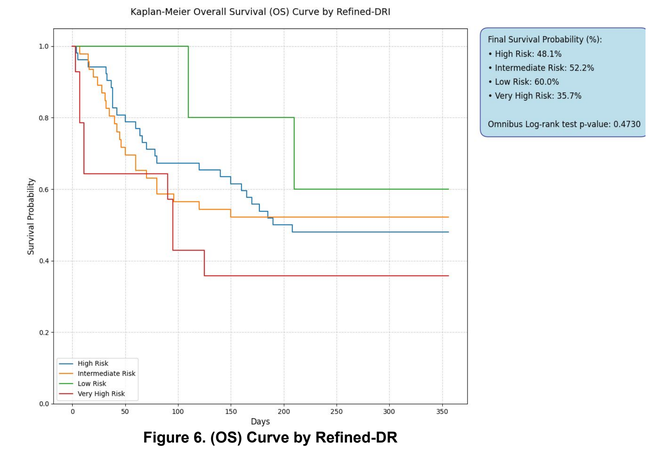

Figure 6. (OS) Curve by Refined-DR

Table 1. Baseline Patient and Transplant Characteristics Stratified by Cytomegalovirus (CMV) Reactivation Status

Characteristic	CMV Reactivation (N = 72)	No CMV Reactivation (N = 45)	P-value
Sex, n (%)			
Female	20 (27.8)	7 (15.6)	0.193
Male	52 (72.2)	38 (84.4)	
Age (years)			0.915
Mean	28.62	28.31	
Median	31.0	27.0	
Range	8–55	7–58	
Diagnosis, n (%)			
AML	44 (61.1)	21 (46.7)	0.180
B-ALL	18 (25.0)	13 (28.9)	0.803
T-ALL	6 (8.3)	6 (13.3)	0.579
CML	2 (2.8)	1 (2.2)	1.000
MDS	0 (0.0)	4 (8.9)	-
MPAL	2 (2.8)	0 (0.0)	-
Recipient CMV immunodominant alleles, n (%)	44 (61.1)	17 (37.8)	0.023*
Donor CMV immunodominant alleles, n (%)	38 (52.8)	13 (28.9)	0.019*
Refined-DRI, n (%)			
High risk	31 (43.1)	21 (46.7)	0.848
Intermediate risk	5 (6.9)	0 (0.0)	0.181
Low risk	6 (8.3)	8 (17.8)	0.216
Very high risk	39 (54.2)	20 (44.4)	0.405

Table 2. Post-Transplant Outcomes and Complications Stratified by Cytomegalovirus (CMV) Reactivation Status

Outcome	CMV Reactivation (N = 72)	No CMV Reactivation (N = 45)	P-value
Relapse, n (%)			1.000
No relapse	60 (83.3)	38 (84.4)	
Relapsed	12 (16.7)	7 (15.6)	
Progression-free survival at ~350 days (%)	38.9	42.2	0.523
Overall survival at ~350 days (%)	51.4	44.4	0.169
Acute GVHD, n (%)			
Any aGVHD	47 (65.3)	17 (37.8)	0.007*
Grade 3	15 (20.8)	0 (0.0)	0.003*
Grade 4	23 (31.9)	27 (60.0)	0.005*
Steroid-responsive aGVHD, n (%)	32 (68)	11 (65)	0.8
Hemorrhagic cystitis (HC)			
Incidence, n (%)	35 (48.6)	12 (26.7)	0.031*
Duration, mean (days)	9.69	2.94	0.008*
Chimerism, n (%)			
Full donor chimerism	71 (98.6)	37 (82.2)	0.004*

Discussions

CMV reactivation was found not to be linked measurable graft-versus-leukemia (GvL) benefit in the setting of Haplo-HSCT with PTCy. Instead, reactivation correlated with increased acute GVHD, particularly more Grade 3 and Stage I-II liver aGVHD. Patients with CMV reactivation also experienced higher incidence and longer duration of hemorrhagic cystitis, likely reflecting synergistic viral and inflammatory damage. Differences in donor and recipient CMV immunodominant alleles and higher rates of full donor chimerism in the CMV group highlight a genetic and immunologic contribution to reactivation risk and immune reconstitution. Despite these associations, relapse risk remained primarily driven by established prognostic factors such as Refined-DRI rather than CMV status, and OS was unaffected, possibly due to short follow-up (~200–225 days) and competing risks. Overall, in the context of PTCy and modern CMV preemptive therapy, CMV reactivation primarily increases short-term morbidity—via GVHD and hemorrhagic cystitis—without exerting a major influence on long-term survival or disease control. Limitations include the retrospective, single-center design, modest sample size, absence of multivariate analysis, and lack of detailed CMV kinetics or immune reconstitution markers.

Conclusions

In this cohort of haploidentical HSCT recipients receiving PTCy, CMV reactivation was frequent and associated with certain immunogenetic factors, delayed engraftment, and increased morbidity (aGVHD, HC). However, CMV reactivation did not show a significant association with the risk of malignant relapse, PFS, or OS in unadjusted analyses. These findings support the notion that while CMV reactivation is a significant clinical event associated with short-term morbidity, it may not positively impact disease control or long-term survival in the context of PTCy-based haplo-HSCT with proactive CMV management.