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LETTER TO EDITOR

Epstein-Barr viremia and post-transplant lymphoproliferative disorders in patients undergoing haploidentical stem cell transplantation with post-transplant cyclophosphamide

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To the Editor,

Historically, haploidentical hematopoietic stem cell transplant (haplo-HSCT) protocols have utilized intensive immunosuppression strategies to overcome the bidirectional alloreactivity [1]. However, this results in high risk of infectious complications such as Epstein—Barr virus (EBV) viremia and post-transplant lymphoproliferative disorders (PTLD) [2,3]. T-cell replete haplo-HSCT utilizing post-transplant cyclophosphamides (PTCy) for Graft Versus Host Disease (GVHD) prophylaxis are now being increasingly utilized [1—3].

We analyzed the incidence and outcomes of EBV viremia including subsequent PTLD in adult patients receiving haplo-HSCT for hematological malignancies. We also analyzed the use of rituximab for preemptive treatment of EBV viremia.

A total of 63 patients were included in this study (Table 1). All patients received post-transplant cyclophosphamide followed by tacrolimus and mycophenolate mofetil for GVHD prophylaxis. All patients received EBV monitoring weekly starting 20 days post-transplant, continuing for 6 months after immunosuppression ended or when CD4 count >200. EBV reactivation was defined as EBV polymerase chain reaction (PCR) load >1000 copies/mL. EBV titer was confirmed by repeat testing when viral load was 1000 copies/mL and treatment with rituximab was initiated if repeat titer was >1000 copies/mL. Patients could receive up to four doses of rituximab.

Among the 63 patients reviewed, 18 (28.5%) developed EBV viremia. The median time to detection of EBV viremia from the time of transplant was 99 days (range: 20—277). The median peak level for the EBV reactivation cohort was 7650 viral copies/mL. Amongst these 18 patients, 12 had no evidence of GVHD, with five patients having mild and one having severe GVHD at the time of EBV viremia diagnosis.

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Table 1 Study population characteristics ($n = 63$), as well as univariate analysis for risk factors.

	Entire cohort	Patients with EBV reactivation ($n = 18$)	Patients without EBV reactivation ($n = 45$)	p
Patient age, median	50.69	49.18	51.29	.60
Sex				.10
Male	20	3	17	
Female	43	15	28	
Diagnosis				.60
Acute myeloid leukemia	30	7	23	
Acute lymphoblastic leukemia	8	2	6	
Myelodysplastic syndrome	7	4	3	
Non-Hodgkin lymphoma	10	3	7	
Myeloproliferative neoplasms	2	1	1	
Hodgkin disease	2	0	2	
Other	4	1	3	
CIBMTR score (median)	64.54	59.43	67.65	.06
HCT-CI score (median)	1	1	1	.75
Disease status at time of transplant				
Complete remission	43	9	34	**.05**
Incomplete remission	20	9	11	
Prior hematopoietic stem cell transplants (HSCT)				.16
No prior HSCT	50	17	33	
Prior autotransplant	9	1	8	
Prior allotransplant	4	0	4	
Conditioning regimen used				.87
Myeloablative conditioning	4	1	3	
Reduced intensity conditioning	59	17	42	
Stem cell source				.81
Bone marrow	35	10	25	
Peripheral blood stem cell	28	8	20	
GVHD prophylaxis regimen received				n/a
Tacrolimus/cyclophosphamide/mycophenolate mofetil	63	18	45	
Acute GVHD at 100-day mark				.79
Grades 0—I	27	8	19	
Grade II	24	8	16	
Grade III—IV	4	1	3	

CIMBTR = The Center for International Blood and Marrow Transplant Research; EBV = Epstein—Barr virus; HCT-CI = Hematopoietic Stem Cell Transplantation Comorbidity Index; HSCT = hematopoietic stem cell transplant; n/a = not applicable.

Eight of the 18 (44.4%) patients that developed EBV viremia required rituximab due to rising or persistent EBV viremia. The median EBV level at initiation of therapy was 31,000 copies/mL. EBV seronegativity was achieved in six patients (75%) with treatment at a median of 13.5 days (range: 3—26). All patients who received rituximab received dose of 375 mg/m^2 with each administration. For all six patients who achieved seronegativity after receiving rituximab, they only needed to receive one dose to achieve this goal One other patient only required two doses of rituximab and was able to obtain EBV level to <500 copies. None of the patients in either cohort developed probable or proven PTLD. There was no statistically significant difference in mortality (44.4% vs. 48.9%, $p = .79$, using Kaplan-Maier survival analysis or GVHD incidence (1.8% vs. 5.5% Grade III/IV at 100 days, $p = .55$, using Pearson chi-square test (Table 1) between those who developed EBV viremia versus those who did not develop EBV viremia.

In our study, we observed a 28.5% incidence of EBV viremia. However, no cases of PTLD were observed, even in those patients with sustained elevation in EBV titers. This is consistent with previous studies which reported no cases of PTLD with use of PTCy [1,3—5]. A possible reason for this phenomenon includes destruction of EBV infected B-cells with PTCy with relative sparing of EBV-specific memory T-cells [4]. It contrasts with the rate of ~3% of PTLD seen in haploidentical transplants utilizing anti-thymocyte globulin (ATG) in their conditioning regimens [6,7]. Rituximab was also seen to be effective in preemptive treatment of EBV viremia with 75% of patients in our cohort achieving seronegativity.

In conclusion, the utility of rituximab for preemptive treatment of EBV viremia was observed as the majority of patients who received even just one dose of rituximab were able to achieve seronegativity. In addition, no cases of PTLD were seen throughout the cohort. It is possible that routine monitoring of EBV viral load in patients who received PTCy following haploSCT may contribute to the absence of PTLD in this cohort; however, there is also a possibility of inherently low risk of PTLD with the PTCy platform. A prospective trial can help determine whether routine monitoring of EBV viral load is even necessary, or whether the incidence is low enough to avoid routine monitoring in the PTcy era.

Conflicts of interest

The authors declare no conflict of interest.

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