Epstein Barr Virus (EBV) reactivation after reduced intensity conditioning (RIC) unrelated umbilical cord blood transplantation (UCBT)

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Introduction

Umbilical cord blood has been increasingly used as an alternative stem cell source for allogeneic hematopoietic stem cell transplantation (allo-SCT). RIC regimens have been increasingly used prior to allo-HSCT with the aim to decrease transplantation-related mortality (TRM) in patients ineligible for standard conditioning. Because of the slow kinetics of immune reconstitution after UCBT, previous studies showed that EBV reactivation and EBV induced lymphoprolipherative disease (LPD) may be of matter of concern, particularly in the reduced intensity setting. The aim of this analysis was to investigate the features of EBV reactivation in 33 patients who underwent RIC UCBT between January 2005 and June 2009.

Patients and methods

During the first six months after allo-SCT and in patients treated for GVHD, all patients were weekly DNA-PCR screened in the peripheral blood for EBV reactivation and were clinically monitored for clinical features attributable to EBV. EBV viremia was defined as 1000 copies of EBV DNA /10^5 cells. EBV LPD was defined as biopsy- or autopsy proven post-transplantation lymphoma, or viremia along with computerized tomography nodal or soft-tissue abnormalities consistent with LPD. Patients with EBV viremia >1000 copies on at least two consecutive occasions were treated with rituximab at a dose of 375 mg/m^2 weekly until clearance of EBV viremia (usually for a maximum of 4 infusions).

Table 1. Characteristics of study population

PATIENTS (n = 33)	
Patient age (median, range)	**50 (18-66)**
Sex ratio (M:F)	**18 : 15 (55% : 45%)**
Diagnosis	
Myeloid malignancies : lymphoid malignancies : AA	**19 : 12 : 2 (58% : 36% : 6%)**
Number of CBT units	
Single : Double	**3 : 30 (9% : 91%)**
HLA matching	
1 mismatch : 2 mismatches	**14 : 19 (43% : 57%)**
Conditioning regimen	
with ATG : without ATG	**8 : 25 (24% : 76%)**
with TBI : without TBI	**29 : 4 (86% : 12%)**
Imunosupression:	
CsA : CsA + MMF	**1 : 32 (3% : 97%)**

AA = aplastic anemia; ATG = antithymoglobulins; BM = bone marrow; CsA = cyclosporine A; MMF = mycophenolate mofetil, TBI = total body irradiation

Results

Engraftment occurred in 25 patients (76%) at a median time of 12 days after UCBT (range, 8–60). Clinically significant grade II to IV acute GVHD occurred in 5 of cases (15%). The cumulative incidence of EBV reactivation at 6 months and three years after allo-HSCT was 13% and 17%. EBV reactivation was observed at a median of 132 (range 85-438) days after allo-HSCT, with 3 (60%) reactivations occurring during the first 6 months. In 28 patients (85%), the EBV load remained less than 1000 EBV copies/10^5 cells at all time, and none of these patients experienced any sign or symptom of LPD. The remaining 5 patients (15%) experienced at least one EBV reactivation episode. Among the 5 patients experiencing EBV reactivation, 2 patients received ATG as part of their RIC. Among these 5 patients, 1 patient experienced an EBV load superior to 1000/10^5 cells at a single time point after allo-HSCT. In this patient, there were no concomitant clinical symptoms and the EBV load normalized spontaneously. Only this patient had a normal T-lymphocyte count at the time of reactivation.

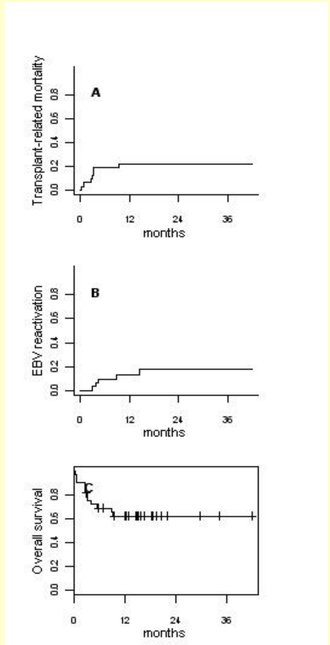

Figure 1. Outcome after RIC allo-HSCT. Cumulative incidence of transplant-related mortality in the study population (A), EBV reactivation in the study population (B), overall survival in the study population (C).

Table 2. Characteristics of patients who developed EBV reactivation

CHARACTERISTICS OF PATIENTS WITH EBV REACTIVATION											
Patient	**Conditioning**	**Time[a] (days)**	**EBV event**	**Coinfection**	**Imunosupressive treatment at reactivation**	**CD3+ cell count at reactivation**	**Peak EBV titer at reactivation (copies/10 5 cells)**	**Treatment**	**Dose s of Rx**	**Other**	**Outcome**
1	Cy-Flu-TBI	438	viremia	VZV	CS	1264	1301	no	-	-	alive at 35 months
2	Cy-Flu-TBI	271	LPD	HHV6	CS	605	36009	yes	1	no	death after 13 days
3	Cy-Flu-TBI	132	viremia	HHV6	CsA+MMF	124	2689	yes	3	no	alive at 19 months
4	Cy-Flu-TBI-ATG	85	viremia	None	CsA	128	3088	yes	3	no	alive at 13 months
5	Cy-Flu-TBI-ATG	119	LPD	HHV6	CsA+CS	131	9733	yes	8	yes[b]	alive at 12 months

[a] Time from transplantation to EBV event
[b] Patient 5 received 2 cycles of CHOP chemotherapy, 1 cycle of R-DHAP chemotherapy, radiotherapy and 2 infusions of EBV specific cytotoxic T cell lines (CTL-s),;
ATG = antithymocyte globulin 5 mg/kg; CS=corticosteroids; CSA = cyclosporine; Cy = cyclophosphamide 50 mg/kg; Flu = fludarabine 200 mg/m^2; MMF = mycophenolate mofetil; EBV = Epstein-Barr Virus; HHV6 = Human Herpes Virus 6 ; LPD = lymphoproliferative disease; Rx = Rituximab; TBI = total body irradiation; VZV = Varicella Zoster Virus;

Four patients who had EBV DNA levels exceeding 1000 copies/10^5 cells on 2 or more occasions were treated with a median of 3 (range, 1-8) rituximab infusions. Two patients responded to rituximab, but 2 patients developed LPD (cumulative incidence of 6 % at three years). Both of our patients were severely immunosupressed with high dose corticosteroid therapy at the time of the occurrence of EBV LPD. One of these 2 patients died before receiving any other anti-EBV therapy. In the other patient, LPD could be controlled after additional chemotherapy, radiotherapy and 2 infusions of EBV specific Cytotoxic T-cell Lines (CTLs). Three of five patients (60%) who experienced EBV reactivation had Human Herpes Virus 6 (HHV 6) detected in the same blood sample by PCR. With a median follow-up of 468 (range, 92-1277) days post allo-HSCT among surviving patients, 21 patients (64%) were still alive and the overall survival (OS) was 62% at 3 years. 5 patients died of disease progression and 7 patients died of transplant-related complications. One patient died of LPD. There was no statistically significant difference in terms of OS or TRM between those patients who experienced an EBV reactivation after UCBT and those who did not (OS: log rank test, p=0.33, TRM: Gray test, p= 0.82). Univariate analysis did not find any risk factors significantly different between subgroups with and without EBV reactivation

Conclusions

Overall, this study shows the rate of EBV reactivation after RIC UCBT to be comparable to the incidence expected with RIC mismatched unrelated bone marrow or peripheral blood SCT. Despite small numbers, our observations support close EBV monitoring and the use of pre-emptive rituximab treatment since some cases may progress to LPD requiring additional interventions such as EBV-specific CTLs.

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