Epstein-Barr Virus (EBV) reactivation after reduced intensity conditioning (RIC) allogeneic stem cell transplantation (allo-SCT)

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Introduction

Following allo-SCT, EBV reactivation and EBV lymphoprolipherative disease (LPD) are well recognized complications. To date, few data has been reported regarding the features of EBV LPD following RIC allo-HSCT. The aim of this study was to define the incidence and risk factors of EBV reactivation in 175 consecutive adult patients undergoing RIC allo-SCT between January 2005 and June 2009 in our institution and to assess its impact on clinical outcome.

Patients and methods

Table 1. Study population characteristics

PATIENTS (n = 175)	
Patient age (median, range)	**56 (18-71)**
Sex ratio (M:F)	**106 : 69 (61%:39%)**
Diagnosis	
Myeloid malignancies	**85 (49%)**
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Aplastic anemia	**4 (2%)**
Stem cell source	
BM : PBSC	**10:165 (6%:94%)**
Donor	
MRD	**84 (48%)**
MUD	**80 (46%)**
MIS	**11 (6%)**
Conditioning	
with ATG	**134 (77%)**
without ATG	**41 (23%)**
Imunosupression:	
CsA	**77 (44%)**
CsA + MMF	**93 (52%)**
CsA + MTX	**5 (4%)**

ATG = antithymoglobulins; BM = bone marrow; CsA = cyclosporine A; MIS = mismatched unrelated donor; MMF = mycophenolate mofetil; MRD = matched related donor; MUD = matched unrelated donor; MTX = methotrexate; PBSC = peripheral blood stem cell

EBV reactivation was defined as any EBV PCR load above 1000 copies of EBV DNA /10^5 cells. EBV LPD was defined as biopsy or autopsy proven post-transplantation lymphoma, or reactivation along with computerized tomography nodal or soft tissue abnormalities consistent with LPD. Patients with EBV viral load >1000 copies/10^5 cells on at least two consecutive occasions were treated with rituximab at a dose of 375 mg/m² weekly until clearance of viremia.

Results

Table 2. Transplant – related events

TRANSPLANT-RELATED EVENTS	
Engraftment days (ANC>0.5) *(median, range)*	**17 (6-48)**
Acute GVHD	
Grade 0-I	**114 (65%)**
Grade II-IV	**61 (35%)**
Acute GVHD onset days after allo-SCT *(median, range)*	**34 (6-181)**
Chronic GVHD	**59 (34%)**
limited	**17 (10%)**
extensive	**42 (24%)**
Chronic GVHD onset (days) after allo-SCT *(median, range)*	**189(100-768)**
EBV reactivation *(EBV load > 1000 copies)*	**34 (19%)**
EBV reactivation onset (days) after allo-SCT *(median, range)*	**58 (0-930)**

ANC = absolute neutrophile count; GVHD = graft vs host disease

The cumulative incidence of EBV reactivation at 6 months after allo-SCT was 15% (95% CI, 10-21%). EBV reactivation was observed at a median of 58 (range 0-930) days after allo-HSCT, with 27 (79%) of reactivations occurring during the first 6 months. In 141 patients (81%), the EBV load remained less than 1000 EBV copies/10^5 cells at all time. The remaining 34 patients (19%) experienced at least one EBV reactivation episode. Among these 34 patients, 17 patients had an EBV load superior to 1000/10^5 cells at a single time point after allo-HSCT. In these 17 cases, there were no concomitant clinical symptoms and the EBV load normalized spontaneously. The 17 patients who had EBV DNA levels exceeding 1000 copies/10^5 cells on 2 or more occasions were pre-emptively treated with a median number of 3 (range, 1-4) rituximab infusions which resulted in complete clearance of EBV viremia in all, but one patient (97%). This patient was severely immunosupressed, experienced both EBV and adenovirus (ADV) infection, had symptoms mainly related to ADV infection, and died of multiorgan failure. Most importantly, none of the patients from this series developed EBV induced LPD. With a median follow-up of 655 (range, 92-1542) days post allo-HSCT among surviving patients, 104 patients (59%) were still alive and the overall survival (OS) was 47% at 4 years. There was no statistically significant difference in terms of OS or transplant related mortality (TRM) between patients who experienced an EBV reactivation and patients who did not (OS: log rank test, p=0.62; TRM: Gray test, p=0.99). In univariate analysis for risk factors associated with EBV reactivation only the use of ATG as part of the RIC regimen prior to allo-HSCT was significantly different between subgroups with and without EBV reactivation (Fisher's exact test, p=0.006). In the multivariate analysis, the use of ATG remained the only independent risk factor associated with EBV reactivation (Fine and Gray test; RR=4.9; 95%CI, 1.1-21.0; p=0.03).

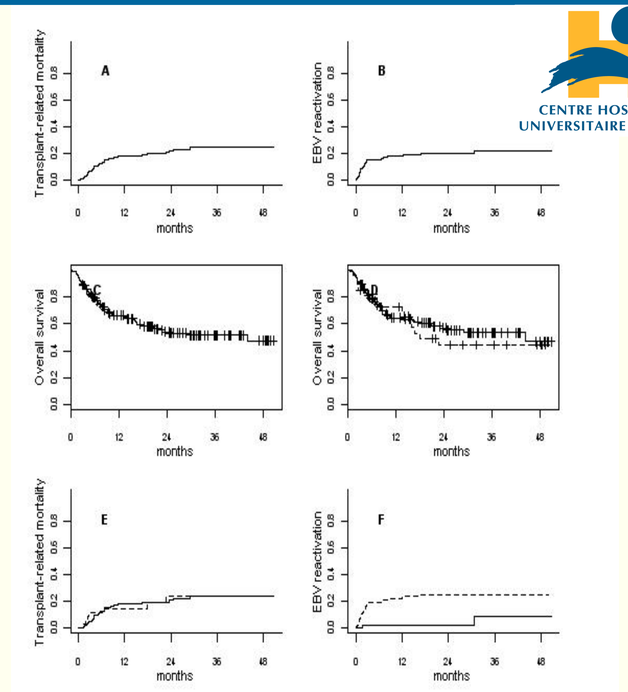

Figure 1. Outcome after RIC allo-HSCT. Cumulative incidence of transplant-related mortality in the study population (A), EBV reactivation in the study population (B), overall survival in the study population (C), overall survival according to EBV reactivation (dashed line: with EBV reactivation) (D), cumulative incidence of transplant-related mortality according to EBV reactivation (dashed line: with EBV reactivation) (E), and cumulative incidence of EBV reactivation according to the use of ATG as part of the RIC regimen (dashed line: with ATG) (F). x-axis: months post allo-HSCT.

Conclusions

In all, we conclude that patients undergoing RIC allo-HSCT using ATG as part of the preparative regimen are at higher risk for EBV reactivation. However, this did not translate into a significant impact on outcome since monitoring of EBV viral load with quantitative PCR and early systematic pre-emptive rituximab therapy allowed for significantly reducing the risk of EBV-related LPD.

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