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Serological Status of Epstein-Barr Virus in Bone Marrow Donor and Recipient and its Impact on Post-Transplant Outcomes

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ABSTRACT

The Epstein-Barr Virus (EBV) is a highly immunogenic herpesvirus that infects more than 90% of healthy individuals and can remain latent in B lymphocytes for years. In this context, in immunocompromised patients, such as those undergoing Bone Marrow Transplantation (BMT), viral reactivation can occur in up to 63% of cases. Among the main risk factors for viral reactivation are donor-recipient incompatibility, EBV IgG-positive donors, and conditioning regimens using lymphodepleting drugs such as anti-thymocyte immunoglobulin, high-dose cyclophosphamide, and corticosteroids. Therefore, weekly EBV monitoring is recommended during the first 100 days post-transplant to detect viremia early and enable preemptive intervention, either by reducing immunosuppression or using anti-CD20 monoclonal antibodies. These strategies aim to reduce viremia progression and the incidence of Post-Transplant Lymphoproliferative Disease (PTLD). This study seeks to estimate the serological profile of bone marrow donors and recipients and its relationship with the incidence of post-BMT viral reactivation. Additionally, it aims to evaluate monitoring and preemptive treatment strategies for managing high-risk patients at the Walter Cantídio University Hospital from 2020 to 2024, while also defining the incidence of PTLD secondary to BMT.

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Introduction

The Epstein-Barr virus is a highly immunogenic herpesvirus that infects more than 90% of healthy individuals [1]. It is generally associated with asymptomatic infections; however, this virus can remain latent in B lymphocytes for many years. In immunocompromised patients, such as those undergoing Bone Marrow Transplantation (BMT), viral reactivation may occur [2].

The incidence of post-transplant reactivation can reach 63% [2]. The most well-known risk factors for EBV reactivation include a high degree of HLA incompatibility, conditioning regimens using anti-thymocyte immunoglobulin, post-transplant cyclophosphamide (CyPost) at 50 mg/kg, alemtuzumab, the intensity and duration of immunosuppression used for Graft-Versus-Host Disease (GVHD) prophylaxis or treatment, and EBV-positive donors with EBV-negative recipients [3,4].

Recent guidelines recommend routine EBV monitoring via polymerase chain reaction (PCR) in high-risk patients [5]. especially within the first 100 days post-transplant, as this is the most common period for EBV reactivation [6,7].

In the absence of specific antiviral medications for EBV, strict monitoring and preemptive treatment are effective strategies for reducing EBV-associated morbidity and mortality, as well as the incidence of PTLD post-BMT. Weekly PCR monitoring of EBV in peripheral blood is recommended for these patients.[1] However, there is still no standardization regarding the exact EBV viral load threshold required to initiate preemptive treatment, and therapeutic strategies are highly heterogeneous, often based on the experience of each transplant center [8].

To prevent EBV viremia progression to PTLD, some transplant centers use an intervention threshold of 1,000–5,000 copies of EBV/mL of plasma, typically beginning with immunosuppression reduction whenever possible. Rituximab, an anti-CD20 monoclonal antibody, is frequently administered at a dose of 375 mg/m² once weekly for four weeks in selected cases until EBV negativity is achieved [8].

It is important to note that EBV reactivation can present as an isolated febrile episode, asymptomatic lymphadenopathy, and, in rare cases, the development of Post-Transplant Lymphoproliferative Disease (PTLD) [9]. The incidence of PTLD post-BMT is approximately 2% and usually occurs within the first six months after transplantation.[4] It's a severe and life-threatening condition with a mortality rate of up to 84% in the absence of treatment [10].

Thus, this study seeks to estimate the serological profile of bone marrow donors and recipients and its relationship with the incidence of post-BMT viral reactivation. Additionally, it aims to assess monitoring and preemptive treatment strategies and their effectiveness in managing high-risk patients at Walter Cantídio University Hospital from 2020 to 2024, while also defining the incidence of PTLD secondary to BMT.

This study aims to estimate the serological profile of Epstein-Barr virus in bone marrow donors and recipients pre-transplant and its impact on post-transplant viral reactivation, as well as define monitoring strategies and treatment indication criteria. Additionally, it seeks to identify risk factors for reactivation and the incidence of PTLD post-BMT during this period.

Materials and Methods

This is a retrospective, observational, descriptive study evaluating the serological profile of Epstein-Barr virus in bone marrow donors and recipients and its impact on post-transplant viral reactivation between January 2020 and December 2024 in the bone marrow transplant unit at Walter Cantídio University Hospital (HUWC-UFC).

Data collection was conducted via medical record review using, either in handwritten or digital form, and through the RedCap platform. The data will be published in aggregate form, with data confidentiality being a potential study risk.

In this study, EBV reactivation was defined as a PCR EBV viral load exceeding 1,000 copies. Data were analyzed using descriptive statistics, and categorical variables were compared using the chi-square test, while continuous variables were compared using the Mann-Whitney test. Statistical analysis was performed using the R platform. The project was approved by the Research Ethics Committee (CEP-HUWC) under approval number 7.315.669.

Results

A total of 131 patients who underwent allogeneic bone marrow transplantation at Walter Cantídio University Hospital between January 2020 and December 2024 were analyzed for Epstein-Barr virus reactivation. Patients undergoing unrelated, haploidentical, or related transplants with risk factors were monitored biweekly using PCR-EBV until 100 days post-transplant or until the discontinuation of immunosuppressive therapy. In this study, EBV reactivation was defined as a PCR EBV viral load exceeding 1,000 copies.

The mean time to post-BMT reactivation was approximately 88 days, with a median of 120 days. When separated into groups, the median reactivation time for untreated patients was 48 days compared to 115 days in patients who did not require treatment. Although not statistically significant (p=0.11), this data suggests that early positivity may resolve in some cases without targeted treatment.

Donor type analysis showed that 78 patients underwent transplants with a matched related donor, 31 with an Unrelated Donor (URD), and 22 with a haploidentical donor. Among the 131 patients, 49 (37.4%) experienced EBV reactivation at some point post-transplant, with 21 (42.8%) in the matched related donor group, 20 (40.8%) in the URD group, and 8 (16.3%) in the haploidentical group.

Univariate analysis by donor type showed reactivation rates of 64% in URD, 36% in haploidentical, and 26% in matched related donors, confirming a higher incidence of reactivation in unrelated and haploidentical transplants.

Pre-transplant donor and recipient serology was a significant risk factor for reactivation, with 96% of donors and 94% of recipients testing positive.

No cases of PTLD were observed in this study period at this transplant center.

Discussion

In this retrospective study, 131 patients were evaluated regarding EBV reactivation post-HSCT and associated risk factors. In the univariate analysis, the use of lymphodepletion, particularly with ATG, significantly impacted the higher incidence of viral reactivation (p=0.0005, OR 3.7). Historically, the use of ATG, PTCY, and alemtuzumab has been widely associated with an increased incidence of viral reactivations, making this result consistent with other studies [6].

Additionally, patients undergoing systemic immunosuppression for GVHD treatment also showed a significant increase in EBV PCR reactivations (p=0.01, OR=2.5), as corticosteroids—the cornerstone of GVHD treatment—are highly lymphodepleting medications, often combined with other immunosuppressive agents such as calcineurin inhibitors, further enhancing their immunosuppressive effect.

Patients with unrelated (64%) and haploidentical donors (36%) had a higher incidence of reactivation (p=0.0012) compared to related donors (26%), which can also be explained by the more intense lymphodepletion performed in these transplant conditioning regimens. Among these patients, 35% of unrelated donor transplants, 33% of related donor transplants, and 25% of haploidentical transplants required rituximab therapy.

When analyzing the 21 patients with related donors who experienced EBV reactivation, 12 had GVHD, and 7 underwent conditioning with ATG for aplastic anemia; only 2 of the 21 patients had no identifiable risk factors and did not require treatment.

Among the 49 patients who experienced EBV reactivation, 6 (12.2%) had more than one reactivation during the study period. Five had undergone conditioning with ATG, and three were on immunosuppression for GVHD. Of these six patients, 50% received preemptive treatment and subsequently achieved viral load negativity.

The conditioning protocol for unrelated donor transplants at this center includes ATG as GVHD prophylaxis, which may explain the higher reactivation rates and treatment needs observed in this type of transplant.

It is important to emphasize that rituximab indication was guided by increasing viral load in patients without prospects of immunosuppression tapering or with late reactivations—i.e., no specific cutoff was defined for treatment initiation. Nevertheless, all treated patients achieved viral load negativity following preemptive treatment, an approach that is effective in approximately 90% of EBV reactivation cases [2]. Moreover, untreated patients also achieved viral load negativity during follow-up.

The median reactivation time in treated patients was 115 days, compared to 48 days in untreated patients (p=0.11). Although not statistically significant, this data suggests that early positivity

tends to resolve with immunosuppression tapering alone, as seen in these cases, without requiring targeted treatment. Additionally, the lack of statistical significance may be due to the small sample size with high standard deviation.

Pre-transplant serological status of both donor and recipient is considered the main risk factor for reactivation and PTLD (RR up to 75), particularly when the donor is positive, and the recipient is negative [5,11]. In this study, 94% of recipients and 96% of donors had positive pre-transplant serology. As a result, it was not possible to establish a correlation between serological status and reactivation incidence, but the positivity in over 90% of cases could itself be considered a risk factor for higher reactivation rates in this population.

The use of ATG, haploidentical transplants, and the presence of GVHD are independent risk factors for viral reactivation that, when combined, can further amplify this risk [2,6]. These findings are consistent with this study's results. A meta-analysis published in 2023 also highlighted that PTCY, compared to ATG, was less associated with reactivation and PTLD [7,12].

Monitoring viral load is a crucial strategy and should be performed for at least the first 100 days post-transplant for the follow-up of these high-risk patients, enabling preemptive treatment and improved outcomes by reducing PTLD incidence after HSCT [13]. However, there is still no consensus on the exact viral load threshold for guiding treatment, meaning it should not be the sole criterion for therapeutic decision-making [7,8,12].

In conclusion, EBV PCR reactivation post-HSCT is common, occurring in up to 60% of cases within six months [8]. High-risk patients should be routinely monitored, as preemptive treatment is a safe and effective strategy for reducing PTLD incidence, as evidenced by the absence of PTLD cases in this center over the past four years. Treatment decisions based solely on viremia levels are not ideal and may lead to indiscriminate use of rituximab without clear benefits, given that many patients achieve spontaneous viral clearance, especially those undergoing immunosuppression tapering and with early reactivations.

Table 1: Correlation between the Number of Reactivations and Donor Type

DONOR TYPE	PATIENTS(n)	REACTIVATIONS (n)	%
Related	78 (59,5%)	21	26,92%
Unrelated	31 (23,6%)	20	64,52%
Haploidentical	22 (16,7%)	8	36,36%
Total	n= 131	49 (37,4%)	p = 0,0012

Table 2: Presence of GVHD, use of Lymphodepletion and EBV Reactivation

LYMPHODEPLETION	PATIENTS (n)	REACTIVATIONS (n)	%	Chi-sq
No Lymphodepletion	66 (50,4%)	15	22,73%	p = 0,0005
Lymphodepletion	65 (49,6%)	34	52,31%	OR = 3,729
• ATG	39	26	66,67%	
• PTCY	26	8	30,77%	
GVHD				
Yes	49 (37,4%)	25	51,02%	p = 0,0128
No	82 (62,6%)	24	29,27%	OR = 2,517

Table 3: Number of Reactivations Versus Treatment Requirement

TREATMENT	Patients (n)	%
Yes	16 (32,6%)	% of reactivations needing treatment
• Unrelated	7/20	35,00%
• Haploidentical	2/8	25,00%
• Related	7/21	33,33%

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