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CONFRONTING DIAGNOSTIC AND THERAPEUTIC CHALLENGES IN VIRAL REACTIVATION AFTER ALLOGENEIC TRANSPLANTATION: EXPERIENCE OF A BRAZILIAN PUBLIC CENTER

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ABSTRACT

BACKGROUND. Despite recent advances of allogeneic hematopoietic stem cell transplantation (HSCT), viral infections are still a significant complication and remain a frequent cause of morbidity.

OBJECTIVE. To evaluate the profile of viral infection in patients undergoing HSCT in a Brazilian reference hospital.

STUDY DESIGN. This is a retrospective, descriptive, analytical and quantitative study. Allogeneic transplants performed in the last 5 years, in patients aged 16 years or older, were analyzed.

RESULTS. A total of 117 allo-HCT recipients were included. Of these, 50.43% were women and 49.57% were men, with a median age of 36 years. Acute myeloid leukemia was the most frequent underlying disease (27,35%). 88,33% of the patients had some virus detected (in any value) during the post-BMT period. There was a prevalence of viral reactivation in haploidenticals, with 90.91% of detection. CMV reactivation was the most frequent. We found a prevalence of CMV infection after allo-HSCT (70.94%) with 62 patients (52.99%) above the cut-off of 1,000 IU/mL and 21 (17.95%) below this value. EBV was the second virus with the highest reactivation rate.

CONCLUSIONS. CMV remains in the first place among viral reactivations. CMV and EBV were predominant in unrelated transplants, while BKV and HHV6 predominated in haploidentical.

Keywords. Hematopoietic Stem Cell Transplantation. Transplantation, Homologous. Virus Activation.

BACKGROUND

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative therapy for numerous hematological diseases. Conditioning regimens used to reduce the risk of allograft rejection increase considerably the risk of viral infections.[1] As consequence, viral infections remain a leading cause of morbidity and mortality after transplant, including DNA viruses such as cytomegalovirus (CMV), BK polyomavirus (BKV), Epstein Barr virus (EBV) and human herpesvirus-6 (HHV-6).[2]

Effective screening and early preemptive therapy are essential for minimizing unfavorable outcomes, however they still represent a challenge in several Brazilian transplant centers, especially in the public health system. Part of this challenge is to draw the

reactivation profile of each region, as it can vary intensely, according to access to appropriate screening methods, GVHD incidence, and standardized types of conditioning, prophylaxis and immunosuppression in each center.

Current literature lacks clinical-epidemiological studies with cohorts of Brazilian population, especially northeastern, which has socioeconomic peculiarities reflected in unequal access to infrastructure and health services. Therefore, the key force of the present study was to draw a viral reactivation profile in a public transplant center, in order to guide our screening and treatment preemptive strategies. We also hope to encourage other northeastern centers to do the same.

METHODS

We retrospectively analyzed patients who underwent a allogeneic HSCT from January 2017 through December 2021 at the Walter Cantídio University Hospital, Fortaleza, Brazil. The minimum age was 16 years. Only patients with at least 100 days of follow-up were included, unless the reason of death was our endpoint. Second allogeneic transplants were also included, but no patient underwent both within the study period.

The local ethics committee approved the study protocol and the analyses were based on medical records and tests results only, with anonymity guaranteed for patients. Data were anonymized before analysis. Demographics, transplant characteristics, and viral events are presented as absolute numbers, percentages or medians and range, according to the type of transplant.

Conditioning regimens varied according to the indication for transplantation and the donor type. Patients diagnosed with aplastic anemia received anti-thymocyte globulin. Most patients received GVHD prophylaxis with cyclosporine combined with methotrexate or cyclophosphamide.

Before starting the conditioning regimen, all patients underwent serology for HIV, hepatitis virus, syphilis, chagas disease, toxoplasmosis, HTLV, CMV, and EBV. Conditioning regimens varied according to the indication for transplantation and the donor type. All patients received standard prophylaxis with trimethoprim-sulfamethoxazole, acyclovir and antifungal (fluconazole, micafungin or voriconazole).

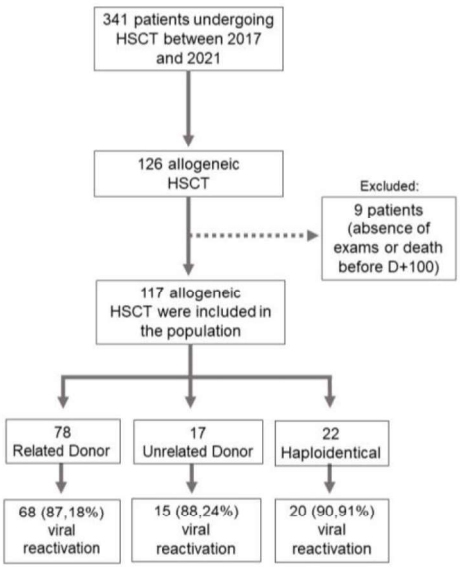
Reactivation was monitored weekly, by real-time quantitative PCR in plasma (for CMV, EBV and HHV-6) and in urine (for BKV). Viral reactivation was defined by detection of virus by PCR technique. Time to reactivation was calculated from the day of transplantation until the date of detectable PCR. The diagnosis of CMV infection was established by the detection of a viral load >1.000 UI/mL. The cut-off is not consensual in the literature and diversify among transplantation centers and according to the laboratory technique used. Recurrent CMV infection was defined as new CMV infection in a patient with previous evidence of CMV infection without the virus detected for 4 weeks during active surveillance.

Patients were treated preemptively for CMV and EBV. In the case of CMV infection, ganciclovir was the first-line therapy. Valganciclovir, Letermovir and Foscarnet are currently unavailability in the Brazilian Public Health System. In EBV infection, rituximab treatment was initiated. Preemptive treatment was performed for patients above the cut-off and individualized according to the assessment of risk factors, type of transplant, presence of GVHD and immunosuppression for those below the cut-off.

RESULTS AND DISCUSSION

Between January 2017 and December 2021, 341 patients underwent HSCT at the Walter Cantídio University Hospital. Of these, 126 were allogeneic. Nine patients (5 related and 4 unrelated) were excluded due to lack of viral screening records or death before D+100. A total of 117 allo-HCT recipients were included in the final study cohort, as detailed in figure 1.

FIGURE 1. Flow chart of patients included in the study.



The patients age at the time of transplant ranged from 17 to 70 years (median = 36 years) and was similar in all groups. 50.43% were women and 49.57% were men. Baseline clinical features are presented in Table 1.

Acute myeloid leukemia was the most frequent underlying disease (27,35%), followed by Acute Lymphoblastic Leukemia (23,93%), Aplastic Anemia (16,24%), Chronic Myeloid Leukemia (10,26%) and Myelodysplasia (8,55%). Other diagnoses represented 13,67% of patients.

Myeloablative conditioning was the most utilized (82,91%; n=97). Graft source was peripheral blood (83,76%; n=98) or bone marrow (16,24%; n=19). No patient underwent cord blood transplantation.

Studies find that 90% of alloHCT recipients have at least 1 DNA virus infection.[1]

TABLE 1. Overall demographics and clinical characteristics of patients undergoing Allogeneic Stem Cell Transplantation.

Characteristic	Total (n=117)	Haploidentical (n=22)	Unrelated Donor (n=17)	Related Donor (n=78)
Patient's Age (years)	36	36	36	36
Median				
Range	(16-70)	(17-64)	(17-58)	(17-70)
Donor's Age (median, in years)	35	35	35	35
Sex of patient	58 (49,47%)	12 (54,55%)	8 (47%)	38 (48,72%)
Male				
Female	59 (50,43%)	10 (45,45%)	9 (53%)	40 (51,28%)
Diagnosis				
Acute myeloid leukemia	32 (27,35%)	9 (40,91%)	1 (5,88%)	22 (28,21%)
Acute lymphocytic leukemia	28 (23,93%)	6 (27,27%)	8 (47,06%)	14 (17,95%)
Myelodysplastic syndrome	10 (8,55%)	1 (4,55%)	3 (17,65%)	6 (7,69%)
Aplastic anemia	19 (16,24%)	2 (9,09%)	1 (5,88%)	16 (20,51%)
Chronic myeloid leukemia	12 (10,26%)	2 (9,09%)	3 (17,65%)	7 (8,97%)
Other disease	16 (13,67%)	2 (9,09%)	1 (5,88%)	13 (16,67%)
ABO compatibility				
Major ABO Incompatibility	17 (14,53%)	3 (13,64%)	4 (23,53%)	10 (12,82%)
Minor ABO Incompatibility	20 (17,1%)	4 (18,18%)	3 (17,65%)	13 (16,67%)
Bidirectional	3 (2,56%)	0	2 (11,76%)	1 (1,28%)
Isogroup	77 (65,81)	15 (68,18%)	8 (47,06%)	54 (69,23%)

Our findings are consistent with those reported, with some virus being detected in 88,33% of the population, equivalent to 103 patients. These numbers correspond to 68 related donor (87.18%), 15 unrelated donor (88.24%) and 20 haploidentical (90.91%) transplantations. The distribution pattern of viral reactivations is specified in Table 2.

TABLE 2. Distribution of viral reactivation by type of HSCT

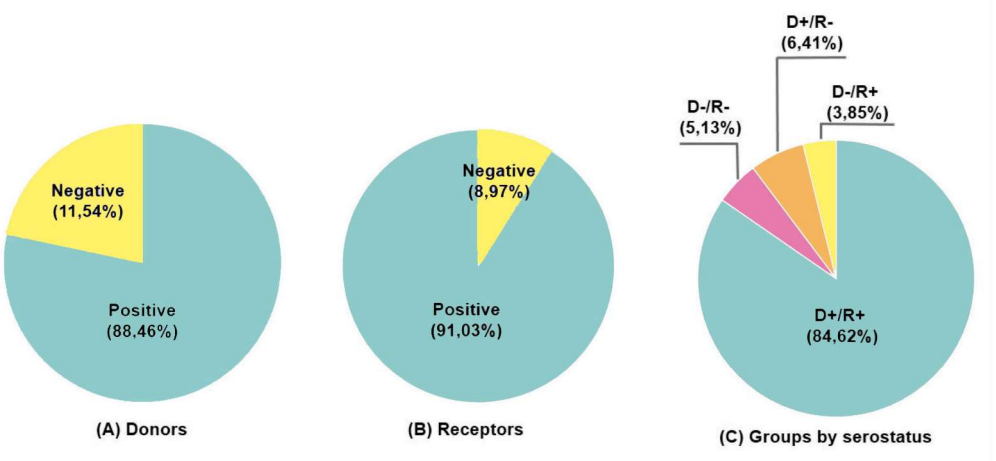
Type of HSCT	CMV (117 tested)			EBV (90 tested)			BKV (64 tested)		HHV6 (58 tested)	
	Indetectable	Detectable		Indetectable	Detectable		Indetectable	Detectable	Indetectable	Detectable
		<1000 UI/mL	>1000 UI/mL		<1000 UI/mL	>1000 UI/mL				
Allogeneic HSCT	34 (29,06%)	21 (17,95%)	62 (52,99%)	30 (33,33%)	24 (26,67%)	36 (40%)	39 (60,94%)	25 (39,06%)	34 (58,62%)	24 (41,38%)
Related Donor	26 (33,33%)	12 (15,38%)	40 (51,28%)	21 (41,18%)	16 (31,37%)	14 (27,45%)	26 (74,29%)	9 (25,71%)	23 (71,43%)	11 (28,57%)
Unrelated Donor	4 (23,53%)	3 (17,65%)	10 (58,82%)	2 (11,76%)	3 (17,65%)	12 (70,59%)	6 (50%)	6 (50%)	6 (66,67%)	3 (33,33%)
Haploidentical	4 (18,18%)	6 (27,27%)	12 (54,55%)	7 (31,82%)	5 (22,73%)	10 (45,45%)	7 (41,18%)	10 (58,82%)	5 (33,33%)	10 (66,67%)

A substantial proportion of patients (67.52%) reactivated more than one virus during follow-up, respectively: 50.43% with 2 viruses (the most frequent association was between CMV and EBV, with 40.17% of cases), 10.24% with 3 viruses and 6.84% with 4 viruses. It is reported that multiviral infections are frequently encountered. The number of post-HSCT patients with more than one virus is described in the literature as 60%, which is similar to our study, and numerous studies have demonstrated a dose-response relationship between the cumulative burden of virus exposure and mortality.[1]

CMV reactivation remains one of the most common infectious complications after allogeneic HSCT.[3] This was maintained in our study. Consistent with literature, we found a prevalence of CMV infection after allo-HSCT (70.94%) with 62 patients (52.99%) above the cut-off of 1,000 IU/mL and 21 (17.95%) below this value. A similarly high incidence of CMV infection was reported by Diaz and collaborators, who describe a total of 59%.[4] That is also consistent with previous literature, that fluctuate between 34% and 90% of incidence. This wide range is attributable to diversity of populational pre transplant CMV serostatus and laboratory techniques used in the diagnosis. A report from Latin America showed an incidence of 69%.[4,5] Other factors may influence this incidence. Goldsmith and collaborators published a CIBMTR analysis whose findings strongly suggest that PTCy contributes significantly to the development of CMV infection, regardless of donor source.[6]

Recipient and donor serologic status is a critical risk factor for CMV infection and disease.[2] Therefore, knowing the serological profile of the transplant center is essential to plan screening strategies. An overall CMV seroprevalence of 83% is estimated in the general population, varying among nationalities, with 90% in the Eastern Mediterranean region and 66% in the European region.[7] In Brazil, seroprevalence is historically high. Data from the Brazilian registry of SBTMO/CIBMTR evaluating 5697 patients between 2008 and 2021 demonstrate 78% positivity among recipients and 88% among donors.[8] In our population, 88.46% of donors and 91.03% of recipients had positive pre-transplantation serology for CMV. The relatively smaller *n* in our study may explain this lower proportion of seroprevalence compared to the national.

FIGURE 2. Subdivision based on the serological status of the donor (A), recipient (B), and their relationship (C).



CMV infection usually occurs within the first 100 days, related to an immunosuppressed state.[4] In particular, we found that time to CMV reactivation ranged from 11 to 182 days (median = 32); duration of DNAemia ranged from 7 to 70 days (median = 14); viral load at reactivation ranged from 1.037 to 32.250 UI/mL (median 2.644) and maximal viral load ranged from <500 to 114.177 UI/mL (median 3.066). Recurrent CMV infection range 1 from 5 episodes per patient (median 1).

High initial viral load (>20.000 copies/mL) would be related with the likelihood of CMV disease, as does the presence of leukopenia (white blood cell count < 3.000/mL) at diagnosis.[9] When we consider each type of transplant separately, our data suggest that the unrelated and haploidentical transplantations reactivate slightly earlier and present more recurrence, longer duration of viremia and higher viral loads (initial and maximum). Table 3 exposes these findings.

TABLE 3. CMV reactivation characteristics by transplantation type

CMV features	Total	Related Donor	Unrelated Donor	Haploidentical
Viremia Frequency Median (in number of episodes) Range	 1 (1-5)	 1 (1-4)	 1 (1-4)	 2 (1-5)
Reactivation date Median (in days post HSCT) Range	 32 (11-182)	 34 (15-182)	 32 (13-59)	 32 (11-42)
Duration of viremia Median (in days) Range	 14 (7-70)	 14 (7-49)	 18 (7-70)	 21 (7-70)
Viral load at reactivation Median (in UI/mL) Range	 2.644 (1.037 - 32.250)	 2.429 (1.037 - 13.369)	 3.490 (1.049 - 32.205)	 2.684 (1.202 - 10.112)
Largest viral load Median (in UI/mL) Range	 3.066 (<500 - 114.177)	 3.030 (<500 - 114.177)	 3.486 (<500 - 105.582)	 3.486 (<500 - 10.112)

Preemptive therapy based on CMV viremia has become the standard prevention of CMV diseases after transplantation.[14] The first line used for the treatment of CMV reactivation in our study was ganciclovir 5mg/kg intravenously every 12h, with a minimum duration of 2 weeks. Accordingly Chan and Logan[9], when treated with pre-emptive antiviral therapies, <5% of cases with CMV reactivation progress to CMV disease. In our study, 20.97% of patients had viremia above the cutoff point after the second week of treatment. In the Literature, this occurs in half (50.6%) of patients experiencing CMV viremia, and is associated with increased risk for CMV disease and treatment-related mortality when it occurs within the first 100 days. In this setting, the toxicities of prolonged treatment may contribute to myelosuppression and renal impairment.[9]

Accordingly Wei et al[10], the infection EBV rate exceeds 90% worldwide. Regarding the pre-transplant serological status, the profile of our population is 96.1% positivity for recipients and 97.4% for donors. Reactivation is a common complication post alloHSCT, which has increased significantly with the development of haploid, unrelated donor transplantation, and the application of antithymocyte globulin (ATG) in pretreatment. The reported incidence post HSCT ranges from 0.1 to 63% according to different GVHD prevention, conditioning regimens and monitoring techniques.[10]

Ru and collaborators conducted a retrospective study that enrolled 890 allo-HCT recipients. Independent risk factors for EBV reactivation were use of ATG, haploidentical donor, and the presence of chronic GVHD. The cumulative incidence of EBV reactivation for patients with 0, 1, 2, and 3 risk factors was 2.9%, 11.7%, 27.3%, and 41.9%, respectively.[11]

These findings are consistent with our study: EBV was the second virus with the highest reactivation rate (40% of patients had more than 1.000UI/mL), as described in table 2. Thirty-four (29.06%) patients used ATG. Of these, 29 (85.29%) reactivated some virus and 14 (56%) reactivated EBV.

Kerbauy et al[2] observed higher rates of EBV reactivation in the UD group in comparison with haploidentical, and occurring earlier in UD. In our results, EBV reactivation was predominant in patients undergoing unrelated HSCT, followed by haploidentical patients. The median time reactivation was 48 days (ranging from 15-159), but 12 patients had later reactivation (after D+180). Unrelated HSCT reactivated earlier and had higher viral loads. Table 4 details the characteristics of EBV reactivation.

TABLE 4. EBV reactivation characteristics by transplantation type.

EBV features	Total	Related Donor	Unrelated Donor	Haploidentical
Reactivation date (until D+180 follow up) Median (in days post HSCT) Range	48 (15-159)	48 (15-159)	38 (21-126)	42 (20-127)
Viral load at reactivation Median (in UI/mL) Range	7.220 (1.060 - 1.078.290)	6.913 (1.060 – 1.078.290)	10.520 (1.270 – 108.301)	2.973 (1.669 - 79.124)
Largest viral load Median (in UI/mL) Range	7.373 (1.060 – 108.301)	7.391 (1.060 – 1.078.290)	10.520 (5.459 – 108.301)	5.972 (1.669 – 79.124)
Reactivations after d+180 (in nº of cases)	12	9	2	1

After HSCT, loss of immune surveillance promotes opportunistic growth of EBV-infected cells, causing EBV reactivation, which can progress to post-transplant lymphoproliferative disorder (PTLD).[12] Therefore, adequate screening and preventive treatment is essential to prevent this feared condition. At our transplant center, preemptive treatment with rituximab was given according to EBV-DNAemia, risk factors and clinical assessment of each patient.

Reactivation of HHV-6 is common after HSCT, especially cord blood transplantation. Like other herpesviruses, HHV-6 establishes chronic latency, and its reactivation can cause a range of central nervous system symptoms, like post-transplant acute limbic encephalitis-PALE, in severely immunocompromised hosts.[13,19] In our cohort, HHV6 had a general detection rate of 41.38% among allogenes, predominantly haploidentical and unrelated (66.67% and 33.33%, respectively), as shown in Table 2. This is consistent with reported in the studies: approximately 30% to 50% of recipients with HHV-6 reactivation after transplantation.[13,14,15] It was the virus with the earliest reactivation (median of 26 days; ranging from 11 to 98). No sample of cerebrospinal fluid was positive in the studied population.

BK polyomavirus infection results in significant morbidity in post TCTH, mainly due to hemorrhagic cystitis. This complication can occur early, after conditioning, or later, approximately from the tenth day to six months after HSCT. The consequences can be tubulointerstitial nephritis and even renal failure.[16] Studies evaluating a BKV viral load cut-off for the development of hemorrhagic cystitis suggest the value above 10^7 copies/mL in urine.[17] Second ECIL guidelines for BK polyomavirus, the observed incidence of BKV is 8%–25% and 7%–54% in paediatric and adult patients, respectively, being higher after allogeneic than after autologous HSCT and particularly after haploidentical HSCT with post-transplant exposure to cyclophosphamide as prophylaxis for graft versus host disease (GVHD).[18] In our study, similarly, BKV reactivation was found in 39.06% of patients, with a predominance of haploidentical patients, followed by unrelated patients. Median reactivation was 45 days. The median of the highest viral load was 2.166.085, with a predominance of unrelated (median 36.048.373) and haploidentical (median 2.166.085).

CONCLUSION

Allogeneic HSCT is associated with substantial rates of viral reactivation resulting in the need for prolonged antiviral therapy and considerable morbidity as well. Optimal management of viral infections is a essencial objective in every HSCT strategy in order to limit virus-related morbidity and mortality. Therefore, strategies to prevent viral infection are strongly warranted.

In our study, CMV remains in the first place among viral reactivations. CMV and EBV were predominant in unrelated transplants, while BKV and HHV6 predominated in haploidentical. The earliest reactivation was HHV6, with a median of 26 days.

There are limitations to our study related to retrospective characteristic and difficult to access the information collected in the medical records.

Despite access and infrastructure challenges of the public health system, it is possible to develop adequate screening and timely preemptive treatment in the alogenic transplantation.

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