Long-term follow-up of human herpesvirus 6 infection in autologous bone marrow transplant recipients

While in allogeneic bone marrow transplantation human herpes virus 6 (HHV-6) has been correlated with severe clinical manifestations, the role of this virus in autologous bone marrow transplantation (ABMT) is not yet well known. The aim of this study was to investigate possible active HHV-6 infection during the post-ABMT period and to evaluate whether there were correlations with clinical manifestations.

Seroepidemiologic surveys show that HHV-6 is ubiquitous throughout the world; infection is generally contracted in infancy, and can reactivate in conditions of immunosuppression.[1,2]

The present study updates and extends a preliminary report on HHV-6 infection in a group of ABMT recipients, followed-up for only 6 months.[3] We extended the number of patients from 23 to 28, four of whom were tested again for HHV-6 DNA in peripheral blood mononuclear cells (PBMC) 1 year after ABMT since recent reports suggested that late graft failure may be caused by HHV-6 infection.[4]

Twenty-eight consecutive patients undergoing ABMT were evaluated for HHV-6 DNA in PBMC and plasma specimens and underwent serologic tests.[3] Two of them received a double ABMT.

Clinical events possibly correlated with active HHV-6 infection were carefully evaluated during the follow-up period.[5-8]

HHV-6 was evaluated before starting the conditioning regimen (time 0) and 7, 14, 30, 45, 60, and 180 days after the peripheral blood stem cell (PBSC) reinfusion. In the cases positive at 180 days, investigations for the virus were repeated 6 months later.

HHV-6 DNA was not detected in the PBMC of 19 of the 28 (67.8%) ABMT recipients. The remaining 9 patients (32.2%) showed intermittent (6 patients) or persistent (3 patients) positivity for HHV-6 DNA, as illustrated in Table 1. Before their transplant, 2 patients were positive for HHV-6 cellular DNA, while the remaining positive ABMT recipients developed positivity at different times. All the samples of each positive patient tested also for HHV-6 DNA in plasma, were negative. All the 10 healthy controls were negative.

Six of the 9 positive PBMC patients carried variant B of HHV-6, while the other 3 positive patients carried both variants A and B. The 4 patient samples evaluated at day 360 remained positive for HHV-6 DNA in PBMC and negative in the respective plasma specimens.

Only 2 patients were positive for anti-HHV-6 antibodies, one from day 90 to 360 and one from day 0 to 45. Neither had HHV-6 DNA in PBMC. All control samples were negative for HHV-6 antibodies.

Fever was the only early symptom that occurred in the majority of cases (26/30), and was attributed to an infection in 14 cases (11 sepsis and 3 clinically documented infections), while in 12 the fever was of unknown origin (FUO). In one single case, fever was associated with a skin rash apparently caused by allopurinol since it disappeared once administration of this drug was stopped. During this period 6 of the 30 cases were intermittently positive for viral DNA in PBMC, and 2 of them were already positive at the beginning of the study (time 0). No clinical symptoms occurred in three of these 6 cases, while one case had sepsis and two had FUO. Only in these last two cases might the fever have been related to HHV-6 infection, but the absence of viral DNA in plasma does not allow it to be stated with certainty that there was an active infection.

No late clinical symptoms were described. There was a moderate increase of serum ALT in three cases simultaneously positive for HHV-6 in PBMC. HHV-6 DNA was possibly related to this increase in ALT because none of the patients was infected by other hepatotropic viruses. The late and low increase of the serum ALT also rules out hepatic toxicity due to conditioning therapy. In these three cases, the presence of HHV-6 DNA in PBMC was observed at +30, +45, and +90 days. In all cases, the serum ALT normalized at +120 days, while HHV-6 DNA positivity persisted in two cases at +180 and +360 days.

The increase of the serum ALT and the contemporary presence of HHV-6 DNA in PBMC could indicate a possible reactivation of HHV-6 because viral cellular DNA had never been found in PBMC of these patients before. However, although the presence of HHV-6 DNA in PBMC demonstrates an increase of the viral load, the negative finding in plasma samples does not confirm an active viral infection.[9]

The presence of HHV-6 DNA in PBMC even after a long-term follow-up (4 cases after 180 days) may be due to the mild immunosuppression, which could support an increased viral load without clinical signs.

Table 1. HHV-6 DNA positivity pattern in PBMC of ABMT recipients.

ABMT recipient number	Day 0	Day 7	Day 14	Day 30	Day 45	Day 60	Day 90	Day 180	Day 360
Patients with intermittent positivity									
1	+ (A,B)*	-	+ (A,B)	-	+ (A,B)	+ (A,B)	-	-	
3	+ (A,B)	+ (A,B)	-	+ (A,B)	-	-	nd	-	
5	-	-	+ (A,B)	-	+ (A,B)	-	-	+ (A,B)	+ (A,B)
6	-	nd	-	-	+(B)[a]	-	+ (B)	-	
7	-	+ (B)	-	-	-	-	+ (B)	-	
27	-	+ (B)	+ (B)	-	-	+ (B)	-	-	
Patients with persistent positivity									
11	-	-	-	-	-	+ (B)	+ (B)	+ (B)	+ (B)
17	-	-	-	+ (B)	+ (B)	+ (B)	+ (B)	+ (B)	+ (B)
25	-	-	-	-	-	+ (B)	+ (B)	+ (B)	+ (B)

*(A, B) = sample positive for both A and B HHV-6 DNA variants. [a](B) = sample positive for B HHV-6 DNA variant

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Finally, our results confirm existing data reporting a very low occurrence of active HHV-6 infection in ABMT recipients (both early and late after the transplant)[10] possibly because of the transient and relatively weak immunosuppression induced in ABMT recipients. Thus, our data do not suggest systematic HHV-6 infection monitoring is necessary in ABMT, except in the case of symptoms possibly correlated to HHV-6.

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