Human herpesvirus-6 DNAemia in immunosuppressed adult patients with leukemia at risk for mold infection

Little is known about human herpesvirus-6 (HHV-6) in leukemia patients. We prospectively followed 37 leukemia patients at risk for mold infection. HHV-6 DNA was detected from whole blood specimens in 11 patients (30%). History of granulocyte transfusions (p=0.05) and prior relapse of leukemia (p=0.07) were the only independent predictors of HHV-6 DNAemia.

Haematologica. 2008 Jan; 93:(1)157-158. DOI: 10.3324/haematol.11638

Little is known about Human Herpesvirus-6 (HHV-6) infection in patients with leukemia.[1] We aimed to determine the frequency, risk factors, clinical characteristics, and outcome of HHV-6 DNAemia in adult patients with leukemia. We prospectively followed a cohort of leukemia patients seen at our institution (October 2002-March 2004) enrolled in a study assessing molecular diagnostic methods for *Aspergillus*, Cytomegalovirus (CMV), and HHV-6. Consecutive patients were enrolled if they were at risk for, or had a possible, probable, or proven invasive mold infection according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria.[2] Our institutional review board approved the study.

Whole blood specimens were examined for HHV-6 using real-time PCR. Sequences for HHV-6 dual-labeled probe and primers used in the study were as follows:

HHV6L: CGTTAATAAGCCAGC
HHV6U: TACATCCTAGCTCAGTCC
Probe: 5'FAM - TTGGTGCATCAGTTGAAGGCTGCCAT - 3'TAMARA.

Characteristics of patients with and without HHV-6 DNAemia were compared. The variables on univariate analysis with a p value <0.1 were entered into a multivariate unconditional logistic regression model. All statistical tests were 2-sided, and $p \leq 0.05$ were considered significant. The statistical analyses were performed using Epi Info (version 3.2.2.) software (Centers for Disease Control and Prevention, Atlanta, GA, USA) and SAS 9.1 statistical software (SAS Institute Inc., Cary, NC, USA).

Thirty-seven patients with leukemia were enrolled, with HHV-6 DNAemia detected in 11 of them (30%) *(Online Supplementary Table 1)*. Four of the 11 patients (36%) had received transfusions of irradiated granulocytes prior to the onset of HHV-6 DNAemia from donors whose granulocyte counts had been stimulated with hematopoietic growth factors and who had not been screened for HHV-6. The median number of granulocyte transfusions was 11 (range 3-16), with a median time from first granulocyte transfusion to onset of HHV-6 DNAemia of 44 days (range 2-117 days). HHV-6 infection was not suspected in any patient. Presentations at the first positive result for HHV-6 were mainly unexplained fever and lower respiratory infection *(Online Supplementary Table 2)*. Compared to the 26 patients without HHV-6 DNAemia, those with HHV-6 DNAemia were more likely to have diarrhea, and apparently a higher incidence of rash. Neurological symptoms were comparable between the two groups *(Online Supplementary Table 2)*.

By univariate analysis, HHV-6 DNAemia was significantly associated with a history of granulocyte transfusions, diarrhea and viral coinfections (CMV and respiratory viruses in 2 patients each), with a trend towards prior relapse of leukemia. By multivariate analysis, history of granulocyte transfusions (p=0.05) and prior relapse of leukemia (p=0.07) were the only independent factors associated with HHV-6 DNAemia (*Online Supplementary Table 2*). The mortality rate was comparable among patients with or without HHV-6 DNAemia *(Online Supplementary Table 2)*. Our study is the first to report the risk factors, clinical characteristics, and outcome of leukemia patients with HHV-6 DNAemia. Our results indicate that HHV-6 DNAemia can be observed in approximately one third of severely immunosuppressed leukemia patients. By comparison, HHV-6 infection/reactivation occurs in 48% (range 28-75%) of hematopoietic stem cell transplantation (HSCT) recipients.[3,4]

This report is the first that associates granulocyte transfusions with HHV-6 DNAemia in leukemia patients. Granulocyte transfusions have been more widely used in recent years as adjuvant therapy.[5] We found that more than one third of the patients with HHV-6 DNAemia had received such transfusions.

Granulocytes contributed to HHV-6 viral load in peripheral blood of patients,[6] suggesting that HHV-6 may replicate in these cells. Whether or not the use of unscreened granulocyte transfusions represents a source of HHV-6 must be determined in future studies. However, it seems reasonable that granulocyte transfusion products should be tested for HHV-6 by molecular methods. Prospective studies in healthy blood donors have identified HHV-6-DNA in antibody-negative individuals.[7]

Therefore, identification of the HHV-6 antibody may not be sufficient to identify potentially infectious donors.[7] On the other hand, among HSCT recipients, pre-transplantation HHV-6 serostatus does not tell us anything about the risk of developing HHV-6 infection post-transplant,[8] which may reflect a loss of specific anti-HHV-6 antibodies. In fact, some authors have suggested that the HHV-6 serostatus of the recipient does not allow differentiation of reactivation from primary infection, especially in the context of immunosuppression.[8] HHV-6 reactivation due to alloactivation or incidental HHV-6 genome integration has been previously described.[9] This phenomenon could have occurred following granulocyte transfusion, which may explain the detection of HHV6 DNA in our patients.

Two out of 11 patients in this series had persistent HHV-6 DNAemia, which is evidence of a limited duration of viral replication in the majority of high-risk leukemia patients. In our study, patients with HHV-6 DNAemia commonly presented with fever, diarrhea and rash mimicking primary HHV-6 infection in immunocompetent children.[10]

Our results need to be interpreted with caution as they only apply to a group of severely immunosuppressed patients with leukemia at risk for mold infection and may not apply to the general leukemia population.

To summarize, severely immunosuppressed leukemia patients with fever, respiratory symptomatology, rash, and/or diarrhea should be considered at risk

for HHV-6 DNAemia. In these patients, HHV-6 DNAemia appears to be associated with granulocyte transfusions and prior relapse of leukemia.

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The online version of this article contains a supplemental appendix.

Funding: supported by The University of Texas M.D. Anderson Cancer Center (RFC).

Redundant publication: presented in abstract form at the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Washington, DC, USA, December, 2005.

Key words: human herpesvirus-6, DNAemia, polymerase chain reaction, leukemia, granulocytes transfusion.

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References

1. Ma XT, Song YH, Lu DM, Mu GF, Li G, Ji LX, et al. Human herpesvirus 6 in hematologic diseases in China. Haematologica 2000;85:458-63.
2. Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002;34:7-14.
3. Wilborn F, Brinkmann V, Schmidt CA, Neipel F, Gelderblom H, Siegert W. Herpesvirus type 6 in patients undergoing bone marrow transplantation: serologic features and detection by polymerase chain reaction. Blood 1994; 83:3052-8.
4. Zerr DM, Corey L, Kim HW, Huang ML, Nguy L, Boeckh M. Clinical outcomes of human herpesvirus 6 reactivation after hematopoietic stem cell transplantation. Clin Infect Dis 2005;40:932-40.
5. Safdar A, Rodriguez GH, Lichtiger B, Dickey BF, Kontoyiannis DP, Freireich EJ, et al. Recombinant interferon γ1b immune enhancement in 20 patients with hematologic malignancies and systemic opportunistic infections treated with donor granulocyte transfusions. Cancer 2006; 106:2664-71.
6. Palleau S, Boutolleau D, Bonnafous P, Agut H, Gautheret-Dejean A. Polymorphonuclear leukocytes mainly contribute to human herpesvirus-6 load in the peripheral blood of patients. Clin Infect Dis 2006;42:1342-3.
7. Wilborn F, Schmidt CA, Zimmermann R, Brinkmann V, Neipel F, Siegert W. Detection of herpesvirus type 6 by polymerase chain reaction in blood donors: random tests and prospective longitudinal studies. Br J Haematol 1994; 88:187-92.
8. Imbert-Marcille BM, Tang XW, Lepelletier D, Besse B, Moreau P, Billaudel S, et al. Human herpesvirus 6 infection after autologous or allogeneic stem cell transplantation: a single-center prospective longitudinal study of 92 patients. Clin Infect Dis 2000;31:881-6.
9. Clark DA, Nacheva EP, Leong HN, Brazma D, Li YT, Tsao EH, et al. Transmission of integrated human herpesvirus 6 through stem cell transplantation: implications for laboratory diagnosis. J Infect Dis 2006;193:912-6.
10. Zerr DM, Meier AS, Selke SS, Frenkel LM, Huang ML, Wald A, et al. A population-based study of primary human herpesvirus 6 infection. N Engl J Med 2005; 352: 768-76.