The role of human herpesvirus 6 in delayed engraftment in stem cell transplant patients in China

We studied the relationship between human herpesvirus 6 (HHV-6) infection and delay in engraftment of stem cell transplantation (SCT) recipients. We found that active HHV-6 infection could occur in both autologous and allogeneic transplant recipients. Active HHV-6 infection in the early post-transplant period was not associated with delayed engraftment.

Human herpesvirus 6 (HHV-6) shares several molecular and biological properties with human cytomegalovirus (CMV),[1] which is known to increase morbidity and mortality after bone marrow transplantation. Several studies have shown that HHV-6 can be reactivated after transplantation,[2,3] most frequently in the third week, and is associated with the development of skin rash, fever, interstitial pneumonitis, and fatal encephalitis.[4] The association between HHV-6 infection and delay in engraftment remains controversial.[5-8] This study was aimed at assessing the role of HHV-6 in delayed engraftment in stem cell transplantation (SCT) recipients in China.

Twenty SCT patients entered this study. The cohort was limited to CMV DNA negative transplant patients so that the clinical manifestations of CMV infection would not confound interpretation of the HHV-6 data. The patients' characteristics, as regards age, sex, diagnosis, type of transplant and pretransplant regimen, are summarized in Table 1. Graft-versus-host disease (GVHD) prophylaxis for allogeneic transplant recipients consisted of cyclosporine and methotrexate. No T-lymphocyte depletion was performed. Bone marrow and blood samples were obtained from all the recipients one week before SCT and four weeks after SCT. Criteria for neutrophil and platelet engraftment have been described elsewhere.[5] HHV-6 infection was studied in recipients using the following methods: detection of HHV-6 DNA in bone marrow mononuclear cells (BMMC) by polymerase chain reaction (PCR);[7] evaluation of increased serologic response to HHV-6 using an indirect immunofluorescent assay (IFA)[8] and virus isolation[9] in BMMC after transplantation. Isolation of HHV-6 or a significant increase in HHV-6-specific antibody titers was considered as evidence of *active* HHV-6 infection. The role of active HHV-6 infection in delayed neutrophil and platelet engraftment was evaluated using the method of Kaplan-Meier with log-rank analysis.

We observed that HHV-6 DNA was detected in 5 of 20 (25%) and 7 of 20 (35%) recipients before and after SCT, respectively. Before and after SCT, 14 of the 20 (70%) and 17 of the 20 patients (85%) were seropositive for HHV-6, respectively. A significant increase in HHV-6 antibody titer was observed in 7 patients, 4 and 3 of whom underwent autologous and allogeneic transplantation, respectively. All the seronegative patients were negative for DNA detection. Virus isolation was attempted in all recipients after SCT, but no isolate was obtained. Figure 1 shows the time course of engraftment for patients with and without active HHV-6 infection. There was no statistically significant difference in the rate of engraftment or frequency of neutrophil and platelet engraftment in patients with active HHV-6 infec-

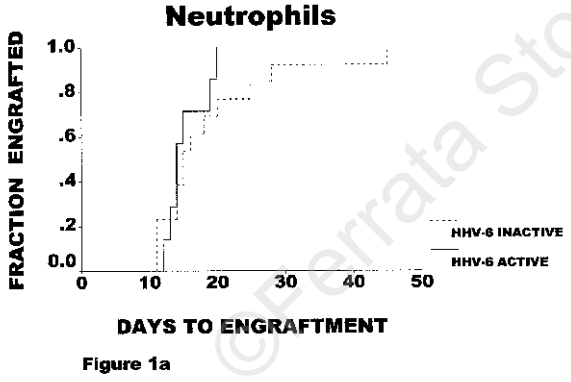

Figure 1a

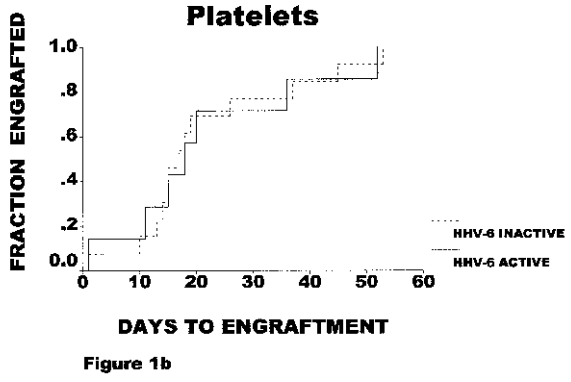

Figure 1b

Figure 1. Time course of neutrophil (a) and platelet (b) engraftment in patients with and without active HHV-6 infection.

Table 1. Characteristics of the transplant recipients.

Age (yr)	28 (range: 14-46)
Sex (M/F)	12/8
Diagnosis	
AML	8
ALL	5
CML	3
MDS	1
CAA	1
NHL	1
HD	1
Type of transplantation	
Allo-BM	3
Allo-PBSC	10
Auto-BM	6
Auto-PBSC	1
Pretransplant regimen	
TBI+CY	13
BCNU+ VP16+ Ara-C+ Mel	2
BU+CY	2
Mel+Ara-C+ CY	1
BU	2

Abbreviations: AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CML: chronic myelogenous leukemia; MDS: myelodysplastic syndrome; CAA: chronic aplastic anemia; NHL: non-Hodgkin's lymphoma; HD: Hodgkin's disease; Allo: allogeneic transplantation; Auto: autologous transplantation; TBI: total body irradiation; CY: cyclophosphamide; BCNU: 1,3-bis-(2-chloroethyl)-1-nitrosourea; VP16: etoposide; Ara-C: cytosine triphosphate; Mel: melphalan; BU: busulphan.

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tion when compared to those without active HHV-6 infection (Figure 1, $p > 0.05$ by log rank test).

Considering other results in the literature, Cone *et al*. reported from the US that 18 of 20 (90%) post-BMT patients had increased peripheral blood mononuclear cell HHV-6 levels,[7] Takemoto *et al.*[8] reported from Japan that 18 of 54 (33%) post-BMT patients had detectable HHV-6 DNA. In this report 7 of 20 (35%) post-SCT patients showed HHV-6 DNA, which coincides with the frequency of HHV-6 infection in patients with hematologic diseases in China.[9] It seems that the incidence of HHV-6 infection is low in East Asia.

To conclude, after SCT, the increase of HHV-6 DNA positivity, seropositivity and antibody titers suggests the reactivation of HHV-6 in some patients during their immunocompromized state. Active HHV-6 infection can appear in both autologous and allogeneic transplant recipients. HHV-6 was not isolated in any of the recipients, suggesting that the viral load was not high. Active HHV-6 infection was not found to be significantly associated with delay in neutrophil and platelet engraftment.

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