American Journal of Hematology 77:410–412 (2004)

Stimulation of Kaposi's Sarcoma-Associated Herpesvirus Viremia During Hematopoietic Stem Cell Mobilization With Filgrastim

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The effects of hematopoietic stem cell (HSC) mobilization on Kaposi's sarcoma-associated herpesvirus (KSHV) were evaluated in three KSHV and human immunodeficiency virus type 1 co-infected subjects. KSHV DNA was not detected in purified $CD34^+$ cell preparations from the period of filgrastim treatment. However, two of 3 subjects had transiently increased cell-free plasma KSHV DNA during filgrastim treatment. Peak plasma KSHV DNA (2,600 and 4,300 copies/mL) occurred on day 4 and declined to below the limit of detection by day 7. These findings suggest that, although $CD34^+$ cell preparations do not have evidence of KSHV infection, HSC mobilization may stimulate KSHV replication in other cellular compartments that contribute to KSHV viremia. Am. J. Hematol. 77:410–412, 2004. © 2004 Wiley-Liss, Inc.

Key words: filgrastim; hematopoietic stem cells; HHV-8; HIV-1

INTRODUCTION

Increased plasma human immunodeficiency virus type 1 (HIV-1) RNA occurs during hematopoietic stem cell (HSC) mobilization in HIV-1-infected persons [1]. The effects of filgrastim on other viral co-infections in HIV-1-infected persons are unknown. Because co-infection with Kaposi's sarcoma-associated herpesvirus (KSHV or human herpesvirus 8) is common among HIV-1-infected gay men, and B lymphocytes are infected by KSHV [2] and express G-CSF receptor [3], we hypothesized that HSC mobilization with filgrastim would stimulate KSHV replication. This hypothesis was tested by studying the effects of filgrastim treatment on cell-free KSHV viremia in HIV-1/KSHV co-infected persons.

PATIENTS AND METHODS

Informed consent was obtained from all study participants. Eighteen HIV-1-seropositive participants received daily subcutaneous injections of 10 μg/kg/day of filgrastim (Neupogen, Amgen Inc., Thousand Oaks, CA) on study days 1 through 7 as reported previously [4]. The characteristics of $CD34^+$ cells purified from leukapheresis products collected on days 4 and 5 have been reported [4].

Plasma samples collected at study entry were tested for antibody to KSHV latent nuclear antigen as described [5]. Plasma dilutions $\geq$1:40 were scored as positive. Cell-free KSHV DNA in plasma collected before and after filgrastim treatment, and cell-associated KSHV DNA in purified $CD34^+$ cell preparations, was quantified by real-time PCR amplification of a conserved region of the ORF 26 minor capsid gene as described [6].

Contract grant sponsor: National Institutes of Health; Contract grant numbers: CA79389 (to T.B.C.), AI32257 (to R.T.S.); Contract grant sponsor: University of Colorado General Clinical Research Center; Contract grant number: RR00051; Contract grant sponsor: University of Colorado Cancer Center Quantitative PCR Core.

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Received for publication 24 May 2004; Accepted 29 May 2004

Published online in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.20175

RESULTS

There was no history of prior or current KS, or other KSHV-associated diseases, for any subject. Antibody to KSHV LANA was detected in three subjects (17%) at titers of 1:640 for two subjects (61145 and 61146) and 1:320 for the third subject (610051). All KSHV co-infected subjects had increased plasma HIV-1 RNA during filgrastim treatment (maximum 101, 258, and 60,363 copies/mL, respectively; Fig. 1A–C).

Increased plasma KSHV DNA occurred during filgrastim treatment in two subjects (61145 and 610051; Fig. 1D and F, respectively). In both cases, peak plasma KSHV DNA occurred on day 4 of filgrastim treatment (maximum 4,301 and 2,553 copies/mL, respectively) and decreased to less than the lower limit of detection on days 6 and 7. Peak plasma KSHV DNA during filgrastim treatment of these subjects was within the range of plasma KSHV DNA observed in untreated AIDS-KS (median 197 copies/mL; range < 30 to $> 10^6$ copies/mL) [7]. Plasma KSHV DNA was again detected in follow-up samples from subject 61145 on days 27 and 55 (2,800 and 2,200 copies/mL, respectively) when $CD4^+$ lymphocytes were decreased 32% and 69% below baseline but was undetectable on day 167 when $CD4^+$ lymphocytes returned to slightly above baseline. Plasma KSHV DNA was not detected in follow-up specimens from subject 610051 on days 27, 55, or 167. Plasma KSHV DNA was not detected during filgrastim treatment of KSHV-infected subject 61146 (Fig. 1E) or three HIV-1-infected subjects who did not have detectable antibody to KSHV.

DISCUSSION

Our findings provide evidence that filgrastim treatment activated KSHV replication in two of 3 KSHV/HIV-1 co-infected subjects. KSHV DNA was not detected in three KSHV uninfected subjects, or in two consecutive samples taken prior to filgrastim administration (days −3 and 0) from the KSHV-infected subjects. Thus, activation of KSHV replication was associated with filgrastim treatment of KSHV/HIV-1 co-infected subjects. Worsened immunosuppression may have contributed to the reoccurrence of intermittent KSHV viremia during a period of transient $CD4^+$ lymphocytopenia after filgrastrim treatment in one subject.

The finding that KSHV replication was activated in only two of 3 KSHV co-infected subjects is similar to the finding that HIV-1 replication was activated in only 9 of the 18 HIV-1-infected subjects [1] and could be due to variability in G-CSF receptor expression in B-cell populations. Because soluble factors secreted by HIV-1 infected cells stimulate KSHV replication [8] and increased plasma KSHV DNA occurred concomitantly with increased plasma HIV-1 RNA, it is also possible that filgrastim stimulation of HIV-1 replication led to increased KSHV replication. The lack of detectable KSHV DNA in purified $CD34^+$ cells collected from the KSHV co-infected subjects on day 4 of filgrastim treatment suggests that increased

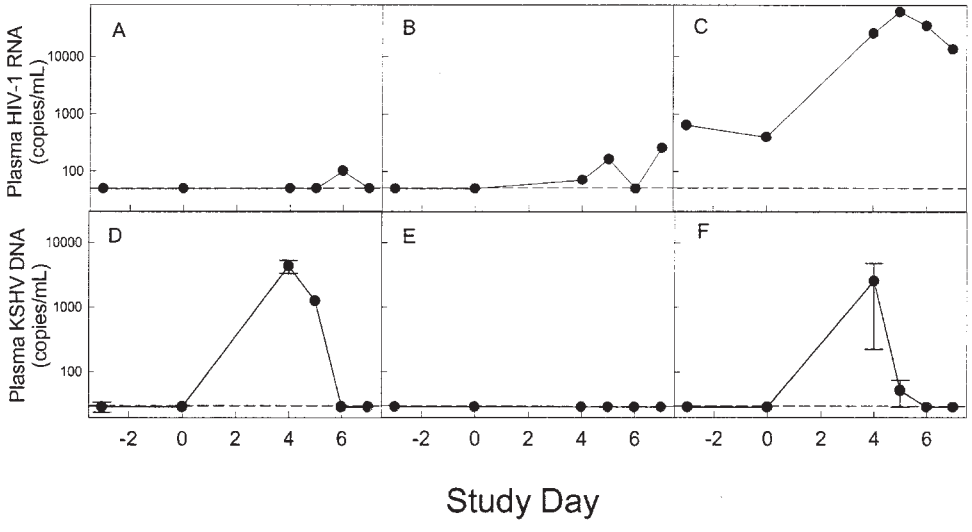

Fig. 1. Effect of filgrastim treatment on plasma HIV-1 RNA and KSHV DNA in HIV-1 and KSHV co-infected subjects. Filgrastim was administered on days 1–7. Duplicate plasma KSHV DNA samples were analyzed for select time points and values for these time points are the mean ± range of the duplicates. (A, D) Subject 61145; (B, E) subject 61146; (C, F) subject 610051. Horizontal dashed lines indicate the lower limit of quantification for each assay.

plasma KSHV DNA during HSC mobilization was not due to recruitment of KSHV-infected hematopoietic progenitor cells into the circulatory compartment.

It is important to note that filgrastim is a safe and effective treatment of neutropenia in patients with AIDS-KS and does not have untoward effects on KS disease [9]. Although our findings help to explain a previous observation that KSHV virus load increased during filgrastim treatment of a patient with AIDS-KS [10], our findings do not imply that use of filgrastim in HIV-1/KSHV co-infected persons is detrimental.

ACKNOWLEDGMENTS

We are grateful to the AACTG 285 study team, especially the study co-chairs Steve Miles and Roger Pomerantz, for providing the samples used in this study.

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