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Human herpesvirus 8-associated neoplasms: the roles of viral replication and antiviral treatment

Soren Gantt[1,5,6,*] and **Corey Casper**[2,3,4,6,7,8]

[1]Department of Pediatrics, University of Washington

[2]Department of Medicine, University of Washington

[3]Department of Epidemiology, University of Washington

[4]Department of Global Health, University of Washington

[5]Seattle Children's Hospital, Fred Hutchinson Cancer Research Center

[6]Vaccine and Infectious Disease, Fred Hutchinson Cancer Research Center

[7]Public Health Sciences, Fred Hutchinson Cancer Research Center

[8]Clinical Research Divisions, Fred Hutchinson Cancer Research Center

Abstract

Purpose of review—In this review, we highlight the importance of human herpesvirus 8 (HHV-8) lytic replication and the potential for antiviral therapies to prevent or treat HHV-8-related neoplasms.

Recent findings—Dieases caused by HHV-8 infection include Kaposi sarcoma (KS), multicentric Castleman disease (MCD), and primary effusion lymphoma (PEL), which occur primarily in patients with HIV infection. KS is the most common AIDS-associated malignancy worldwide. MCD and PEL occur less commonly but, like KS, are associated with poor treatment outcomes. Like all herpesviruses, HHV-8 is capable of either latent or lytic infection of cells. Although HHV-8 infection of tumor cells is predominately latent, accumulating data point to the importance of both lytic phase viral gene products and production of infectious virus. Antiviral agents that target herpesvirus DNA synthesis, such as ganciclovir, inhibit HHV-8 lytic replication and can prevent KS. Several HIV protease inhibitors may interfere with tumor growth and angiogenesis, and one PI, nelfinavir, directly inhibits HHV-8 replication *in vitro*.

Summary—Controlled trials are indicated to determine the clinical utility of antiviral suppression of HHV-8 replication, and identify the optimal antiretroviral regimens, for the prevention and treatment of KS.

Keywords

Human herpesvirus 8; replication; antiviral; Kaposi sarcoma

[*]Corresponding Author: Seattle Children's Hospital, 1900 Ninth Ave. Mailstop C9S-8, Seattle, WA 98101. sgantt@uw.edu, Telephone: 1 (206) 987-1160, Fax: 1 (206) 884-7311.

Introduction

Human herpesvirus 8 (HHV-8; also known as Kaposi sarcoma-associated herpesvirus, KSHV) was identified in KS lesions by representational difference analysis in 1994 [1], and belongs to the gamma group of human herpesviruses along with Epstein-Barr virus (EBV). KS is the most common AIDS-defining malignancy in the world; in some parts of East Africa, KS is the most common cancer in the general population [2]. Multicentric Castleman disease (MCD) and primary effusion lymphoma (PEL) are uncommon neoplasms typically associated with HIV infection. Emerging insights into the pathogenesis of these disorders suggest that targeting viral functions- including lytic replication and the elaboration of lytic gene products- may be a viable strategy for preventing disease and improving response to therapy. A number of excellent reviews of HHV-8 pathobiology have been published recently [3**,4,5]. Here, we will focus on the clinical importance of HHV-8 lytic replication, and discuss the potential uses of antiviral therapies for the prevention and treatment of HHV-8-related diseases.

Role of HHV-8 lytic replication in HHV-8-associated diseases

Like all herpesviruses, HHV-8 infection of cells results in one of two discrete viral programs, latency and lytic replication. During latent infection, few viral genes are expressed and the HHV-8 genome is maintained as an episome. The HHV-8 gene products that are expressed in latently infected KS tumor (“spindle”) cells appear limited to LANA-1, viral (v) cyclin, vFLIP, kaposins A, B and C, numerous miRNAs, and possibly ORF K1 (reviewed in [3**,4]). Each of these latent-phase proteins has functions that likely promote tumorigenesis, including promoting cell growth and division, inhibiting apoptosis, modulating inflammation, and inducing angiogenesis. Importantly, however, latent infection of primary cells with HHV-8 does not result in immortalization [6,7,8,9].

Although spindle cells in KS lesions are predominately (∼99%) latently infected with HHV-8, careful studies have consistently shown that a proportion undergoes lytic replication and produce virions [10,11,12]. Most infected cell types in culture display a progressive loss of the HHV-8 episomal genome within 5-10 divisions in the absence of genetic selection or reinfection [13], such that the HHV-8 genome is eventually lost from most spindle cell lines isolated from KS lesions [14,15,16]. This indicates that persistence of HHV-8 within KS tumors requires ongoing lytic replication and infection of new cells [13]. The majority of infected cells in PEL and MCD is also latent, but a greater proportion express lytic phase genes compared to KS, with MCD demonstrating the highest frequency of lytic replication (up to 25%) [11,12,17].

Numerous lytic viral gene products are detected in KS tumors and mediate central aspects of KS pathobiology. Proteins expressed by spindle cells during lytic replication directly or indirectly mediate several aspects of KS pathogenesis, including inflammation (vGPCR, vIL-6, K15), angiogenesis (vIL-6, vGPCR, K1, vCCL1, vCCL2), cell growth (vIL-6, vGPCR, K1), and inhibition of apoptosis (vCCL1, vCCL2, vBcl2, vIRF1, K1), among others (reviewed in [3**,5]). Of note, lytically infected cells are destroyed, and thus their effects in KS lesions should be limited to either increasing the number of infected cells or

paracrine effects of lytic viral gene products. Similarly, MCD appears to be driven largely by the paracrine effects of HHV-8 lytic phase proteins (e.g. vIL-6) [18].

HHV-8 DNA is detected more frequently and at higher copy numbers in plasma of KS patients compared to controls with asymptomatic HHV-8 infection [19,20,21*,22*]. A large proportion of this HHV-8 DNA in plasma is encapsidated in virions [21*,23], indicating an association between KS and systemic viral replication and dissemination. HHV-8 viremia appears to be in the causal pathway for KS, rather than a consequence, since HHV-8 viremia predicts subsequent KS in cohorts of asymptomatic people with HHV-8 and HIV co-infection [24,25]. In addition, ganciclovir, which inhibits HHV-8 lytic replication, prevents incident KS (see below). Thus, lytic replication in viral reservoirs, likely the oropharynx [22*] and lymph nodes [26], may seed the blood and increase infection of spindle cell precursors. Based on this body of evidence (Table 1), therefore, HHV-8 replication appears central to the pathogenesis of KS.

Utility of measuring HHV-8 replication in the management of HHV-8-associated disease

HHV-8 testing could have three potential clinical applications: diagnosing HHV-8-related disease, assessing the risk of developing disease, and predicting treatment success (Table 2). Each possibility is reviewed in turn.

Viral testing to diagnose HHV-8-related neoplasms

In spite of its value for epidemiologic studies, serologic diagnosis of HHV-8 infection is rarely informative in clinical practice, given the relative lack of sensitivity of most assays (reviewed in [34,35]) combined with the fact that the majority of HHV-8 infected individuals remain asymptomatic. HHV-8 testing of biopsy specimens of suspected PEL or MCD lesions is required for diagnostic purposes [36]. Immunohistochemical staining for nuclear staining of LANA is most commonly performed, although PCR detection of HHV-8 DNA is also reasonable. HHV-8 testing of KS biopsy material by immunohistochemistry or PCR is not essential, but may be helpful if the diagnosis is in doubt. HHV-8 PCR testing of blood or other specimens for the diagnosis of HHV-8-related neoplasms has limited utility, but may be supportive when biopsy is not feasible. Although detected more often than in people with asymptomatic infection, HHV-8 viremia is only present in between ∼10-60% of KS patients [19,21*,22*,24,25]. HHV-8 viremia in a patient with suspected PEL or MCD would be suggestive, but not definitive, and absence of viremia would not preclude either diagnosis.

HHV-8 testing to assess risk of incident disease

PCR testing of viral DNA can provide a quantitative measure of HHV-8 lytic replication, which has been correlated with the risk of subsequent KS [24,25]. Therefore, it is likely that HHV-8 viral load measurement could be used to guide selective prophylaxis or preemption strategies to prevent progression from asymptomatic infection to disease, as is used for EBV and cytomegalovirus in transplant patients [37,38]. In order to develop such applications,

however, the predictive value of levels of HHV-8 replication in specific patient populations must be better defined.

HHV-8 testing to predict response to therapy or recurrent disease

The quantity of HHV-8 DNA in clinical samples has been correlated with disease progression and response to treatment in KS [28,39,40,41**], and may prove useful in guiding type or duration of therapy. Symptomatic flares of MCD are universally associated with the detection of HHV-8 DNA from the peripheral blood [42,43,44], and declines in HHV-8 DNA levels in blood is associated with treatment response. Additional longitudinal studies are needed to determine how best to base management decisions on measures of HHV-8 replication in these diseases.

Use of HHV-8 DNA synthesis inhibitors

A large number of drugs that block herpesvirus DNA synthesis have been reported to inhibit HHV-8 replication (Table 3) [45,46,47,48,49]. Of these agents, ganciclovir (or its oral pro-drug valganciclovir) is the only one proven to either suppress HHV-8 replication *in vivo* or prevent the development of KS in randomized trials. In a randomized placebo-controlled cross-over trial, valganciclovir was shown to reduce HHV-8 oral shedding frequency by 46% and quantity by 0.44 log copies/mL [50]. Ganciclovir treatment of CMV retinitis in HIV-infected patients statistically significantly reduced the incidence of KS by 75% when given orally and 93% when given intravenously compared to intraocular treatment alone, in a randomized trial [33]. Numerous observational studies have also suggested that ganciclovir and foscarnet, but not acyclovir, may prevent KS [29,30,31,32]. Thus, there is ample evidence for using valganciclovir to prevent KS in high-risk individuals. Operationally, however, it is not yet clear who might benefit most from preventive use of antivirals (see above).

The efficacy of antivirals for the treatment, as opposed to prevention, of KS is less clear. Case reports have suggested that cidofovir or foscarnet may have improved KS treatment outcomes [55,56,57]. However, data from small observational studies did not indicate better KS outcomes with inhibitors of HHV-8 DNA synthesis [40,58]. Furthermore, the largest trial of cidofovir to date, which included 7 patients with KS, found no apparent effect on progression or HHV-8 viremia [51]. Even if continuous HHV-8 lytic replication is important for the persistence of KS tumors, it is possible that once KS has developed these drugs may not suppress HHV-8 replication effectively enough to have clinical benefits. In this case, more potent antiviral regimens could improve outcomes. Alternatively, it may be that despite complete inhibition of viral DNA synthesis, expression of early lytic gene products (e.g. vIL-6 and vGPCR) may still occur at levels sufficient to support KS progression [59,60]. The impact of antivirals on KS treatment might be augmented if combined with agents that induce the activation of HHV-8 latently infected cells to undergo lytic replication *in vitro*, such as valproic acid, hydroxyurea, or glycyrrhizinic acid [61,62], but such approaches have not been validated in clinical trials to date. A final potential role for antivirals might be as secondary prophylaxis after a response to ART and/or chemotherapy in order to reduce the risk of relapse [63], which has not yet been evaluated in clinical trials.

The benefit of various antiviral treatment strategies for other HHV-8-related diseases, particularly MCD, is suggested by some reports [44,64,65,66,67,68], but not others [69], and definitive data do not exist to recommend specific therapies.

The effects of antiretroviral therapy (ART) on HHV-8-related diseases

In resource-rich areas, the widespread availability of ART has resulted in a dramatic decline in KS incidence [70]. Rates of KS began slowing with the advent of zidovudine monotherapy, and then fell precipitously with the use of “highly active” ART combining nucleoside reverse transcriptase inhibitors (NRTIs) with a non-NRTI (NNRTI) or protease inhibitor (PI). The mechanisms by which ART prevents KS have not been entirely defined, but it is clear that restoration of immune function plays a central role. HIV itself may also promote the development of KS through actions of Tat (reviewed in [71,72]).

One recurring and controversial hypothesis is that the individual antiretroviral components of ART regimens, specifically PIs, may have differential effects on HHV-8 or tumorigenesis that affect KS development or response, independently of their effects on HIV replication and immune reconstitution. It should be stressed that a number of observational studies have found similar rates of KS incidence and response between HIV-infected patients treated with PI-based and NNRTI-based ART [28,73,74,75,76*]. However, these studies were all limited by small numbers of KS cases and/or incomplete detail regarding the type and use of ART regimen. Some of these same data suggest that complete remission of KS may occur more often in patients treated with PIs despite similar control of HIV infection (HIV RNA and CD4 T-cell levels) [28]. In addition, numerous KS relapses have been reported after switching from PI-based to NNRTI-based ART regimens without virologic or immunologic deterioration [77,78,79]. In the absence of convincing clinical evidence for the superiority of PIs for KS, there has been much interest in the fact that individual PIs variably affect angiogenesis, cell division and invasion, and apoptosis (reviewed in [80,81]). Some of these actions by PIs appear to be mediated through inhibition of the PI3K/Akt signaling, which is upregulated both by latent HHV-8 infection and by vGPCR [82,83]. The attractiveness of the PI3K/Akt pathway as a target for KS treatment is illustrated by the success of the immunosuppressant rapamycin (sirolimus), an inhibitor of mTOR (a signaling molecule that is downstream of and activated by PI3K/Akt) that is remarkably effective for KS in transplant patients [54] and has activity against PEL cell lines [84]. Interestingly, a recent study shows that rapamycin inhibits expression of HHV-8 RTA *in vitro*, blocking virion production [53**]. Other mechanisms by which PIs may interfere with HHV-8 tumorigenesis include inhibition of matrix metalloprotease and proteasome activities. Notably, these properties have sparked an interest in the use of PIs for other cancer types, leading to clinical trials for a wide variety of solid tumors (reviewed in [80,85]).

Another intriguing possibility is that some antiretrovirals directly affect HHV-8 replication. Among several PIs screened for their ability to inhibit HHV-8 replication using a recombinant virus assay, only nelfinavir showed potent activity at concentrations that are achieved in plasma with standard oral dosing (Table 3) [52**]. PIs act on the HIV aspartyl protease, an enzyme not encoded by human herpesviruses. However, nelfinavir modulates numerous basic cellular processes [80], one or more of which might disrupt HHV-8

replication. The NRTIs zidovudine and stavudine are phosphorylated by the HHV-8 thymidine kinase (ORF 21) [86,87], but appear to have minimal effects on HHV-8 replication *in vitro* [52**].

The varied effects of different PIs on HHV-8 replication, tumor growth, and angiogenesis indicate the possibility that all ART regimens may not be equally effective for preventing or treating KS. This could explain why observational studies that combine all PIs together, perhaps diluting a benefit of a subset of these agents, may not have discerned an effect of PI-based compared to NNRTI-based ART regimens, especially when the number of events is small [28,73,74,75]. Disappointingly, unlike in the U.S. and Europe, rates of KS in sub-Saharan Africa have not declined appreciably even where ART has been provided to a large proportion of those requiring treatment [88]. The vast majority of ART delivered in sub-Saharan Africa has been nevirapine (NNRTI)-based, raising the possibility that different first-line regimens might offer an advantage in KS-endemic populations. Controlled trials are needed to determine which individual ART regimens are optimal for the prevention and treatment of KS. Although the use of PI-based ART as first line treatment of KS has already been adopted by some clinicians [89], there are currently no controlled studies to support this practice or guide the choice of individual PI. An uncontrolled trial of indinavir in 28 patients with refractory Classic (HIV-negative) KS observed tumor regression in a minority of subjects [90*], and a phase 3 randomized trial of ART containing a PI combination (ritonavir-boosted lopinavir) versus a NNRTI (efavirenz) for mild-moderate AIDS-KS is ongoing in Uganda (ClinicalTrials.gov Identifier: NCT00444379). Additional trials are required to determine how best to use available agents- and to guide the development of new therapies- to improve KS outcomes.

Conclusion

Despite our increased understanding of HHV-8 pathobiology, the exact mechanisms by which HHV-8 infection causes KS, MCD, and PEL remain unclear. KS and MCD in particular differ from classical cancers in ways that in part reflect the requirement for ongoing lytic replication. This paradigm squarely frames HHV-8 replication as a therapeutic target for the prevention or treatment of these diseases. Importantly, several drugs that inhibit HHV-8 replication, including (val)ganciclovir and nelfinavir, are already in wide clinical use for other indications and can therefore be easily evaluated and repositioned for the specific management of KS. Other PIs may have specific benefits for KS by interfering with cellular processes that are driven by HHV-8 infection. However, the role of HHV-8 DNA synthesis inhibitors and the optimal ART regimen for prevention and treatment of KS have yet to be defined. Given the enormous burden of KS in sub-Saharan Africa and the poor outcomes of current standard therapies, controlled clinical trials are urgently needed to evaluate these approaches.

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Key points

1. Lytic replication plays a central role in HHV-8 tumorigenesis, particularly in KS and MCD.
2. (Val)ganciclovir inhibits HHV-8 replication and prevents KS, but additional studies are required to characterize the patient populations in whom the benefits of antiviral suppression outweigh the cost and toxicity.
3. PIs have numerous cellular effects that may interfere with HHV-8 replication and tumorigenesis, but these activities vary significantly among individual agents within the PI class, and the superiority of PI-based ART regimens for KS remains unproven.
4. Controlled trials are urgently needed to evaluate the role for HHV-8 DNA synthesis inhibitors as well as to determine the optimal ART regimens for preventing and treating KS in people with HIV infection.

Table 1

Evidence suggesting a causal role for HHV-8 lytic replication in the pathogenesis of Kaposi sarcoma

1	A proportion of HHV-8-infected spindle cells in KS lesions are consistently found to undergo lytic replication [10-12].
2	Lytic replication is required for the maintenance of the HHV-8 genome in spindle cells [13].
3	Gene products expressed during lytic replication mediate angiogenesis and inflammation central to KS pathogenesis (reviewed in [3**]).
4	HHV-8 viremia is a strong predictor for the development of KS, and has been associated with a poor response during KS treatment [19,20,23-25,32,90].
5	Ganciclovir or foscarnet for treatment of cytomegalovirus reduce the incidence of KS [45-49].

Table 2
Clinical Utility of Assays to Detect HHV-8 in Biologic Specimens

Clinical scenario	Specimen type	Frequency of HHV-8 Detection	Clinical Utility of Test
Asymptomatic HHV-8 infection	Peripheral blood	Among seropositive people, HHV-8 detection by PCR ranges from 0% in the US and Europe to 30% in areas where KS is endemic	Insensitive for determination of HHV-8 infection status; correlated with risk of subsequent KS
KS	Tumor	HHV-8 is detectable in >95% of KS tumors	Immunohistochemistry, *in situ* hybridization or PCR may assist in the diagnosis of KS
	Peripheral blood	∼10-60% of patients with KS will have HHV-8 DNA detected in peripheral blood	Levels of viremia during treatment may be correlated with poor outcomes
PEL	Pleural or ascitic fluid	HHV-8 DNA is reliably detected in the effusions of patients with PEL	Detection of HHV-8 by immunohositochemistry, *in situ* hybridization or PCR in effusion is required for definitive diagnosis
	Peripheral blood	HHV-8 DNA is frequently detected in the peripheral blood of persons with PEL	Unclear
MCD	Lymph node	HHV-8 DNA is reliably detected in lymph node biopsies in cases of MCD in HIV+ patients	Detection of HHV-8 by immunohositochemistry, *in situ* hybridization or PCR establishes specific diagnosis, and can guide therapy (i.e. use of antiviral therapy)
	Peripheral blood	Detection of HHV-8 DNA in blood of persons with MCD is correlated with symptoms and is usually undetectable between “flares”	Helpful in determining etiology of constitutional symptoms in MCD patients

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Table 3

Drugs in clinical use with reported inhibitory activity on HHV-8 replication

Drug	EC_{50} range *in vitro* (uM)	Peak plasma conc. (uM)	Comments	References
Ganciclovir/valganciclovir	0.96 - 8.9	50 (IV ganciclovir); 22 (oral valganciclovir)	Inhibited oropharyngeal HHV-8 replication in a placebo-controlled trial; associated with reduced KS incidence in one randomized trial and some cohort studies	[39-45,47-49]
Foscarnet	80 - 177	990 – 5,900	Associated with reduced KS incidence in cohort studies	[39-41,46-48]
Cidofovir	0.05 – 6.3	30 – 70	No benefit for treatment of KS in one uncontrolled trial of 11 patients	[39-43,54]
Acyclovir	80 – 95.5	102 (IV); 38 (valacyclovir PO)	Observational data have suggested no benefit	[39,41,42,46-49]
Adefovir	20 - 39	36.7		[39,42]
Brivudin	7.2 - 24	5.1		[39,42]
Nelfinavir	2.0 – 7.4	6.6 - 9	Activity appears to be specific to nelfinavir in contrast to a protease inhibitor “class effect”	[84**]
Rapamycin (sirolimus)	EC_{50} not reported; significant inhibition at 12 nM	Trough targets up to 16.4 nM in organ transplant recipients	Immunosuppressant drug that is effective for prevention and treatment of KS in organ transplant recipients	[80,82**]