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KSHV-associated Malignancies: Epidemiology, Pathogenesis, and Advances in Treatment

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Abstract

Kaposi sarcoma associated herpesvirus (KSHV), a γ2-herpesvirus, also known as human herpesvirus-8, is the etiologic agent of three virally associated tumors: Kaposi sarcoma, a plasmablastic form of multicentric Castleman disease (KSHV-MCD) and primary effusion lymphoma. These malignancies are predominantly seen in people with acquired immunodeficiencies, including acquired immunodeficiency syndrome and iatrogenic immunosuppression including organ transplantation, but can also develop in elderly. Kaposi sarcoma (KS) is most frequent in regions with high KSHV seroprevalence, such as sub-Saharan Africa and some Mediterranean countries. In the era of combination antiviral therapy, inflammatory manifestations associated with KSHV-infection, including KSHV-MCD, a recently described KSHV-associated inflammatory cytokine syndrome and KS immune reconstitution syndrome are also increasingly appreciated. Our understanding of viral and immune mechanisms of oncogenesis continues to expand and lead to improved molecular diagnostics as well as novel therapeutic strategies that employ immune modulatory agents, manipulations of the tumor microenvironment, virus activated cytotoxic therapy, or agents that target interactions between specific virus-host cell signaling pathways. This review focuses on the epidemiology and advances in molecular and clinical research that reflects the current understanding of viral oncogenesis, clinical manifestations and therapeutics for KSHV-associated tumors.

Introduction

Kaposi sarcoma-associated herpesvirus (KSHV) was first isolated from Kaposi sarcoma (KS) lesions in patients with acquired immunodeficiency syndrome (AIDS) by Chang and Moore in 1994[1] and was later established to be the etiologic agent for KS in several

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Conflict of Interest: The spouse of one of the authors (R.Y.) is a co-inventor on an assay to measure KSHV v-IL6. This invention was made when this scientist was an employee of the US Government under 45 Code of Federal Regulations Part 7. All rights, title, and interest to this patent have been assigned to the U.S. Department of Health and Human Services. The government conveys a portion of the royalties it receives to its employee-inventors under the Federal Technology Transfer Act of 1986 (P.L. 99-502).

epidemiologically distinct populations[2-4]. Subsequent studies showed it to be the etiologic agent of several other lymphoproliferative disorders, including primary effusion lymphoma (PEL), a plasmablastic form of multicentric Castleman disease (KSHV-MCD) and large cell lymphoma arising in the setting of KSHV-MCD[5, 6]. We will review clinical aspects of KSHV-associated malignancies, including risk factors for tumor development, the relationship with human immunodeficiency virus (HIV), rarer manifestations of KSHV infection, select KSHV-encoded genes implicated in oncogenesis, as well as clinical presentation and treatment approaches for KS, KSHV-MCD and PEL.

KS was initially described in 1872 as a lower extremity tumor among elderly men by the dermatologist Moritz Kaposi, and this form, which develops in Mediterranean or Ashkenazi Jewish men, has been called *classic* KS. KS was subsequently noted to be a relatively common tumor in sub-Saharan Africa in the 1950s-1970s, prior to the HIV epidemic[7]. Later, an association with immunosuppressive drugs was reported[8].

In 1981 an unusual clustering of KS cases among young men who have sex with men (MSM) in the United States (US) was a harbinger of the AIDS epidemic[9] and KS was considered an AIDS-defining malignancy by the Centers for Disease Control and Prevention[10]. AIDS was subsequently found to be caused by a newly discovered human retrovirus, HIV. Between 20 and 50% of AIDS patients developed KS during the early epidemic in US. An epidemiologic clue to the origin of KS came from the observation that KS incidence was much higher in HIV-infected MSM than in other HIV risk groups (e.g. injection drug users), leading to the hypothesis that KS was caused by a transmissible agent other than HIV that was better transmitted by sexual contact than by exposure to blood[11]. The nature of this putative agent was initially elusive. However, this mystery was solved in 1994 when a novel γ2-herpesvirus, KSHV, was discovered by representational difference analysis of KS lesions compared to normal skin[1]. Subsequent studies showed PEL, an unusual lymphoma associated with AIDS, and KSHV-MCD were also associated with and caused by KSHV[5, 6]. Cases of PEL and KSHV-MCD have also been described in patients without HIV. KSHV is a necessary etiologic agent for KS based on epidemiologic studies demonstrating temporality and strength of association as well as experimental and laboratory evidence confirming biologic plausibility[12, 13]. KSHV is classified as group 1 biological carcinogenic agent, with sufficient evidence to link to carcinogenicity in humans, by International Agency for Research on Cancer[14]. However, only a small percentage of KSHV infected individuals develop KSHV-associated tumors, thus KSHV infection is not sufficient to cause oncogenesis.

Epidemiology of KSHV Infection

The incidence of KS largely mirrors KSHV seroprevalence, although KS risk is dramatically increased by HIV co-infection. Several epidemiologic patterns of KS have been described: *classic* KS, discussed above; *endemic* KS occurring in men and women in Africa and often occurring at a younger age; *epidemic* KS associated with HIV infection; and *iatrogenic* KS, generally seen in the setting of transplantation. In regions with access to combination antiretroviral therapy (cART), AIDS-associated KS incidence has decreased by up to 80% since its peak in the early AIDS epidemic[15], largely due to improved control of HIV viremia

and preserved CD4+ T-cell counts and immune function. Nonetheless, KS incidence in patients on long-term cART remains markedly elevated compared to the general population, even in patients with preserved CD4+ counts. Furthermore, despite decreased HIV incidence in the US since the peak of the AIDS epidemic, there are still 50,000 incident cases of HIV per year in MSM in the US[16], and there continues to be a high rate of KSHV infection in this population. KS represents a major public health problem in sub-Saharan Africa, where KSHV infection is endemic and resources to treat HIV/AIDS related complications are limited. In some areas and countries in Africa, it is the most common tumor in men[17].

KSHV Serologic Assays

KSHV seroprevalence has been estimated in several large population-based studies. The primary means of assessing for KSHV infection is antibody testing. KSHV has a large genome with more than 85 genes, most of which have the potential to be antigenic. In KSHV-infected individuals, antibody response to viral antigens is variable, with certain antigens such as latency associated nuclear antigen (LANA) or the capsid antigen K8.1 eliciting strong responses. Intensity of immune response may also depend on HIV status, as well as the co-existence of a KSHV-associated malignancy[18]. Current serologic studies employ either immunofluorescent assays (IFA)[19] or enzyme-linked immunoassays (ELISA) against one or more KSHV-encoded latent and/or lytic proteins[20, 21]. The sensitivity of these assays is variable, while the specificity is generally greater than 95%[22]. With ELISAs, definition of KSHV-seropositivity based on a combination of tests for reactivity against a lytic (K8.1) and latent (LANA) antigen increases sensitivity while preserving specificity, and this approach generally performs well in epidemiologic studies. However, there is no US Food and Drug Administration (FDA)-approved diagnostic test for clinical purposes such as documentation of acute infection. Additionally, challenges exist related to a gold-standard confirmatory test for KSHV infection in subjects without a documented KSHV-associated malignancy or detectable KSHV in the blood or saliva.

In addition to limitations in the accuracy of IFA and ELISA assays, these assays are technically burdensome. Newer recombinant antigen-based serologic assays employing either a luciferase immunoprecipitation system against 4 KSHV antigens[23] or a magnetic-bead based multiplex assay using 6 KSHV antigens[18] have been recently developed. These newer assays appear to be dynamic across a wider range of antibody concentrations and have a higher sensitivity and preserved specificity compared to earlier assays. However, they are currently performed only in a few research laboratories, and require validation in additional populations.

Estimates of KSHV seroprevalence in different populations

KSHV was established in populations of endemic areas in the distant past and appears to have migrated with humans as they colonized the world. Subtypes of KSHV defined on the basis of strain variability of KSHV-encoded K1 and K15[24] have been used to evaluate the spread of KSHV. It has been speculated that KSHV was present in the origins of modern humans in Africa (B subtype), and that migrations of human out of Africa, first to the Middle East, and then South Asia (D subtype), and later to Europe, North Asia, and the Americas (A and C subtypes) established the other epidemiologic patterns[24]. An increase of

KSHV in MSM appears to have preceded the rise of HIV[25]; HIV may then have facilitated further spread of KSHV.

Unlike most herpesviruses, which are almost universally prevalent in adults, KSHV prevalence currently varies substantially in different populations. Three major patterns are noted: a) high-level endemic areas including many parts of Africa[19]; b) intermediate-level endemic areas featuring seroprevalences between 10 and 25%, such as the Mediterranean area[19, 26]; and c) non-endemic areas where seroprevalences are less than 10%; these include North America, Northern Europe, and most of Asia[19]. Prevalence estimates vary widely in different regions and populations in the Caribbean, Latin America, and South America. Within a country, substantial regional variation can be noted. For example, among blood donors in Italy, prevalence was estimated to be 7.3% in Northern and Central Italy and 24.6% in Southern Italy[26]. Interestingly, outside of KSHV endemic regions, high KSHV antibody prevalence has been reported in several distinct populations, for example an estimated seroprevalence of 65% among Brazilian Amerindians greater than 30 years of age[27], 33% among adults in Papua New Guinea[28], 20%-46% in Xinjiang, China[29] and 25% among Hispanic children in South Texas, US[30]. While KSHV seroprevalence is less than 5% in the general US population, it is markedly elevated in MSM, with estimates ranging from 25% to 60% among HIV-infected and 20% to 30% of HIV-uninfected MSM[31, 32]. KSHV infection in HIV-uninfected MSM in other countries also appears common[33]. In Africa, regional differences appear to be correlated with malaria, HIV, and socioeconomic status[34-37].

Modes of transmission

Behavioral risk factors for KSHV transmission are incompletely understood, and appear to vary in endemic and non-endemic regions. Saliva exchange appears to an important factor. KSHV DNA sequences are detectable in saliva[38] and oral tissues of some KSHV infected individuals. Exposure to KSHV-infected saliva is believed to be a major route of KSHV transmission in both MSM in non-endemic regions and in children in endemic regions. In a study in Seattle, salivary shedding of KSHV DNA was detected in 61% of 44 KSHV-infected MSM on at least one day tested[39]. Saliva exchange appears to be the main mode of KSHV transmission to children, due in some cases to practices such as pre-mastication of food by the mother[35]. KSHV salivary shedding is also common among adults with endemic infection; approximately one-third of commercial sex workers in Kenya[40] and one-fourth of mothers of children with sickle cell disease in Uganda[41] had KSHV DNA in saliva. Increased oral shedding is associated with untreated HIV infection, malaria parasitemia, and perhaps other infections[36].

In high-level endemic areas, KSHV is predominantly transmitted during childhood by a horizontal non-sexual route rather than vertical transmission. In such areas, KSHV seropositivity is relatively uncommon in infants and there is an age-dependent increase in KSHV seroprevalence during childhood. Children are more likely to be infected if they are residing with an affected or seropositive mother, siblings or family members. Other risk factors include type of water supply and low socioeconomic status[37]. Among adults, KSHV

risk also increases with increased number of sexual partners in both endemic and non-endemic areas[42-44].

For MSM in the US, a sexual route of acquisition is likely to be particularly important, with seropositivity associated with history of sexually transmitted diseases (STD) and higher number of sex partners[31]. Saliva exchange during certain sexual activities such as deep kissing, oro-genital sex, or use as saliva as a lubricant for anal sex appears to be the major source of transmission among MSM[38, 42, 45, 46]. Identification of KSHV in semen is relatively infrequent in immunocompetent hosts[38, 47]. While slightly more common in HIV-infected patients[47, 48], KSHV viral load in semen is much lower than in saliva, further suggesting semen exchange is a less common route of transmission.

Additional sexual risk-factors associated with KSHV transmission in presumed heterosexual populations have not been clearly established. In the US, KSHV seroprevalence in heterosexual men is associated with number of lifetime partners and history of herpes simplex-1[44]. Some[49] but not all studies[50] from high endemic areas have reported higher prevalence of KSHV-seropositivity among commercial sex workers and heterosexual individuals attending STD clinics, and those with HIV[51]. Circumcision and condom use were found to have a modest protective effect in one study of heterosexual men in Kenya[49]. Although a steady increase in seroprevalence observed beyond puberty provides evidence that sexual transmission also occurs in areas where KSHV is highly prevalent, KSHV infection appears to be commonly established during childhood and later sexual transmission may be relatively less important[35].

KSHV transmission via blood and blood products is possible, as KSHV-infected persons could have circulating KSHV-infected mononuclear cells. However, such transmission is usually rare as evidenced by the substantially lower KS incidence observed in US AIDS populations whose risk factor for HIV was intravenous drug use or transfusion[11, 43]. Additionally, KSHV seroprevalence in HIV-infected injection drug users is substantially lower than in HIV-infected MSM[20, 52], further suggesting that blood exchange through sharing contaminated needles is a relatively unimportant route of KSHV transmission, especially when compared to transmission of other viruses such as HIV, hepatitis C virus or hepatitis B virus[53].

In non-endemic settings, where modern blood-banking techniques, including stringent donor screening, laboratory testing of products for other infectious agents, leukodepletion of fresh components, and proper storage of blood components are routinely practiced, the risk of transmission appears to be extremely low. In US, approximately 3% of blood donors are seropositive for KSHV, and even if seropositive, these healthy donors have extremely low risk of detectable viremia[54]. In contrast, in resource-poor endemic areas, e.g. Uganda, with less stringent donor screening and less advanced blood component processing (including the use of non-leukodepleted red cells or unprocessed whole blood), the KSHV seroprevalence among blood donors is about 40% and the risk of infection associated with receipt of a transfusion from a seropositive donor may be as high as 5%[55].

On the other hand, transmission of KSHV through solid organ transplantation is relatively more common and because of the immunosuppression that is utilized post transplantation it is clinically important[56]. Interestingly, cases of KS of donor cell origin developing in solid tissue transplant recipients who were KSHV seronegative at time of transplant have been reported, suggesting KS can originate from transmission of KSHV-infected progenitor cells from the donor to the host through the graft[57, 58]. Primary KSHV infection with severe inflammatory symptoms in seronegative recipients who received renal[59] or liver transplantation from KSHV positive donors[60], and fatal visceral KS and KSHV-associated lymphoproliferations after a heart or liver transplant have also been reported. In a French multicenter transplant study, where 217 seronegative solid organ recipients who received organs from KSHV seropositive donors were followed[61], approximately 30% of these KSHV-negative recipients seroconverted. However, KSHV viremia was only detected in 4 of the liver transplant patients, 2 of whom developed KSHV-associated malignancies. Also, one renal transplant patient who seroconverted developed KS[61]. Given the risk for infection as well as increased risk for development of KSHV-associated malignancies in the setting of immunosuppression, these data support a role for evaluating KSHV serostatus in solid organ transplants donors and recipients, and appropriate monitoring for KSHV associated conditions in cases of a KSHV infected recipient and/or donor.

Risk Factors for Developing KS and Other KSHV-associated Malignancies

HIV-induced immunosuppression is an important cofactor in the induction of KS. Both absolute decreases in CD4+ counts and lack of KSHV-specific T-cell immunity[62, 63] are associated with incident KS. Also, KS is independently associated with the degree of HIV viremia[64]. Before the widespread use of cART, patients co-infected with HIV and KSHV were estimated to be 400 to 2000 times more likely to develop KS than those with just KSHV infection. The widespread use of cART in the US and Western Europe resulted in an initial 80% decrease in the incidence of KS[65]. However, further decreases after 2000 have been more modest, and KS remains the second commonest tumor arising in HIV-infected persons in the US, after non-Hodgkin lymphoma, with a cumulative incidence of approximately 2% in the cART era[66]. KS is still the commonest AIDS-defining malignancy in parts of sub-Saharan Africa where both HIV and KSHV seroprevalence is elevated.

A number of immunosuppressive drugs are implicated in the development of *iatrogenic* KS, including cyclosporine, azathioprine, glucocorticoids and rituximab[8, 67, 68]. These are particularly important in the setting of transplantation, but are also relevant in the setting of chronic immunosuppression for rheumatologic conditions or treatment of KSHV-infected patients with other malignancies. Solid organ transplantation increases the risk of KS in the general US population by 60-fold[69]. Overall, among Italian and French organ transplant recipients, risk of KS is 125-fold greater than the general population and the cumulative risk for KS in renal transplant in Italy is approximately 1%[70]. However, among KSHV-seropositive renal transplant recipients, the cumulative risk appears substantially higher, and is estimated at greater than 10%[59].

Inherited immunodeficiencies are a rare cause of KS, and such cases can present in childhood. KS cases have been reported in the setting of *OXO40* deficiency[71], *STIM1*

deficiency[72], *interferon-γR1* deficiency[73], and Wiskott-Aldrich syndrome[74]. Additionally, hemophagocytic syndrome has been noted after KSHV infection in infants with heterozygous mutations in perforin alleles resulting in undetectable perforin expression[75]. Polymorphisms in certain immune genes may also modulate KS risk in adults. An *IL13* promoter region variant 98A[76] has been associated with a 1.9-fold increased risk, and the 1235T/-1010G *IL8RB* haplotype was associated with a 2-fold decreased risk for classic KS. In patients with HIV, an *IL6* promoter polymorphism (G174C) is also associated with KS[77].

Age is an important risk factor for KS, and *classic* KS typically develops in elderly men. *Classic* KS is associated with decreased lymphocyte counts[78], and KS development may be promoted by immunosenescence. Given the increased longevity and aging of the HIV-infected population, an increase in KS in future years is possible. In this regard, a recent study of T-lymphocyte phenotype in AIDS-associated KS occurring in the setting of controlled HIV suggested KS is associated with immunologic disturbances generally associated with aging, including decreased naive (CD27+CD28+) T-cells and a skewing towards a immunosenescence phenotype (CD57+CD28-) T-cells[79]. Evaluation of the risk of KSHV-associated malignancies in an aging population of HIV/KSHV co-infected populations remains an important research area.

In contrast to the epidemiology of KS, which has been extensively studied, relatively little is known about the epidemiology of KSHV-MCD and PEL, in part because these diseases are relatively newly described. Also, KSHV-MCD is not monitored in cancer registries, and PEL was only recently included. There is some evidence that KSHV-MCD incidence has increased in the cART era[80]. Interestingly, there may be virus-specific risks for KSHV-MCD, as polymorphisms in KSHV-encoded microRNA (miRNA) appear to be related to MCD and other inflammatory manifestations of KSHV[81]. PEL is generally viewed as arising primarily in HIV patients with low CD4+ counts; however, recent data indicates that it can arise in patients with relatively preserved CD4+ counts and even in HIV-negative individuals.

Pathogenesis of KSHV-associated Tumors

KSHV can infect a variety of cells including those of endothelial lineage, monocytes, and B cells. While PEL and MCD are B cell lymphoproliferative disorders, KS is an angioproliferative tumor that is endothelial in origin[82]. KSHV has a large double stranded DNA genome that encodes for a number of mimics of human genes, several of which have immunologic or angiogenic properties[83, 84]. The KSHV genome is encoded in a circularized, extra-chromosomal episome, which is tethered to the host chromosome, thus maintaining its replication during host cell division. Like other herpesviruses, it has two main programs in cells: latent infection, in which only a few genes are expressed and lytic infection in which multiple genes are expressed and viral replication occurs. Lytic replication can be induced by a number of factors, including hypoxia[85], oxidative stress[86], or co-infections with agents including HIV[87]. In addition, lytic activation can be induced by certain cytokines or exposure to certain chemicals, including those that have histone deacetylase or proteasome inhibitor activity[88, 89]. Lytic activation is largely coordinated by a virally encoded replication and transcription activator, *Rta*, which in turn activates other lytic genes[90]. Some KSHV-

encoded genes, such as a viral homologue of interleukin-6 (vIL-6) are expressed at low levels during latency, but upregulated with lytic activation[91]. While the primary function of latency-expressed genes is to enable chronically infected cells to remain in the body, in part through immune evasion, these same genes, as well as some lytically expressed genes can also promote tumorigenesis. KSHV-associated malignancies can be seen as an accidental byproduct of KSHV's survival strategies, particularly those aimed at developing persistent infection and thwarting cellular defenses against viral infection. The potential contributions of individual latent and lytic KSHV gene products vary by tumor type. In KS and PEL, the predominant populations of tumor cells harbor latent KSHV, and only up to 5% of cells undergo lytic replication at any time[92]. In KSHV-MCD, however, a higher percentage of the plasmablasts express vIL-6, and to a lesser extent, a fuller array of lytic genes, which are important in the pathophysiology of MCD. Several KSHV genes of interest are discussed below.

KSHV latently expressed genes

The KSHV latent genes include open reading frame (ORF)K12/Kaposin, ORF71/K13/vFLIP, ORF72/v-Cyclin, ORF3/LANA, ORFK10.5/LANA-2/vIRF3, and the 12 virus-encoded miRNAs. KSHV latent transcripts, including genes and miRNAs, function to subvert host signaling pathways and favor viral persistence.

Latency-associated nuclear antigen (LANA)

The LANA, encoded by ORF73, plays an important role in tethering KSHV to cellular histones and is required for the establishment of viral latency[93] as well as replication and maintenance of the episomal KSHV genome. It also modulates transcription of certain interferon response genes[94] and plays a role in maintaining viral latency through inhibition of *Rta*[95]. LANA also inhibits the activities of p53 and RB, thereby affecting cell cycle progression and suppressing apoptosis in the infected cells[96, 97]. In addition, LANA deregulates growth inhibitory Wnt signaling pathway by nuclear trapping of glycogen synthase kinase 3β, hence stabilizing β-catenin, and upregulating MYC expression[98]. LANA contributes to an upregulation of hypoxia inducible factor (HIF) and angiogenesis, in part by stabilizing HIF-1α and by targeting von Hippel Lindau for degradation[99].

Viral-cyclin (v-cyclin)

v-cyclin is a viral homologue of cellular cyclin D that deregulates cell cycle progression. v-cyclin interacts with cyclin dependent kinase-6 (CDK6) to mediate phosphorylation of target proteins. v-cyclin-CDK6 plays a role in maintaining viral latency through phosphorylation of the histone chaperone, nucleophosmin (NPM1)[100], which then interacts with LANA. v-cyclin-CDK6 also mediates phosphorylation and subsequent downregulation of Rb[101] and inhibition of p27(Kip1)[102], which contribute to blocking G1 cell cycle arrest.

Viral FLICE-inhibitory protein (*vFLIP*)

vFLIP is a viral homologue of FLIP[103]. It activates nuclear factor-κB (NF-κB) signaling by binding to the inhibitor of IκB kinase-γ[104]. *In vitro* and mouse model experiments implicate vFLIP in both endothelial derived spindle cell tumors[105] and PEL[106]. Constitutive NF-κB

activation by vFLIP leads to enhanced *IRF4* gene transduction[107] that may contribute to PEL oncogenesis, as well as upregulation of antiapoptotic members of the Bcl-2 family[106]. Interestingly, vFLIP also suppresses autophagy, an important pro-oncogenic activity, by preventing the autophagocytosis associated protein ATG3 from binding and processing microtubule associated protein light chain 3[108]. vFLIP activation of NF-κB also leads to transcriptional upregulation of NF-κB-responsive genes that are involved in inflammation and immune responses[107], thereby playing an important role in modulating the tumor microenvironment in KSHV-associated malignancies.

Kaposins

Kaposins are proteins encoded by the alternatively spliced ORF K12. Kaposin A is a latent protein with transforming potential in rodent fibroblasts[109]. Kaposin B functions as adapter protein in signal transduction by binding to MK2, a MAPK-associated protein kinase. Kaposin B-mediated activation of MK2 blocks the decay of mRNAs with AU-rich elements (AREs) in their 3′ untranslated regions. Kaposin B stabilization of prospero homeobox 1, PROX1 mRNA specifically may play an important role in tumorigenesis through lymphatic reprogramming of KSHV-infected endothelial cells[110]. Additionally, several cytokine mRNAs have ARE elements, and kaposin B expression results in an increase in the production of pro-inflammatory cytokines[111]. Like, vFLIP, kaposin A and kaposin B are likely to contribute to the inflammatory microenvironment of KS.

Viral interferon response factor-3/ latency associated nuclear factor-2 (vIRF-3/LANA-2)

KSHV encodes 4 viral interferon response factors (vIRF1-4), which are homologues of cellular IRFs[112]. While vIRF1, 2 and 4 are generally considered lytic genes, vIRF3, also known as LANA-2, is constitutively expressed in KSHV infected hematopoietic cells and thus considered a latent gene[113]. However, it is not expressed in KS. There is evidence that vIRF-3 is required for proliferation and survival of PEL cells *in vitro*[114]. Besides its effect on proliferation, vIRF-3 also stabilizes HIF-1α and contributes to upregulation of vascular endothelial growth factor (VEGF)[115].

KSHV-encoded microRNAs

More recently, miRNAs derived from 12 precursor miRNAs (pre-miRNAs) were identified in the latency locus of the KSHV genome[116]. miRNA are approximately 22-nucleotide single stranded RNAs that inhibit the translation of mRNAs. Recent studies indicate they contribute to KSHV induced growth transformation by targeting cellular genes, including regulatory members of the NF-κB pathway[117]. Additionally these miRNAs are thought to influence endothelial cell differentiation and angiogenesis. At least four KSHV miRNAs, including an orthologue of cellular miR-155, target the cellular oncogene MAF to induce reprogramming of lymphatic endothelial cells[116]. Other activities of distinct KSHV miRNAs include targeting of TWEAKR, IRAK1, and MYD88, resulting in downregulation of IL-8 and other inflammatory cytokines, and upregulation of HIF-1α[118, 119], as well as targeting of C/EBPβ leading to upregulation of IL-10[120].

Select KSHV-genes expressed during lytic induction

During lytic infection, KSHV expresses a number of lytic proteins that enable viral replication and production of infectious progeny; this process eventually leads to cell death. Additionally, various KSHV lytic genes can have effects on the host cell, resulting in reprogramming of cellular metabolism, upregulation of survival pathways, stimulation of angiogenesis and inflammation, and escape of immune control. In tumors caused by Epstein-Barr virus (EBV), latent genes are considered most important for tumor development. However, in the case of KSHV, there is evidence that some lytic genes also play key roles in oncogenesis. Select KSHV-encoded lytic genes are discussed below.

Viral interferon response factors (vIRFs)

As noted, KSHV encodes for 4 vIRFs; vIRF-3 has been previously mentioned. The expression of the other vIRFs is low during latency but is induced during lytic infection[113, 121]. Major functions of vIRFs are modulation of interferon signaling, immune evasion through downregulation of MHC-I and MHC-II[122, 123], and inhibition of activation-induced death signaling[124]. However vIRFs may also play a role in oncogenesis, in part through their effects on immune evasion and downregulation of p53[113].

Viral G-protein coupled receptor (vGPCR)

KSHV ORF74 encodes a constitutively active transmembrane viral G-protein coupled receptor (vGPCR) that is a homologue of the IL-8 receptor, CXCR1. It is expressed at early phases during lytic replication[125] and confers important tumorigenic properties. Transgenic expression of vGPCR results in angioproliferative tumors resembling KS in mice[126], suggesting that it may have a key role in KS pathogenesis. vGPCR induces the activation of MAPKs, PI3K/AKT and NF-κB anti-apoptosis pathways resulting in endothelial cell survival and proliferation[127, 128]. vGPCR has a prominent role in the angiogenic switch in infected cells. vGPCR activates secretion of VEGF[128, 129] via MAPK phosphorylation of HIF-1α[129] and through activation of the PI3K-AKT-mTORC1 pathway, making mTOR a potential therapeutic target in KS[130]. Moreover, vGPCR activates other pro-angiogenic and inflammatory cytokines[131]. Through paracrine interactions with other growth factors and by directly triggering the PI3K-AKT pathway, vGPCR in concert with other lytic proteins K1, and ORF45 can activate mTORC1[130], which has important effects on protein synthesis, suppression of autophagy, and regulation of cellular metabolism that facilitate proliferation of tumor cells.

Viral interleukin-6 (vIL-6)

KSHV encoded vIL-6 is expressed at low levels during latency, and is upregulated during lytic activation[91, 132]. Unlike its cellular IL-6 homologue, whose signaling requires binding of both gp80 (IL-6Rα) and gp130, vIL-6 binding and signaling occurs through gp130 alone[133]. In a xenographic mouse model, vIL-6 leads to a phenotype similar to that seen in MCD[134]. vIL-6 can be detected in serum of patients with KSHV-MCD and KICS[135, 136] as well in pleural effusions in patients with PEL[137]. Much of vIL-6 activity occurs through binding gp130 intracellularly in the endoplasmic reticulum compartment[138]; however vIL-6 also appears to play an important role in the pathogenesis of MCD and other KSHV tumors

through additional autocrine and paracrine mechanisms[134, 139]. vIL-6 collaborates with human IL-6 for full expression of a MCD phenotype in mice[140], although some cases of symptomatic KSHV-MCD in humans have elevated vIL-6 but normal human IL-6 serum levels[136]. vIL-6 along with other viral-encoded factors such as vMIP-I, vMIP-II, and vMIP-III have proangiogenic properties in several experimental systems[83, 134].

Clinical characteristics and management of KSHV-associated malignancies and related conditions

Kaposi Sarcoma

KS lesions typically involve the skin or mucosal surfaces. They are purplish, reddish blue or dark brown/black macules, plaques, and nodules that may bleed and ulcerate easily. With extensive spread, KS lesions may become cosmetically disfiguring and associated with lymphedema, pain, and secondary infection (Figure 1). Age of presentation varies between epidemiologic subtypes of KS, with AIDS and transplantation-related KS more commonly affecting younger patients. Besides age at presentation, other clinical differences exist. Outside the setting of immune suppression, KS usually occurs in the lower extremities, and may have a more indolent course. Post-transplantation KS and AIDS-associated KS may be more diffuse in presentation, often involving the face or trunk or lymph nodes[141], oral mucosa, and visceral organs. Visceral disease sometimes occurs in the absence of skin lesions. Besides lung and gastrointestinal (GI) involvement, KS has been observed in the liver, pancreas, heart, testes, bone marrow, bone, and skeletal muscle. In HIV-infected children, severe KS, often involving lymph nodes has been described[142]. Similar presentations occasionally occur in adults with HIV or transplant-related immunosuppression.

Biopsy is required for definitive diagnosis. Characteristic angioproliferative histologic features include a variable combination of spindle-shaped cells, aberrant proliferation of leaky blood vessels with extravasated erythrocytes, and inflammatory infiltrates. Immunohistochemical staining of biopsy specimens is generally performed to confirm diagnosis by detection of KSHV LANA within the spindle cells. KS spindle cells are proliferating KSHV-infected endothelial cells that have undergone reprogramming and differentiation[143]. Immunohistochemistry studies to demonstrate panendothelial cell markers such as CD31, CD34, and Factor VIII, as well as markers of lymphatic endothelial cells, such as lymphatic vessel endothelial receptor 1[144] are sometimes useful to support a diagnosis of KS. The leukocyte infiltrates often predominantly involve CD3+ T-cells and CD68+ macrophages[145]. Regressed lesions frequently lack spindle cells, but in partially regressed cases may have some residual spindle cells. More often, regressed lesions have residual perivascular lymphocytes and hemosiderin-laden macrophages that may be responsible for a residual darkening of the skin in the absence of tumor cells[146].

In evaluating patients with KS, the extent of cutaneous disease should be documented, as well as any tumor associated phenomenon such as edema, pain or ulceration. Complete physical exam should include evaluation of the oral palate and rectal exam with evaluation of fecal occult blood. Evaluation for visceral disease is reserved for patients with symptoms,

adenopathy, occult blood in the stool, or unexplained iron deficiency anemia. Patients with respiratory symptoms require chest imaging and bronchoscopy, while those with unexplained gastrointestinal symptoms, iron deficiency or fecal occult blood require GI endoscopic evaluation (Figure 1). Patients with adenopathy or B-symptoms should undergo computerized tomography (CT) imaging of the neck, chest, abdomen and pelvis to evaluate for concurrent KSHV-associated lymphoproliferative disorders.

AIDS-associated KS is usually staged according to the classification developed by the AIDS Clinical Trials Group (ACTG) Oncology Committee[147, 148]. As KS is of viral etiology, tumor, node, metastasis (TNM) staging as used in other sarcomas is not appropriate. The ACTG TIS staging system risk-stratifies patients (low risk subscript 0, high risk subscript 1) based on tumor burden ($T_{0\ or\ 1}$), immune status ($I_{0\ or\ 1}$), and presence of any systemic illness ($S_{0\ or\ 1}$). For tumor burden (T), poor risk (T_1) is defined by the presence of extensive cutaneous or oral disease, tumor-associated edema, ulceration or visceral disease; for immune status, poor risk (I_1) is defined by CD4+ <150 cells/mm^3 (I_1); and for systemic illness, poor risk (S_1) is defined by the presence of other opportunistic infections, constitutional symptoms, or poor performance status. The ACTG staging system was developed and initially validated in the pre-cART era. In the cART era, baseline CD4+ count appears relatively less important, with a cut-off of 100 cells/mm^3 a significant predictor of death in some studies[149] but not others[150], and it has been proposed that patients can largely be dichotomized into two main risk categories: good risk (T_0S_0, T_1S_0, or T_0S_1) and poor risk (T_1S_1)[150].

Despite improvements in overall survival, in the cART era, patients with AIDS-associated KS have an increased risk of death, especially in the first year after starting cART, compared to other HIV-infected patients, even after correcting for CD4+ counts[151]. HIV-infected patients starting cART occasionally demonstrate new KS or KS progression, and an immune reconstitution inflammatory syndrome (IRIS) has been proposed that may contribute to morbidity and mortality[149]. Additionally, in AIDS-associated KS, several studies have demonstrated that women and patients with pulmonary disease have a worse prognosis[149, 150]. There is no validated staging system for KS in other epidemiologic groups. Nonetheless, the approach to the initial evaluation for extent of KS should be similar.

For patients with KS associated with AIDS or other immunodeficiency, correcting the immunodeficiency should be done when possible. Effective control of HIV viremia with cART is imperative in patients with AIDS-KS and in patients with limited KS, is often sufficient[152]. While there is some pre-clinical evidence that HIV protease inhibitors have specific anti-KS activity, most studies indicate that prevention or control of KS is related to the degree of control of HIV, rather than the specific cART regimen utilized[153] Additional studies, however, will be needed to clarify this issue. In renal transplant patients on cyclosporine-based immunosuppression, switching to the mTOR inhibitor, sirolimus, has been associated with tumor regression[154]. Steroids can exacerbate KS in both HIV and transplantation patients, and their use should be minimized or avoided when possible.

The goal of KS specific therapy in all patients with KS is symptom palliation and improved quality of life. In patients with limited KS and either no immune dysfunction or those on cART or appropriate post-transplant therapy, observation is reasonable. Indications to administer specific KS therapy include cutaneous disease that is rapidly progressive, bulky, causing pain or lymphedema, impairing function, or causing psychological distress. Visceral disease generally requires KS specific therapy, occasionally urgently in the setting of severe pulmonary KS. Although KSHV infection cannot be eradicated, long-term remissions are possible, especially in patients whose immune system can be modulated by cART or, for transplant patients, a change in immunosuppression. For other patients chronic intermittent therapy may be needed, and limiting cumulative toxicities is important. Information on the effectiveness of treatments of KS is largely from either prospective studies in patients with AIDS-associated KS (Table 1)[149, 155-166], or retrospective series.

Localized, symptomatic lesions are sometimes treated using local approaches, such as intralesional injection of low dose vinblastine (0.1mL of 0.1mg/mL), liquid nitrogen, laser therapy, localized radiotherapy or surgical resection. Topical 9-*cis*-retinoic acid (Panretin gel) is approved by the FDA for KS, and is associated with up to a 45% response in treated lesions. However, all of these approaches only treat limited areas of disease and have toxicities that often limit their utility. Surgical intervention is rarely indicated, except to make a pathological diagnosis or to remove or debulk a single lesion that is dangerous or particularly symptomatic by virtue of its location, (e.g. urethral or airway obstruction). Systemic therapies are often required for patients with symptomatic relatively localized disease, especially in those for whom additional immune modulation is not anticipated to further control KS.

In patients with KS requiring systemic therapy, pegylated liposomal doxorubicin (Doxil™) or liposomal daunorubicin are usually the first-line choice where available. In randomized multicenter trials in patients with AIDS-associated KS, each of these agents was as effective as or superior to the previously utilized conventional combination chemotherapy (bleomycin and vincristine with or without doxorubicin) in terms of response rates, and had a better toxicity profile[155, 157]. Liposomal doxorubicin 20 mg/m^2 every 3 weeks is considered by many physicians to be the first-line therapy for patients with KS requiring chemotherapy. In the cART era, response rates in AIDS-associated KS range from 45 to 85% depending on the extent of disease and immune status of the baseline population. While risk of cardiac toxicity from liposomal anthracyclines is substantially less than that from bolus non-liposomal anthracyclines, the FDA warns against cumulative lifetime doses exceeding 550 mg/m^2, and cardiac monitoring is required for patients approaching or exceeding this value. Palmar-plantar erythrodysesthesia or cumulative bone marrow toxicity may also limit the use of liposomal doxorubicin.

Paclitaxel, a microtubule stabilizing agent with anti-angiogenic properties, is FDA approved as second-line treatment for KS[167, 168], and may be an alternative first-line treatment, though it is generally less well tolerated than liposomal doxorubicin[161]. Response rates range from 59%-71% in phase II studies. Paclitaxel 100 mg/m^2 every two weeks is a common dosing schedule. Adverse events include neuropathies, cytopenias, and alopecia. Other agents with activity in KS include vincristine, vinblastine, vinorelbine[166], bleomycin and etoposide[164].

Oral etoposide 50 mg/day on days 1 through 7 of a 14-day cycle has an overall response rate of 36% in previously treated patients[164], and this approach may be useful in resource-limited settings, although the risk of secondary myeloid leukemia is a concern with long-term administration.

Because of the cumulative toxicities of existing therapies together with the frequent need for periodic retreatment of KS, improved and less toxic therapies are needed. Various targeted and immunomodulatory approaches have been evaluated in KS. The best-studied agent, interferon-α (IFN-α), is a cytokine with immune modulatory, anti-viral, and anti-angiogenic activity. In HIV-associated KS, it is best utilized for patients with limited disease and preserved CD4+ counts[169]. Systemic side effects including constitutional symptoms, cytopenias, mood disturbances including major depression, and hypothyroidism are common and may be severe. Most practitioners begin with IFN-α 1 to 5×10^6 units subcutaneous injection daily and gradually increase the dose as tolerated. IFN-α should be used in combination with cART in AIDS-associated KS[169]. Subcutaneous interleukin-12, a cytokine that enhances type I immunity, has anti-angiogenic effects, and downregulates vGPCR, was found to have a 71% overall response rate in AIDS-associated KS. The side effect profile was similar to that of IFN-α. Thalidomide is a small molecule immunomodulatory agent that also has direct anti-tumor and anti-angiogenic effects and was shown to have a 35-47% overall response rate, but it can be associated with neurologic side effects[170, 171]. Second and third generation immunomodulatory derivatives (IMiDs) of thalidomide, lenalidomide (NCT01057121) and pomalidomide (NCT01495598), are currently being evaluated for the treatment of KS. Interestingly, IMiD activity is mediated at least in part through binding to cereblon, a protein that is part of E3 ubiquitin ligase. The mTOR inhibitor, sirolimus, which targeting downstream effectors of the vGPCR appears particularly useful in transplant associated KS, but is less useful in AIDS-associated KS, and may have many drug-drug interactions with common anti-retroviral agents[154, 172].

Several approaches targeting angiogenesis and the tumor microenvironment have been evaluated prospectively in the therapy of AIDS-associated KS. Matrix metalloproteinases (MMP) are highly expressed in KS lesions and may contribute to angiogenesis via degradation of extracellular matrix. A Phase II study of the MMP inhibitor COL-3 demonstrated a 41% overall response rate[173]. Activation of the c-kit and platelet-derived growth factor receptor (PDGFR) signaling is implicated in the induction of angiogenesis and growth of KS cells. Imatinib, a partially selective blocker of c-kit and PDGFR, induced partial response in one third of AIDS-associated KS patients when given for up to 52 weeks in a multicenter phase II study by AIDS Malignancy Consortium[174]. In a phase II study, the monoclonal anti-VEGF antibody, bevacizumab had an overall response rate of 31%[175], and evaluation of sorafenib, a tyrosine kinase inhibitor with activity against several VEGF receptors as well as PDGFR is underway (NCT00287495). Angiogenesis inhibitors may have a role in combination therapy, and the combination of bevacizumab with liposomal doxorubicin is being evaluated (NCT00923936).

Several antiviral agents including ganciclovir, foscarnet, and cidofovir have been shown to inhibit KSHV replication *in vitro*[176], and ganciclovir when used to treat CMV retinitis lowered the risk of KS in patients with AIDS in a study conducted in the pre-cART era[177].

However, anti-herpetic agents have not been shown to have activity in treating established KS. Further studies of antiviral agents may be warranted in select patients with KSHV-associated malignancies (see KSHV-MCD and KICS).

KSHV-associated multicentric Castleman disease (KSHV-MCD)

KSHV is the etiologic agent of a plasmablastic form of MCD that is most common in the setting of HIV but can also arise in transplant recipients and in other HIV-negative patients. Unlike KS, KSHV-MCD appears to be becoming more frequent with the widespread use of cART[80]. KSHV-associated MCD has some clinical overlap with an IL-6-related spectrum of diseases known as idiopathic (KSHV-negative) MCD. Despite high KSHV and HIV seroprevalence in some parts of Africa, KSHV-MCD has rarely been reported. Our group has seen a number of cases in African immigrants[81], and it is possible that KSHV-MCD is relatively common, but underdiagnosed and underreported in Africa.

Clinically, KSHV-MCD is dominated by intermittent flares of inflammatory symptoms, including fevers, night sweats, fatigue, and cachexia, and edema, together with lymphadenopathy and/or hepatosplenomegaly[178]. Non-specific respiratory and GI symptoms are also common. Pulmonary symptoms often include cough or dyspnea. Rashes after administration of drugs such as trimethoprim-sulfamethoxazole are commonly reported in patients with symptomatic KSHV-MCD. Patients may have waxing and waning course with exacerbations and subsequent remissions. Symptom flares can at times be severe and fatal. Without therapy, patients generally die from severe inflammatory syndromes, multiorgan failure, or concurrent infections. Hemophagocytic syndromes have also been described. Concomitant KS is present in up to 70% of individuals. Some patients with KSHV-MCD progress to large B-cell lymphoma arising in KSHV-associated MCD (previously described as “plasmablastic lymphoma”), which lacks EBV infection, or else PEL.

KSHV-MCD symptoms are thought to be caused by an excess of certain cytokines, especially human IL-6, KSHV vIL-6, and human IL-10[179]. Several KSHV genes are implicated in upregulating human IL-6, including vFLIP, vGPCR and kaposin B through activation of NF-kB[180, 181]. vIL-6 is believed to play an important role in pathogenesis of KSHV-MCD, which may be independent or complimentary to that of human IL-6[106, 136, 182].

Common laboratory abnormalities of KSHV-associated MCD include anemia, cytopenias, hypoalbuminemia, hyponatremia, hypergammaglobinemia and elevated inflammatory markers such as C-reactive protein (CRP)[179]. Flares are typically associated with high KSHV viral loads[179, 183]. A high index of suspicion is necessary, as the differential diagnosis of fever and adenopathy, even with other laboratory abnormalities, in HIV infected individuals is quite broad[183].

The diagnosis of KSHV-MCD is based on a biopsy. Affected lymph nodes demonstrate involuted germinal centers with vasculature hyperplasia and expansion of KSHV-infected and reactive interfollicular plasmablasts, which are polyclonal but monotypic, expressing IgM lamdba. Using immunohistochemical stains for LANA and vIL-6, KSHV-infected cells

are found predominantly in the mantle zones and centers of the follicles but are also seen scattered as single cells in the interfollicular area[184]. The majority of the cells within affected nodes however are reactive plasmacytoid B-lymphocytes, and only a portion of KSHV-infected cells express KSHV vIL-6 and other lytic genes[184]. Concurrent microscopic KS is often noted in the same lymph node with MCD[185]. In pathology cases suspicious for lymphoma, IgH gene rearrangement studies for B cell clonality, EBV testing, and flow cytometry should be performed on the lymph node or effusions (if present) to rule out a clonal disorder (e.g. PEL)[186].

There is no single consensus definition of KSHV-MCD flare or symptomatic activity. The French ANRS (Agence Nationale de Recherche sur le SIDA) CastlemaB trial group and the NCI have each described criteria to evaluate MCD flares that require therapy[68, 186] based on clinical symptoms and laboratory abnormalities. KSHV-viral load has at times been used to assess symptomatic patients with KSHV-MCD[187], although assays vary between groups and elevated KSHV viral load is not-specific for KSHV-MCD, and therefore should not be performed in place of a biopsy. Patients with KSHV-MCD should undergo CT of the neck, chest, abdomen, and pelvis to evaluate the degree of adenopathy and splenomegaly and to assess other potential abnormalities. CT-imaging generally shows diffuse, symmetric adenopathy and hepatosplenomegaly (Figure 2). ^{18}Fluorodeoxyglucose positron emission tomography is sometimes used to evaluate for concurrent lymphoma. Patients with effusions should undergo pathologic evaluation for PEL. Patients with concurrent KS should be staged as noted above.

There is no standard therapy for KSHV-MCD. HIV positive patients with KSHV-MCD are generally treated with concurrent cART in addition to specific therapy[188]. The reduction in HIV viral load and improvement in immune function associated with cART is expected to result in better KS outcome and may decrease inflammatory triggers of KSHV-lytic activation[87]. Specific treatment directed at KSHV-MCD is generally reserved for symptomatic patients. In critically ill patients, treatment may have to be instituted in the setting of an intensive care unit.

Emerging evidence supports the use of rituximab, given alone or in conjunction with chemotherapy. It is postulated that rituximab targets a small fraction of KSHV-infected malignant cells exhibiting low-level expression of CD20, but a major mechanism of action may be elimination of reactive B cells, thus depriving the KSHV-infected plasmablasts of proliferation and survival signals by breaking virus and cytokine driven feedback loops with the reactive B cells. Rituximab monotherapy 375 mg/m^2 weekly for 4 weeks has been evaluated in two prospective studies[67, 68, 189]. In both studies more than 90% patients had sustained resolution of their MCD attack and one study reported two-year overall survival of 95% with one- and two-year relapse-free survivals of 92 and 79%, respectively. The commonest side effect of rituximab is an infusion reaction during the first dose, which can be managed by holding the infusion, and resuming at a slower rate after administration of appropriate supportive care. A retrospective study showed significant decrease in the incidence of NHL in patients who had been treated with rituximab (hazard ratio, 0.09; 95% confidence interval, 0.01-0.70) compared with those who were not[190].

For patients with evidence of organ failure, poor performance status related to the disease, or concurrent or worsening KS, the addition of concurrent chemotherapy is an important consideration. Rituximab was associated with exacerbations of cutaneous KS in 35-67% of patients in prospective studies. Rituximab 375 mg/m^2 in combination with liposomal doxorubicin 20 mg/m^2 in patients with concurrent KSHV-MCD and Kaposi sarcoma or severe KSHV-MCD is being evaluated prospectively (NCT00099073) and preliminary results reveal that this combination is highly effective, even in heavily pretreated patients.

KSHV-targeted virus activated cytotoxic therapy using high dose zidovudine and valganciclovir has also been evaluated in patients with symptomatic KSHV-MCD, based on the rationale that KSHV-encoded ORF36 and ORF21 phosphorylate these agents to triphosphate moieties that are toxic to cells[191]. Zidovudine 600 mg orally every 6 hours combined with valganciclovir 900 mg orally every 12 hours generally administered days 1-7 of a 21-day cycle was associated with an 86% major clinical response rate using NCI KSHV-MCD response criteria; however, median time to progression was 6 months[192].

Human IL-6 is an important to the pathogenesis of MCD, and siltuximab, a chimeric anti IL-6 monoclonal antibody, was approved by the FDA for treatment of KSHV-negative MCD. However, because vIL-6 is antigenically different from human IL-6, a potential role for siltuximab in the treatment of KSHV-MCD remains to be explored. We are currently conducting a clinical study of tocilizumab, a humanized monoclonal antibody targeted at anti-IL-6 receptor (gp80), in patients with symptomatic KSHV-MCD (NCT01441063). While human IL-6 is elevated in KSHV-MCD and contributes to symptoms and disease pathogenesis, given the additional role of vIL-6 and other KSHV genes, it is unknown whether anti-human IL-6 therapy alone will be sufficient. For KSHV-MCD, therapies targeting human IL-6 might optimally be combined with complementary pathogenesis-based treatments such as high dose zidovudine combined with valganciclovir.

KSHV Inflammatory Cytokine Syndrome (KICS)

Inflammatory symptoms similar to those in KSHV-MCD have been described in KSHV-infected patients without KSHV-MCD[135]. As in KSHV-MCD, symptoms may include fevers, cachexia and laboratory abnormalities including cytopenias, hypoalbuminemia, and elevated CRP and elevated KSHV viral load. However, splenomegaly, and lymphadenopathy do not appear to be prominent features, and KSHV-MCD should be excluded through evaluation for adenopathy and biopsy of pathologically enlarged nodes if noted. This syndrome has been provisionally named KSHV inflammatory cytokine syndrome (KICS) and a working case definition that includes at least two characteristic clinical abnormalities, elevated CRP, elevated KSHV viral load, and exclusion of KSHV-MCD has been proposed. Disturbances of vIL-6, human IL-6 and IL-10 similar to those seen in KSHV-MCD contribute to KICS pathophysiology[135], although the source of vIL-6 is unknown at this time. KICS may accompany KSHV-associated tumors (KS or PEL) or occur in their absence.

Primary effusion lymphoma (PEL)

PEL accounts for 1-4% of all AIDS-related lymphomas. PEL occurs primarily in HIV-infected patients, but also may be seen following solid organ transplantation, in elderly patients, and in chronic hepatitis C virus infection. Besides being KSHV infected, in 70-80% of cases, the lymphoma cells have co-existing EBV infection[5]. Gene expression profiling has shown that PEL cells, unlike other AIDS-related NHLs, are not of germinal center or memory cell origin; rather, they more likely correspond to a post-germinal stage of B cell development, intermediate between that of immunoblasts and plasma cells, with only partially activated uncoupled protein response[193, 194]. Other human genes upregulated in gene expression profiling include *IRF4, VDR, VEGF*, as well as integrins, which may be involved in leukocyte extravasation. Gene amplification of the selectin-P ligand (*SELPG*), also associated with cell migration, has also been described in some cases[195].

PEL is classically characterized by lymphomatous effusions; pleural involvement is the most common, seen in 60 to 90% of patients, followed by involvement of other body cavity membranes, including peritoneal (30 to 60%), pericardial (up to 30%), joint spaces, and rarely meninges[196, 197]. An extracavitary variant of PEL has been recognized[198], and indeed PEL can involve the GI tract, lung, central nervous system (CNS), skin, and lymph nodes[198]. PEL is often associated with other KSHV-associated malignancies, such as KS and KSHV-MCD. Recent studies by our group have shown that PEL patients with no pathologic evidence of KSHV-MCD generally have MCD-like symptoms and laboratory abnormalities and meet criteria for KICS; essentially all PEL patients presented with inflammatory symptoms, elevated CRP, hypoalbuminemia, and cytopenias. Severe KICS associated laboratory abnormalities such as hypoalbuminemia and thrombocytopenia have been associated with inferior survival in patients with PEL[197].

Diagnosis of PEL requires the demonstration of KSHV in the neoplastic cells, which may vary in morphology from anaplastic to large cells with immunoblastic or plasmablastic features. EBV co-infection can be demonstrated through *in situ* staining for EBV encoded small RNAs. PEL cells have a characteristic phenotype highlighted by CD45, CD30, CD38, CD138 and IRF4 co-expression. Classic B-cell markers (CD19, CD20) are often not seen, however, clonal rearrangements of heavy and light chain immunoglobulin genes can be demonstrated[196, 198]. PEL can sometime have aberrant expression of T-cell markers (CD3, CD7)[199], although often these and other T-cell markers (CD2, CD4, CD5, and CD8) are also not seen. Classic PEL should be differentiated from lymphomas complicated by effusions (a.k.a. secondary lymphomatous effusion), which may mimic phenotypic clinical features of PEL but are devoid of KSHV infection. Complex and recurrent cytogenetic abnormalities in the tumor cells have been reported in PEL. Evaluation with chest radiographs and CT of chest/abdomen/pelvis is required to document initial extent of disease. Lumbar puncture and CNS imaging should be performed to evaluate for CNS involvement, and endoscopy should be performed if clinically indicated based on symptoms. Bronchoscopy may be important to exclude concurrent infections. Patients with concurrent KS should be evaluated as noted above.

There is no standard therapy for PEL. The effectiveness of combination chemotherapy with or without cART in patients with PEL has been evaluated in uncontrolled retrospective

series. Historically, median survival ranges between 3 to 9 months; with 2-year overall survival rates of 33 to 39% in reported series employing CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like regimens[197]. Evaluation of pathogenesis-based approaches for the treatment of PEL is urgently needed. Bortezomib, a proteasome inhibitor that induces KSHV-lytic activation, has demonstrated activity in preclinical studies and is being evaluated in combination with chemotherapy as second-line therapy in patients with EBV and KSHV-associated lymphomas (NCT00598169). Other targeted agents that have demonstrated activity in mouse models include the mTOR inhibitor, sirolimus[200], and the anti-CD30 immunotoxin, brentuximab vedotin[201]. Although PEL is a CD20-negative tumor, advances in the understanding the biology of KSHV-infection of B-cells[189] in relation to the pathobiology of IL-6 syndromes, and frequent clinical overlap with KSHV-MCD support a role for use of rituximab in the treatment of PEL, especially in patients with concurrent KSHV-MCD. Clinical experience using novel approaches is scant and clinical trials will be critical to advance the field and improve outcomes for patients with PEL.

CONCLUSIONS

KSHV-associated malignancies continue to cause substantial morbidity and increased mortality in HIV-infected and transplant patients, as well as some non-immunosuppressed patients in areas of the world with high KSHV seroprevalence. Improved therapies for KS are needed, both for the developed world and for resource-limited regions where infusional therapy is often challenging to administer. KSHV-associated lymphoproliferative disorders are increasingly recognized, but likely remain under diagnosed in sub-Saharan Africa. The heterogeneity of KSHV-associated malignancies likely reflects the interplay of various pathophysiologic mechanisms including chronic antigenic stimulation, immunosuppression, genetic abnormalities, cytokine release and dysregulation, and co-infection with HIV. Increased recognition that inflammatory manifestations of KSHV-associated malignancies such as KSHV-MCD, KICS and KS-IRIS can be associated with a high mortality, especially in the setting of HIV, is leading to more comprehensive initial evaluation of such patients, and can be expected to lead to new diagnostic and therapeutic approaches. An improved understanding of KSHV-mediated oncogenesis is providing exciting opportunities for development of targeted and immune-modulatory treatment approaches in each of the major KSHV-associated malignancies that employ small molecules or monoclonal antibodies. Effective oral agents that can be used in resource-limited settings are urgently needed.

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References

1. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi’s sarcoma. Science. 1994; 266:1865–9. [PubMed: 7997879]
2. Moore PS, Chang Y. Detection of herpesvirus-like DNA sequences in Kaposi’s sarcoma in patients with and without HIV infection. N Engl J Med. 1995; 332:1181–5. [PubMed: 7700310]

3. Chang Y, Ziegler J, Wabinga H, Katangole-Mbidde E, Boshoff C, Schulz T, et al. Kaposi's sarcoma-associated herpesvirus and Kaposi's sarcoma in Africa. Uganda Kaposi's Sarcoma Study Group. Arch Intern Med. 1996; 156:202–4. [PubMed: 8546554]

4. Dupin N, Grandadam M, Calvez V, Gorin I, Aubin JT, Havard S, et al. Herpesvirus-like DNA sequences in patients with Mediterranean Kaposi's sarcoma. Lancet. 1995; 345:761–2. [PubMed: 7891488]

5. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. N Engl J Med. 1995; 332:1186–91. [PubMed: 7700311]

6. Soulier J, Grollet L, Oksenhendler E, Cacoub P, Cazals-Hatem D, Babinet P, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood. 1995; 86:1276–80. [PubMed: 7632932]

7. Cook-Mozaffari P, Newton R, Beral V, Burkitt DP. The geographical distribution of Kaposi's sarcoma and of lymphomas in Africa before the AIDS epidemic. Br J Cancer. 1998; 78:1521–8. [PubMed: 9836488]

8. Klepp O, Dahl O, Stenwig JT. Association of Kaposi's sarcoma and prior immunosuppressive therapy: a 5-year material of Kaposi's sarcoma in Norway. Cancer. 1978; 42:2626–30. [PubMed: 728865]

9. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men--New York City and California. MMWR Morb Mortal Wkly Rep. 1981; 30:305–308. [PubMed: 6789108]

10. Selik RM, Haverkos HW, Curran JW. Acquired immune deficiency syndrome (AIDS) trends in the United States, 1978-1982. Am J Med. 1984; 76:493–500. [PubMed: 6322585]

11. Beral V, Peterman TA, Berkelman RL, Jaffe HW. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? Lancet. 1990; 335:123–8. [PubMed: 1967430]

12. Whitby D, Howard MR, Tenant-Flowers M, Brink NS, Copas A, Boshoff C, et al. Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma. Lancet. 1995; 346:799–802. [PubMed: 7674745]

13. Gao SJ, Kingsley L, Hoover DR, Spira TJ, Rinaldo CR, Saah A, et al. Seroconversion to antibodies against Kaposi's sarcoma-associated herpesvirus-related latent nuclear antigens before the development of Kaposi's sarcoma. N Engl J Med. 1996; 335:233–41. [PubMed: 8657239]

14. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al. A review of human carcinogens--Part B: biological agents. Lancet Oncol. 2009; 10:321–2. [PubMed: 19350698]

15. Shiels MS, Pfeiffer RM, Gail MH, Hall HI, Li J, Chaturvedi AK, et al. Cancer burden in the HIV-infected population in the United States. J Natl Cancer Inst. 2011; 103:753–62. [PubMed: 21483021]

16. Center for Disease Control and Prevention. Estimated HIV incidence in the United States, 2007–2010. HIV Surveillance Supplemental Report. 2012

17. Wabinga HR, Nambooze S, Amulen PM, Okello C, Mbus L, Parkin DM. Trends in the incidence of cancer in Kampala, Uganda 1991-2010. Int J Cancer. 2014; 135:432–9. [PubMed: 24615279]

18. Labo N, Miley W, Marshall V, Gillette W, Esposito D, Bess M, et al. Heterogeneity and breadth of host antibody response to KSHV infection demonstrated by systematic analysis of the KSHV proteome. PLoS Pathog. 2014; 10:e1004046. [PubMed: 24675986]

19. Gao SJ, Kingsley L, Li M, Zheng W, Parravicini C, Ziegler J, et al. KSHV antibodies among Americans, Italians and Ugandans with and without Kaposi's sarcoma. Nat Med. 1996; 2:925–8. [PubMed: 8705864]

20. Simpson GR, Schulz TF, Whitby D, Cook PM, Boshoff C, Rainbow L, et al. Prevalence of Kaposi's sarcoma associated herpesvirus infection measured by antibodies to recombinant capsid protein and latent immunofluorescence antigen. Lancet. 1996; 348:1133–8. [PubMed: 8888167]

21. Mbisa GL, Miley W, Gamache CJ, Gillette WK, Esposito D, Hopkins R, et al. Detection of antibodies to Kaposi's sarcoma-associated herpesvirus: A new approach using K8.1 ELISA and a newly developed recombinant LANA ELISA. J Immunol Methods. 2010

22. Engels EA, Whitby D, Goebel PB, Stossel A, Waters D, Pintus A, et al. Identifying human herpesvirus 8 infection: performance characteristics of serologic assays. J Acquir Immune Defic Syndr. 2000; 23:346–54. [PubMed: 10836758]

23. Burbelo PD, Leahy HP, Groot S, Bishop LR, Miley W, Iadarola MJ, et al. Four-antigen mixture containing v-cyclin for serological screening of human herpesvirus 8 infection. Clin Vaccine Immunol. 2009; 16:621–7. [PubMed: 19261774]
24. Zong J, Ciufo DM, Viscidi R, Alagiozoglou L, Tyring S, Rady P, et al. Genotypic analysis at multiple loci across Kaposi's sarcoma herpesvirus (KSHV) DNA molecules: clustering patterns, novel variants and chimerism. J Clin Virol. 2002; 23:119–48. [PubMed: 11595592]
25. Osmond DH, Buchbinder S, Cheng A, Graves A, Vittinghoff E, Cossen CK, et al. Prevalence of Kaposi sarcoma-associated herpesvirus infection in homosexual men at beginning of and during the HIV epidemic. JAMA. 2002; 287:221–5. [PubMed: 11779265]
26. Whitby D, Luppi M, Barozzi P, Boshoff C, Weiss RA, Torelli G. Human herpesvirus 8 seroprevalence in blood donors and lymphoma patients from different regions of Italy. J Natl Cancer Inst. 1998; 90:395–7. [PubMed: 9498490]
27. Biggar RJ, Whitby D, Marshall V, Linhares AC, Black F. Human herpesvirus 8 in Brazilian Amerindians: a hyperendemic population with a new subtype. J Infect Dis. 2000; 181:1562–8. [PubMed: 10823754]
28. Rezza G, Danaya RT, Wagner TM, Sarmati L, Owen IL, Monini P, et al. Human herpesvirus-8 and other viral infections, Papua New Guinea. Emerg Infect Dis. 2001; 7:893–5. [PubMed: 11747707]
29. Wang X, He B, Zhang Z, Liu T, Wang H, Li X, et al. Human herpesvirus-8 in northwestern China: epidemiology and characterization among blood donors. Virol J. 2010; 7:62. [PubMed: 20236530]
30. Baillargeon J, Leach CT, Deng JH, Gao SJ, Jenson HB. High prevalence of human herpesvirus 8 (HHV-8) infection in south Texas children. J Med Virol. 2002; 67:542–8. [PubMed: 12116002]
31. Martin JN, Ganem DE, Osmond DH, Page-Shafer KA, Macrae D, Kedes DH. Sexual transmission and the natural history of human herpesvirus 8 infection. N Engl J Med. 1998; 338:948–54. [PubMed: 9521982]
32. Casper C, Wald A, Pauk J, Tabet SR, Corey L, Celum CL. Correlates of prevalent and incident Kaposi's sarcoma-associated herpesvirus infection in men who have sex with men. J Infect Dis. 2002; 185:990–3. [PubMed: 11920325]
33. Giuliani M, Cordiali-Fei P, Castilletti C, Di Carlo A, Palamara G, Boros S, et al. Incidence of human herpesvirus 8 (HHV-8) infection among HIV-uninfected individuals at high risk for sexually transmitted infections. BMC Infect Dis. 2007; 7:143. [PubMed: 18053246]
34. Sitas F, Carrara H, Beral V, Newton R, Reeves G, Bull D, et al. Antibodies against human herpesvirus 8 in black South African patients with cancer. N Engl J Med. 1999; 340:1863–71. [PubMed: 10369849]
35. Butler LM, Dorsey G, Hladik W, Rosenthal PJ, Brander C, Neilands TB, et al. Kaposi sarcoma-associated herpesvirus (KSHV) seroprevalence in population-based samples of African children: evidence for at least 2 patterns of KSHV transmission. J Infect Dis. 2009; 200:430–8. [PubMed: 19534596]
36. Wakeham K, Webb EL, Sebina I, Nalwoga A, Muhangi L, Miley W, et al. Risk factors for seropositivity to Kaposi sarcoma-associated herpesvirus among children in Uganda. J Acquir Immune Defic Syndr. 2013; 63:228–33. [PubMed: 23403859]
37. Mbulaiteye SM, Biggar RJ, Pfeiffer RM, Bakaki PM, Gamache C, Owor AM, et al. Water, socioeconomic factors, and human herpesvirus 8 infection in Ugandan children and their mothers. J Acquir Immune Defic Syndr. 2005; 38:474–9. [PubMed: 15764964]
38. Pauk J, Huang ML, Brodie SJ, Wald A, Koelle DM, Schacker T, et al. Mucosal shedding of human herpesvirus 8 in men. N Engl J Med. 2000; 343:1369–77. [PubMed: 11070101]
39. Casper C, Krantz E, Selke S, Kuntz SR, Wang J, Huang M-L, et al. Frequent and asymptomatic oropharyngeal shedding of human herpesvirus 8 among immunocompetent men. J Infect Dis. 2007; 195:30–6. [PubMed: 17152006]
40. Taylor MM, Chohan B, Lavreys L, Hassan W, Huang M-L, Corey L, et al. Shedding of human herpesvirus 8 in oral and genital secretions from HIV-1-seropositive and -seronegative Kenyan women. J Infect Dis. 2004; 190:484–8. [PubMed: 15243920]
41. Mbulaiteye SM, Biggar RJ, Bakaki PM, Pfeiffer RM, Whitby D, Owor AM, et al. Human herpesvirus 8 infection and transfusion history in children with sickle-cell disease in Uganda. J Natl Cancer Inst. 2003; 95:1330–5. [PubMed: 12953087]

42. Dukers NH, Renwick N, Prins M, Geskus RB, Schulz TF, Weverling GJ, et al. Risk factors for human herpesvirus 8 seropositivity and seroconversion in a cohort of homosexual men. Am J Epidemiol. 2000; 151:213–24. [PubMed: 10670545]
43. Kedes DH, Operskalski E, Busch M, Kohn R, Flood J, Ganem D. The seroepidemiology of human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus): distribution of infection in KS risk groups and evidence for sexual transmission. Nat Med. 1996; 2:918–24. [PubMed: 8705863]
44. Engels EA, Atkinson JO, Graubard BI, McQuillan GM, Gamache C, Mbisa G, et al. Risk factors for human herpesvirus 8 infection among adults in the United States and evidence for sexual transmission. J Infect Dis. 2007; 196:199–207. [PubMed: 17570106]
45. Beral V, Bull D, Darby S, Weller I, Carne C, Beecham M, et al. Risk of Kaposi's sarcoma and sexual practices associated with faecal contact in homosexual or bisexual men with AIDS. Lancet. 1992; 339:632–5. [PubMed: 1347337]
46. Grulich AE, Kaldor JM, Hendry O, Luo K, Bodsworth NJ, Cooper DA. Risk of Kaposi's sarcoma and oroanal sexual contact. Am J Epidemiol. 1997; 145:673–9. [PubMed: 9125993]
47. Ambroziak JA, Blackbourn DJ, Herndier BG, Glogau RG, Gullett JH, McDonald AR, et al. Herpes-like sequences in HIV-infected and uninfected Kaposi's sarcoma patients. Science. 1995; 268:582–3. [PubMed: 7725108]
48. Monini P, de Lellis L, Fabris M, Rigolin F, Cassai E. Kaposi's sarcoma-associated herpesvirus DNA sequences in prostate tissue and human semen. N Engl J Med. 1996; 334:1168–72. [PubMed: 8602183]
49. Baeten JM, Chohan BH, Lavreys L, Rakwar JP, Ashley R, Richardson BA, et al. Correlates of human herpesvirus 8 seropositivity among heterosexual men in Kenya. AIDS. 2002; 16:2073–8. [PubMed: 12370507]
50. Malope BI, MacPhail P, Mbisa G, MacPhail C, Stein L, Ratshikhopha EM, et al. No evidence of sexual transmission of Kaposi's sarcoma herpes virus in a heterosexual South African population. AIDS. 2008; 22:519–26. [PubMed: 18301065]
51. Campbell TB, Borok M, Ndemera B, Fiorillo S, White IE, Zhang X-q, et al. Lack of evidence for frequent heterosexual transmission of human herpesvirus 8 in Zimbabwe. Clin Infect Dis. 2009; 48:1601–8. [PubMed: 19400749]
52. Renwick N, Halaby T, Weverling GJ, Dukers NH, Simpson GR, Coutinho RA, et al. Seroconversion for human herpesvirus 8 during HIV infection is highly predictive of Kaposi's sarcoma. AIDS. 1998; 12:2481–8. [PubMed: 9875587]
53. Cannon MJ, Dollard SC, Smith DK, Klein RS, Schuman P, Rich JD, et al. Blood-borne and sexual transmission of human herpesvirus 8 in women with or at risk for human immunodeficiency virus infection. N Engl J Med. 2001; 344:637–43. [PubMed: 11228278]
54. Kleinman S, King MR, Busch MP, Murphy EL, Glynn SA. The National Heart, Lung, and Blood Institute retrovirus epidemiology donor studies (Retrovirus Epidemiology Donor Study and Retrovirus Epidemiology Donor Study-II): twenty years of research to advance blood product safety and availability. Transfus Med Rev. 2012; 26:281–304. 304 e1-2. [PubMed: 22633182]
55. Hladik W, Dollard SC, Mermin J, Fowlkes AL, Downing R, Amin MM, et al. Transmission of human herpesvirus 8 by blood transfusion. N Engl J Med. 2006; 355:1331–8. [PubMed: 17005950]
56. Regamey N, Tamm M, Wernli M, Witschi A, Thiel G, Cathomas G, et al. Transmission of human herpesvirus 8 infection from renal-transplant donors to recipients. N Engl J Med. 1998; 339:1358–63. [PubMed: 9801396]
57. Barozzi P, Luppi M, Facchetti F, Mecucci C, Alu M, Sarid R, et al. Post-transplant Kaposi sarcoma originates from the seeding of donor-derived progenitors. Nat Med. 2003; 9:554–61. [PubMed: 12692543]
58. Dudderidge TJ, Khalifa M, Jeffery R, Amlot P, Al-Akraa M, Sweny P. Donor-derived human herpes virus 8-related Kaposi's sarcoma in renal allograft ureter. Transpl Infect Dis. 2008; 10:221–6. [PubMed: 18086278]
59. Frances C, Marcelin AG, Legendre C, Chevret S, Dussaix E, Lejeune J, et al. The impact of preexisting or acquired Kaposi sarcoma herpesvirus infection in kidney transplant recipients on morbidity and survival. Am J Transplant. 2009; 9:2580–6. [PubMed: 19775317]

60. Pietrosi G, Vizzini G, Pipitone L, Di Martino G, Minervini MI, Lo Iacono G, et al. Primary and reactivated HHV8 infection and disease after liver transplantation: a prospective study. Am J Transplant. 2011; 11:2715–23. [PubMed: 21966899]

61. Lebbe C, Porcher R, Marcelin AG, Agbalika F, Dussaix E, Samuel D, et al. Human herpesvirus 8 (HHV8) transmission and related morbidity in organ recipients. Am J Transplant. 2013; 13:207–13. [PubMed: 23057808]

62. Biggar RJ, Chaturvedi AK, Goedert JJ, Engels EA. AIDS-related cancer and severity of immunosuppression in persons with AIDS. J Natl Cancer Inst. 2007; 99:962–72. [PubMed: 17565153]

63. Guihot A, Dupin N, Marcelin AG, Gorin I, Bedin AS, Bossi P, et al. Low T cell responses to human herpesvirus 8 in patients with AIDS-related and classic Kaposi sarcoma. J Infect Dis. 2006; 194:1078–88. [PubMed: 16991082]

64. Silverberg MJ, Chao C, Leyden WA, Xu L, Horberg MA, Klein D, et al. HIV infection, immunodeficiency, viral replication, and the risk of cancer. Cancer Epidemiol Biomarkers Prev. 2011; 20:2551–9. [PubMed: 22109347]

65. Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, et al. Trends in cancer risk among people with AIDS in the United States 1980-2002. AIDS. 2006; 20:1645–54. [PubMed: 16868446]

66. Simard EP, Pfeiffer RM, Engels EA. Cumulative incidence of cancer among individuals with acquired immunodeficiency syndrome in the United States. Cancer. 2011; 117:1089–96. [PubMed: 20960504]

67. Bower M, Powles T, Williams S, Davis TN, Atkins M, Montoto S, et al. Brief communication: rituximab in HIV-associated multicentric Castleman disease. Ann Intern Med. 2007; 147:836–9. [PubMed: 18087054]

68. Gerard L, Berezne A, Galicier L, Meignin V, Obadia M, De Castro N, et al. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus associated multicentric Castleman's disease: ANRS 117 CastlemaB Trial. J Clin Oncol. 2007; 25:3350–6. [PubMed: 17664482]

69. Engels EA, Pfeiffer RM, Fraumeni JF Jr, Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011; 306:1891–901. [PubMed: 22045767]

70. Tessari G, Naldi L, Boschiero L, Minetti E, Sandrini S, Nacchia F, et al. Incidence of primary and second cancers in renal transplant recipients: a multicenter cohort study. Am J Transplant. 2013; 13:214–21. [PubMed: 23057816]

71. Byun M, Ma CS, Akcay A, Pedergnana V, Palendira U, Myoung J, et al. Inherited human OX40 deficiency underlying classic Kaposi sarcoma of childhood. J Exp Med. 2013; 210:1743–59. [PubMed: 23897980]

72. Byun M, Abhyankar A, Lelarge V, Plancoulaine S, Palanduz A, Telhan L, et al. Whole-exome sequencing-based discovery of STIM1 deficiency in a child with fatal classic Kaposi sarcoma. J Exp Med. 2010; 207:2307–12. [PubMed: 20876309]

73. Camcioglu Y, Picard C, Lacoste V, Dupuis S, Akcakaya N, Cokura H, et al. HHV-8-associated Kaposi sarcoma in a child with IFNgammaR1 deficiency. J Pediatr. 2004; 144:519–23. [PubMed: 15069403]

74. Picard C, Mellouli F, Duprez R, Chedeville G, Neven B, Fraitag S, et al. Kaposi's sarcoma in a child with Wiskott-Aldrich syndrome. Eur J Pediatr. 2006; 165:453–7. [PubMed: 16602009]

75. Grossman WJ, Radhi M, Schauer D, Gerday E, Grose C, Goldman FD. Development of hemophagocytic lymphohistiocytosis in triplets infected with HHV-8. Blood. 2005; 106:1203–6. [PubMed: 15840696]

76. Brown EE, Fallin D, Ruczinski I, Hutchinson A, Staats B, Vitale F, et al. Associations of classic Kaposi sarcoma with common variants in genes that modulate host immunity. Cancer Epidemiol Biomarkers Prev. 2006; 15:926–34. [PubMed: 16702372]

77. Foster CB, Lehrnbecher T, Samuels S, Stein S, Mol F, Metcalf JA, et al. An IL6 promoter polymorphism is associated with a lifetime risk of development of Kaposi sarcoma in men infected with human immunodeficiency virus. Blood. 2000; 96:2562–7. [PubMed: 11001912]

78. Brown EE, Whitby D, Vitale F, Marshall V, Mbisa G, Gamache C, et al. Virologic, hematologic, and immunologic risk factors for classic Kaposi sarcoma. Cancer. 2006; 107:2282–90. [PubMed: 16998933]

79. Unemori P, Leslie KS, Hunt PW, Sinclair E, Epling L, Mitsuyasu R, et al. Immunosenescence is associated with presence of Kaposi's sarcoma in antiretroviral treated HIV infection. AIDS. 2013; 27:1735–42. [PubMed: 23435301]

80. Powles T, Stebbing J, Bazeos A, Hatzimichael E, Mandalia S, Nelson M, et al. The role of immune suppression and HHV-8 in the increasing incidence of HIV-associated multicentric Castleman's disease. Ann Oncol. 2009; 20:775–9. [PubMed: 19179554]

81. Ray A, Marshall V, Uldrick T, Leighty R, Labo N, Wyvill K, et al. Sequence analysis of Kaposi sarcoma-associated herpesvirus (KSHV) microRNAs in patients with multicentric Castleman disease and KSHV-associated inflammatory cytokine syndrome. J Infect Dis. 2012; 205:1665–76. [PubMed: 22448005]

82. Flore O, Rafii S, Ely S, O'Leary JJ, Hyjek EM, Cesarman E. Transformation of primary human endothelial cells by Kaposi's sarcoma-associated herpesvirus. Nature. 1998; 394:588–92. [PubMed: 9707121]

83. Moore PS, Boshoff C, Weiss RA, Chang Y. Molecular mimicry of human cytokine and cytokine response pathway genes by KSHV. Science. 1996; 274:1739–44. [PubMed: 8939871]

84. Boshoff C, Endo Y, Collins PD, Takeuchi Y, Reeves JD, Schweickart VL, et al. Angiogenic and HIV-inhibitory functions of KSHV-encoded chemokines. Science. 1997; 278:290–4. [PubMed: 9323208]

85. Davis DA, Rinderknecht AS, Zoeteweij JP, Aoki Y, Read-Connole EL, Tosato G, et al. Hypoxia induces lytic replication of Kaposi sarcoma-associated herpesvirus. Blood. 2001; 97:3244–50. [PubMed: 11342455]

86. Li X, Feng J, Sun R. Oxidative stress induces reactivation of Kaposi's sarcoma-associated herpesvirus and death of primary effusion lymphoma cells. J Virol. 2011; 85:715–24. [PubMed: 21068240]

87. Zeng Y, Zhang X, Huang Z, Cheng L, Yao S, Qin D, et al. Intracellular Tat of human immunodeficiency virus type 1 activates lytic cycle replication of Kaposi's sarcoma-associated herpesvirus: role of JAK/STAT signaling. J Virol. 2007; 81:2401–17. [PubMed: 17151125]

88. Shin HJ, DeCotiis J, Giron M, Palmeri D, Lukac DM. Histone deacetylase classes I and II regulate Kaposi's sarcoma-associated herpesvirus reactivation. J Virol. 2014; 88:1281–92. [PubMed: 24227836]

89. Brown HJ, McBride WH, Zack JA, Sun R. Prostratin and bortezomib are novel inducers of latent Kaposi's sarcoma-associated herpesvirus. Antivir Ther. 2005; 10:745–51. [PubMed: 16218174]

90. Sun R, Lin SF, Gradoville L, Yuan Y, Zhu F, Miller G. A viral gene that activates lytic cycle expression of Kaposi's sarcoma-associated herpesvirus. Proc Natl Acad Sci U S A. 1998; 95:10866–71. [PubMed: 9724796]

91. Sarid R, Flore O, Bohenzky RA, Chang Y, Moore PS. Transcription mapping of the Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) genome in a body cavity-based lymphoma cell line (BC-1). J Virol. 1998; 72:1005–12. [PubMed: 9444993]

92. Staskus KA, Zhong W, Gebhard K, Herndier B, Wang H, Renne R, et al. Kaposi's sarcoma-associated herpesvirus gene expression in endothelial (spindle) tumor cells. J Virol. 1997; 71:715–9. [PubMed: 8985403]

93. Ballestas ME, Chatis PA, Kaye KM. Efficient persistence of extrachromosomal KSHV DNA mediated by latency-associated nuclear antigen. Science. 1999; 284:641–4. [PubMed: 10213686]

94. Renne R, Barry C, Dittmer D, Compitello N, Brown PO, Ganem D. Modulation of cellular and viral gene expression by the latency-associated nuclear antigen of Kaposi's sarcoma-associated herpesvirus. J Virol. 2001; 75:458–68. [PubMed: 11119614]

95. Lan K, Kuppers DA, Verma SC, Robertson ES. Kaposi's sarcoma-associated herpesvirus-encoded latency-associated nuclear antigen inhibits lytic replication by targeting Rta: a potential mechanism for virus-mediated control of latency. J Virol. 2004; 78:6585–94. [PubMed: 15163750]

96. Friborg J, Kong W, Hottiger MO, Nabel GJ. p53 inhibition by the LANA protein of KSHV protects against cell death. Nature. 1999; 402:889–94. [PubMed: 10622254]

97. Radkov SA, Kellam P, Boshoff C. The latent nuclear antigen of Kaposi sarcoma-associated herpesvirus targets the retinoblastoma-E2F pathway and with the oncogene Hras transforms primary rat cells. Nat Med. 2000; 6:1121–7. [PubMed: 11017143]

98. Fujimuro M, Wu FY, ApRhys C, Kajumbula H, Young DB, Hayward GS, et al. A novel viral mechanism for dysregulation of beta-catenin in Kaposi's sarcoma-associated herpesvirus latency. Nat Med. 2003; 9:300–6. [PubMed: 12592400]

99. Lan K, Verma SC, Murakami M, Bajaj B, Kaul R, Robertson ES. Kaposi's sarcoma herpesvirus-encoded latency-associated nuclear antigen stabilizes intracellular activated Notch by targeting the Sel10 protein. Proc Natl Acad Sci U S A. 2007; 104:16287–92. [PubMed: 17909182]

100. Sarek G, Jarviluoma A, Moore HM, Tojkander S, Vartia S, Biberfeld P, et al. Nucleophosmin phosphorylation by v-cyclin-CDK6 controls KSHV latency. PLoS Pathog. 2010; 6:e1000818. [PubMed: 20333249]

101. Godden-Kent D, Talbot SJ, Boshoff C, Chang Y, Moore P, Weiss RA, et al. The cyclin encoded by Kaposi's sarcoma-associated herpesvirus stimulates cdk6 to phosphorylate the retinoblastoma protein and histone H1. J Virol. 1997; 71:4193–8. [PubMed: 9151805]

102. Mann DJ, Child ES, Swanton C, Laman H, Jones N. Modulation of p27(Kip1) levels by the cyclin encoded by Kaposi's sarcoma-associated herpesvirus. EMBO J. 1999; 18:654–63. [PubMed: 9927425]

103. Thome M, Schneider P, Hofmann K, Fickenscher H, Meinl E, Neipel F, et al. Viral FLICE-inhibitory proteins (FLIPs) prevent apoptosis induced by death receptors. Nature. 1997; 386:517–21. [PubMed: 9087414]

104. Chaudhary PM, Jasmin A, Eby MT, Hood L. Modulation of the NF-kappa B pathway by virally encoded death effector domains-containing proteins. Oncogene. 1999; 18:5738–46. [PubMed: 10523854]

105. Sakakibara S, Pise-Masison CA, Brady JN, Tosato G. Gene regulation and functional alterations induced by Kaposi's sarcoma-associated herpesvirus-encoded ORFK13/vFLIP in endothelial cells. J Virol. 2009; 83:2140–53. [PubMed: 19091861]

106. Guasparri I, Keller SA, Cesarman E. KSHV vFLIP is essential for the survival of infected lymphoma cells. J Exp Med. 2004; 199:993–1003. [PubMed: 15067035]

107. Forero A, Moore PS, Sarkar SN. Role of IRF4 in IFN-stimulated gene induction and maintenance of Kaposi sarcoma-associated herpesvirus latency in primary effusion lymphoma cells. J Immunol. 2013; 191:1476–85. [PubMed: 23804715]

108. Lee J-S, Li Q, Lee J-Y, Lee S-H, Jeong JH, Lee H-R, et al. FLIP-mediated autophagy regulation in cell death control. Nat Cell Biol. 2009; 11:1355–62. [PubMed: 19838173]

109. Muralidhar S, Pumfery AM, Hassani M, Sadaie MR, Kishishita M, Brady JN, et al. Identification of kaposin (open reading frame K12) as a human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus) transforming gene. J Virol. 1998; 72:4980–8. [PubMed: 9573267]

110. Yoo J, Kang J, Lee HN, Aguilar B, Kafka D, Lee S, et al. Kaposin-B enhances the PROX1 mRNA stability during lymphatic reprogramming of vascular endothelial cells by Kaposi's sarcoma herpes virus. PLoS Pathog. 2010; 6:e1001046. [PubMed: 20730087]

111. McCormick C, Ganem D. The kaposin B protein of KSHV activates the p38/MK2 pathway and stabilizes cytokine mRNAs. Science. 2005; 307:739–41. [PubMed: 15692053]

112. Baresova P, Pitha PM, Lubyova B. Distinct roles of Kaposi's sarcoma-associated herpesvirus-encoded viral interferon regulatory factors in inflammatory response and cancer. J Virol. 2013; 87:9398–410. [PubMed: 23785197]

113. Rivas C, Thlick AE, Parravicini C, Moore PS, Chang Y. Kaposi's sarcoma-associated herpesvirus LANA2 is a B-cell-specific latent viral protein that inhibits p53. J Virol. 2001; 75:429–38. [PubMed: 11119611]

114. Wies E, Mori Y, Hahn A, Kremmer E, Sturzl M, Fleckenstein B, et al. The viral interferon-regulatory factor-3 is required for the survival of KSHV-infected primary effusion lymphoma cells. Blood. 2008; 111:320–7. [PubMed: 17890449]

115. Shin YC, Joo CH, Gack MU, Lee HR, Jung JU. Kaposi's sarcoma-associated herpesvirus viral IFN regulatory factor 3 stabilizes hypoxia-inducible factor-1 alpha to induce vascular endothelial growth factor expression. Cancer Res. 2008; 68:1751–9. [PubMed: 18339855]

116. Samols MA, Hu J, Skalsky RL, Renne R. Cloning and identification of a microRNA cluster within the latency-associated region of Kaposi's sarcoma-associated herpesvirus. J Virol. 2005; 79:9301–5. [PubMed: 15994824]

117. Zhu Y, Haecker I, Yang Y, Gao SJ, Renne R. gamma-Herpesvirus-encoded miRNAs and their roles in viral biology and pathogenesis. Curr Opin Virol. 2013; 3:266–75. [PubMed: 23743127]

118. Gallaher AM, Das S, Xiao Z, Andresson T, Kieffer-Kwon P, Happel C, et al. Proteomic screening of human targets of viral microRNAs reveals functions associated with immune evasion and angiogenesis. PLoS Pathog. 2013; 9:e1003584. [PubMed: 24039573]

119. Abend JR, Ramalingam D, Kieffer-Kwon P, Uldrick TS, Yarchoan R, Ziegelbauer JM. Kaposi's sarcoma-associated herpesvirus microRNAs target IRAK1 and MYD88, two components of the toll-like receptor/interleukin-1R signaling cascade, to reduce inflammatory-cytokine expression. J Virol. 2012; 86:11663–74. [PubMed: 22896623]

120. Qin Z, Kearney P, Plaisance K, Parsons CH. Pivotal advance: Kaposi's sarcoma-associated herpesvirus (KSHV)-encoded microRNA specifically induce IL-6 and IL-10 secretion by macrophages and monocytes. J Leukoc Biol. 2010; 87:25–34. [PubMed: 20052801]

121. Gao SJ, Boshoff C, Jayachandra S, Weiss RA, Chang Y, Moore PS. KSHV ORF K9 (vIRF) is an oncogene which inhibits the interferon signaling pathway. Oncogene. 1997; 15:1979–85. [PubMed: 9365244]

122. Lagos D, Trotter MW, Vart RJ, Wang HW, Matthews NC, Hansen A, et al. Kaposi sarcoma herpesvirus-encoded vFLIP and vIRF1 regulate antigen presentation in lymphatic endothelial cells. Blood. 2007; 109:1550–8. [PubMed: 17047149]

123. Schmidt K, Wies E, Neipel F. Kaposi's sarcoma-associated herpesvirus viral interferon regulatory factor 3 inhibits gamma interferon and major histocompatibility complex class II expression. J Virol. 2011; 85:4530–7. [PubMed: 21345951]

124. Kirchhoff S, Sebens T, Baumann S, Krueger A, Zawatzky R, Li-Weber M, et al. Viral IFN-regulatory factors inhibit activation-induced cell death via two positive regulatory IFN-regulatory factor 1-dependent domains in the CD95 ligand promoter. J Immunol. 2002; 168:1226–34. [PubMed: 11801659]

125. Cesarman E, Nador RG, Bai F, Bohenzky RA, Russo JJ, Moore PS, et al. Kaposi's sarcoma-associated herpesvirus contains G protein-coupled receptor and cyclin D homologs which are expressed in Kaposi's sarcoma and malignant lymphoma. J Virol. 1996; 70:8218–23. [PubMed: 8892957]

126. Yang TY, Chen SC, Leach MW, Manfra D, Homey B, Wiekowski M, et al. Transgenic expression of the chemokine receptor encoded by human herpesvirus 8 induces an angioproliferative disease resembling Kaposi's sarcoma. J Exp Med. 2000; 191:445–54. [PubMed: 10662790]

127. Arvanitakis L, Geras-Raaka E, Varma A, Gershengorn MC, Cesarman E. Human herpesvirus KSHV encodes a constitutively active G-protein-coupled receptor linked to cell proliferation. Nature. 1997; 385:347–50. [PubMed: 9002520]

128. Bais C, Santomasso B, Coso O, Arvanitakis L, Raaka EG, Gutkind JS, et al. G-protein-coupled receptor of Kaposi's sarcoma-associated herpesvirus is a viral oncogene and angiogenesis activator. Nature. 1998; 391:86–9. [PubMed: 9422510]

129. Sodhi A, Montaner S, Patel V, Zohar M, Bais C, Mesri EA, et al. The Kaposi's sarcoma-associated herpes virus G protein-coupled receptor up-regulates vascular endothelial growth factor expression and secretion through mitogen-activated protein kinase and p38 pathways acting on hypoxia-inducible factor 1alpha. Cancer Res. 2000; 60:4873–80. [PubMed: 10987301]

130. Sodhi A, Chaisuparat R, Hu J, Ramsdell AK, Manning BD, Sausville EA, et al. The TSC2/mTOR pathway drives endothelial cell transformation induced by the Kaposi's sarcoma-associated herpesvirus G protein-coupled receptor. Cancer Cell. 2006; 10:133–43. [PubMed: 16904612]

131. Schwarz M, Murphy PM. Kaposi's sarcoma-associated herpesvirus G protein-coupled receptor constitutively activates NF-kappa B and induces proinflammatory cytokine and chemokine production via a C-terminal signaling determinant. J Immunol. 2001; 167:505–13. [PubMed: 11418689]

132. Chatterjee M, Osborne J, Bestetti G, Chang Y, Moore PS. Viral IL-6-induced cell proliferation and immune evasion of interferon activity. Science. 2002; 298:1432–5. [PubMed: 12434062]

133. Molden J, Chang Y, You Y, Moore PS, Goldsmith MA. A Kaposi's sarcoma-associated herpesvirus-encoded cytokine homolog (vIL-6) activates signaling through the shared gp130 receptor subunit. J Biol Chem. 1997; 272:19625–31. [PubMed: 9235971]

134. Aoki Y, Jaffe ES, Chang Y, Jones K, Teruya-Feldstein J, Moore PS, et al. Angiogenesis and hematopoiesis induced by Kaposi's sarcoma-associated herpesvirus-encoded interleukin-6. Blood. 1999; 93:4034–43. [PubMed: 10361100]

135. Uldrick TS, Wang V, O'Mahony D, Aleman K, Wyvill KM, Marshall V, et al. An interleukin-6-related systemic inflammatory syndrome in patients co-infected with Kaposi sarcoma-associated herpesvirus and HIV but without Multicentric Castleman disease. Clin Infect Dis. 2010; 51:350–8. [PubMed: 20583924]

136. Polizzotto MN, Uldrick TS, Wang V, Aleman K, Wyvill KM, Marshall V, et al. Human and viral interleukin-6 and other cytokines in Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. Blood. 2013; 122:4189–98. [PubMed: 24174627]

137. Aoki Y, Yarchoan R, Braun J, Iwamoto A, Tosato G. Viral and cellular cytokines in AIDS-related malignant lymphomatous effusions. Blood. 2000; 96:1599–601. [PubMed: 10942415]

138. Chen D, Sandford G, Nicholas J. Intracellular signaling mechanisms and activities of human herpesvirus 8 interleukin-6. J Virol. 2009; 83:722–33. [PubMed: 18987143]

139. Cousins E, Nicholas J. Role of human herpesvirus 8 interleukin-6-activated gp130 signal transducer in primary effusion lymphoma cell growth and viability. J Virol. 2013; 87:10816–27. [PubMed: 23903842]

140. Suthaus J, Stuhlmann-Laeisz C, Tompkins VS, Rosean TR, Klapper W, Tosato G, et al. HHV-8-encoded viral IL-6 collaborates with mouse IL-6 in the development of multicentric Castleman disease in mice. Blood. 2012; 119:5173–81. [PubMed: 22490805]

141. Herts BR, Megibow AJ, Birnbaum BA, Kanzer GK, Noz ME. High-attenuation lymphadenopathy in AIDS patients: significance of findings at CT. Radiology. 1992; 185:777–81. [PubMed: 1438762]

142. Davidson A, Wainwright RD, Stones DK, Kruger M, Hendricks M, Geel J, et al. Malignancies in South African children with HIV. J Pediatr Hematol Oncol. 2014; 36:111–7. [PubMed: 24552745]

143. Hong YK, Foreman K, Shin JW, Hirakawa S, Curry CL, Sage DR, et al. Lymphatic reprogramming of blood vascular endothelium by Kaposi sarcoma-associated herpesvirus. Nat Genet. 2004; 36:683–5. [PubMed: 15220917]

144. Pantanowitz L, Otis CN, Dezube BJ. Immunohistochemistry in Kaposi's sarcoma. Clin Exp Dermatol. 2010; 35:68–72. [PubMed: 19874352]

145. Hussein MR. Immunohistological evaluation of immune cell infiltrate in cutaneous Kaposi's sarcoma. Cell Biol Int. 2008; 32:157–62. [PubMed: 17950633]

146. Pantanowitz L, Dezube BJ, Pinkus GS, Tahan SR. Histological characterization of regression in acquired immunodeficiency syndrome-related Kaposi's sarcoma. J Cutan Pathol. 2004; 31:26–34. [PubMed: 14675282]

147. Krown SE, Metroka C, Wernz JC. Kaposi's sarcoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response, and staging criteria. AIDS Clinical Trials Group Oncology Committee. J Clin Oncol. 1989; 7:1201–7. [PubMed: 2671281]

148. Krown SE, Testa MA, Huang J. AIDS-related Kaposi's sarcoma: prospective validation of the AIDS Clinical Trials Group staging classification. AIDS Clinical Trials Group Oncology Committee. J Clin Oncol. 1997; 15:3085–92. [PubMed: 9294471]

149. Mosam A, Shaik F, Uldrick TS, Esterhuizen T, Friedland GH, Scadden DT, et al. A randomized controlled trial of highly active antiretroviral therapy versus highly active antiretroviral therapy and chemotherapy in therapy-naive patients with HIV-associated Kaposi sarcoma in South Africa. J Acquir Immune Defic Syndr. 2012; 60:150–7. [PubMed: 22395672]

150. Nasti G, Talamini R, Antinori A, Martellotta F, Jacchetti G, Chiodo F, et al. AIDS-related Kaposi's Sarcoma: evaluation of potential new prognostic factors and assessment of the AIDS Clinical Trial Group Staging System in the Haart Era--the Italian Cooperative Group on AIDS and Tumors and the Italian Cohort of Patients Naive From Antiretrovirals. J Clin Oncol. 2003; 21:2876–82. [PubMed: 12885804]

151. Maskew M, Fox MP, van Cutsem G, Chu K, Macphail P, Boulle A, et al. Treatment response and mortality among patients starting antiretroviral therapy with and without Kaposi sarcoma: a cohort study. PLoS One. 2013; 8:e64392. [PubMed: 23755122]

152. Bower M, Fox P, Fife K, Gill J, Nelson M, Gazzard B. Highly active anti-retroviral therapy (HAART) prolongs time to treatment failure in Kaposi's sarcoma. AIDS. 1999; 13:2105–11. [PubMed: 10546864]

153. Martinez V, Caumes E, Gambotti L, Ittah H, Morini JP, Deleuze J, et al. Remission from Kaposi's sarcoma on HAART is associated with suppression of HIV replication and is independent of protease inhibitor therapy. Br J Cancer. 2006; 94:1000–6. [PubMed: 16570046]

154. Stallone G, Schena A, Infante B, Di Paolo S, Loverre A, Maggio G, et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. N Engl J Med. 2005; 352:1317–23. [PubMed: 15800227]

155. Gill PS, Wernz J, Scadden DT, Cohen P, Mukwaya GM, von Roenn JH, et al. Randomized phase III trial of liposomal daunorubicin versus doxorubicin, bleomycin, and vincristine in AIDS-related Kaposi's sarcoma. J Clin Oncol. 1996; 14:2353–64. [PubMed: 8708728]

156. Northfelt DW, Dezube BJ, Thommes JA, Miller BJ, Fischl MA, Friedman-Kien A, et al. Pegylated-liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial. J Clin Oncol. 1998; 16:2445–51. [PubMed: 9667262]

157. Stewart S, Jablonowski H, Goebel FD, Arasteh K, Spittle M, Rios A, et al. Randomized comparative trial of pegylated liposomal doxorubicin versus bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma. International Pegylated Liposomal Doxorubicin Study Group. J Clin Oncol. 1998; 16:683–91. [PubMed: 9469358]

158. Cooley T, Henry D, Tonda M, Sun S, O'Connell M, Rackoff W. A randomized, double-blind study of pegylated liposomal doxorubicin for the treatment of AIDS-related Kaposi's sarcoma. Oncologist. 2007; 12:114–23. [PubMed: 17227906]

159. Welles L, Saville MW, Lietzau J, Pluda JM, Wyvill KM, Feuerstein I, et al. Phase II trial with dose titration of paclitaxel for the therapy of human immunodeficiency virus-associated Kaposi's sarcoma. J Clin Oncol. 1998; 16:1112–21. [PubMed: 9508198]

160. Tulpule A, Groopman J, Saville MW, Harrington W, Friedman-Kien A, Espina BM, et al. Multicenter trial of low-dose paclitaxel in patients with advanced AIDS-related Kaposi sarcoma. Cancer. 2002; 95:147–54. [PubMed: 12115328]

161. Cianfrocca M, Lee S, Von Roenn J, Tulpule A, Dezube BJ, Aboulafia DM, et al. Randomized trial of paclitaxel versus pegylated liposomal doxorubicin for advanced human immunodeficiency virus-associated Kaposi sarcoma: evidence of symptom palliation from chemotherapy. Cancer. 2010; 116:3969–77. [PubMed: 20564162]

162. Krown SE, Li P, Von Roenn JH, Paredes J, Huang J, Testa MA. Efficacy of low-dose interferon with antiretroviral therapy in Kaposi's sarcoma: a randomized phase II AIDS clinical trials group study. J Interferon Cytokine Res. 2002; 22:295–303. [PubMed: 12034036]

163. Shepherd FA, Beaulieu R, Gelmon K, Thuot CA, Sawka C, Read S, et al. Prospective randomized trial of two dose levels of interferon alfa with zidovudine for the treatment of Kaposi's sarcoma associated with human immunodeficiency virus infection: a Canadian HIV Clinical Trials Network study. J Clin Oncol. 1998; 16:1736–42. [PubMed: 9586886]

164. Evans SR, Krown SE, Testa MA, Cooley TP, Von Roenn JH. Phase II evaluation of low-dose oral etoposide for the treatment of relapsed or progressive AIDS-related Kaposi's sarcoma: an AIDS Clinical Trials Group clinical study. J Clin Oncol. 2002; 20:3236–41. [PubMed: 12149296]

165. Schwartsmann G, Sprinz E, Kromfield M, Kalakun L, Sander E, Prolla G, et al. Clinical and pharmacokinetic study of oral etoposide in patients with AIDS-related Kaposi's sarcoma with no prior exposure to cytotoxic therapy. J Clin Oncol. 1997; 15:2118–24. [PubMed: 9164226]

166. Nasti G, Errante D, Talamini R, Rizzardini G, Fasan M, Landonio G, et al. Vinorelbine is an effective and safe drug for AIDS-related Kaposi's sarcoma: results of a phase II study. J Clin Oncol. 2000; 18:1550–7. [PubMed: 10735904]

167. Welles L, Saville MW, Lietzau J, Pluda JM, Wyvill KM, Feuerstein I, et al. Phase II trial with dose titration of paclitaxel for the therapy of human immunodeficiency virus-associated Kaposi's sarcoma. J Clin Oncol. 1998; 16:1112–21. [PubMed: 9508198]

168. Gill PS, Tulpule A, Espina BM, Cabriales S, Bresnahan J, Ilaw M, et al. Paclitaxel is safe and effective in the treatment of advanced AIDS- related Kaposi's sarcoma. J Clin Oncol. 1999; 17:1876–83. [PubMed: 10561228]

169. Krown SE, Lee JY, Lin L, Fischl MA, Ambinder R, Von Roenn JH. Interferon-alpha2b with protease inhibitor-based antiretroviral therapy in patients with AIDS-associated Kaposi sarcoma: an AIDS malignancy consortium phase I trial. J Acquir Immune Defic Syndr. 2006; 41:149–53. [PubMed: 16394845]

170. Fife K, Howard MR, Gracie F, Phillips RH, Bower M. Activity of thalidomide in AIDS-related Kaposi's sarcoma and correlation with HHV8 titre. Int J STD AIDS. 1998; 9:751–5. [PubMed: 9874123]

171. Little RF, Wyvill KM, Pluda JM, Welles L, Marshall V, Figg WD, et al. Activity of Thalidomide in AIDS-Related Kaposi's Sarcoma. J Clin Oncol. 2000; 18:2593–2602. [PubMed: 10893291]

172. Krown SE, Roy D, Lee JY, Dezube BJ, Reid EG, Venkataramanan R, et al. Rapamycin with antiretroviral therapy in AIDS-associated Kaposi sarcoma: an AIDS Malignancy Consortium study. J Acquir Immune Defic Syndr. 2012; 59:447–54. [PubMed: 22067664]

173. Dezube BJ, Krown SE, Lee JY, Bauer KS, Aboulafia DM. Randomized phase II trial of matrix metalloproteinase inhibitor COL-3 in AIDS-related Kaposi's sarcoma: an AIDS Malignancy Consortium Study. J Clin Oncol. 2006; 24:1389–94. [PubMed: 16549833]

174. Koon HB, Krown SE, Lee JY, Honda K, Rapisuwon S, Wang Z, et al. Phase II trial of imatinib in AIDS-associated Kaposi's sarcoma: AIDS Malignancy Consortium Protocol 042. J Clin Oncol. 2014; 32:402–8. [PubMed: 24378417]

175. Uldrick TS, Wyvill KM, Kumar P, O'Mahony D, Bernstein W, Aleman K, et al. Phase II study of bevacizumab in patients with HIV-associated Kaposi's sarcoma receiving antiretroviral therapy. J Clin Oncol. 2012; 30:1476–83. [PubMed: 22430271]

176. Kedes DH, Ganem D. Sensitivity of Kaposi's sarcoma-associated herpesvirus replication to antiviral drugs. Implications for potential therapy. J Clin Invest. 1997; 99:2082–6. [PubMed: 9151779]

177. Martin DF, Kuppermann BD, Wolitz RA, Palestine AG, Li H, Robinson CA. Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. Roche Ganciclovir Study Group. N Engl J Med. 1999; 340:1063–70. [PubMed: 10194235]

178. Oksenhendler E, Duarte M, Soulier J, Cacoub P, Welker Y, Cadranel J, et al. Multicentric Castleman's disease in HIV infection: a clinical and pathological study of 20 patients. AIDS. 1996; 10:61–7. [PubMed: 8924253]

179. Oksenhendler E, Carcelain G, Aoki Y, Boulanger E, Maillard A, Clauvel JP, et al. High levels of human herpesvirus 8 viral load, human interleukin-6, interleukin-10, and C reactive protein correlate with exacerbation of multicentric castleman disease in HIV-infected patients. Blood. 2000; 96:2069–73. [PubMed: 10979949]

180. An J, Sun Y, Sun R, Rettig MB. Kaposi's sarcoma-associated herpesvirus encoded vFLIP induces cellular IL-6 expression: the role of the NF-kappaB and JNK/AP1 pathways. Oncogene. 2003; 22:3371–85. [PubMed: 12776188]

181. Keller SA, Hernandez-Hopkins D, Vider J, Ponomarev V, Hyjek E, Schattner EJ, et al. NF-kappaB is essential for the progression of KSHV- and EBV-infected lymphomas in vivo. Blood. 2006; 107:3295–302. [PubMed: 16380446]

182. Aoki Y, Tosato G, Fonville TW, Pittaluga S. Serum viral interleukin-6 in AIDS-related multicentric Castleman disease. Blood. 2001; 97:2526–7. [PubMed: 11307774]

183. Polizzotto MN, Uldrick TS, Hu D, Yarchoan R. Clinical Manifestations of Kaposi Sarcoma Herpesvirus Lytic Activation: Multicentric Castleman Disease (KSHV-MCD) and the KSHV Inflammatory Cytokine Syndrome. Front Microbiol. 2012; 3:73. [PubMed: 22403576]

184. Du MQ, Liu H, Diss TC, Ye H, Hamoudi RA, Dupin N, et al. Kaposi sarcoma-associated herpesvirus infects monotypic (IgM lambda) but polyclonal naive B cells in Castleman disease and associated lymphoproliferative disorders. Blood. 2001; 97:2130–6. [PubMed: 11264181]

185. Naresh KN, Rice AJ, Bower M. Lymph nodes involved by multicentric Castleman disease among HIV-positive individuals are often involved by Kaposi sarcoma. Am J Surg Pathol. 2008; 32:1006–12. [PubMed: 18469709]

186. Uldrick TS, Polizzotto MN, Yarchoan R. Recent advances in Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. Curr Opin Oncol. 2012; 24:495–505. [PubMed: 22729151]

187. Bower M, Pria AD, Coyle C, Nelson M, Naresh K. Diagnostic criteria schemes for multicentric Castleman disease in 75 cases. J Acquir Immune Defic Syndr. 2014; 65:e80–2. [PubMed: 24442228]

188. Mylona EE, Baraboutis IG, Lekakis LJ, Georgiou O, Papastamopoulos V, Skoutelis A. Multicentric Castleman's disease in HIV infection: a systematic review of the literature. AIDS Rev. 2008; 10:25–35. [PubMed: 18385778]

189. Rappocciolo G, Hensler HR, Jais M, Reinhart TA, Pegu A, Jenkins FJ, et al. Human herpesvirus 8 infects and replicates in primary cultures of activated B lymphocytes through DC-SIGN. J Virol. 2008; 82:4793–806. [PubMed: 18337571]

190. Gerard L, Michot JM, Burcheri S, Fieschi C, Longuet P, Delcey V, et al. Rituximab decreases the risk of lymphoma in patients with HIV-associated multicentric Castleman disease. Blood. 2012; 119:2228–33. [PubMed: 22223822]

191. Davis DA, Singer KE, Reynolds IP, Haque M, Yarchoan R. Hypoxia enhances the phosphorylation and cytotoxicity of ganciclovir and zidovudine in Kaposi's sarcoma-associated herpesvirus infected cells. Cancer Res. 2007; 67:7003–10. [PubMed: 17638913]

192. Uldrick TS, Polizzotto MN, Aleman K, O'Mahony D, Wyvill KM, Wang V, et al. High-dose zidovudine plus valganciclovir for Kaposi sarcoma herpesvirus-associated multicentric Castleman disease: a pilot study of virus-activated cytotoxic therapy. Blood. 2011; 117:6977–86. [PubMed: 21487108]

193. Jenner RG, Maillard K, Cattini N, Weiss RA, Boshoff C, Wooster R, et al. Kaposi's sarcoma-associated herpesvirus-infected primary effusion lymphoma has a plasma cell gene expression profile. Proc Natl Acad Sci USA. 2003; 100:10399–404. [PubMed: 12925741]

194. Klein U, Gloghini A, Gaidano G, Chadburn A, Cesarman E, Dalla-Favera R, et al. Gene expression profile analysis of AIDS-related primary effusion lymphoma (PEL) suggests a plasmablastic derivation and identifies PEL-specific transcripts. Blood. 2003; 101:4115–21. [PubMed: 12531789]

195. Luan SL, Boulanger E, Ye H, Chanudet E, Johnson N, Hamoudi RA, et al. Primary effusion lymphoma: genomic profiling revealed amplification of SELPLG and CORO1C encoding for proteins important for cell migration. J Pathol. 2010; 222:166–79. [PubMed: 20690162]

196. Nador RG, Cesarman E, Chadburn A, Dawson DB, Ansari MQ, Sald J, et al. Primary effusion lymphoma: a distinct clinicopathologic entity associated with the Kaposi's sarcoma-associated herpes virus. Blood. 1996; 88:645–56. [PubMed: 8695812]

197. Boulanger E, Gérard L, Gabarre J, Molina J-M, Rapp C, Abino J-F, et al. Prognostic factors and outcome of human herpesvirus 8-associated primary effusion lymphoma in patients with AIDS. J Clin Oncol. 2005; 23:4372–80. [PubMed: 15994147]

198. Chadburn A, Hyjek E, Mathew S, Cesarman E, Said J, Knowles DM. KSHV-positive solid lymphomas represent an extra-cavitary variant of primary effusion lymphoma. Am J Surg Pathol. 2004; 28:1401–16. [PubMed: 15489644]

199. Dong HY, Wang W, Uldrick TS, Gangi M. Human herpesvirus 8- and Epstein-Barr virus-associated solitary B cell lymphoma with a T cell immunophenotype. Leuk Lymphoma. 2013; 54:1560–3. [PubMed: 23228024]

200. Gasperini P, Tosato G. Targeting the mammalian target of Rapamycin to inhibit VEGF and cytokines for the treatment of primary effusion lymphoma. Leukemia. 2009; 23:1867–74. [PubMed: 19554030]

201. Bhatt S, Ashlock BM, Natkunam Y, Sujoy V, Chapman JR, Ramos JC, et al. CD30 targeting with brentuximab vedotin: a novel therapeutic approach to primary effusion lymphoma. Blood. 2013; 122:1233–42. [PubMed: 23838350]

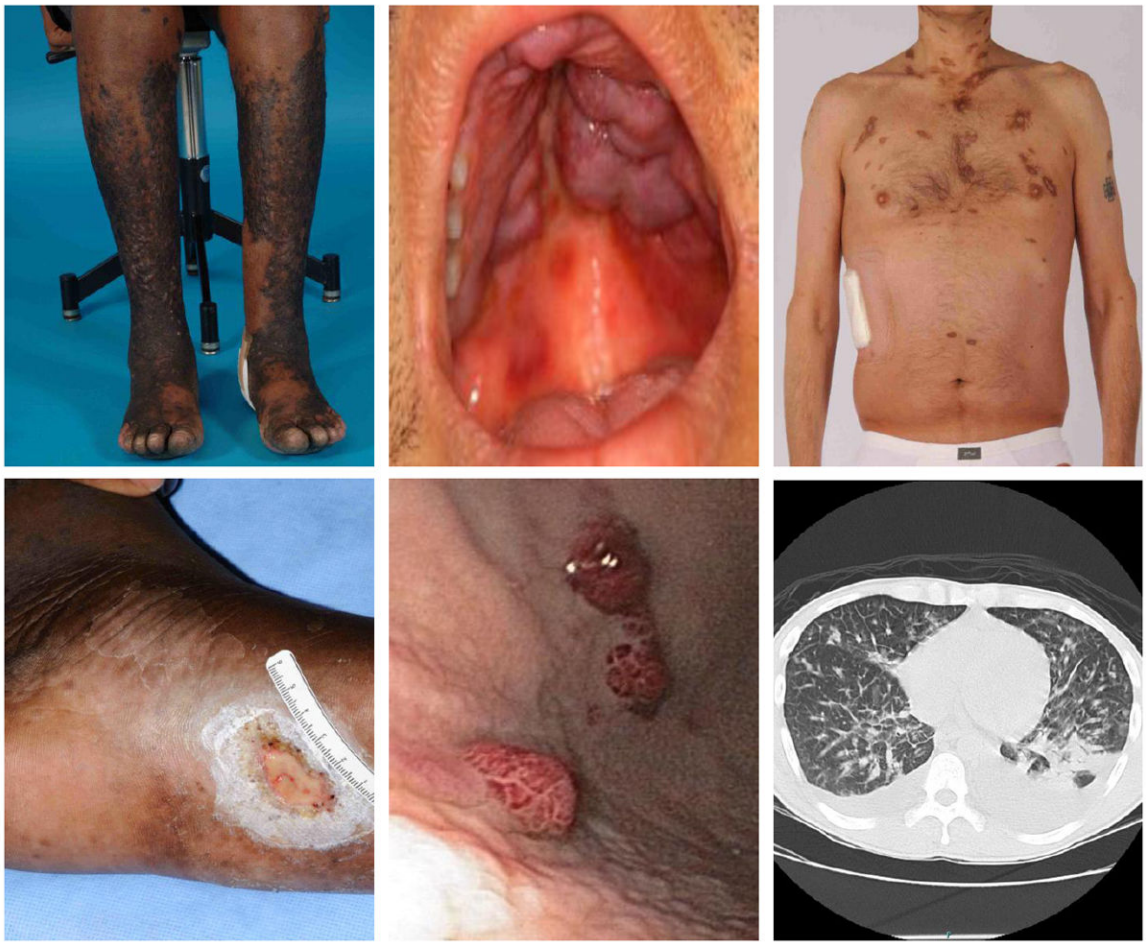

Figure 1.

Kaposi sarcoma A) Multiple confluent violaceous papules on both lower extremities with tumor associated edema B) Nodular lesions on the hard palate C) Multiple oval, violaceous plaques on the upper extremities and trunk D) An ulcerated hyperkeratotic plaque with ulceration on the sole of the foot E) Esophagogastroduodenoscopy showing discrete, raised, violaceous plaques in the body of stomach F) Axial computerized tomography of chest shows diffuse peribronchovascular thickening, multiple nodules, and pleural effusion bilaterally; evaluation of the pleural fluid demonstrated an exudative, non-chylous effusion with no evidence of primary effusion lymphoma

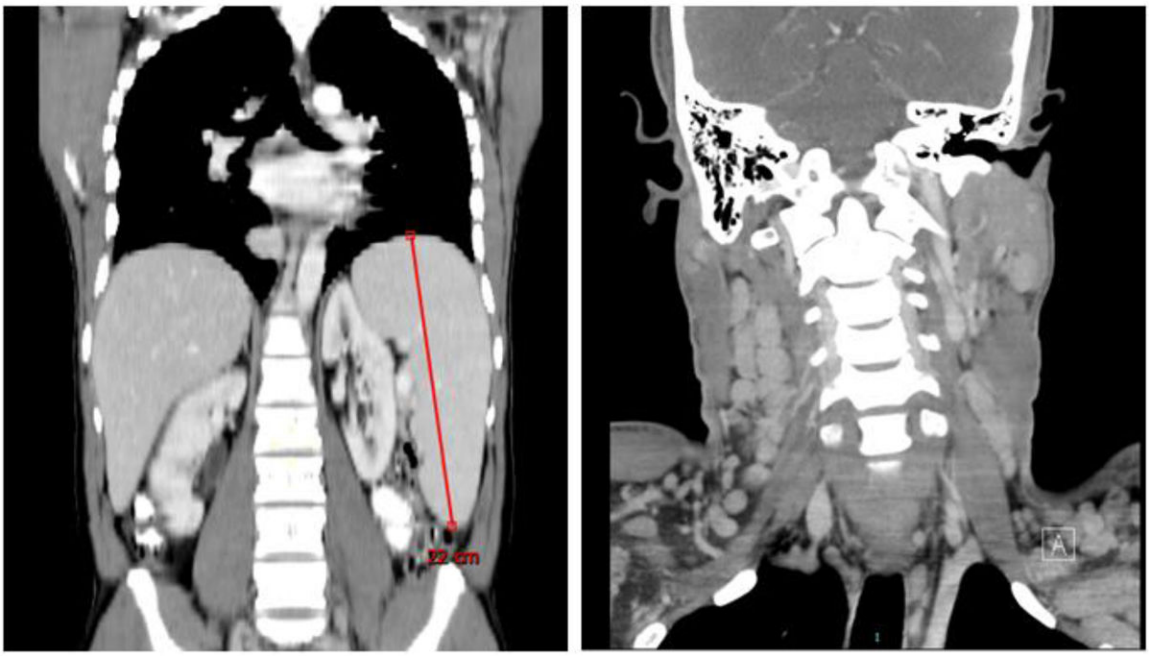

Figure 2.

Computerized tomography (CT) in KSHV-associated multicentric Castleman disease A) Coronal reformatted image from a contrast-enhanced CT scan of abdomen shows massive hepatosplenomegaly (upper limit of normal for spleen length = 12 cm) B) Coronal reformatted image from CT of the neck shows multiple enlarged bilateral cervical and supraclavicular lymph nodes

Table 1

Prospective studies of chemotherapy and interferon for the treatment of AIDS-associated Kaposi sarcoma

Study	Study design	N	Median CD4 count (cells/uL)	Prior systemic KS therapy	On cART	Response rate (CR+PR)	Differences in long-term outcomes	Important side effect considerations
Liposomal anthracyclines								
Gill et. al.[155] (1996)	RCT: ***liposomal daunorubicin*** 40 mg/m^2 IV every 2 weeks vs. ***ABV*** Treatment continued until 2 cycles beyond CR, or PD or unacceptable toxicity	116 vs. 111	29	0%	0% *	25% vs. 28% (NS)	No significant difference in duration of response or OS	• Cardiotoxicity with liposomal anthracyclines less even at high doses; FDA black box warning to limit to 550 mg/m^2 lifetime dosing, monitor cardiac function if additional therapy required • Occasional emesis • Significant myelosuppression • Infusion related hypotension • Hand -foot syndrome
Northfelt et. al. [156] (1998)	RCT: ***pegylated liposomal doxorubicin*** 20 mg/m^2 IV every 2 weeks for 6 cycles vs. ***ABV***	133 vs. 125	13	78%	0% *	46% vs. 25% (p<0.001)	No significant difference in duration of response or OS	
Stewart et. al.[157] (1998)	RCT: ***pegylated liposomal doxorubicin*** 20 mg/m^2 IV every 3 weeks for 6 cycles vs. **BV**	121 vs. 120	30	0%	0% *	59% vs. 23% (p<0.001)	No significant difference in duration of response	
Cooley et. al.[158] (2007)	RCT: ***pegylated liposomal doxorubicin*** 20 mg/m^2 IV vs. ***liposomal daunorubicin*** 40 mg/m^2 IV every 2 weeks	60 vs. 19	131 vs. 168	45% vs. 37%,	96%	55% vs. 32% (NS)	No significant difference in duration of response	
Paclitaxel								
Welles et. al.[159] (1998)	Phase II study ***paclitaxel*** 135 mg/m^2 titrated up to 135 mg/m^2 IV every 3 weeks	29	15	66%	0%	69%	NA	• Alopecia • Myalgia • Neuropathy • Myelosuppression • More grade 3–5 toxicity with paclitaxel compared to liposomal doxorubicin (84% vs. 66%, p=0.077)
Tulpule et. al.[160] (2002)	Phase II study ***paclitaxel*** 100 mg/m^2 every 2 weeks	107	41	100%	77%	56%	NA	
Cianfrocca et. al. [161] (2010)	RCT of ***pegylated liposomal doxorubicin*** 20 mg/m2 IV every 3 weeks vs. ***paclitaxel***	37 vs. 36	CD4 <150 60% vs. 56%	0%	73%	46% vs. 56% (NS)	No significant difference in duration of response or OS	

Study	Study design	N	Median CD4 count (cells/uL)	Prior systemic KS therapy	On cART	Response rate (CR+PR)	Differences in long-term outcomes	Important side effect considerations
	100 mg/m2 IV every 2 weeks							
Interferon-α2b								
Krown et. al.[162] (2002)	RCT: ***interferon-α2b***; 1 million units vs. 10 million units SQ daily; each with didanosine	35 vs. 33	192 vs. 230	1%	24%	40% vs. 55% (NS)	No significant difference in duration of response	• Fevers and chills • Cytopenias • Depression • Hypothyroidism
Shepherd et. al. [163] (1998)	RCT: ***Interferon α-2b***; 1 million units vs. 8 million units SQ daily; each with zidovudine	54 vs. 54	CD4 <150 39% vs. 50%	0%	0% *	8% vs. 31% (p=0.011)	Median time to progression: 13 vs. 18 weeks (p=0.002)	
Select other chemotherapies active against KS, but not specifically FDA approved for KS								
Evans et. al.[164] (2002)	Phase II study of ***oral etoposide*** 50 mg/d daily for 7 days every 2-weeks. Provision to escalate dose to 100 mg, if no toxicity after 2 cycles	36	NA	100%	80%	36%	NA	• Neutropenia • Thrombocytopenia • Emesis • Alopecia • Possible secondary MDS with long term therapy
Schwartsmann et. al.[165] (1997)	Phase II study of ***oral etoposide*** 25 mg/m^2 twice a day for 7 days, every 2 weeks	25	153	20%	0% *	32%	NA	
Nasti et. al.[166] (2000)	Phase II study of ***vinblastine*** 30 mg/m^2 IV every 2 weeks, continued until CR or 2 cycles beyond maximum response	35	20	100%	0% *	43%	NA	• Neurologic toxicity mild and reversible • Neutropenia
Mosam et. al.[149] (2012)	RCT: ***cART alone*** vs. ***cART and chemotherapy - ABV or oral etoposide*** 50-100 mg for 1-21 days of a 28-day cycle	59 vs. 53	136 vs. 192	0% (Also 100% treatment naïve to cART)	100%	39% vs. 66%; (p=0.005)	1-year PFS 31% vs. 56% in chemo arm, hazard ratio = 0.52 (0.31-0.93). No difference in OS	• KS-IRIS in 23 (21%) patients. • Other common effects seen in both arms were abnormal liver function tests, anemia, and infections.

cART: combination antiretroviral therapy consisting of at least three agents, including a protease inhibitor or a nucleoside reverse transcriptase inhibitor. RCT: randomized controlled trial. IV: intravenously. SQ: by subcutaneous injection. ACTG: AIDS clinical trial group. ABV (Gill): doxorubicin 10 mg/m^2, bleomycin 15 U, and vincristine 1 mg, administered intravenously every 2 weeks. ABV (Northfelt) doxorubicin 20 mg/m^2, bleomycin 10 mg/m^2 and vincristine 1 mg every 14 days for six cycles. BV: bleomycin 15 IU/m^2 and vincristine 2 mg. OS: Overall survival. PFS: Progression-free survival

Pre-medications for paclitaxel: Dexamethasone 10–20 mg iv 30 min prior, or 10 mg orally 12 and 6 h prior) to prevent allergic reactions, with the provision to reduce the dose to 8 mg if no allergic reactions were noted. Cimetidine 300 mg or ranitidine 50 mg, and diphenhydramine 50 mg, were also given IV 1 hour prior. NS = Not significant.

*Many patients on antiretroviral therapy including one or two antiretroviral agents