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Update on KSHV-Epidemiology, Kaposi Sarcoma Pathogenesis, and Treatment of Kaposi Sarcoma

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Abstract

Much has been learned since the discovery of KSHV in 1994 about its epidemiology and pathology but much of what has been learned has yet to be translated into clinical practice. In this review, we survey the current state of knowledge on KSHV epidemiology and KS pathogenesis and highlight therapeutic opportunities in both the developed and developing world.

Introduction

Kaposi sarcoma (KS) was suspected to be caused by an infectious agent long before the AIDS epidemic because of the distinctive geographical distribution of incidence[1] and the association with immune suppression[2]. KS was one of the earliest manifestations of the AIDS epidemic and the severe morbidity and mortality associated with AIDS-KS prompted a vigorous research effort into it's aetiology which lead eventually to the discovery of Kaposi's sarcoma-associated herpesvirus (KSHV)[3]. KSHV was later shown to be associated with primary effusion lymphoma (PEL)[4] and multicentric Castelman disease[5]. The spectrum of diseases associated with KSHV may yet expand with more thorough study, especially in the HIV infected population.

The introduction of effective antiretroviral therapies in the mid-1990s lead to a sharp decrease in the incidence of KS in HIV infected subjects in developed countries where such therapies were widely available[6; 7]. However, the risk of KS remains substantially increased in HIV infected subjects and further decreases have not been observed[7]. KS has recently been reported in subjects with well controlled HIV infection and CD4 counts >200[8; 9] and it remains to be seen what further changes in the incidence of KS may occur as the substantial HIV/KSHV co-infected population ages. In resource-poor countries, many of which have a high prevalence of both HIV and KSHV, effective anti-retroviral therapies have been introduced more recently or are yet to be introduced. Few studies exist on the impact of ART in these settings.

Much has been learned since the discovery of KSHV in 1994 about its epidemiology and pathophysiology but much of what has been learned has yet to be translated into clinical

practice. An understanding of the overlap of KSHV transmission and related seroprevalence with additional modifiable risk factors for the development of KS in KSHV infected individuals, such as uncontrolled HIV or immunosuppression from medications used in organ transplant, continue to inform approaches for KS prevention and treatment. In this review, we survey the current state of knowledge on KSHV prevalence and transmission, as well as select aspects of Kaposi Sarcoma pathophysiology and therapy, highlighting opportunities for KS therapeutic interventions in both the developed world and resource-limited settings.

Epidemiology of KSHV Infection and Transmission

The discovery of KSHV in 1994[3] was followed by a substantial effort to understand the epidemiology of KSHV infection and routes of transmission. The earliest studies relied on PCR detection of viral DNA in tissue biopsies[10; 11; 12] and nested PCR detection of viral DNA in PBMC[10; 13]. The development of serological assays to detect antibodies to KSHV enabled more extensive studies to be conducted. KSHV serology remains controversial and there are no universally accepted standard assays. There are a number of challenges intrinsic to KSHV serology. KSHV has a large genome with more than 85 genes all of which have the potential to be antigenic. The host humoral response to these antigens is variable and not predictable. In addition, antibody levels are low in subjects without disease and “sero-reversion” in which antibody levels fall to below the level of detection of assays has been reported [14]. Currently used serological assays include immunofluorescence assays (IFA) based on KSHV infected primary effusion lymphoma (PEL) cell, with or without induction of lytic viral replication [15; 16; 17]. In addition, ELISAs have been developed based on either recombinant proteins or peptides representing the major antigens identified to date, K8.1, ORF 65 and ORF 73/LANA[16; 18] [19]. All of these methods have advantages and disadvantages and show only moderate concordance[20]. Most of these assays perform very well in epidemiological studies but are not as well suited for diagnostic applications. It is likely that modern multiplexing technologies will facilitate the development of improved assays in the future. An example of a newer approach to KSHV serology using a novel detection platform was recently reported[21].

Prevalence of KSHV

Unlike most human herpesviruses, KSHV is not a ubiquitous infection and major variations occur in prevalence geographically. KSHV infection is very common in sub-Saharan Africa with seropositivity rates of >50%; moderately prevalent in Mediterranean countries (20–30%) but much less common (<10%) in most of Europe, Asia and the US. In addition prevalence is elevated in some ethnic or behavioral groups. Most strikingly prevalence is elevated in men who have sex with men (MSM) in the US and Europe[22; 23; 24]. In South America, KSHV prevalence is markedly increased in Amerindians compared to other ethnic groups[25; 26; 27]. Recent reports describe a similar increased prevalence in some ethnic groups in China[28; 29; 30; 31; 32; 33; 34].

KSHV Transmission

KSHV is now known to be transmitted largely via saliva. The elevated prevalence of KSHV in MSM was suggestive that it could be transmitted sexually. The reported evidence for sexual transmission of KSHV is mixed with some studies suggesting evidence for sexual transmission but many more finding no such evidence. It is clear that in MSM, KSHV risk is associated with sexual risk factors such as number of sexual partners[22; 23; 24] but even in this case, many investigators now believe that transmission is via saliva and that sexual risk factors likely are a surrogate marker for close contact[35]. Reports of KSHV transmission

via heterosexual routes are inconsistent with some studies reported an association [36; 37; 38; 39] but many more reporting no association between KSHV risk and heterosexual risk factors[29; 40; 41; 42].

KSHV is detectable in peripheral blood [43; 44] suggesting that KSHV transmission via blood and blood products is possible. This is obviously an area of great concern particularly with regard to the safety of blood donations. KSHV transmission via blood transfusion is rare but evidence of both risk and actual transmission has been reported[45; 46; 47]. Risk of transmission is likely to be greatly reduced by depleting the blood of leucocytes since KSHV is known to be largely cell associated. Storing blood for several hours or days would also likely reduce the risk of transmission since we have observed that KSHV DNA detection is frequently reduced or abolished if blood from KSHV infected subjects is stored overnight before DNA extraction [Whitby and Uldrick, unpublished observations] These measures seem to be preferable to the introduction of screening blood or blood products for KSHV antibodies given the limitations of currently available assays[47] [48]. Such screening may even be counter-productive since a recent report demonstrated that transmission of KSHV occurred less frequently when donors had higher levels of antibodies[49]. The relationship between antibody titre, KSHV viral load and transmissibility of KSHV is clearly complex[50; 51]and is an area that warrants further study.

Transmission of KSHV via solid organ donation is an issue of great clinical concern especially since transplant recipients require immune suppression. KS is documented to occur both in recipients of organs from KSHV infected donors and in KSHV infected recipients due to KSHV reactivation, raising the question of whether donors, recipients or both should be screened for KSHV antibodies (reviewed by Marcelin, et. al. [52]). A recently reported large prospective study showed that KS occurred threefold more frequently in KSHV seropositive recipients of solid organ donations than in seronegative recipients of organs[53]. “In this study, overall survival and graph loss rates were comparable between three groups of patients: KSHV seropositive organ recipients, KSHV seronegative recipients who received organs from KSHV seropositive donors, and seronegative recipients of organs from seronegative donors[53].”

This would suggest that while screening of recipients and donors may be warranted as a pointer for follow-up clinical monitoring, the presence of antibodies in either donor or recipient should not preclude transplantation.

Reports of KSHV transmission via injecting drug use have also been mixed. Some studies suggested that injecting drug users (IDU) are not at increased risk of KSHV infection[54; 55], while others have shown an increased risk of KSHV infection in IDU, especially with prolonged use[56; 57].

KSHV infection occurs in children in Italy[58], sub-Saharan Africa[14; 36; 59; 60] and South American Amerindian populations[61]. Children are most likely to be infected if they have an infected mother [14; 59; 60] or other family member[62]. HIV infection of both the mother and child is an important risk factor for KSHV transmission in children [14; 36; 60]. This is of great concern in regions where both viruses are common as it may lead to increasing prevalence of KSHV and subsequently a greater burden of KS. Other risk factors for KSHV transmission in childhood include type of water supply and socioeconomic status of mothers[14; 59]. There is some evidence that the patterns of transmission of KSHV may differ in different parts of sub-Saharan Africa and this is an area that warrants further study[63]

Pathogenesis of Kaposi Sarcoma

KS is a multicentric angioproliferative spindle cell tumor of endothelial origin [64] that is remarkable for pathologic [65] and clinical heterogeneity, as well as its ability to progress or regress based on host immune factors. In addition to proliferation of spindle cells that are mostly latently infected with KSHV, tumors are notable for inflammatory infiltrates and leaky vasculature. KSHV infection is necessary but insufficient cause of KS. The 165 kb KSHV genome is notable for molecular piracy of several genes homologous to cellular regulatory genes that are likely to contribute to the pathogenesis of KS through complex interactions with human immune and endothelial systems [64; 66; 67]. The molecular biology of KSHV specific genes implicated in tumorigenesis was recently reviewed. [67]. Here, we will mainly focus on a review of immunologic, angiogenic, and KSHV viremia in relation to the pathogenesis and treatment of KS.

Immune Dysregulation and Kaposi Sarcoma

The evidence for host immune dysregulation in the pathogenesis of KS is based on evaluation of populations at high-risk of KS, as well as an increasing understanding of specific immune defects. The association of KS with immunosuppression was first noted in solid organ transplant patients [68] and other patients on chronic immunosuppressive agents [69]. Furthermore, the appearance of a cluster of cases in MSM in San Francisco and New York in the early 1980s was an early harbinger of the AIDS epidemic [70]. HIV co-infection dramatically increases the risk of developing KS [71], especially in the absence of combination antiretroviral therapy (cART) to suppress HIV. Prior to the availability of cART, the 10-year risk of developing KS among men in San Francisco co-infected with HIV and KSHV approached 50%. [22]. The effect of uncontrolled HIV viremia and associated T-cell immunodeficiency in the pathogenesis of KS was further emphasized by an 80% decrease in KS incidence among people with AIDS in the US that corresponded with the widespread adoption of combination antiretroviral therapy (cART) [72].

Risk for KS is strongly associated with defects in cellular immunity. Decreasing CD4 cell count is associated with increasing risk of KS in both AIDS-associated KS [72] and classic KS [73]. Furthermore, KSHV infected patients that develop KS have decreased KSHV-specific CD4 response as measured by an interferon-γ ELISPOT assay utilizing 52 synthetic peptides from the KSHV-specific proteins, LANA, K12, and K15 [74], when compared to HIV-KSHV co-infected individuals without KS. Response to therapy has been associated with increases in both absolute CD4 count and KSHV-specific T-cell responses, as measured by ELISPOT, in treatment naive patients with AIDS-associated KS [75], as well as in transplant patients whose KS regressed with decrease dosing of cyclosporine [76].

Interestingly, renal transplant patients who develop KS on cyclosporine-based immunosuppression have KS regression when immunosuppression is switched from cyclosporine to rapamycin, a mammalian target of rapamycin (mTOR) inhibitor [77], and rapamycin may have direct anti-tumor activity. Transgenic mouse models have shown that the KSHV gene, ORF74/vGPCR, activates the PI3K-akt pathway and promotes proliferation through the mTOR pathway, and that rapamycin inhibits tumorigenesis in this model via inhibition of mTOR. [78]. Furthermore, rapamycin may have anti-KS effect due to its ability to decrease VEGF-A secretion and signaling [79], as well as secretion of interleukin-6 and interleukin-10 by KSHV infected cells [79; 80]. The anti-proliferative and anti-angiogenic effects of rapamycin in KS are posited to be due effects both a small compartment of lytically active KSHV infected cells, as well as the paracrine effects of decreased growth signaling through vascular endothelial growth factor-A (VEGFA). However, other immune modulatory effects of rapamycin are also likely to be at play. Effects on innate immunity are hypothetically possible, as rapamycin has been noted to inhibit interleukin-10 and induce

interleukin-12p70 secretion by monocytes outside of the setting of KSHV infection [81; 82]. Given the proliferative effect of interleukin-10 of KSHV infected cells, and anti-tumor effect of pharmacologic levels of interleukin-12 demonstrated in clinical studies of patients with HIV-associated KS[82; 83], these changes would be predicted to favor to KS regression. Together with the demonstration of development of KSHV-specific T-cell responses in renal transplant patients switching from cyclosporin to rapamycin, these data suggest the anti-KS effects of rapamycin in the setting of renal transplant related KS are likely to be multifactorial[76].

While intact T-cell function is important in preventing KS, several lines of evidence suggest that defects in humoral immunity may also play a role in KS pathogenesis. At the population level, development of KS correlates with decreased CD19 cell counts in both HIV-negative[84] and HIV –infected individuals[85]. One potential mechanism by which the humoral immune system could protect from the development of KS is through neutralizing antibodies. In a comparison of subjects with KS to those who were KSHV infected with no evidence of KS, a neutralizing antibody assay demonstrated significantly lower levels of neutralizing antibodies in the serum of patients with clinical KS. This remained true after correcting for CD4 count and total anti-KSHV antibody titers[86]. More recently, rituximab, a monoclonal antibody targeting CD20, has been evaluated in the treatment of KSHV-associated multicentric Castleman disease.[87; 88]. Interestingly, this anti-B-cell therapy was associated with mild exacerbations of KS in 33–36% of patients. A transient increase in KSHV viremia was detected during the first month of rituximab therapy in study subjects[87], but the association of transient KSHV viremia and the development of KS were not evaluated in this phase II clinical study. Despite these observations, the exact processes by B-cells and perhaps neutralizing antibodies protect against KS and other KSHV-associated malignancies remains incompletely understood.

Vascular Endothelial Growth Factor and KS

Several models of KS pathogenesis, based either on endothelial or primary effusion lymphoma derived cell lines derived from AIDS patients, systems in which individual KSHV genes are transduced into other cell lines, or cells infected with whole KSHV, have focused on the role dysregulated autocrine and paracrine angioproliferative signaling in the pathogenesis of KS. Correlative studies performed on human samples in many cases support preclinical models. Early work demonstrated that various KS cell lines, which were no longer infected with the KSHV genome, expressed elevated basic fibroblast growth factor (bFGF) mRNA levels. Cultured media from these KS cell lines was able to stimulate both human umbilical cord endothelial cell (HUVEC) and KS cell growth, while anti-bFGF antibodies inhibited this paracrine signaling[89]. Similarly, cultured media of AIDS-KS cell lines has high levels of VEGFA, and HUVEC proliferation that occurs in the presence of this cultured media is inhibited by anti-VEGF antibodies[90] or VEGFA siRNA[91]. Furthermore, anti-bFGF antibodies and anti-VEGFA antibodies are synergistic in inhibiting paracrine signaling[90]. VEGFR2, a receptor for VEGFA, is detected in both stromal vessels and spindle cells by both immunohistochemical stains of KS biopsies[92], and KS tumor samples express increased vascular endothelial growth factor receptor 1(VEGFR1) and vascular endothelial growth factor receptor 2(VEGFR2) mRNA compared to normal skin biopsies[91]. Antibodies against VEGFR2 and VEGFR2 siRNA also inhibit cell proliferation, again supporting the importance of autocrine signaling[93]. More recently, vascular endothelial growth factor receptor 3(VEGFR3), a receptor whose expression is generally limited to lymphoid endothelial cells, has been noted to be robustly expressed in KS cell lines[94; 95], as well as spindle cells from KS biopsy samples.[95; 96; 97]. When KSHV infected HUVEC cell cultures are compared to uninfected HUVEC cultures, increases in mRNA by RT-PCR for VEGFA, VEGFB, VEGFC, and VEGFD as well as

VEGFR1, VEGFR2, and VEGFR3 are noted, and IHC confirmed the strong expression of all three receptors in the KSHV infected HUVEC cells[93].

Evaluation of KSHV lytic and latent genes suggests that the virus has developed redundant mechanisms for up-regulation of multiple cellular VEGF signaling pathways. Signaling pathways involving several KSHV genes, including vGPCR, viral interleukin-6 (vIL-6), K1 and LANA lead to upregulation of VEGF. The vGPCR, encoded by ORF74, is a constitutively activated lytic gene most closely related to the human chemokine receptor CXCR2. Transfection of NIH3T3 cells or a PEL cell line (BC3) with vGPCR leads to cells that produce VEGFA[98; 99]. Cultured media from these transfected cells support HUVEC cell cultures, while anti-VEGFA antibodies inhibit proliferation. Furthermore, inoculation of these transfected cells in nude mice leads to the formation of vascular tumors with histological features of KS. vGPCR stimulated upregulation of VEGF is associated with stabilization of hypoxia-inducible factor 1-alpha (HIF-1α,), and upregulation of VEGF depends on the hypoxia response element (HRE) in the VEGF promoter. [100]. HUVEC cell lines transfected with vGPCR also maintain high mRNA expression of VEGFR2, and these cells undergo apoptosis when exposed PTK787, a small molecule tyrosine kinase inhibitor that inhibits all VEGF receptors[101]. vIL-6 is also KSHV lytic gene product with 25% amino acid homology to human interleukin-6. Transfection of vIL-6 into NIH 3T3 leads to 6–8 fold increases in VEGF-A mRNA, while subcutaneous injection of vIL-6 transfected NIH3T3 cells in nude mice also leads to spindle shaped tumors[102]. The K1 gene of KSHV encodes a transmembrane glycoprotein related to the immunoglobin receptor family with a constitutively active signaling through an intracellular immunoreceptor tyrosine-based activation motif (ITAM). K1 transgenic mice develop plasmacytoid and sarcomatoid tumors[103], and the lymph nodes from the K1 transgenic mouse show high levels of VEGFA by immunohistochemistry. Transfection of K1 into various B-cell lymphoma cell lines also lead to increased VEGF compared to the same cell lines transfected with a K1-mutant that lacked the ITAM sequence[104]. In an endothelial cell model, K1 transduction into HUVECs leads to an immortalized cell that produce high levels of VEGFA through increased transcriptional activity. Lastly, LANA, which is a latent KSHV gene may also have an effect on VEGF transcription. 293T cells transduced with LANA have increased VEGF-A transcription and increased VEGF-A in cell culture supernatant[105]. The ability of LANA to affect VEGF-A expression may be due to effects on HIF-1. LANA interacts with HIF-1α, and LANA and HIF-1 complex co-localize in the nucleus. Furthermore, LANA appears to regulate HIF-1α transcription, and may enhance HIF-1α transcriptional activating activity in the setting of hypoxia[106].

KSHV lytic activation, KSHV Viremia, and KS

While controlling HIV viremia has a clear benefit in preventing KS, a related area that is pertinent to prevention and treatment of KS and other KS-associated malignancies is the role of interventions designed to decrease KSHV lytic activation and associated expression of pathogenic lytic gene products as well as associated KSHV viremia. Both cohort studies and clinical studies suggest that KSHV viremia is a risk factor for development of KS, and that pharmacologic interventions that alter KS lytic replication may alter the natural history of KS. Several cohort studies have demonstrated that detectable KSHV viremia is a risk factor for development of KSHV among patients with HIV, and that this remains true after correcting for KSHV seropositivity.[43; 107] Controlling KSHV lytic replication decreases the risk of developing KS in patients with AIDS. In a randomized controlled trial of oral ganciclovir, intravenous ganciclovir and intraocular ganciclovir implants in patients with AIDS and CMV retinitis, there was a 75% –93% decrease in the development of KS in the arms randomized to receive oral or intravenous ganciclovir as compared to the implant arm. [108] However, a pilot study of intermittent use of anti-KSHV agent cidofovir[109] as

monotherapy did not adequately control KSHV as detected in the peripheral blood, and patients in this study had progressive KS.[110] While cidofovir as administered did not demonstrate efficacy in the treatment of KS, use of chemotherapy in addition to cART in patients with advanced KS does appear to be associated with decreasing KSHV viremia. In a small nested case-control study within a randomized clinical study of cART compared to cART and chemotherapy, patients who received doxorubicin, bleomycin and vincristine (ABV) in addition to cART had a 3 log decrease in KSHV at month 11, compared to the cART only arm, in which no decrease was observed.[75] Evaluation of the mature data from this study will help further define the association of decreased KSHV viremia to clinical outcomes. It will be important to further evaluate the extent to which measures of KSHV viremia in clinical studies represent a measure of KSHV infected circulating cells (i.e. KSHV infected B-cells that may be eliminated by chemotherapy itself), active KSHV lytic replication, or both. Indeed, future clinical studies evaluating drugs that interrupt KSHV viral replication in the treatment of KSHV-associated diseases would benefit from this distinction. Antiherpetic agents may be of particular interest in the management of patients with KS and concurrent multicentric Castleman disease, a disease where the role KSHV lytic activation is better established in disease pathogenesis.[111]

The role of KSHV lytic activation in inflammatory syndromes associated with KS is an area of future research interest.[112] Patients with HIV-associated KS can manifest inflammatory syndromes in the setting concurrent MCD, KS immune reconstitution inflammatory syndrome (IRIS), or other concurrent infections. Interestingly, some of these inflammatory syndromes, such as MCD or KS-IRIS, may occur in the setting of effective control of HIV.

Treatment of Kaposi Sarcoma

Effective cART prevents the development of KS in patients with HIV[113; 114]and the incidence of KS has decreased dramatically in countries such as the United States, where cART is broadly available[71]. Yet despite broadly available cART, risk of KS remains elevated in people infected with HIV, and KS is the second most common tumor in people with HIV/AIDS in the US[71]. In sub-Saharan Africa where the burden of HIV and KSHV co-infection is high, and widespread access to cART is expanding but still limited and surveillance programs for KS are lacking, KS remains a growing public health problem[115; 116].

Treating KS through Effective Combination Antiretroviral Therapy

Treatment of HIV-associated KS requires cART, which leads to both immune reconstitution and control of HIV viremia. Without cART, approaches that employ chemotherapy or radiotherapy in AIDS-associated KS are associated with extremely poor overall survival despite minor palliative benefit[117], whereas, the introduction of cART has lead to dramatic improvements in overall survival[118]. Furthermore, regression with cART alone has been well documented, and a pooled analysis of patients with early disease (T_0 = KS with low tumor volume, no associated ulceration or edema, and no visceral disease) who had not received cART previously suggest that approximately 80% will have disease regression with cART alone, with median time to response ranging from 3–9 months[119]. In a 254 patients from the Chelsea and Westminster HIV Cohort diagnosed with KS after the availability of cART (1996) 175 patients had early stage KS (T_0). With a median follow up of 4 years, 158 (90%) of these early stage patients were managed with cART alone, and when chemotherapy was used in this cohort, it was generally for concurrent malignancies such as KSHV-associated multicentric Castleman disease or non-Hodgkin lymphoma. Despite the excellent results, it is worth noting that there was a small cohort of patients (7%) who were diagnosed with KS despite undetectable HIV. The median age, CD4 count and time since diagnosis was each higher than the general cohort, suggesting that with an aging

population, there will continue to be a subset of patients who are optimally controlled on cART, yet will require additional modalities for the management of KS.[120] There are few good estimates of response rates with cART alone for treatment naive patients with advanced KS (T_1 KS with high tumor volume, associated ulceration or edema, and/or visceral disease), given most of these patients have been managed with chemotherapy. The best estimates are available from a randomized controlled trial of cART versus cART combined with chemotherapy in South Africa[121]. By intention to treat analysis, 39% of patients randomized to cART alone had a partial response or better by month 12, compared to 66% in the cART combined with chemotherapy ($p = 0.001$, Fischer exact test). However, it should be noted that 21 of 59 (36%) patients in the cART alone arm required the addition of chemotherapy or palliative radiation within 12 months of randomization. In an as-treated analysis, 52 patients with advanced disease were managed with cART alone, and 17/52 (33%) had partial response and 1/52 (2%) had a complete response with cART alone [personal communication, Mosam]. There was no difference between arms in terms of overall survival[121]. Results from this randomized study support the palliative benefit chemotherapy in patients with advanced KS, and suggests that an approach that incorporates chemotherapy may be feasible in resource-limited settings. Further evaluation of quality-of-life from this study will better inform the relative palliative benefits of cART and chemotherapy.

Choice of Antiretroviral Regimen

Effective combination antiretroviral therapy consists of a combination of either a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) with two nucleoside reverse transcriptase inhibitors (NRTI). *In vitro* and mouse models suggested that certain PIs, indinivir and saquinivir, inhibit development and induce regression of angioproliferative KS-like lesions[122]. This finding led to interest in potential direct anti-KS effects of PIs through “off target” effects of this class of agents. However, to date, non-randomized clinical studies do not support this hypothesis. In the Chelsea and Westminster Cohort of 8640 patients with HIV, 1240 patients with KS were identified, and NNRTI and PI based regimens had the same protective effect against the development of KS[114]. Time to treatment failure was also evaluated in 78 patients treated with chemotherapy or radiotherapy, and subsequently started on cART, with no significant differences noted between PI based and NNRTI based regimens[113]. Similarly, disease-free survival among 254 patients with KS treated with cART was not significantly effected by whether their first cART regimen included a PI.[120]. “Additional retrospective studies failed to show differences in tumor regression between patients treated with PI based regimens and those treated with NNRTI based regimens.” [123; 124] A randomized controlled trial of a PI based regimen (lopinavir/ritonavir plus emtricitabine/tenofovir) versus an NNRTI based regimen (efavirenz plus emtricitabine/tenofovir) in treatment naïve patients with KS in Uganda (NCT00444379) is currently enrolling patients to further evaluate this question. In addition to the potential effects of PIs on KS, the nucleoside analogue zidovudine (AZT) is a substrate for the KSHV thymidine kinase, ORF21[125] and is toxic to lytically activated KSHV infected cells[126]. However, the individual impact on KS of AZT within a combination regimen is difficult to ascertain, and practically, is a less pressing clinical question given the trend toward use second generation NTRIs with less hematotoxicity than AZT.

Immune Reconstitution Inflammatory Syndrome Manifesting as Worsening of KS

It should be noted that some patients with HIV-associated KS have worsening of KS with the initiation of cART due to immune reactivation inflammatory syndrome (IRIS). KS IRIS is generally distinguished from failure of cART by improvements in CD4 count and control

of HIV viremia. Although exact definitions of KS IRIS may vary between studies, The AIDS Clinical Trial Group Defines KS IRIS clinically by:

1. Initiation, reintroduction, or change in cART AND
2. Evidence of
    a. Increase of CD4 by ≥ 50 cells/mL or ≥ 2-fold rise in CD4 count and/or
    b. Decrease in HIV-1 viral load > 0.5 $\log_{10}$ AND
3. A sudden or more dramatic progression of disease than expected as part of natural history that occurs within 12 weeks of initiation of ART.

Estimates of the incidence of KS-IRIS vary. The incidence of rapid progression of KS in 150 cART naive patients in the Chelsea and Westminster Cohort with HIV-associated KS who were started cART was 6.6%. However, changes in CD4 count were not part of the case description in this study[127]. In a case series of 9 cases of KS-IRIS from Seattle in which all cases had > 1 $\log_{10}$ decrease in HIV-1 viral load, the mean time to KS-IRIS was 5 weeks (range 3–7 weeks). KS-IRIS manifested as a flare of cutaneous disease in all patients, and increased lymphadenopathy or mucocutaneous involvement was also noted.[128] A prospective study of treatment naive HIV and KSHV co-infected adults in Mozambique showed that 8/69 (11.6%) developed KS-IRIS during the first 10 months of therapy. The median time to diagnosis of KS-IRIS in this cohort was 13.8 weeks. KS-IRIS was associated with baseline clinical KS, detectable plasma KSHV DNA, anemia (hematocrit <30%), and increasing KSHV viral load[129]. KS-IRIS is treated by continuation of cART, however, the addition of chemotherapy may be necessary, especially in patients with pulmonary involvement. More research is needed to better define and evaluate the natural history of KS-IRIS.

Additional Therapy for the Treatment of HIV-associated KS

Effective treatment of KS with additional agents is dependent on the risks, benefits and goals of the proposed therapy. KS is not a curable tumor. However, durable remission may be a reasonable goal of therapy, especially in patients who have low CD4 lymphocyte counts at diagnosis and immune reconstitution once HIV viremia is controlled with cART. Indications to initiate treatment for KS include rapidly progressive disease, visceral disease, bulky cutaneous disease, or cutaneous disease associated with edema and ulceration, as well as cosmesis. Several modalities, including radiotherapy, topical therapy, cryotherapy, or intralesional injection historically have been employed for control of localized KS, but their use has been largely been replaced by cART. However, systemic therapy remains indicated for bulky, rapidly progressing, symptomatic, or life-threatening disease[119]. Evaluation of the treatment studies of HIV-associated KS is complicated by the complexity of grading responses, the variability in the natural history of KS with changes in immune status, and variable use of cART within clinical studies, and the improved outcomes in cART naïve patients[119]. Furthermore, the treatment of early stage disease has generally differed from that of advanced disease, and evaluation of response rates must take into account the relative distribution of T_1 versus T_0 disease. Estimates of the effectiveness of individual interventions must be interpreted with an appreciation of the strong impact of these patient related factors, differences in timing of responses, and potential effect of concurrent KSHV-associated inflammatory cytokine syndromes[112]. Giving the waxing and waning nature of KS, the diversity of presenting symptoms, and the need to retreat in many cases, evaluation of response rates provide only some information required to personalize therapy for a given patient. Furthermore, although KS can cause a great deal of morbidity, patients often do not die from KS, and attention to long term side effects of interventions must also be considered. Lastly, as HIV-associated KS appears to be an increasing public health problem in parts of

sub-Saharan Africa where HIV and KSHV co-infection rates are high[115], creative treatment approaches that take into account resource limitations, as well as cost of medications for cancer care in resource limited settings[130] are urgently needed. Despite these limitations, response rates do provide some insight into drug activity. We will review treatment options for KS using both standard therapies and select novel pathogenesis-based approaches. (Table 1) A review of treatment of other KSHV-associated tumors is beyond the scope of this review.

Liposomal doxorubicin is currently the chemotherapeutic agent of choice for advanced KS. Preclinical data showed that pegylated liposomes preferentially accumulate in highly vascularized KS lesions, and provided a rationale for their evaluation in KS. Prior to the availability of cART, a randomized controlled study of 232 patients with AIDS-associated KS compared overall response rates of liposomal daunorubicin as compared to doxorubicin, bleomycin and vincristine (ABV)[131]. Most patients in this study received NRTI monotherapy, however, no patients were receiving a current standard 3-drug regimen. Overall response rates (25% versus 28%) and overall survival were similar between the two groups. Two separate studies performed in the same time period randomized patients to receive either liposomal doxorubicin or a combination of bleomycin and vincristine (BV) or ABV. Approximately half the patients were receiving one or more antiretroviral agent, but again none received the current standard 3-drug regimen. In these study, the overall response rate with liposomal doxorubicin was superior to BV (58.7% versus 23.3%)[132] and ABV (45.9% versus 24.8%)[133], and in the later study, health related quality-of-life measured also favored liposomal doxorubicin[134]. All three studies demonstrated an improved toxicity profile with the use of liposomal anthracyclines when compared to BV or ABV. With the availability of cART and dramatic decrease in patients with KS, there have been no large randomized treatment studies in HIV-associated KS in the United States or Europe, and liposomal doxorubicin has not been compared to regimens like ABV in the cART era due to the improved toxicity profile of the former. A small multicenter study of 28 patients with HIV, who were not on an effective antiretroviral regimen and at least 10 cutaneous lesions, randomized patients to receive cART alone or cART combined with liposomal doxorubicin. By intention-to-treat analysis, the overall best response rates were 76% versus 20% ($p= 0.003$)[135], showing a strong treatment effect of the addition of chemotherapy to cART. Given this cumulative data, liposomal doxorubicin has become the standard of care for KS. Long-term follow-up of 98 patients treated with liposomal doxorubicin combined with cART in 2 prospective studies demonstrated that approximately 78% of patients treated with this combination had a partial response or better, and among responders, the relapse rate was 13.5% per year[136]. While outcomes from this combination are superior to historical controls, approximately one third of patients with HIV-associated KS may require additional or second-line therapy. Additional commercially available agents which have activity in KS include paclitaxel[137; 138] which is FDA approved for this indication, interferon-α[139], and oral etoposide[140]. Other agents with immune modulating activity, such as high dose thalidomide[141] or IL-12[83; 142], also have activity in HIV-associated KS. However, their use is limited by toxicities or lack of drug availability. Several agents are under clinical investigation for use in patients with KS. Studies evaluating the vascular endothelial growth factor (VEGF) pathway inhibitors bevacizumab (NCT00055237, NCT00923936) and sorafenib (NCT0030412 are underway, as are studies of the mammalian target of rapamycin (mTOR) inhibitor sirolimus (NCT00450320) and the immune modulating agent, lenolidomide (NCT01057121).

In sub-Saharan Africa, where the burden of advanced KS is high, the optimal therapeutic approach is unknown. A randomized controlled study of cART combined with chemotherapy showed a 66% overall response rate with a combination approach[121]. However, liposomal anthracyclines have not been evaluated in this setting due to lack of

drug availability. Furthermore, implementation of chemotherapy for the treatment of advanced AIDS-associated KS has to take into account issues of infrastructure, such as lack of infusion centers and trained personnel to administer chemotherapy, and ability to monitor blood work, as well as a high rate of co-morbid tuberculosis. Oral agents such as etoposide may have the benefit of ease of administration. In sub-Saharan Africa, where the burden of AIDS-associated KS is greatest, prospective evaluation of novel approaches to treating KS in resource limited settings as well as randomized studies of established agents are needed to better define an optimal and affordable approach to therapy for AIDS-associated KS in this setting.

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Table 1

Select Systemic Therapies in the Treatment of Kaposi Sarcoma

Intervention	Mechanism of Action/Drug Target	Estimated Overall Response Rate	Common and Select Late Toxicities	Notes
Immune modulation				
Combination antiretroviral therapy	Suppress HIV replication and viremia through drug specific mechanisms. Restoration of T-cell immunity.	Sufficient in up to 90% of patients with early stage (T0) KS. Partial response rate in advanced (T1) KS ≈35%[120; 121].	Dependent on agents used.	Combination antiretroviral therapy is required for all HIV-associated KS, but has no role in the treatment non-HIV-associated KS. Five classes of drugs and >25 agents are available. Drug-drug interactions must be considered.
Rapamycin	mTOR Inhibitor Immune-modulation	Discontinuing cyclosporine and initiating rapamycin ≈100% effective in renal transplant patients with KS[77]	Edema, hypertension, elevated creatinine, hyperlipidemia,	Rapamycin has a role in renal-transplant related KS, its use in HIV associated KS is being evaluated in an early phase clinical study. (NCT00450320) Drug-drug interactions must be considered.
Interferon-α	Pleotropic effects: Immune modulation, antiviral, and anti-angiogenic effects	In combination with protease inhibitor based therapy, 33%. [139]	Flu-like symptoms and fatigue(decrease with continued therapy) Neutropenia, elevated transaminases, hypothyroidism Neuropsychiatric	May be more effective in patients with preserved CD4 counts. Rarely used in the era of combination antiretroviral therapy. May have a role in patients with concurrent hepatitis C.
Interleukin-12	Enhances TH1 Immune responses, upregulates Interferon-γ. Through Inducible Protein 10 (IP10), may down regulate the pathogenic KSHV-encoded protein, vGPCR.	71% alone, 83% in combination with liposomal doxorubicin[83; 142]	Constitutional symptoms, neutropenia, elevated transaminases, depression	In early stage development, not commercially available.
Thalidomide	Immune modulator, anti-angiogenic effects	High dose thalidomide, 40–47%[141]	Fatigue, somnolence, depression, neuropathy, rash	Not generally used. Dosing evaluated phase II study in KS higher than that currently used in multiple myeloma.
Lenalidomide	Immune modulator, anti-angiogenic effects	In early phase clinical study.	Fewer neuropathic side effects than thalidomide. More cytopenias. Also edema, rash, infections and fatigue.	Patients currently being accrued to an early phase study in AIDS-associated KS by the AIDS Malignancy Clinical Trial Consortium. (NCT01057121)
Cytotoxic Agents				
Doxorubicin	DNA intercalating agent, Topoisomerase II inhibitor	Prior to broadly available antiretroviral therapy, treatment of AIDS KS with either a combination of bleomycin, vincristine +/− doxorubicin (BV/ABV) 25–50% In an intention to	Agents generally used in combination regimens: ABV or BV. Side effects include: nausea and vomit, mucositis, neutropenia. Hair loss	ABV and BV have largely been replaced by liposomal anthracyclines in the developed world given improved efficacy and decreased toxicity. The use of BV or ABV may still have a roll in some resource-limited settings where liposomal preparations are not available.
Bleomycin	Formation of free radicals and resultant DNA damage			

Intervention	Mechanism of Action/Drug Target	Estimated Overall Response Rate	Common and Select Late Toxicities	Notes
Vincristine/Vinblastine	Disruption of microtubule function	treat analysis of treatment naive patients assigned to antiretroviral therapy + ABV: 66% at 12 months.[131; 121]	(ABV), increasing risk of cardiomyopathy with cumulative doses of doxorubicin > 400 mg/m2. Risk of pulmonary toxicity with bleomycin.	
Etoposide	Topoisomerase II inhibitor	In AIDS-associated KS with no antiretroviral therapy, or in the setting of multiply relapsed disease: 33–36%[117; 140]	Neutropenia, anemia, alopecia. Etoposide use has a small risk of secondary acute myelogenous leukemia.	Studies in AIDS-associated KS usually employ low dose oral etoposide. While generally not used where liposomal doxorubicin is available, it has the benefit of oral administration
Pegylated Liposomal Doxorubicin	Liposomal preparation of doxorubicin, liposomes preferentially accumulate in vascularized KS lesions.	In the era of cART: 46 – 78% [132; 133; 135; 136]	Anemia, thrombocytopenia, leukopenia. Hand-foot syndrome. Although less cardiotoxic than doxorubicin, recommended cumulative life time dose <550 mg/m2.	Standard therapy where available, FDA approved for use in Kaposi sarcoma. In the cART era, paclitaxel was compared to pegylated liposomal doxorubicin in a small randomized study. Neither drug was clearly superior. Doxil is generally better tolerated.
Paclitaxel	Microtubule Stabilizer	56%–71% [137; 138]	Hair loss, anemia, thrombocytopenia, neutropenia, peripheral neuropathy, myalgia infusion reactions.	FDA approved for use in Kaposi sarcoma. Often used as second line therapy or in advanced cases.
Experimental Approaches Targeting Vascular Endothelial Growth Factor (VEGF)				
Bevacizumab	Humanized monoclonal anti-VEGF antibody	In a phase II study of patient on a stable antiretroviral regimen: 33% [143]	Hypertension, proteinuria, epistaxis. Increased thrombotic risk when used to treat other malignancies.	Bevacizumab is being further evaluated in combination with pegylated liposomal doxorubicin at the NCI. (NCT00923936) Bevacizumab may be particularly useful in managing pleural effusions.
Sorafenib	Tyrosine kinase inhibitor targeting VEGFR1, VEGFR2, and PDGFR	In early phase clinical study.	Potential drug-drug interaction with some antiretroviral agents. Rash, hand-foot syndrome. gastrointestinal symptoms, fatigue, elevated lipase.	Patients currently being accrued to a Phase I study at the NCI. (NCT00304122)