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Targeted therapy in Kaposi sarcoma

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Abstract

Kaposi sarcoma (KS) occurs as a result of Kaposi sarcoma-associated virus (KSHV) infection, typically in the context of one of several immunodeficient states. In the United States, patients with KS may either be co-infected with human immunodeficiency virus (HIV) or on immunosuppressant therapy following solid-organ transplantation. Systemic treatment of KS traditionally involved one of several chemotherapeutic agents either in combination or as single agents, which typically provides reasonable response rates and short term control. However recurrence is common and progression free intervals are under one year. For these reasons, new therapies have been sought and with the elucidation of novel pathogenic mechanisms of KS, rationale targets identified. These include KSHV replication, restoration of immune competence, and signal transduction pathways utilized by KSHV in the propagation of KS.

Keywords

Kaposi sarcoma; herpesvirus 8; Kaposi sarcoma associated herpesvirus

Introduction

Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8) is the causal agent of Kaposi sarcoma (KS), primary effusion lymphoma (PEL), and many cases of multicentric Castleman disease (MCD).([1-3]) Since its discovery in 1996, much has been learned about KSHV interactions with its infected host which lead to these conditions. Though infection is not sufficient for tumor development, it is clear that KSHV has developed various ways to manipulate host cell signal transduction, and thereby lead to the activation of numerous pro-growth and anti-apoptotic pathways. As several of these mechanisms of oncogenesis have been elucidated, potential therapeutic targets have been identified and inhibitors of these targets have been developed. Since KS is currently the most common KSHV-associated neoplasm, the majority of clinical investigation and research effort has been devoted to this low-grade vascular neoplasm. This review will focus on KS with a description of important clinicopathological characteristics, oncogenesis, and highlight “targeted” therapeutic interventions.

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Major Clinical Characteristics

KS is a multifocal angioproliferative neoplasm that occurs in several clinical-epidemiologic settings. It is the most common tumor in HIV-infected patients and is a leading cause of mortality and morbidity in acquired immune deficiency syndrome (AIDS).([4]) Tumorigenesis is driven by KSHV infection, predominantly in those who are immunosuppressed. This includes (i) Classic KS, a disease that mainly affects elderly Mediterranean men, (ii) iatrogenic KS, which develops in patients taking immunomodulatory agents in the context of solid-organ transplantation, and (iii) AIDS-related KS.([5-7]) African-KS is endemic to Africa and unrelated to HIV infection. KSHV infection and an ineffective host immune response towards this gamma herpes virus are common to all of the aforementioned KS clinical subtypes. Reversal of immune suppression, either with highly active antiretroviral therapy (HAART) or by decreasing the levels of immunomodulatory agents in transplant recipients, has been associated with regression of lesions.([8, 9]) In addition, the incidence of KS has decreased over 6-fold with the advent of widespread use of HAART in treated HIV-infected individuals. (10)

Despite its decrease in incidence, KS remains a disease with a wide spectrum of severity. This ranges from single skin or mucosal lesions to rapidly progressing, extensive cutaneous, and/or visceral disease. For patients with advanced disease, systemic therapy is indicated and three FDA-approved agents are available. These include the liposomal anthracyclines (pegylated liposomal doxorubicin and liposomal daunorubicin) and the taxane paclitaxel. Pegylated liposomal doxorubicin use is associated with response rates ranging from 46% and 59% and median duration of response ranges from three to five months.([11, 12]) Liposomal daunorubicin has shown a response rate of 25%, disease stability in an additional 62% with a median duration of response of 175 days and median time to progression of 115 days.(13) Both liposomal anthracyclines have been associated with limited toxicity and were better tolerated than the comparative treatment of adriamycin-bleomycin-vincristine in two trials and bleomycin-vincristine in another study. Paclitaxel received FDA-approval based upon the results of a phase II trial of 28 patients with significant immunosuppression (mean CD4 cell count 15 cells/microliter) in whom 20 had a major response.(14) Mean progression free survival was 6.3 months and median duration of response 7.4 months; grade 3 and 4 toxicity were reported to be rare. Despite the effectiveness of these agents, most patients afflicted with KS progress within six to seven months of treatment and require additional therapy. Although patients may initially benefit from further cycles of chemotherapy, durable chemotherapy-free remissions tend to be shorter with each successive treatment regimen. Clearly, novel therapeutic strategies are needed.

Key Pathologic Findings

KS lesions of all epidemiologic forms are similarly comprised of KSHV positive (LNA-1 immunoreactive) spindled shaped tumor cells, vessels and chronic inflammatory cells (Figure 1). KS lesions evolve from early patch, to plaque, and later tumor nodules. Early patch lesions are characterized by a proliferation of irregular, thin-walled vascular channels. As the cellularity of the lesion increases a palpable plaque forms. Continued proliferation of spindle cells eventually results in a nodular tumor. KS regression can rarely occur spontaneously, but as alluded to above is seen most often following appropriate therapy or after removal of immunosuppressive therapy.(15) KS flare (or exacerbation) can occur with either the immune reconstitution inflammatory syndrome (IRIS) following HAART, after corticosteroids, and with rituximab therapy.(16) Unique staging systems available for Classic and AIDS-associated KS (e.g. AIDS Clinical Trials Group staging classification) are used mainly for patients on trials.

Targeting KSHV

Like all herpesviruses, the KSHV lifecycle includes a latent and lytic phase. Gene expression in the latent phase is limited, even though these gene products play an important role in oncogenesis.(17) The lytic phase is characterized by the expression of many genes that culminate in viral replication followed by cell lysis and the release of viral replicants. It is during this lytic phase that KSHV is susceptible to the effects of anti-viral agents.(18) Notably, in KS lesions only a small percentage of cells are infected with KSHV in the lytic phase, as the great majority harbor KSHV in the latent phase.(19) In KSHV-related MCD, by comparison, a much greater degree of KSHV lytic gene expression is seen in lesional tissue. (20)

Given its causal role in KS, there has been great optimism that therapy aimed directly against KSHV may provide benefit in the treatment of KS. Several antiviral agents including ganciclovir, foscarnet, and cidofovir have been shown to inhibit KSHV replication *in vitro*, and a randomized controlled trial has recently established the efficacy of valganciclovir in reducing KSHV replication.(21, 22) In addition, a trend towards a lower incidence of KS in CMV infected patients with concomitant HIV who received ganciclovir and foscarnet, but not acyclovir which has little *in vitro* activity against KSHV, has been reported.(23) As of yet, however, this has not translated into the successful therapeutic use of these antiviral agents in KS.

Specifically, cidofovir was shown to be ineffective in the treatment of patients with KS.(24, 25) This is in contrast to reports of improvement of patients with MCD treated with ganciclovir. (26) Also, cases of prolonged survival in persons with PEL treated adjunctively with ganciclovir or cidofovir have been reported.(27, 28) The reason for this variable activity of antiviral therapy for each of the KSHV-associated diseases is unclear, but likely lies in the relative proportion of lytic-phase virus present in each disease.(18)

Histone deacetylase (HDAC) inhibitors are agents capable of inducing lytic replication in latently infected cells.(29) The HDAC inhibitor valproic acid was initially shown to induce lytic replication of KSHV in cultured PEL cells.(30) This was followed by a pilot clinical trial of valproic acid in patients with AIDS-associated KS on HAART.(31) Although only 6% (1/18 patients) showed a partial response after short-course treatment, none of the patients in this study had KS progression. This pilot study supports further research of more potent HDAC inhibitors over longer treatment courses in patients with KS.

Targeting KSHV-directed immunity

The regression of KS with the reduction of immunosuppressive treatment following solid organ transplant, and the clinical improvement of KS in subjects with immune reconstitution following HAART, is evidence that the immune system plays a critical role in the control of KS. The exact mechanisms have not been elucidated to fully describe the immune system's interaction with KSHV infected cells, nor its overseeing of the above mentioned clinical regression. What is clear is that diminished immune status is a critical contributing factor to KS development, and its improvement is an important therapeutic goal.

Highlighting this approach is the effectiveness of antiretroviral regimens in treating AIDS-related KS. This strategy is so important that it is considered standard practice for all patients with AIDS-associated KS to receive HAART when availible.(8) This is based on the fact that HAART is associated with both a reduction in the incidence of AIDS-related KS and regression in size and number of existing lesions.(32, 33) It is difficult to know exactly at what rate KS responds to HAART alone, since in many patients with advanced KS, cytotoxic chemotherapy was administered concurrently. While there is minimal data comparing the efficacy of various

HAART regimens in the treatment of KS, the use protease-inhibitor-containing regimens have a theoretical advantage based on experimental models and anecdotal data. (34) Discontinuation of chemotherapy without subsequent KS recurrence can be achieved in certain individuals with more advanced KS once their HIV infection is successfully suppressed with effective HAART.

In patients with iatrogenic (transplant-associated) KS, reduction of immunosuppression, while not always feasible, is desired.(9) In patients where such reductions would incur undue risk (e.g. graft rejection), changes in the immunomodulatory regimen may be warranted. For example, a series of patients had notable regression of KS when the cyclosporine-based regimens on which they developed KS where changed to one that included rapamycin.(35) While the degree of immunosuppression was likely unaltered based upon the absence of graft rejection in these patients, the improvement documented was more likely the result of inhibiting constitutively active KSHV-mediated signal transduction. The use of rapamycin and its analogs is discussed below.

Targeting KSHV-mediated signaling

Through intricate and varied utilization of critical signal transduction pathways, KSHV gene products drive the transformation of KSHV-infected cells into KS lesions. Some of these virally encoded proteins are cellular homologues of oncogenes which play critical roles in cell cycle regulation and apoptosis. Others are homologues of cytokines, chemokines, or chemokine receptors which promote cellular growth and transformation when abnormally regulated. The ramification of activating these proteins and oncogenic pathways include abnormal regulation of the cell cycle, promotion of angiogenesis, and the propagation of an anti-apoptotic signal. Recent advances made in our understanding of the KSHV genome and the many sequential and parallel signaling pathways it activates has identified several drugable targets.(36)

Perhaps the most promising therapeutic targets in KS are the downstream signaling pathways upregulated by a viral G-protein coupled receptor (vGPCR).([37]) Encoded by KSHV in the lytic phase of replication, vGPCR shares significant homology with the high-affinity interleukin (IL)-8 receptor, and its dysregulated expression contributes to oncogenesis.(38) The consequence of its activation is best highlighted by the fact that transgenic mice expressing vGPCR develop angioproliferative tumors resembling KS in multiple organs. These tumorigenic effects are potentially mediated through numerous cellular proliferation, transformation, pro-angiogenic and anti-apoptotic signaling pathways, the most important of which appears to be the phosphatidylinositol 3-kinase (PI3K) pathway.([37-41])

PI3K is a lipid kinase that activates Akt, a serine-threonine kinase that has multiple targets including the mammalian target of rapamycin (mTOR), a kinase that plays a crucial role in cell proliferation and survival in KS.([41, 42]) The activation of this pathway and the implications of its inhibition have been well described in vGPCR-transfected cells and in AIDS-related KS samples. *In vitro*, cells expressing constitutively active vGPCR have high levels of activated Akt, inactivated TSC2 (a tumor suppressor which is inactivated by Akt), and activated mTOR.([43, 44]) This has been reversed with either a PI3K inhibitor (LY 294002) or an mTOR inhibitor (rapamycin) *in vitro* and *in vivo* murine models; the latter also associated with decreased tumor growth.(44) As mentioned previously, all 15 patients described with iatrogenic KS who developed lesions on cyclosporine-based immunosuppression regimens had complete clinical and histological regression of KS in response to discontinuing cyclosporine and commencing rapamycin.(35) Additionally, intense staining of mTOR pathway mediators including expression of phosphorylated Akt, vascular endothelial growth factor (VEGF), VEGF receptor 2 (VEGFR1), and phophorylated p70S6 kinase was seen in the KS lesions compared with comparative normal skin biopsies.(35) A clinical trial is underway to determine the safety and efficacy of rapamycin in AIDS-related KS.

Activation of mTOR has numerous effects including the enhancement of a pro-angiogenic signal through increased expression of vascular endothelial growth factor (VEGF).([45]) In KS, VEGF as well as VEGF receptor 2 (VEGFR2) and VEGFR3 expression are seen and deemed important for its development.([46-50]) Furthermore, the expression of vGPCR in HUVEC (human umbilical vein endothelial cells) leads to immortalization which occurs with concomitant expression of VEGFR2 (KDR).([51]) This further activates PI3K/Akt/mTOR and leads to the increased secretion of VEGF, which enhances VEGFR2 activation. This autocrine loop enhances survival of these cells and is thought to be a major transforming mechanism. (51) Inhibition of VEGF, either through monoclonal antibodies (bevacizumab) or with small molecule tyrosine kinase inhibitors (sorafenib, sunitinib), has proven clinical efficacy in many solid tumors including breast cancer, renal cell carcinoma, lung cancer, and colon cancer. Currently, the use of VEGF inhibitors is an area of active investigation for patients with KS, and NCI-sponsored clinical trials are ongoing with bevacizumab, sunitinib, and sorafenib.

Targeting downstream effectors of the vGPCR in the treatment of KS, including PI3K, mTOR, or VEGF, offers considerable rationale and promise, however downmodulation of the receptor activation itself may provide a more direct and effective strategy. Interleukin-12 (IL-12) is a proinflammatory cytokine which promotes expression of the type I immune response, at least in part through stimulation of interferon gamma production and is known to mediate an antiangiogenic signal.(52) In addition, IL-12 upregulates interferon-induced-protein-10 (IP-10) which is a known negative regulator of vGPCR and IL-12 may thus inhibit vGPCR signal transduction through this mechanism.([53, 54]) Given these properties, it is not surprising that IL-12 has been investigated as a potential treatment for KS. In a phase I exploratory study of patients with AIDS-related KS, 17 of 24 (70 %) patients treated at higher doses near or above the MTD of 500 ng/kg experienced a partial or complete response.(55) Following this, IL-12 was combined with pegalated liposomal doxorubicin (PLD) in a phase two study. In this trial patients received both IL-12 and PLD for up to six cycles and then received IL-12 maintenance for up to three years.(56) 30 of the 36 (83 %) patients enrolled had a major clinical response and the median progression free survival had not been reached with a median follow up of over four years.

While targeting mTOR and VEGF are promising therapeutic strategies, the inhibition of other upregulated pathways in KS have been the focus of recently completed clinical trials. Based on the pathologic findings of increased expression of the platelet derived growth factor receptor (PDGFR) and the receptor tyrosine kinase c-kit in KS, a pilot study with imatinib was performed.([57-61]) Imatinib is a small molecule inhibitor of multiple tyrosine kinases including bcr-abl, PDGFR, and c-kit. A total of ten patients with AIDS-related KS were treated with imatinib, and clinical and histological response was seen in four patients.(62)

Finally, another promising therapeutic strategy for KS is the inhibition of matrix metalloproteinases (MMPs). MMPs are endopeptidases that assist in angiogenesis via degradation of extracellular matrix. While they play a role in normal angiogenesis and wound healing, several MMPs such as MMP2 and MMP9 are associated with malignancy and are both expressed in KS.([63, 64]) COL3, a tetracycline, is a known MMP inhibitor which showed promising activity in a phase I trial of advanced malignancies.(65) Based on MMP expression in KS, a phase I trial was performed and was well tolerated and showed anti-tumor activity in patients with AIDS-related KS. A subsequent phase II trial confirmed the antitumor activity of COL3 in treating KS.(66)

Conclusions

Over the past 10-15 years, the ability to molecularly target intricate pathways in cancer has been transformed from a hopeful idea to a definitive reality. This has revolutionized the way

cancer is being treated, and AIDS-related malignancies are no exception. In particular, Kaposi Sarcoma is an ideal example of a disease whose clinical characteristics inspired elegant bench research which has translated into improved clinical decision making. Its association with immunodeficiency and certain regions stimulated investigators to search out a culprit infectious agent. Once discovered, elegant research on KSHV has elucidated intricate sequential and parallel signaling pathways that can be inhibited by small molecule tyrosine kinase inhibitors and antibodies to key cell surface receptors. In total, this has translated to a multifaceted therapeutic approach which includes targeting the causal agent (KSHV), the deficient immune system (ie. HAART in AIDS-related KS), and the molecular pathways which fuel tumor growth and new blood vessel formation. Continued efforts remain essential in determining the optimal treatment for KS which will minimize toxicity and enhance patient's quality and quantity of life. In seems clear that the application of state-of-the art bench and clinical research tools will help us achieve this, now, attainable goal.

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