Kaposi’s sarcoma in HIV-infected patients: a review of the literature

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ABSTRACT: Kaposi’s sarcoma (KS) is a multicentric angioproliferative cancer of endothelial origin that usually occur in patients with immunodeficiency, such as Human Immunodeficiency Virus (HIV) or transplantation. KS-associated herpesvirus (KSHV), also known as human herpesvirus-8 (HHV-8), is associated with the development of KS. In the setting of HIV infection, the incidence of KS has dramatically decreased after the introduction of Highly Active Antiretroviral Therapy (HAART). In fact, HAART represents the first treatment step for slowly progressive disease, while chemotherapy (CT) plus HAART is indicated for visceral and/or rapidly progressive disease. Target therapies, based on anti-angiogenic agents as well as metalloproteinase and cytokine signaling pathway inhibitors, have been developed more recently and used for patients with progressive disease despite chemotherapy and/or HAART. In this paper, we review the most recent data on KS epidemiology, pathogenesis and therapy.

Key words: HIV, Kaposi, Herpes virus, ART.

INTRODUCTION

With the introduction of Highly Active Antiretroviral Therapy (HAART), the natural history of Human Immunodeficiency Virus (HIV) infection has changed significantly⁴. However, HAART is not able to eradicate HIV infection, due to the persistence of latent viral reservoirs²-¹³. On the other hand, a significant increase in the risk of non-HIV-related morbidity and mortality, including bone and cardiovascular disease, and malignancies, has been observed¹⁴-⁴⁹. Although the incidence of Kaposi’s sarcoma (KS), an AIDS-related malignancy, has dramatically decreased in both USA and Europe after the introduction of HAART⁵⁰, KS remains the second most frequent tumor worldwide and the most common cancer in Sub-Saharan Africa⁵¹. KS usually occurs in late stages of HIV infection and is characterized by an extremely aggressive clinical course. KS is less aggressive in patients on HAART. However, KS has recently been reported as occurring in subjects with well-controlled HIV infection and CD4⁺ T-cell count >200 cells/μl; in addition, it remains to be seen if further changes in the incidence of KS may occur as the HIV/KSHV coinfected population ages⁵².

In this paper, we review the most recent data on KS epidemiology, pathogenesis and therapy.

EPIDEMIOLOGY

KSHV is one of the most oncogenic human viruses⁵³. The prevalence of KSHV infection is estimated to be around 1.3%-4.4% in Southeast Asia and the Caribbean regions and significantly higher in Sub-Saharan Africa, with seropositivity rates >50%. In Europe, the prevalence is around 20-30%, whereas in the US is 1.5%-7%⁵⁴. KS is one of the most common cancers in several Sub-Saharan African countries, where the vast majority of cases of KS occur, and it can affect all HIV patients populations, including homosexual and heterosexual individuals, men and women⁵⁵. In the US and Europe, the prevalence of KSHV is elevated in men who have sex with men (MSM) and bisexual male AIDS patients⁵²-⁵⁵.

The incidence of KS is 1 in 100,000 in the general population, whereas in HIV-infected individuals it is around 1 in 20, reaching the value of 1 in 3 in HIV-infected homosexual men before the introduction of HAART. The majority of cases
of KS occur in individuals with low CD4+ T-cell counts. However, one-third of cases have been reported to occur in subjects on successful long-term HAART.

KS occurring during effective antiretroviral therapy has many characteristics of that seen in elderly HIV-uninfected men (i.e. classical KS). In fact, the clinical presentation is much less aggressive compared to KS of untreated individuals with advanced disease. It has been hypothesized that certain markers of immunosenescence may be associated with KS in the context of effective therapy. Specifically, increased frequency of T cells with an immunosenescent phenotype (CD28- and CD57+) has been reported in patients with KS, as well as lower frequencies of naive T cells and higher frequencies of effector T cells.

Almost 50% of individuals acquiring KSHV infection with pre-existing HIV infection develop KS. This observation suggests that an already damaged immune system may predispose to a higher KSHV load, with subsequent KS development.

- There are four different epidemiological forms of KS:
  - Classic KS, affecting elderly men of Mediterranean or Eastern European ancestry;
  - Endemic KS, existing in Central and Eastern Africa, which has been described long before The HIV pandemic and often affects children;
  - Iatrogenic KS, developing in immunosuppressed individuals;
  - Epidemic or AIDS-KS, a major AIDS-defining malignancy.

KSHV can be isolated from several fluids and cells, including saliva, semen, cervico-vaginal secretions and prostate glands, and peripheral blood mononuclear cells (PBMCs). Saliva represents the main route of transmission of KSHV. Other possible routes of transmission, although less common, include the sexual one and blood transfusion. In transplant recipients, KS may result from a new infection or KSHV reactivation, as a consequence of immune suppression.

In endemic areas, where the seroprevalence of KSHV is high in children, vertical transmission from mother to child has been hypothesized.

**PATHOGENESIS**

KS is a multicentric angioproliferative cancer of endothelial origin, which is characterized by clinical heterogeneity, as well as by its ability to progress or regress on the basis of host immune factors.

KS-associated herpesvirus (KSHV) or human herpesvirus-8 (HHV-8) is the etiological agent associated of KS, as well as multicentric Castleman’s disease and a rare form of B-cell lymphoma called Primary Effusion Lymphoma (PEL). The virus is found in all subtypes of KS, including classical, endemic, epidemic (HIV-associated), and posttransplantation KS.

KSHV can infect endothelial lineage cells, leading either to viral replication, viral clearance, or persistence in a transformed cell. KSHV/HHV-8 has two distinct modes of replication, the latent and lytic phase, which play a different role in the pathogenesis of KS. The infectious cycle of KSHV begins with the attachment of specific viral glycoproteins to the host cell receptors on circulating endothelial cells (EC). This step leads to the release of the viral particles into the cell cytoplasm and to transport of viral DNA into the nucleus, where it is able to maintain itself as a multicopy circular episomal DNA, which is segregated during mitosis as a host chromosome. During the latent phase, there is a little expression of viral genes and no production of new virions. As a consequence, viral latency allows KSHV to escape the host immune response. On the other hand, the KSHV lytic phase has an important role in tumorigenesis, as it favors viral spread to target cells, sustains the population of latent infected cells, and provides paracrine regulation for KS development. During both the lytic and latent phase, KSHV encodes an arsenal of viral oncogenes and anti-apoptotic genes that induce infected EC proliferation, transformation, cytokine production, immune evasion, antiapoptosis, and angiogenesis. Moreover, the expression of Matrix metalloproteinases (MMPs) and proangiogenic molecules allows vessel destabilization and infected cells migration. NF-κB activation induced immediately after infection stimulates the expression of viral genes, including the cluster of latent genes, that are controlled from a single latent promoter, as well as many cellular genes that play a role in the establishment of latency. NF-κB activity is essential for the survival of latently infected PEL cells and the selective inhibition of this pathway results in downregulation of a very specific set of antiapoptotic genes, apoptosis of cells in culture, and tumor responses in mice.

**Co-expression**

The expression of Kaposin B may enhance cytokine release. Cytokines have an important role in promoting angiogenesis and inflammatory infiltrates in KS. Oncostatin M, a cytokine produced by microphages and activated T-lymphocytes, can be a mitogen for HIV-KS derived spindle cells. Moreover, the production of basic fibroblast growth factor (bFGF) represents a crucial autocrine growth factor for spindle cells. In addition, KSHV seems to downregulate Th1-mediated responses, and hyperactivate Th2- responses, through the secretion of proinflammatory cytokines, activation of signaling molecules, chemotaxis and extravasation of Th2 lymphocytes to the site of infection. Inflammatory cells secrete stimulatory molecules (VEGF, IL-6) that favor the growth of spindle cells (SCs) and angiogenesis.

Recently, it is shown that KSHV-induced expression or secretion of MMP-1, MMP-2, MMP-7, MMP-9, VEGF-A dependent by extracellular matrix metalloproteinase inducer (EMMPRIN), a heavily glycosylated transmembrane protein, which is a member of the immunoglobulin superfamily. EMMPRIN can bind various cell receptors involved in KSHV-induced migration/invasion, including PGE2 receptors and integrins. KSHV infection induces Cox-2 expression and PGE2 production in human en-
dothelial cells and fibroblasts, and these factors contribute to angiogenesis and invasion by KSHV-infected cells. Cox-2, PGE2, and the PGE2 receptors are all expressed in KS tumors. Inhibition of Cox-2, PGE2, or PGE2 receptors suppresses expression and/or activity of MMP1, MMP2, MMP3, MMP7 and MMP9. LANA induces EMMPRIN expression by direct interaction with gene promoters and or interactions with other transcription factors, including the zinc finger transcription factor Sp1. The EMMPRIN promoter region contains several binding sites for Sp1 and the transcription factor known as the early growth response gene 2 (Egr-2). LANA or other KSHV genes may also induce EMMPRIN expression through activation of intracellular signal transduction. NF-κB and JNK activation increase EMMPRIN expression and function in tumor-associated macrophages; both NF-κB and JNK signaling are induced by vFLIP and vGPCR. SCs are the principal cells in KS lesions and express endothelial markers such as CD31 and CD34. In addition, lesions also contain dendritic cells, macrophages, plasma cells and lymphocytes. The exact origin of SCs remains elusive. At present, KSHV is thought to infect both blood vascular endothelial cells (BECs) and lymphatic endothelial cells (LEC)s and that infected BECs are reprogrammed towards a lymphatic expression profile. Therefore, the virus might favor the switch from one cell type to another, and this capability complicates the possibility to determine SC origin.

CLINICAL FEATURES AND PROGNOSIS

KS may have an indolent slowly progressive behavior, generally limited to the skin, or may present as an aggressive and rapidly progressing disease. KS skin lesions are usually pigmented, varying in size from a few millimeters to several centimeters, involving large areas of the body surface, and often associated with edema, lymph node and visceral involvement.

The earliest foci of KS are called “patch lesions” and are red flat lesions in the dermis, containing a large number of T and B cells, monocytes and abundant neovascularity.

Dermal KS may evolve over time to more advanced lesions (“plaque stage”), which are more indurated, often edematous and more intensely red or even violaceous.

SCs proliferation is associated with the progressive involvement of the deepest part of the dermis, and lesion progression to the “nodular stage”, sometimes associated with ulceration.

Visceral involvement occurs in more than 50% of cases. The oral cavity is affected in approximately 35% of patients at the time of initial diagnosis, the gastrointestinal involvement in 40% of cases at initial diagnosis and up to 80% at autopsy. Gastrointestinal localization can occur in the absence of cutaneous disease and may be asymptomatic or cause abdominal pain, weight loss, malabsorption with diarrhea or obstruction, vomiting or bleeding. Pulmonary KS is the second most common site of extracutaneous involvement and it is the most life-threatening form of the disease. In 15% of cases, pulmonary KS occurs without evidence of mucocutaneous disease. Patients with pulmonary KS may be symptomatic with shortness of breath, cough or hemoptysis, or present with an asymptomatic finding on chest X-ray (nodular or interstitial or alveolar infiltrates, pleural effusion or isolated pulmonary nodule).

In the pre-HAART era, the AIDS Clinical Trials group (ACTG) defined a staging system based upon the three parameters:

- **Extent of the tumor (T):** a favorable prognosis (T0) is associated with disease limited to the skin or with minimal involvement of the oral cavity. Those with associated lymphoedema, more extensive oral cavity involvement or other visceral disease are considered to have a poor prognosis (T1);
- **CD4+ T-cell count (I):** the degree of immunosuppression is an important prognostic factor. A CD4+ T-cell count higher than 200 cells/μl has been associated with a favorable prognosis (I0), while low CD4+ T-cell counts have been associated with poor prognosis (I1);
- **Severity of systemic illness (S):** the following features have been associated with poor prognosis (S1): a history of opportunistic infection, thrush, B symptoms (fever, night sweats, significant weight loss, diarrhoea for more than two weeks).

This classification identified two different risk categories: a good risk category (T0I0S0) with skin +/-, lung +/-, minimal oral disease, CD4+ T-cell count >150/μl, no opportunistic diseases (OI)/B-symptoms and Performance Status (PS) >70, and a poor risk one (T1I1S1) in case of edema or ulcerations or extensive oral KS and visceral involvement, CD4 <150/μl, OI and/or B-symptoms and PS <70. Nasti et al have validated the ACTG staging system by collecting epidemiological, clinical, staging and survival data from 211 patients with AIDS-KS enrolled in two prospective Italian HIV cohort studies: the Italian Cooperative Group on AIDS and Tumors (GICAT) and the Italian Cohort of patients Naïve from Antiretrovirals (ICONA). Tumor extension and systemic disease correlated with survival, whereas CD4+ T-cell count was not a predictor of survival. Pulmonary disease was associated with a significantly poorer survival when compared with the other T1 features. These data differ substantially from the pre-HAART results of the Krown study, in which CD4+ T-cell count independently predicted survival. HAART has probably modified the prognostic value of ACTG classification. Stebbing et al identified four prognostic factors: AIDS-defining illness, age ≥50 years, CD4+ T-cell count, and S stage; these parameters may be used to obtain an accurate prognostic index when diagnosing AIDS-related KS and to guide its therapeutic management. They developed a prognostic score from 0 to 15 starting at 10; increasing score by 1 increased the 1-year hazard ratio by 40%. Having KS as the AIDS-defining illness (-3 points) and increasing CD4+ T-cell count (-1 point for every complete 100 cells per μl) improved prognosis; age of 50 years or older (2 points) and having another AIDS-associated illness at the same time (3 points) conveyed a poorer prognosis. Ac-
Local reactions were observed mainly in large to medium-sized nodules and can be attributed to poor precision in the injection site (drug leakage in the perinodular tissue) or to the amount of drug injected (overdose). No systemic absorption and no systemic adverse events were reported.

Vinblastine and bleomycin are both more painful and less effective than vincristine. These therapeutic agents lead to regression with temporary success rates of up to 88%, but regression is usually limited to about 4 months.

In some centers, intralesional doxorubicin is the standard treatment for cutaneous KS. Doxorubicin acts through intercalation of double-stranded DNA bases and by inhibiting DNA topoisomerase II.

Recently, Kim et al. have demonstrated the efficiency of intralesional injection of 3% (0.2 mg/mL) Sodium Tetradecyl Sulfate in the treatment of cutaneous KS in a HIV-negative 96-year-old woman. STS is a therapeutic agent which can cause endothelial surface damage, inducing an inflammatory reaction that causes sclerosis of vessels. It also causes less complication than other systemic treatments, and is cheaper and easier to handle. Accurate injection of STS into the target is easy in nodular KS, more complicated in patch and plaque KS, because of many vascular slits without true endothelial linings.

Radiotherapy is an effective palliative treatment to reduce pain, bleeding and edema. It has been used in nodular lesions and plaques. Cutaneous KS is highly radiosensitive with more than 90% response, complete remission and good tolerability. For patients with advanced disease a single dose of 8 Gy is preferable. Side effects are rare (minimal skin reactions), with the exception of patients with mucosal lesions, which have a greater risk of experiencing severe mucositis. In particular, severe mucositis and impaired salivary function were reported at doses of 7.5 to 27 Gy, which are generally well tolerated by HIV-uninfected subjects. Oral toxicity from radiotherapy has been reported to be more common in patients with HIV-KS than in HIV-positive patients with other head and neck tumors; as a consequence, it is conceivable that KSHV/HHV-8 itself may contribute to radiotherapy toxicity as seen in KS patients. By contrast, intracavitary radiotherapy was well tolerated when used to treat oral KS lesions, with only mild membrane reactions and no interruption of therapy. Even if uncommon, cutaneous toxicity with pain, skin erythema, desquamation and ulcers have been reported when using 20 Gy in 10 fractions for the treatment of KS of the feet. Unfortunately, patients often develop long-term mucosal and cutaneous changes, including a woody appearance and pigmentation changes.

Electrochemotherapy (ECT) is an emerging local treatment proposed for cutaneous metastatic nodules and different primary skin tumors. This technique is a non-thermal tumor ablation combining the use of electroporation with the administration of two highly cytotoxic drugs, bleomycin and cisplatin. Electroporation leads to the creation of pores on the cell membrane, by using pulsed, high-intensity electric fields to temporarily increase cell membrane permeability. Increased permeabil-
ity facilitates drug delivery into the cell. The resulting high drug concentration obtained within tumor cells enhances the chemotherapeutic cytotoxic activity and allows the administration of a lower dose, thus limiting not only drug-related toxicity but also immunodepression. ECT has been reported to have a good clinical activity and toxicity profile in KS patients, with a clinical response in up to 60.9% of cases after the first session, long remission duration and a significant improvement in the quality of life. The absence of systemic toxicity and the mild general anesthesia needed for ECT treatment permitted repeated sessions. As a consequence, ECT with bleomycin could represent an effective therapy for skin-limited KS, including stage I and stage II disease.

Systemic Therapy

HAART

The widespread introduction of HAART has been associated with a marked reduction of KS incidence in resource-rich countries, which is estimated to range between 33% and 95%.

In the Sub-Saharan Africa (SSA), a similar decrease has not been documented. This may be partly due to the incomplete access to HAART and earlier time of acquisition of KSHV infection.

The effects of HAART on KS are multifactorial and include inhibition of HIV replication, amelioration of the immune response against HHV-8 and perhaps some direct antiangiogenic activity of protease inhibitors as well as the diminished production of HIV-1 transactivating protein Tat. In vitro models suggested that indinavir and saquinavir inhibited the development and induced regression of angioproliferative KS-like lesions. However, non-randomized clinical studies have not supported this hypothesis.

In patients with limited cutaneous lesions, an effective HAART regimen including a PI may represent the first step for the treatment of KS. In these patients the suppression of viral replication and immune restoration are usually associated with a significant reduction of the size of lesions; in most cases, KS lesions disappear completely after a few weeks or months.

KS regression with HAART alone has been well documented, with 66-86% overall response rate and 35% complete remission rate and median time to response ranging from 3 to 9 months.

KS may dramatically flare following the initiation of HAART and may represent a manifestation of the immune reconstitution inflammatory syndrome (IRIS). This syndrome is a heterogeneous and sometimes fatal inflammatory disorder occurring after HAART initiation in HIV-positive patients with initial low CD4+ T-cell count. KS flares are usually observed and diagnosed within 2 months after immunologic and virologic response to HAART.

HAART alone may represent the first step of therapy for T0 and T1 slowly progressive disease. HAART with concomitant chemotherapy is indicated for visceral disease and/or rapidly progressive disease; the maintenance (M)-HAART may be an effective therapeutic option to control KS after debulking chemotherapy (overall response rate of 91%).

Systemic Chemotherapy

Systemic CT is reserved for patients not responding to HAART and/or with widespread, symptomatic, rapidly progressive, life-threatening disease with visceral involvement and in IRIS-associated flares. Several single agent options have been reported to be active in AIDS-related KS (vincristine, vinblastine, vinorelbine, etoposide, teniposide, adriamycin, epirubicin, bleomycin, docetaxel and paclitaxel). Overall response rates range from 30 to 70%, although most of them have been associated only with partial response.

Currently, the first-line therapy for patients with advanced AIDS-KS is represented by liposomal anthracyclines: pegylated liposomal doxorubicin (PLD) and daunorubicin citrate liposome (DNX). The liposomal formulation has a better pharmacokinetic profile and reduced cardiotoxicity. PLD use is associated with response rates ranging from 46 to 59% and median remission time of 3-5 months; DNX has shown a response rate of 25%, disease stability in an additional 62% of cases, with a median duration of response of 175 days. Liposomal anthracyclines have a better tolerability profile than the comparative treatment with adriamycin-bleomycin-vincristine (ABV) in two randomized clinical trials and bleomycin-vincristine (BV) in another study: DNX (40 mg/m² intravenously (iv) every 2 weeks) and PLD (20 mg/m² iv every 2 weeks) had an activity respectively equivalent or superior to combinations ABV or BV, with 76-82% overall response rate and 26-40% complete remission rate. Concerning the side effects, DNX and PLD are associated with less alopecia and gastrointestinal and neurologic impacts compared with BV or ABV. Grade 3-4 myelosuppression is a frequent complication with both drugs, while stomatitis and infusion reactions occur more often with DNX.

One small randomized, open-label, multicentre phase II trial compared the efficacy of PLD (20 mg/m² every 3 weeks) combined with HAART vs HAART alone. In this study, the combined use of PLD and HAART was more effective than HAART alone in the treatment of patients with moderate to advanced AIDS-related KS.

Paclitaxel is used in patients with recurrent or refractory AIDS-related KS after first-line chemotherapy. Paclitaxel is a cytotoxic agent, which exerts its antitumor activity by polymerizing microtubules and inhibiting cell division. Two small phase II trials have demonstrated that intravenous paclitaxel (100 mg/m² given every 2 weeks as a 3-hour infusion) is associated with a response rate of 59% with a median duration of response of 7.4 months in the first trial and 10.4 months in the second one. Possible side effects are represented by significant myelosuppression, peripheral neuropathy, and renal dysfunction.

Unfortunately, a significant number of patients with KS progress within six to seven months and they need...
additional therapy. Remission periods becomes gradually shorter after each treatment course.\textsuperscript{50, 78} Paclitaxel and PLD appear to be active first-line agents for advanced, symptomatic KS. However, paclitaxel has been associated with a higher incidence of grade 3-4 hematologic toxicity, alopecia and sensory neuropathy.\textsuperscript{55, 86}

Some phase II trials have shown that intravenous docetaxel (25 mg/m\textsuperscript{2} over 15-30 minutes weekly for 8 weeks) may represent a safe and effective option in the treatment of advanced-stage epidemic KS with 42% partial remission rate and 33% grade 3 leukopenia. Immuno-suppression and infections are the major problems in patients treated with cytotoxic chemotherapy. The use of granulocyte colony-stimulating factor (G-CSF) subcutaneously at the dose of 5 mcg/kg daily is standard practice.

**Target Therapy**

Target therapy for KS is currently based on the use of anti-angiogenic agents, metalloproteinase and cytokine signaling pathway inhibitors and it represents an option for patients with AIDS-associated KS, which progressed despite chemotherapy and/or HAART.

Irinotecan (CPT-11) is an anti-tumoral agent targeting the enzyme DNA topoisomerase I. In a phase II study, intravenous CPT-11 (150 mg/m\textsuperscript{2} on day 1, 10 mg/m\textsuperscript{2} every 21 days) plus HAART including PIs was reported to be effective and well tolerated for the treatment of HIV-infected patients with relapsing/progressing KS. The most important dose-limiting side effects were grade 3-4 myelotoxicity and diarrhea.\textsuperscript{80}

Matrix metalloproteinases (MMPs) play a fundamental role in the process of neangiogenesis, tumor invasion and metastasis. These endopeptidases, constitutively over-expressed in KS cells, are a class of calcium-dependent proteases with a conserved catalytic motif consisting of three histidine residues that hold a Zn\textsuperscript{2+} ion and a nearby glutamic acid that is essential for peptide bond hydrolysis. MMPs have an important role in KS, because they facilitate the migration of endothelial cells, by disrupting the extracellular matrix, and favor the release of several tumoral growth factors, in particular, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (B-FGF). Also, KS cells overexpress the gelatinases MMP-2 and MMP-9, which have a key role in promoting angiogenesis, as they degrade collagen IV, the major component of basement membranes.\textsuperscript{87} CMT-3 or COL-3 (6-deoxy 6-demethyl 4-dedimethylamino tetracycline), a chemically modified tetracycline, is one of the most potent MMP inhibitors. The use of 50 mg once daily orally has been associated with a response rate of 41%, and a median duration of response of 52 weeks.\textsuperscript{50, 87} Common side effects include dose-related photosensitivity and rash.

Thalidomide (100 mg/day for 12 months) is able to block TNF production, as well as the assembly of basement membrane and intercellular adhesion molecules. Along with the inhibition of vascular endothelial cell proliferation, thalidomide induces a significant decrease in the activity of the nuclear factor SP1, a transcription factor involved in the expression of extracellular matrix genes and moderate inhibition of nuclear factor B activation in nuclear extracts. Toxicities include neutropenia, depression and fever.\textsuperscript{50, 88}

IL-12, a Th1 cytokine, can downregulate a constitutively active G protein-coupled receptor encoded by HHV-8. In preliminary results from a phase I study evaluating the efficacy of the combination of IL-12 plus liposomal doxorubicin and HAART, remission was obtained in a substantial percentage of patients with advanced KS. Imatinib mesylate orally (300 mg twice daily) inhibited the activation of the platelet-derived growth factor (PDGF) and c-kit receptors, which are important targets in mediating the growth of AIDS-related KS. The most common adverse events were diarrhea and leukopenia.\textsuperscript{50, 89}

One phase II study has evaluated the efficacy of bevacizumab, a humanized anti-VEGF-A monoclonal antibody, for the treatment of patients with HIV-associated KS. VEGF-A is an important paracrine and autocrine growth factor in KS and KSHV has developed redundant mechanisms for its upregulation. The observed overall response rate was lower than that reported with liposomal anthracyclines but comparable to that seen when using other angiogenesis inhibitors such as COL-3. A possible explanation is that SCs express VEGF-A receptor 3 and the receptor for platelet-derived growth factor (PDGF) in response to VEGF-A receptors 1 and 2 and proliferate in response to ligands for these receptors (VEGF-C and PDGF). Furthermore, a number of KSHV genes, such as a latency-associated nuclear antigen (LANA), v-FLIP, v-cyclin, and kaposin-A, can inhibit apoptosis or directly contribute to SCs proliferation. Thus, optimal targeted therapy for KS may require targeting two or more pathways simultaneously. Overall, this study suggests that bevacizumab has utility in combination with other drugs or after an initial reduction of the tumor burden with cytotoxic chemotherapy or in patients who are approaching the maximal safe cumulative dose of anthracyclines. In contrast most cytotoxic agents active in KS, bevacizumab does not seem to impair immune reconstitution, an important feature for therapeutic interventions for HIV-associated KS.\textsuperscript{90}

Bortezomib, a novel chemotherapeutic agent currently approved for multiple myeloma treatments, has been shown efficacy against cellular proliferation in cell lines derived from PEL. In particular, it inhibits NF-kappaB pathway and upregulates p53, p21, p27 and the caspase cascade. Preclinical data also suggest that the inhibitory effect of bortezomib on NF-kB can facilitate lytic activation of EBV and KSHV.\textsuperscript{91}

**Immunotherapy**

Interferon-alfa (IFN-\alpha) is known to have several immunomodulatory, antiviral and antiangiogenic effects. An overall response rate of 10-40% has been reported when using high-dose IFN-\alpha monotherapy; on the other hand, equal or better results have been found when using it at lower doses in combination with HAART. Common side effects associated with IFN use include flu-like symptoms and bone marrow suppression. Sirolimus (SRL),
also known as rapamycin, is a potent immunosuppressant drug with anti-angiogenic and anti-proliferative effects. The anti-angiogenic properties of SRL make it an attractive therapeutic option for KS and other malignancies. In a case series of 15 renal transplant recipients with KS, complete clinical remission of cutaneous KS was found after 3 months of treatment with SRL and histological remission after 6 months. Because SRL is a substrate for the drug-metabolizing enzyme cytochrome P450 3A4 (CYP3A4) and the efflux transporter P-glycoprotein, in a recent consortium study Krown et al.22 assessed rapamycin’s safety and toxicity in HIV-infected individuals with KS receiving HAART. In particular, substantial interactions between rapamycin and PI/r were reported, requiring therapeutic monitoring and dose readjustments for rapamycin.93

A large number of drugs blocking herpesvirus DNA synthesis have been reported to inhibit HIV-8 replication. Of these agents, ganciclovir (or its oral pro-drug valganciclovir) is the only one proven to either suppress HIV-8 replication in vivo or prevent the development of KS in randomized trials. In a randomized placebo-controlled cross-over trial, valganciclovir was shown to reduce HIV-8 oral shedding frequency by 46% and viral load by 0.44 log copies/ml. Numerous observational studies have suggested that ganciclovir and foscarnet, but not acyclovir, may prevent KS. Thus, there is ample evidence for using valganciclovir to prevent KS in high-risk individuals.94,96

1α,25-dihydroxyvitamin D3 [1α,25(OH)2D3, calcitriol], the most active form of vitamin D, has several anti-proliferative, pro-apoptotic and pro-differentiating actions on various malignant cells. Moreover, it has anti-inflammatory properties, induced by the inhibition of pro-inflammatory cytokines and NF-κB signalling. In recent years, it has been demonstrated that one of such 1α,25(OH)2D3 analogues, TX 527 [19-nor-14,20-bisepi-23-yne-1,25(OH)2D3], is also characterized by markedly hypocalcemic effects in combination with enhanced anti-proliferative and pro-differentiating capacities on normal and malignant cell types and immune regulatory capacities. Most of the activity of 1α,25(OH)2D3 is mediated by the vitamin D receptor (VDR), a member of the nuclear receptor superfamily. The VDR is present not only in cells and tissues involved in calcium regulation but also in a wide variety of other cells including neoplastic cells. The KS-associated herpes virus GPCR (vGPCR) is a key molecule in the pathogenesis of KS through its potent transforming and pro-angiogenic functions. It has been determined that vGPCR potently activates the NF-κB pathway which is required for direct induction of neoplasia by vGPCR, thus being an important therapeutic target for the treatment of KS. It has been demonstrated that 1α,25(OH)2D3 and TX 527 have anti-proliferative effects on the growth of endothelial cells transformed by the vGPCR in vitro and in vivo by a mechanism that depends on VDR expression. Furthermore, down-regulation of the NF-κB pathway by 1α,25(OH)2D3 in vGPCR cells was found to be part of the mechanism of inhibition. In a recent work, the analogue TX 527 has been reported to inhibit the NF-κB pathway at various levels and control the expression of inflammatory genes and the proliferative properties, induced by the inhibition of activated NF-κB in vGPCR cells.97

CONCLUSIONS

With the introduction of HAART, HIV-infected people have experienced a significant decline in HIV-related morbidity and mortality. However, KS is still the second most frequent tumor in HIV-infected patients worldwide. Unfortunately, there is a lack of well-defined therapeutic protocols. HAART represents the milestone of treatment, either alone or in combination with systemic and local therapy; other options, such as anti-angiogenic agents, metalloproteinase and cytokine signaling pathway inhibitors, are available, but there is the need of large prospective studies to assess their impact on KS prognosis.98

CONFLICT OF INTERESTS:

The Authors declare that they have no conflict of interests.

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