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Kaposi' s sarcoma in HIV-positive patients: the state of art in the HAART-era

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Abstract. – Kaposi's sarcoma (KS) is a multicentric angioproliferative cancer of endothelial origin typically occurring in the context of immunodeficiency, i.e. coinfection with Human Immonodeficiency Virus (HIV) or transplantation. The incidence of KS has dramatically decreased in both US and Europe in the Highly Active Antiretroviral Therapy (HAART) era. However, KS remains the second most frequent tumor in HIV-infected patients worldwide and it has become the most common cancer in Sub-Saharan Africa.

In 1994, Yuan Chang et al discovered a novel γ-herpesvirus in biopsy specimens of human KS. Epidemiologic studies showed that KS-associated herpesvirus (KSHV) or human herpesvirus-8 (HHV-8) was the etiological agent associated with all subtypes of KS.

KS has a variable clinical course ranging from very indolent forms to a rapidly progressive disease. HAART represents the first treatment step for slowly progressive disease. Chemotherapy (CT) plus HAART is indicated for visceral and/or rapidly progressive disease. The current understanding of KS as a convergence of immune evasion, oncogenesis, inflammation and angiogenesis has prompted investigators to develop target therapy, based on anti-angiogenic agents as well as metalloproteinase and cytokine signaling pathway inhibitors. These drugs may represent effective strategies for patients with AIDS-associated KS, which progress despite chemotherapy and/or HAART.

In this review, we focus on the current state of knowledge on KSHV epidemiology, pathogenesis and therapeutic options.

Key Words:
HIV, Kaposi, HAART, Herpesvirus, HHV-8.

Introduction

The introduction of Highly Active Antiretroviral Therapy (HAART) has significantly changed the natural history of Human immunodeficiency virus (HIV) infection[1]. However, despite the significant reduction in the incidence of HIV-related events, HAART is not able to eradicate HIV infection, due to the persistence of latent viral reservoirs[2-13]. On the other hand, the risk of non-HIV-related morbidity and mortality, including cardiovascular and bone disease, neurocognitive impairment and malignancies, has dramatically increased[14-49].

The incidence of Kaposi's sarcoma (KS), an AIDS-related malignancy, has dramatically decreased in both USA and Europe in the HAART era[50]. However, KS remains the second most frequent tumor in HIV-infected patients worldwide and it has become the most common cancer in Sub-Saharan Africa[51].

The viral etiology of KS was already suspected before the onset of AIDS epidemic, because of its distinctive geographical distribution and association with immune suppression; however, it was only in 1994 that Chang et al isolated the genome of a herpesvirus from a KS tumor in an patient with HIV. This virus was termed KS-associated herpesvirus (KSHV) and is also known as human herpesvirus-8 (HHV-8).

At present, the risk of KS is substantially higher among HIV-infected subjects. KS occurs in more than 50% of cases in late stages of HIV infection and is characterized by an extremely aggressive clinical course. Patients with KS on HAART exhibit a less aggressive presentation compared with patients not receiving HAART at the time of KS diagnosis. 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 ages[52].

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Epidemiology

KSHV is one of the most oncogenic human viruses currently known[53]. The prevalence of KSHV infection is estimated to be around 1.3%-4.4% in Southeast Asia and the Caribbean regions. In Sub-Saharan Africa the infection is very common, with seropositivity rates > 50%. In Europe the prevalence is around 20-30%, with the lowest rates (6%-8%) in Spain and Greece and the highest in Italy (20.4%). The range of estimated prevalence in the US general population was found to be 1.5%-7%[54]. Countries in which KS was endemic before the AIDS epidemic have seen a dramatic increase in the incidence of HIV-related KS. Currently, KS is one of the most common cancers in certain Sub-Saharan African countries, where 89% of all cases of KS occur.

The prevalence of KSHV is elevated in men who have sex with men (MSM) in the US and Europe, while in South America it is markedly increased in Brazilian Amerindians. In fact, approximately 50% of the adult population of Amerindians was reported to have antibodies to KSHV, compared with only 11% of HIV-negative injection drug users in Argentina. Recent reports have described a similar increased prevalence in some ethnic groups in China[52].

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. 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 Jewish 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[55].

The main route of transmission of KSHV is saliva, thus in keeping with the observation that KSHV can replicate *in vitro* in primary oral-derived epithelial cells[55].

Considering the elevated prevalence of KSHV in MSM, it was suggested that it could be transmitted sexually[52]. KSHV transmission by blood transfusion is documented, although rare. It occurred less frequently when donors had higher levels of antibodies. The risk of transmission can be greatly reduced by depleting blood of leucocytes (KSHV-associated cells) or by storing blood for several hours or days. In transplant recipients KS may be the consequence of a new infection from KSHV infected donors or KSHV reactivation in infected recipients, as a consequence of immune suppression. Reports on KSHV transmission via injecting drug use have also been mixed. Some studies suggested that injecting drug users (IDUs) were not at increased risk of KSHV infection, while others have shown an increased risk of KSHV infection in IDUs, especially with prolonged drug abuse[52,55].

Several studies have explored the potential contribution of host genetic factors, including genetic polymorphisms of inflammatory and immune response genes. Particularly, it has been observed that classic KS risk is associated with diplotypes of interleukin-8 receptor-β (IL-8Rβ), IL-13 and certain human leukocyte antigen (HLA) haplotypes. Transplant KS risk is associated with an IL-6 promoter polymorphism and genotypes of FcγRIIIA influence the development of KS in HIV-infected men. These data suggest that common host genetic variants, in addition to environmental factors, timing and possibly routes of infection, may contribute to the oncogenic outcome of KSHV infection. However, there is a need for larger studies, extensively evaluating the impact of host genetics on KS[52,55].

Pathogenesis

KS is a multicentric angioproliferative cancer of endothelial origin, which is characterized by a remarkable pathologic and clinical heterogeneity, as well as by its ability to progress or regress on the basis of host immune factors[52].

It is now 19 years since the discovery by Yuan Chang et al of a novel γ-herpesvirus in biopsy specimens of human KS. Epidemiologic studies showed that KS-associated herpesvirus (KSHV) or human herpesvirus-8 (HHV-8) was the etiological agent associated with all subtypes of KS, multicentric Castleman's disease and a rare form of B-cell lymphoma, called Primary Effusion Lymphoma (PEL)[56].

KSHV/HHV-8 has two distinct modes of replication, which play a different role in the patho-

genesis of KS: the lytic and latent phase. The first step of the infectious cycle of KSHV is the attachment of specific glycoproteins present on the virion surface 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 latency, only a minimal number of latent genes are expressed and there is no production of infectious virions. Thus, viral latency has been effectively adopted by KSHV to escape the host antiviral responses by minimizing exposure to the host immune surveillance radar. The KSHV lytic phase contributes to viral tumorigenesis by spreading viruses to target cells, sustaining the population of latently infected cells, thus serving to propagate the infection and provide paracrine regulation for KS development[57,58].

During the lytic and latent phase KSHV encodes an arsenal of viral oncogenes and anti–apoptotic genes that induce infected EC proliferation, transformation (JNK/SAPK, PLC/PKC, PL3K/Akt), cell signalling (NF-kB), cytokine production (vCCL-1, vCCL-2, vCCL3, vGPCR, Kaposin B), immune evasion (KCP, K3, K5), antiapoptosis (vFLIP, K1, Lana-1, vIRF-1, vIRF-3, K8) and angiogenesis (VEGF, IL-6, vCCLs,K1, Angiopoietin-1). The expression of Matrix metalloproteinases (MMPs) and proangiogenic molecules allows vessel destabilization and infected cells migration. More recently, it has been observed that KS cell lines express not only increased vascular endothelial growth factor receptor 1 (VEGFR1) and vascular endothelial growth factor receptor 2 (VEGFR2) mRNA compared to normal skin biopsies, but also vascular endothelial growth factor receptor 3 (VEGFR3), generally limited to lymphoid endothelial cells[52].

During the latent phase, only five viral genes are expressed: LANA (ORF73), v-cyclin (ORF72), v-FLIP (ORF71), kaposin (K12), and vIRF-3 (LANA-2, ORF10.5). LANA promotes the replication of the latent viral episome, specifically binding sequences within the terminal repeats of the viral genome[39]. In addition, it suppresses the elicitation of type I IFNs (IFN-β) by interfering with the functional role of interferon regulatory factor 3 (IRF-3). Although the binding of cellular transcription factors, such as NF-κB and ATF-2/c-Jun, to their respective sites in the IFN-β promoter regions was unaffected, the recruitment of IRF-3 to specific sites (PRD-I/III) in the IFN-β promoter region was inhibited by the central domain of LANA, that specifically binds to the PRD-I/III sites of the IFN-β promoter, competitively inhibiting the ability of IRF-3 to bind to these sites, which generates a defective IFN-β enhanceosome[57,59]. Chronic inflammation plays a role in KS pathogenesis: presence of immune infiltrate in KS lesions suggests it is the result of inflammation-induced reactive hyperproliferation. KSHV downregulates Th1-mediated responses, through IFNs suppression and MHC-1 downregulation. At the same time the virus is able to 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 (SC) and angiogenesis. In particular, the virus codes for an homolog of cellular IL-6 (vIL-6), that signals through IL-6R (IL-6R/CD126/gp80) and gp130, which activate JAK/STAT and MAPK pathways. It has been shown that vIL-6 promotes angiogenesis, tumor growth and plasmacytosis in mice. Nevertheless, only a proportion of KS patients have detectable circulating vIL-6. By contrast, KS tissues often express cellular IL-6, which may be induced by the KSHV genes vFLIP and vGPCR[58].

SCs are the main group of cells within 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 SC remains elusive. At present, KSHV is thought to infect both blood vascular endothelial cells (BEC) and lymphatic endothelial cells (LEC) and that infected BEC are reprogrammed towards a lymphatic expression profile. Therefore, the virus might have the capacity to convert one cell type to another and this aspect complicates the possibility to determine SC origin[50].

Clinical Features

KS may have an indolent behavior, generally confined to the skin and slowly progressing, or may present as an aggressive disease, with significant morbidity and mortality. Typically, KS is characterized by disseminated and pigmented skin lesions, in size from a few millimetres to several centimetres, involving large areas of the body surface, sometimes in a symmetrical fashion, with a characteristic appearance ranging

from pink to purple or brown and often associated with edema, lymph node and visceral involvement[50]. Local nodularity and edema can be marked and profoundly disfiguring.

The earliest recognizable foci of KS are called "patch lesions": they are red flat lesions in the dermis, containing a large number of T and B cells, monocytes and abundant neovascularity. In contrast to classical cancers, the process of neoangiogenesis in the KS begins prior to establishment of a mass[56].

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

As SCs proliferate and involve the deepest part of the dermis, lesions progress to the "nodular stage", which is characterized by visible masses, mainly composed of SCs, but again accompanied by inflammatory cells and the continuous elaboration of slit-like neovascular spaces[56]. These lesions may eventually become ulcerating tumors.

Interestingly, in AIDS-associated KS the temporal pattern of occurrence of multifocal lesions is often not consistent with spread from a primary lesion, but rather suggests independent occurrence (multicentricity). This inference has been supported by molecular analysis of KSHV genomes from KS lesions, which has found out that different lesions from the same patient often harbor genomes with different terminal structure, suggesting they arose from independent infection events[56].

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. Gastrointestinal involvement has been reported in 40% of cases at initial diagnosis and up to 80% at autopsy; it can also 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 haemoptysis, or present with an asymptomatic finding on chest X-ray (nodular or interstitial or alveolar infiltrates, pleural effusion or isolated pulmonary nodule). Gallium and thallium scans may differentiate KS from other more common infections; in fact KS is thallium positive and gallium negative, whereas infections are gallium positive and thallium negative. Planar 99mTc-MIBI imaging has moderate sensitivity, specificity and accuracy for detecting pulmonary KS. Single photon emission computed tomography (SPECT) is more effective in detecting abnormal lymph nodes, pleural/pericardial effusion and ascites. 99mTc-MIBI SPECT followed by planar imaging at 40-60 min can be useful in the evaluation of pulmonary KS[50].

Prognosis

In the pre-HAART era, the AIDS Clinical Trials group (ACTG) defined a staging system based upon the extent of tumor (T), the immune system status in terms of CD4+ T-cell count (I) and the presence of systemic illness (S). This classifications 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. To assess new potential prognostic factors and to validate the ACTG staging system in the HAART era, Nasti et al collected epidemiological, clinical, staging and survival data from 211 patients with a diagnosis of AIDS-KS which had been 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). Multivariate analysis showed that tumor extension and systemic disease correlated with survival, whereas CD4+ T-cell count was not a predictor of survival. The analysis of interaction between tumor stage and systemic disease and its correlation with survival identified two main risk categories: a good-risk group (T0S0-T1S0-T0S1) and a poor-risk group (T1S1). The median survival for patients with T1S1 was significantly lower (38 months) in comparison with that of patients with T0S0, T1S0 and T0S1. The 3-year survival rate of patients with T1S1 was 53%, significantly lower than the 3-year survival rates of patients with T0S0 (88%), T1S0 (80%) and T0S1 (81%). The survival analysis of patients with pulmonary involvement within the T1 risk category indicated that 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, S stage; these parameters may be used to obtain an accurate prognostic index when diagnosing AIDS-related KS and may 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. According to this prognostic index, patients with a score > 12 should be treated with HAART and systemic chemotherapy together or alternatively should be considered for entry into clinical studies with novel agents. Patients with a low risk (score < 5) should be initially treated with HAART alone even if they have T1 disease. Chemotherapy should be reserved for progressive disease[50].

Treatment

HAART has significantly reduced the risk of developing KS among HIV-positive patients; in Sub-Saharan Africa, where the burden of HIV and KSHV co-infection is high and access to HAART is limited, KS remains a growing public health problem[60,61].

Several different therapeutic options are currently available, even though there are no standard therapy protocols.

Treatment decision making depends on the extent and rate of tumor growth, disease stage, lesion distribution and evolution pattern, symptoms, immune status and concurrent complications of HIV infection. Because KS is not a curable tumor, durable remission may be a reasonable therapeutic goal, especially in patients with low CD4+ T-cell count at diagnosis and immune reconstitution once HIV viremia is controlled with HAART.

Local Therapy

Local therapy is reserved for patients with minimal cutaneous disease for cosmesis or as palliative therapy for patients with rapidly progressive disease who had not responded to systemic treatments.

Some topical therapeutic options are represented by cryotherapy and excisional surgery; alitretinoid gel 0.1% (9-cis-retinoic acid) applied to affected areas 2 to 4 times daily may be used. The overall response rate ranges from 35 to 50% with topic skin reactions[50].

Intralesional vincristine can be used locally for nodular lesions. Vincristine is a vinca alkaloid antiblastic drug disrupting microtubular function. Brambilla et al demonstrated a complete clinical response in 76.1% of patients treated with intralesional vincristine and a partial response in 18.5%, with good tolerability and minimal local adverse events. Most cutaneous adverse events were controlled with topical clobetasol and nonsteroidal anti-inflammatory drugs. Local reactions were observed mainly in large to medium-sized nodules. Local adverse events can be attributed to poor precision in the injection site (drug leakage in the perinodular tissue) or to the amount of drug injected (overdose). Poor precision in site injection may explain the correlation between adverse effects and poor efficacy. Some regions, such as fingers or perionychium, are more sensitive because of subtle dermis and scarce hypodermis. In these cases it may be preferable to reduce the dose. No systemic absorption and no systemic adverse events were reported[62].

Other topical treatments include the use of intralesional vinblastine or bleomycin, which are both more painful and not as efficacious as vincristine, and intralesional interferon, which has been associated with inflammatory reactions and pain, elevated costs and reduced compliance[50].

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, 70% 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 has been reported for doses of 20 Gy in 10 fractions when treating KS of the feet. However, patients frequently develop long-term mucosal and cutaneous changes including a woody appearance and pigmentation changes[63].

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 uses pulsed, high-intensity electric fields to temporarily increase cell membrane permeability by creation of pores, which facilitate 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. Curatolo et al showed that ECT had a good clinical activity and toxicity profile in KS patients. In fact, they obtained a clinical response in all cases, regardless of tumor size, with a clinical response of 60.9% after the first session and one further response after a repeated session. The excellent response rates were coupled with a long remission duration and an 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[64-66].

Systemic Therapy

HAART

There is now ample evidence to indicate that 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%[67].

The limited data currently available from Sub-Saharan Africa (SSA) have not documented a similar decrease. This may be partly due to the incomplete access to HAART and earlier time of acquisition of KSHV infection of individuals living in SSA[68]. Although there are no clinical data comparing the efficacy of different HAART regimens for the treatment of KS, the use of protease inhibitor (PI)-containing regimens seems to be indispensable in the treatment of AIDS epidemic KS in all patients, alone or in combination with systemic and local therapy[69].

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 diminished production of HIV-1 transactivating protein Tat[69]. *In vitro* and mouse models suggested that indinivir and saquinivir inhibited the development and induced regression of angioproliferative KS-like lesions[52].

However, non-randomized clinical studies have not supported 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 were found to have the same protective effect against the development of KS. Time to treatment failure was also evaluated in 78 patients treated with chemotherapy or radiotherapy, and subsequently starting HAART, with no significant differences between PI- and NNRTI-based regimens. Similarly, disease-free survival among 254 patients with KS treated with HAART was not significantly affected by the presence of PIs in their first HAART regimen[52].

In patients with limited cutaneous lesions (T0=KS with low tumor volume, no associated ulceration or edema and no visceral disease), 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 KS size reduction; 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. It is difficult to establish the exact response rate to HAART among patients with KS, since in many patients with advanced KS cytotoxic chemotherapy has been administered concurrently[52,69].

KS may dramatically flare following the initiation of HAART and may represent a manifestation of the immune reconstitution inflammatory syndrome (IRIS)[50]. This syndrome is an heterogeneous and sometimes fatal inflammatory disor-

der 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%).

It has been shown that the association of HAART and anthracyclines may induce and/or select a multi-drug resistant (MDR) phenotype. A major cause of this phenomenon is the overexpression in tumor cells of members of a highly conserved family of transmembrane proteins characterized by an ATP-binding cassette (ABC). Furthermore, anthracyclines are substrates of many ABC transporters (such as ABCB1, ABCG2, ABCC1 and ABCC2) and both acute and chronic treatment with anthacyclines alone can induce ABCB1 expression, thus resulting in a MDR phenotype. Long-term exposure of KS cells to doxorubicin has been found to induce dose-dependent resistance together with a significant cross-resistance to the taxane compound paclitaxel, suggesting ABCB1-related resistance. Five different PIs (i.e. indinavir, nelfinavir, atazanavir, ritonavir and and lopinavir) were chosen based on their ability to act as substrates for ABC transporters and their antitumor properties. These compounds were tested either alone or together with doxorubicin at concentrations in line with those achieved in HIV-infected patients undergoing antiretroviral treatment. Physiological concentrations of PIs were able to select a MDR phenotype, because of increased ABCB1 expression and function in KS-derived SCs. Interestingly, the mechanisms resulting in ABCB1 expression of doxorubicin and PIs seem to be different. Whereas doxorubicin induced ABCB1 expression and functionality in SLK cells after acute treatment (72 h), ABCB1 was only expressed in SLK cells after chronic treatment (6 months) with PIs[70].

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, epirubicine, 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 the treatment of patients with advanced AIDS-KS is based on the use of 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. As previously stated, both liposomal anthracyclines have been associated with limited toxicity and were better tolerated than the comparative treatment with adriamycin-bleomycin-vincristine (ABV) in two randomized clinical trials and bleomycin-vincristine (BV) in another study: DNX (40 mg/m^2 intravenously (iv) every 2 weeks) and PLD (20 mg/m^2 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. With regard to 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 common with both drugs; stomatitis and infusion reactions occur with DNX, but hand-foot syndrome is relatively infrequent in the dose schedules used for KS[68]. One small randomized, open-label, multicentre phase II trial compared the efficacy of PLD (20 mg/m^2 every 3 weeks) combined with HAART *vs* HAART alone. In this study, the combination of PLD with HAART was more effective than HAART alone in the treatment of patients with moderate to advanced AIDS-related KS[50,67,71].

Treatment with paclitaxel is restricted to 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/m^2 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, renal dysfunction and the inconvenience of a 3-hour infusion[50,67,72].

Despite the effectiveness of these agents, most patients affected by KS progress within six to seven months of treatment and require additional therapy. Durable remission periods tend to be gradually shorter after each treatment course[50,65]. Dose reductions may be required when these drugs are coadministered with PIs or NNRTI, as they are all metabolized by cytochrome P450.

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[72].

Although clinical experience with docetaxel is more limited than that with paclitaxel, phase II trials suggest that intravenous docetaxel (25 mg/m2 over 15-30 minutes weekly for 8 weeks) is safe and effective in the treatment of advanced-stage epidemic KS with 42% partial remission rate and 33% grade 3 leukopenia. Immunosuppression and infections are the major problem 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

The current understanding of KS as a convergence of immune evasion, oncogenesis, inflammation and angiogenesis has prompted investigators to develop target therapy, based on anti-angiogenic agents, metalloproteinase and cytokine signaling pathway inhibitors. This therapy may represent an effective strategy for patients with AIDS-associated KS, which progressed despite chemotherapy and/or HAART.

Irinotecan (CPT-11), a semi-synthetic camptothecin derivative converted by decarboxylation into the biologically active form SN-38 (7-ethyl-10-hydroxycamptothecin), belongs to a recently established class of anticancer agents with cytotoxic mechanism targeting the cellular enzyme DNA topoisomerase I. Data on a GICAT phase II study showed that intravenous CPT-11 (150 mg/m^2 on day 1, 10 mg/m^2 every 21 days) plus HAART including PIs was active and well tolerated in HIV-infected patients with KS who had relapsed or progressed during HAART. The most important dose limiting side effects were grade 3-4 myelotoxicity and diarrhea. A recent study showed that the coadministration of lopinavir/ritonavir and CPT-11 reduced the clearance of CPT-11 by 47%, the AUC of the oxidized metabolite APC by 81% and inhibited the formation of SN38 glucuronide. These effects globally resulted in increased availability of CPT-11 for SN38 conversion and reduced inactivation of SN38 in SN38 AUC[50].

Matrix metalloproteinases (MMPs) play a fundamental role in the process of neoangiogenesis, tumor invasion and metastasis. These endopeptidases, constitutively overexpressed in KS cells, are a class of calcium-dependent proteases with a conserved catalytic motif consisting of three histidine residues that hold a Zn2+ ion and a nearby glutamic acid that is essential for peptide bond hydrolysis. MMPs are involved not only in the disruption of extracellular matrix, facilitating the migration of endothelial cells, but they also create a favorable microenvironment for tumoral cells by releasing tumor growth factors. In particular, it is known that KS cells secrete *in vitro* vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (B-FGF); moreover, they overexpress the gelatinases MMP-2 and MMP-9, which have a crucial role in the promotion of angiogenesis, as they degrade collagen IV, the major component of basement membranes[73].

CMT-3 or COL-3 (6-deoxy 6-demethyl 4-dedimethylamino tetracycline), a chemically modified tetracycline, is one of the most potent MMP inhibitor. A phase II trial showed that COL-3 inhibited *in vitro* activated neutrophil gelatinase and the expression of MMPs in human colon and breast carcinoma cell lines in a dose-dependent manner, when administered orally 50 mg once daily. This drug was associated with dose-related photosensitivity and rash. The overall response rate was 41%, with a median duration of response of 52 weeks[50,73].

Thalidomide (100 mg/day for 12 months) has been shown to block TNF production and inhibit basement membrane formation and intercellular adhesion molecules. The inhibition of vascular endothelial cell proliferation induced by thalidomide occurs in association with a marked 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[50,74].

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[50,75].

One phase II study has evaluated the efficacy of bevacizumab, an 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. In this study, patients with HIV-KS on a stable HAART regimen received bevacizumab 15 mg/kg every 3 weeks after an initial loading dose. 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 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 initial reduction of the tumor burden with cytotoxic chemotherapy or in patients who are approaching the maximal safe cumulative dose of anthracyclines. In contrast to most cytotoxic agents active in KS, bevacizumab does not seem to impair immune reconstitution, an important feature for therapeutic interventions for HIV-associated KS[76].

Immunotherapy

Interferon-alfa (IFN-α) has been shown to have immunomodulatory, antiviral and antiangiogenic effects, with 10-40% overall response rate when administered at high doses as a single agent and equal or superior efficacy at lower doses when combined with HAART. Appropriate response to IFN-α requires continued treatment for at least 6 months or more. Significant toxicity includes flu-like symptoms and bone marrow suppression.

A large number of drugs blocking herpesvirus DNA synthesis have been reported to inhibit HHV-8 replication. Of these agents, ganciclovir (or its oral pro-drug valganciclovir) is the only one proven to either suppress HHV-8 replication *in vivo* or prevent the development of KS in randomized trials. In a randomized placebo-controlled cross-over trial, valganciclovir was shown to reduce HHV-8 oral shedding frequency by 46% and 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[77,78].

Conclusions

Despite the impact of HAART has resulted in a dramatic decline in HIV-related morbidity and mortality, KS still represents the second most frequent tumor in HIV-infected patients worldwide, whose pathogenic mechanisms are not completely known. Unfortunately, no standard therapy protocols have been defined. HAART either alone or in combination with systemic and local therapy has a crucial role in controlling KS; new therapeutic options, including anti-angiogenic agents as well as metalloproteinase and cytokine signaling pathway inhibitors, are available, but large prospective studies are necessary to better establish their impact on KS control and long-term prognosis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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