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Kaposi's sarcoma: Etiology and pathogenesis, inducing factors, causal associations, and treatments: Facts and controversies

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Abstract Kaposi's sarcoma (KS), an angioproliferative disorder, has a viral etiology and a multifactorial pathogenesis hinged on an immune dysfunction. The disease is multifocal, with a course ranging from indolent, with only skin manifestations to fulminant, with extensive visceral involvement. In the current view, all forms of KS have a common etiology in human herpesvirus (HHV)-8 infection, and the differences among them are due to the involvement of various cofactors. In fact, HHV-8 infection can be considered a necessary but not sufficient condition for the development of KS, because further factors (genetic, immunologic, and environmental) are required. The role of cofactors can be attributed to their ability to interact with HHV-8, to affect the immune system, or to act as vasoactive agents. In this contribution, a survey of the current state of knowledge on many and various factors involved in KS pathogenesis is carried out, in particular by highlighting the facts and controversies about the role of some drugs (quinine analogues and angiotensin-converting enzyme inhibitors) in the onset of the disease. Based on these assessments, it is possible to hypothesize that the role of cofactors in KS pathogenesis can move toward an effect either favoring or inhibiting the onset of the disease, depending on the presence of other agents modulating the pathogenesis itself, such as genetic predisposition, environmental factors, drug intake, or lymph flow disorders. It is possible that the same agents may act as either stimulating or inhibiting cofactors according to the patient's genetic background and variable interactions.

Treatment guidelines for each form of KS are outlined, because a unique standard therapy for all of them cannot be considered due to KS heterogeneity. In most cases, therapeutic options, both local and systemic, should be tailored to the patient's peculiar clinical conditions.

Introduction

Kaposi's sarcoma (KS) is an angioproliferative disease, with a viral etiology and a multifactorial pathogenesis hinged

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on an immune dysfunction. The name is bound to Moritz Kaposi (1837–1902) who described three fatal cases of multiple idiopathic pigmented hemangiosarcoma in elderly men at the University of Vienna in 1872.[1] Since then, KS has been defined as a malignant neoplasm of blood or lymph vessels presenting with multiple vascular nodules in the skin or other organs. The disease is multifocal, with a course ranging from indolent, with only skin manifestations, to fulminant, with extensive visceral involvement.

KS clinical classification

Since Kaposi's description of the *classic type* clinicians have described four distinct types. Although the classic type remains more prevalent among elderly men of Mediterranean origin, it has been diagnosed worldwide and typically follows a benign course. The *African endemic form* of KS was first described in 1914 and occurs predominantly among young black men aged 25 to 40 years.[2] There is also a lymphadenopathic subvariant of the African form that affects children at a mean age of 3 years.[3] In the 1970s, a third form associated with immunosuppressant treatment was described among recipients of organ transplantation, patients on long-term corticosteroids for various disorders, and patients immunosuppressed as a result of other therapeutic regimens, including chemotherapy (*iatrogenic form*).[4,5] Finally, in 1981, an epidemic of KS among young men who had sex with men in the United States served as the harbinger of a new immunodeficiency syndrome, subsequently identified as being associated with HIV infection (*epidemic form*).[6] As the HIV epidemic progressed, KS was found almost exclusively among homosexual men.[7] Due to epidemiologic data indicating the high incidence of KS among persons at greater risk for sexually transmitted infections, a further independent infectious agent was proposed in the etiology of epidemic KS.[7]

Etiology and pathogenesis of KS

From the viral etiology hypothesis to the HHV-8 discovery

Although the onset of KS ensues from complex and multifactorial events, including immunosuppression,[8] a crucial role of viral agents has been supposed since the 1950s.[2,3] In the 1970s, a specific role for herpesviruses was proposed.[9] Giraldo and colleagues observed herpes-type viral particles in five of eight tissue culture cell lines from African patients with KS[10] and subsequently cytomegalovirus genetic sequences were identified in those tumors.[11] In 1994, a major breakthrough in the etiology of KS was reported. Chang and co-workers identified a new human herpesvirus, HHV-8, by representational difference analysis and detected this virus in more than 90% of KS lesions, including those unrelated to HIV.[12] Subsequently, HHV-8 has been documented in more than 95% of KS patients of all four types of KS.[13] HHV-8, found in saliva and semen, may spread through contact with saliva and kissing, as well as sexual activity, similarly to what occurs with other herpesviruses.[14] The prevalence of HHV-8 antibodies increases with age and shows wide fluctuations geographically. Low rates (<5%) of HHV-8 seroprevalence are reported in North Europe and the Americas,[15] high rates (35%) in Sicily,,[16] and very high (87%) in Botswana.[17] The rates are usually related to the prevalence of KS.[18] Nevertheless, there are countries, such as Brazil, Gambia, Ivory Coast, and Thailand, with high HHV-8 seroprevalence and low incidence of KS.[19]

Geographical distribution of HHV-8 variants

Phylogenetic studies performed on the well-conserved open reading frame (ORF) 26 (minor capsid gene) allowed the identification of eight distinctive subtypes designated as A/C, J, K/M, D/E, B, Q, R, or N groups, which are diversely distributed in different geographical regions. In particular, four subtypes (B, N, Q, and R) have been found almost exclusively among Sub-Saharan African samples, one (D/E) has been found only within indigenous South Asian and Polynesian (Pacific Rim) populations, and three (A/C, J, and K) have been identified almost exclusively in Eurasian subjects (European, United States, North Asian, and Middle Eastern).[20] Sequence analysis of the highly variable ORF K1 region has allowed the identification of seven major HHV-8 subtypes (A, B, C, D, E, F, and Z), comprising each several sub-clades, whose distribution in the world parallels that of ORF 26 variants: HHV-8 subtype B predominates in Africa and F has been identified in Ugandan Bantu tribe, subtype D is present in the Pacific islands; subtype E clusters in ancient populations, like Brazilian Amerindians, whereas A and C predominate in Europe and the United States.[21–25] It is still unclear whether different genotypes may have different pathogenic and tumorigenic properties associated with inverse rates of disease progression.[26–29]

The role of co-factors in KS pathogenesis

Pathogen-related diseases do not have the same clinical outcome in all infected patients with a subset developing chronic infections and a smaller subset progressing to cancer, suggesting that cofactors are needed for the different evolution, including genetic and environmental determinants. In the current view, all forms of KS have a common etiology in HHV-8 infection and their differences are due to the involved cofactors.[30] HHV-8 infection, in fact, can be considered a necessary but not sufficient condition for the development of KS because further factors (genetic, immunologic, and environmental) are required.

Gene polymorphisms and risk for KS

It is well known today that HHV-8 is a necessary cause for the development of KS, but given the heterogeneous distribution of the virus, the incidence of KS in different populations, and the datum that only a small percentage of HHV-8 seropositive patients develop KS, other genetic or environmental cofactors are clearly necessary for the development of this tumor.[31–34]

HHV-8, similar to other DNA oncogenic viruses, expresses viral genes that directly or indirectly perturb p53 protein functions and thereby mediate viral oncogenesis.[35] The p53 protein plays a central role in cell cycle control for its ability to induce cell cycle arrest and DNA repair, or senescence and apoptosis in response to a variety of stimuli such as stress signals, genotoxic agents, hypoxia and oncogene activation.[36] The key function of p53 in oncogenesis as tumor suppressor protein is supported by the fact that *TP*53 is the most frequently mutated gene in a variety of human cancer of diverse histologic type.[37] HHV-8 virus interferes with p53 pathway at several levels: (1) the latency-associated nuclear antigen, encoded by ORF 73 of the HHV-8 genome, suppresses p53 transcription and transactivation activity, and interacts directly with the p53 protein inhibiting the ability of p53 to induce cell death[35,38]; (2) the viral interferon (IFN) regulatory factor 4 (vIRF4), encoded by ORFK10/K10.1 of HHV-8, specifically interacts with and stabilizes murine double minute 2 (*MDM2*) human homologue, a well-known negative regulator of p53 via proteasome-mediated degradation, leading to the consequent reduction of p53 levels and thereby concurring to the suppression of p53-mediated apoptosis.[39,40] The relevance of the vIRF4 interference with MDM2 protein is strongly supported by its relevance in cell cycle control.

A number of studies have shown that MDM2 is overexpressed in several human cancers. The higher expression levels of MDM2 are mutually exclusive in respect to p53 mutations suggesting that they may substitute for mutational inactivation of p53.[41,42] A naturally occurring G to T sequence variation (single-nucleotide polymorphism 309 [SNP309]) in the second promoter-enhancer region of *MDM2* gene has been shown to increase the binding affinity of the transcriptional activator Sp1 resulting in high levels of MDM2 protein, formation of transcriptionally inactive p53–MDM2 complexes and alteration of the p53 pathway.[43,44] These observations are consistent with an oncogenic function for the variant SNP309. The *MDM2* SNP309 polymorphism may be associated with earlier onset of breast cancer in Li-Fraumeni patients[43,45,46] and with earlier onset of soft tissue sarcoma, diffuse large B-cell lymphoma, colorectal cancer, and non-small cell lung cancer particularly in women.[47–49]

In a recent study, a significant increase of the heterozygous *MDM2* SNP309 T/G genotype among white classic KS cases was reported.[50] The homozygous *MDM2* SNP309 G/G genotype in classic KS, on the other hand, was lower (9.1%) than observed in controls (15.6%). The decreased frequency of *MDM2* SNP309 G/G genotype in cutaneous KS patients could have several explanations including that G/G carriers with HHV-8 infection could be at increased risk for developing visceral KS, or highly aggressive HHV-8 related lymphoproliferative disorders such as primary effusion lymphoma (PEL) or multicentric Castleman's disease.[51] The analysis of seven PEL cell lines for mutations and SNPs in 10 genes involved in apoptosis and cell cycle regulation, including SNP309 in *MDM2* and codon 31 in *CDKN1A* genes has been demonstrated.[52] Interestingly, three (42.8%) Epstein-Barr virus (EBV)–negative cell lines, namely BC3, BCBL-1 and BCP, were homozygous for SNP309 G, suggesting a major role of this polymorphic allele in cell transformation, particularly in the absence of EBV co-infection. Future researches, however, are needed to accurately address this hypothesis.

Immune deficit and risk for KS

Systemic immunodeficiency. KS prevalence is tremendously higher in post-transplant and AIDS patients, being 500 times and 20,000 times, respectively, greater than in the general population.[30] The incidence of KS has changed markedly during AIDS epidemic, particularly across the African continent. Before the HIV epidemic KS was a disease primarily affecting men, with extreme incidence variation among specific populations in different geographical regions. In Uganda, from 1954 to 1960 and 1968 to 1970, KS represented 6.4% to 6.6% of all male cancer patients, respectively, with rare female cases[53,54]; however, from 1989 to 1991, KS prevalence in male cancer patients rose to 48.6% (incidence of 30.1/100,000), becoming the most frequently reported cancer in men, whereas prevalence in female cancer patients climbed to 17.9% (incidence of 11/100,000).[55] Since the HIV epidemic, KS has become as common in women as in men and has been prevalent also in many African countries where it was almost unknown, but where HHV-8 has been shown to be prevalent.[56] These observations point to a role for other factors in the etiology of KS, including the possibility that different HHV-8 variants might spread during HIV/AIDS epidemic.

Local immunodeficiency. Concerning immunity disorders, systemic immunodeficiency should be considered as well as conditions of local immune destabilization, such as lymphedema, caused by several agents, often environmental factors.[57] In endemic KS, there is a relationship between KS and podoconiosis (non-filarial elephantiasis) and an increased prevalence of KS among rural peasants and cultivators toiling up highland soils containing volcanic clay minerals.[58] Walking barefoot on volcanic soils exposes pores and sweat glands in bare feet permits abrasions and allows aluminosilicates and possibly iron oxides to be taken up by lymphatics. The silicates can cause an obstacle to lymph flow, inflammation of regional lymph nodes, and disruption of the immune control in the feet and legs. As a result, these sites become an *immunocompromised district*, namely, a body region where chronic lymph stasis leads to an

immune stasis, responsible for the local outbreak of opportunistic infections (parasitic, bacterial, fungal) or tumors, as paradigmatically KS is. The link between the impairment of lymph circulation and regional immune dysfunction in classical KS was first proven in 1984.[59] KS appeared on a lymphedematous leg of a patient with altered lymph drainage and lack of cell immune response confined to the lymphedematous limb. Intradermal skin tests to common antigens performed on the four limbs (forearms and legs) revealed no immune responses on the affected limb versus normal or even strong responses on the three unaffected limbs.[59] Five years later, the same patient presented with lymphedema and new KS lesions on the other leg. On this occasion, skin tests were negative on both legs, whereas normal responses were still observed on the forearms.[60] Two years later, KS lesions also appeared on both the forearms: At this time, skin tests were negative on all four limbs.[60] A lymphologic and immunologic investigation performed in patients with classical KS sensitized with dinitrochlorobenzene proved that the affected limbs presented concomitant alteration of the lymph drainage and of the immune response.[61] The role of chronic lymphedema in facilitating the onset of KS was stressed in an unusual localization (penis) of the classical form[62] and even in the epidemic AIDS-related type.[63] Although rarely emphasized in HIV-related KS, a variable degree of lymphedema (overt or subtle, a sort of microlymphedema) of the KS-involved areas is somewhat common in homosexual men and has a wide anatomic distribution, often without notable lymphadenopathy.[64,65] Also a localized trauma may be responsible for facilitating the onset of KS lesions selectively on the traumatized area.[66,67]

Environmental cofactors and risk for KS

In cancer pathogenesis, the possibility exists that following an initial stable, genetic damage (initiation event), a transient post-initiation insult (promotion event), nonsufficient by itself to induce a cancer, could contribute to increase cancer incidence.[68] Viruses, like chemicals, can act both as initiators as well as promoters, depending on their prevalent effects either mutagenic (eg, *herpesviruses*) or epigenetic (eg, *papillomaviruses*).[69–71]

Viruses can interact with several co-carcinogens, which may act simultaneously or sequentially, continuously, repeatedly, or occasionally. These co-carcinogens may act directly on the potential cancer cell or indirectly by affecting other tissues of the host. KS can represent a good model of interaction between different oncogenic factors, useful to identify their role and their mechanisms.[8,72] The role of cofactors can be attributed to their ability to interact with HHV-8, to affect the immune system, or to act as vasoactive agents (Table 1).[57]

In AIDS-related KS, for instance, the use of large quantities of nitrite inhalants among gay men with AIDS was strongly associated with KS onset. Several plausible biologic mechanisms of action have been proposed for nitrites and their metabolites, such as cholesteryl nitrite and nitrosamines to be carcinogenic. Nitrite inhalant use might also contribute to the development of KS through immune suppression or affecting small blood vessels.[73,74]

Drugs as environmental cofactors for risk for KS: Facts and controversies. Some drugs proved to be associated with KS pathogenesis due to their immunomodulatory and proangiogenic effects. Quinine and its analogues, 4-aminoquinolines, are drugs used for many years in malaria treatment. The link between these drugs and KS is based on a series of clues that take into account the geographical distribution and incidence of KS in patients taking these drugs. In fact, HHV-8 seropositivity and KS have a high prevalence in areas such as sub-Saharan Africa, Italy, and Greece and low in northern Europe and Asia, which reflects the same pattern of distribution of malaria.[75,76] There are regions of the world, such as Brazil, Gambia, Ivory Coast, and Thailand, with high HHV-8 seroprevalence where KS and malaria are rare and the use of quinine derivatives is low, thus confirming the possible association of these drugs with KS development. In several regions of sub-Saharan Africa, despite the widespread resistance of *Plasmodium* to quinolines and the availability of more efficacious antimalarial drugs, quinine and its analogues continue to be widely used in the treatment of malaria. In fact, since 2009, 31 African countries have recommended quinine as second-line treatment for uncomplicated malaria, 38 as first-line treatment of severe malaria, and 32 for treatment of malaria in the first trimester of pregnancy.[77] In most of Africa, quinine is still used as monotherapy, contrary to recommendations by the World Health Organization (WHO).[77]

Table 1 Multifactorial etiopathogenesis of Kaposi's sarcoma[a]

KS variant	Herpesvirus	Factors affecting immune system functions	Vasoactive agents
Classic	HHV-8	Aging-related T-cell immune deficiency	ACE inhibitors
Endemic	HHV-8	Environment (parasites, diet, herbs) Drugs (antimalarials)	Aluminosilicates and iron oxides taken up by lymphatics
Iatrogenic	HHV-8	Steroids; immunosuppressants	ACE inhibitors
Epidemic	HHV-8	HIV infection of T-cells; quinine and heroin	Nitrite inhalants

ACE, angiotensin-converting enzyme; HHV, human herpesvirus; KS, Kaposi's sarcoma.
[a] Modified from Haverkos.[57]

Quinine continues to play a significant role in the management of malaria in sub-Saharan Africa and other malaria endemic areas, and its use in routine practice may not be restricted to the stated WHO recommendations. In Cameroon, quinine has continued to be used as first-line therapy, with 45% of adults receiving oral quinine for uncomplicated malaria.[78] Recent surveillance data from sentinel sites in Uganda showed that quinine was prescribed for up to 90% of children younger than age 5 years with uncomplicated malaria.[79] Furthermore, this drug and its analogs are widely distributed to healthy children as preventive treatment (*prophylaxis campaigns*). The still widespread use of antimalarials might contribute to the high incidence of KS in the geographic areas where both KS and malaria are endemic. In fact, KS and its causative agent, HHV-8, have distinctive geographic distributions that are largely unexplained. For this reason, it has been put forward an "oncoweed hypothesis," which suggests that environmental cofactors (such as some plants and natural products deriving from them) present in KS endemic regions may cause frequent reactivation of HHV-8 in infected subjects, thus leading to increased viral shedding and transmission.[33,80] Conversely, it has been hypothesized that quinine and its derivatives might better explain the epidemiology of KS than oncoweeds. This oncodrug hypothesis, specifically hints at quinine and its derivatives.[81] In fact, it is worth noting that quinine, chloroquine, and hydroxychloroquine may affect the effectiveness of the immune response, being immunosuppressive drugs. It is well known that chloroquine and hydroxychloroquine are extensively used in the treatment of autoimmune diseases such as lupus erythematosus and rheumatoid arthritis.[82] The immune-suppressive properties of these drugs may produce deleterious effects in the presence of viral infections or immunizations. For example, a randomized controlled trial to evaluate the antibody response of freshman veterinary students to intradermal human diploid-cell rabies vaccine administered concurrently with chloroquine have demonstrated that this drug taken in the dose recommended for malaria prophylaxis can reduce the antibody response to primary immunization with rabies vaccine.[83] Incidentally, one could reasonably think that the unusually severe course run by the Spanish flu pandemic of 1918–1919 could have been facilitated by the documented large administration of quinine in flu patients, because at the time, quinine was considered the "specific" remedy for fever attacks.[84]

Quinine is also used to "cut" heroin, which contributes to the widespread use of the drug among heroin addicts. In AIDS-related KS, drug addicts represent one of the main populations at risk; in these individuals, the use of quinine combined with heroin can pave the way for the onset of KS due to the interrelated anti-inflammatory and immunosuppressive effects of the two drugs.[85]

Another category of drugs, angiotensin-converting enzyme (ACE) inhibitors, have been widely associated with classic and iatrogenic KS onset. Several cases reported in the literature would indicate that ACE inhibitors might act as a trigger for the development of KS.[86,87] In fact, ACE inhibitors have immmunomodulatory effects. The immunomodulatory action of ACE inhibitors has been attributed to several mechanisms, including: (1) inhibition of the production of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-12 produced by activated monocytes and dendritic cells, (b) antiproliferative activity, (c) inhibition of free radicals, (d) inhibition of metalloproteases and, (e) elevation of immunomodulatory prostaglandins.[88] Suppression of ACE itself may explain immune alteration (possible immunosuppression) because ACE has been shown to be involved in immune function and to be up-regulated in inflammatory conditions. Furthermore, ACE inhibition enhances angiogenesis through the activation of the B2-receptor pathway. This proangiogenic effect may be associated with the up-regulation of endothelial nitric oxide synthase (eNOS) expression, but would be independent by the vascular endothelial growth factor (VEGF) pathway.[89] Other studies, however, have confirmed that the same eNOS up-regulation would be able to stimulate the VEGF pathway,[90] or to stimulate angiogenesis through the production of pro-inflammatory cytokines or activation of cyclooxygenase-2.[91]

Evaluating the role of cofactors in the outbreak of KS is not an easy task. For example, some contradictory data make it difficult to assess the relationship existing between antimalarial drugs and KS (Table 2). Chloroquine and hydroxychloroquine, quinine analogs, have recently being considered potential anticancer agents as well as chemosensitizer when used in combination with anticancer drugs, such as 5-fluorouracil in colon cancer cells or topotecan in lung cancer cells, possibly by inhibiting autophagy-dependent resistance to chemotherapy.[92,93] Autophagy is an evolutionarily conserved cell survival pathway that has been implicated as a potential mechanism of resistance to anticancer agents. In fact, it can promote cell survival in the face of stress induced by chemotherapeutic agents by breaking down cellular components to generate alternative sources of energy. Disruption of autophagy with chloroquine induces the accumulation of ubiquitin-conjugated proteins, stimulating apoptosis in several cancer cells.[94] Chloroquine and hydroxychloroquine also inhibit angiogenesis and production of proinflammatory cytokines such as IL-1β, IL-6, IL-18, VEGF, fibroblast growth factors (FGF)-2, TNF-α, transforming growth factor-β and IFN-β. Most cytokines are involved in the reactivation of the HHV-8 lytic cycle and induction of the microenvironment necessary for lesion formation, which is characterized by a triad of inflammation, angiogenesis, and production of cytokines and chemokines. Thus, these drugs can counteract the molecular targets by which HHV-8 is able to cause the disease and indirectly they can inhibit the action of the virus.[95,96]

Even more complex is the evaluation of the direct effects exerted by antimalarial drugs on HHV-8. In fact, chloroquine

Table 2 Controversies concerning role of antimalarials and ACE inhibitors in KS onset: Pro and con

Favoring effect	Impeding effect
High prevalence of KS in malarial areas with widespread use of quinine and its derivates[18]	Quinolines are potential anticancer agents alone or in combination with other antineoplastic drugs: inhibition of autophagy and apoptosis[92–94]
Low prevalence of KS in areas where malaria is rare and quinine derivates are rarely used[19]	Lysosomotropic effects of quinolines inhibit pH-dependent steps of viral entry and replication[99–101]
Use of quinine to "cut" heroin in drug addicts affected by AIDS-KS[85]	Quinolines inhibit angiogenesis, hallmark of KS pathogenesis[95]
Well-known immunosuppressive properties of quinine and its derivatives, largely used in the treatment of autoimmune diseases (SLE, DLE, rheumatoid arthritis)[82]	Quinolines inhibit production of pro-inflammatory cytokines, involved in HHV-8 lytic cycle reactivation[96]
Antimalarials indirectly encourage the onset of KS, through their inhibitory effect on TNF-α expression[103]	Antimalarials indirectly prevent the onset of KS, through their inhibitory effect on TNF-α expression[102]
Chloroquine can reduce the antibody response to primary immunization[83]	
ACE inhibitor intake can induce KS[86,87]	ACE inhibitor intake can protect from KS[104]

ACE, angiotensin-converting enzyme; DLE, discoid lupus erythematosus; HHV, human herpesvirus; KS, Kaposi's sarcoma; SLE, Systemic lupus erythematosus; TNF, tumor necrosis factor.

and hydroxychloroquine are lysosomotropic amines, substances that are selectively taken up into lysosomes; owing to their accumulation, these drugs are able to increase the intracellular pH and inhibit pH-dependent steps of duplication of several bacteria (*Enterobacterium agglomerans, Staphylococcus aureus*) and replication of viruses including members of the flaviviruses, retroviruses, coronaviruses and herpesviruses through blockade of bacterial and viral entry via inhibition of endosomal acidification.[97–100] Several studies have shown that the same HHV-8 entry is blocked by inhibition of acidification of endosomes.[101]

Also problematic is the role of TNF-α; in fact, this factor seems to play a key role for lytic cycle reactivation of the virus (HHV-8 itself stimulates TNF-α production) and to create the ideal environment for the genesis of the disease.[102] Antimalarial drugs seem able to exert a protective effect by inhibiting the production of TNF-α through inhibition of toll-like receptors; however, some studies have shown the outbreak of KS in patients taking TNF-α blockers such as infliximab; these cases have questioned the role of this factor in the genesis of the disease, especially regarding the role of its production or inhibition in the reactivation of HHV-8 lytic cycle and, in general, in KS pathogenesis.[103]

Concerning ACE inhibitors, some studies have suggested a protective role played by these drugs as a result of the improvement or regression of KS lesions in patients who were administered ACE inhibitors.[104] The matter is controversial because opposite mechanisms of action, protective or inducing, have been alleged (Table 2).[105–107]

Based on these assessments, it is possible to hypothesize that the role of cofactors in KS pathogenesis can move toward an effect either favoring or inhibiting the onset of the disease depending on the presence of other agents modulating the pathogenesis itself, such as genetic predisposition, environmental factors, drug intake, or lymphatic system disorders. It is possible that the same agents may act as either stimulating or inhibiting cofactors based on the patient's genetic background and their variable interactions.

Treatment guidelines

Due to the KS heterogeneity, there are no standard therapeutic guidelines and several different therapeutic options are available for KS treatment. Treatment decisions must take into consideration the extent and the rate of tumor growth, patient's symptoms, immune system conditions, and concurrent HIV-related complications. The best therapeutic results are obtained in the classic KS with only local treatment. Iatrogenic KS usually regresses after withdrawal of the "culprit" drug(s). Endemic KS may require a systemic therapy with cytostatic agents, which results in a variable outcome depending on the extent and severity of the disease. Epidemic KS prevalence has decreased dramatically since the introduction of highly active anti-retroviral therapy (HAART).

Therapeutic options can be distinguished in two groups: local and systemic therapy.

Local therapy

Local therapy allows for a safe, cost-effectiveness approach and is reserved for patients with minimal cutaneous disease or for nonresponders to systemic therapy who have rapidly progressive disease, as palliative therapy. Intralesional vinblastine, oral etoposide, cryotherapy with liquid nitrogen, and excisional surgery may be feasible options. Alitretinoid gel 0.1% (9-*cis*-retinoic acid) may be applied two to four times daily in the affected areas. The overall response rates (ORRs) range between 35% and 50% with cutaneous reactions.

Electrochemotherapy in the treatment of KS

Electrochemotherapy (ECT) is an emerging treatment for cutaneous lesions of different tumor types. The combination of chemotherapy and electroporation enhances drug uptake

into tumoral cells. Twenty-three patients with histologically confirmed unresectable KS, not treatable by radiotherapy or intralesional vincristine therapy, were successfully treated according to the European Standard Operating Procedures of Electrochemotherapy guidelines. In particular, a response to the first ECT session was obtained in all patients, with a complete response in 14 (60.9%) of 23 patients. After a median follow-up of 1.5 years, 16 patients maintained the response. The overall survival rate was 74.4% at 2 years.[108]

Radiotherapy is effective and often represents the best local treatment for palliation of pain, bleeding or edema, with response and complete remission rates of more than 90% and 70%, respectively. For patients with far advanced disease a single dose of 8 Gy is preferable.[109]

Systemic therapy

HAART

HAART is indispensable in the treatment of epidemic KS in all patients, alone or in combination with systemic chemotherapy and local therapy. Some antiretroviral drugs such as foscarnet, ganciclovir, cidofovir, and adefovir are alleged to have anti-HHV-8 activity. In patients with limited cutaneous lesions (T0 early-stage disease and/or slowly proliferating disease) an effective HAART regimen may represent the first step of therapy for KS, with an ORR of 66% to 86% and a complete remission rate of 35%. KS lesions typically start to decrease and disappear completely within a few weeks or months. Frequently, KS may flare dramatically following the initiation of HAART, which seems to be a manifestation of the immune reconstitution inflammatory syndrome (IRIS), that occurs in HIV-positive patients with initial low CD4 counts and an incontrollable viral load. At present, HAART alone may represent the first-line therapy for T0 and T1 slowly progressive disease. HAART with concomitant chemotherapy is indicated for visceral and/or rapidly progressive disease, whereas HAART after systemic chemotherapy may be effective as anti-KS therapy after debunking chemotherapy (ORR 91%).[110,111]

Systemic chemotherapy

Systemic chemotherapy is reserved for patients who do not respond to HAART and/or have widespread, symptomatic, rapidly progressive, life-threatening disease with visceral involvement or an IRIS-associated flare. Several single-agent therapies have been reported to be active in AIDS-related KS (vincristine, vinblastine, vinorelbine, etoposide, teniposide, adriamycin, epirubicine, bleomycin, docetaxel, and paclitaxel), with ORRS ranging between 30% and 70%, although most were partial responses. Liposomal anthracyclines (doxorubicin or daunorubicin) are now considered as first-line therapy for patients with advanced AIDS-KS.[112]

Paclitaxel, a cytotoxic agent that exerts its antitumor activity by polymerizing microtubules and inhibiting cell division, is reserved for patients with recurrent or refractory AIDS-related KS after first-line chemotherapy. Intravenous paclitaxel (100 mg/m^2 given every 2 weeks as a 3-hour infusion) is associated with a response rate of 59% and duration of sustained response of 10 months.

High-dose IFN-α allows obtaining complete and partial response rates between 20% and 40%, if the CD4 + count is greater than 200/mm^3.

Target therapy

Current understanding of KS as a convergence of immune evasion, oncogenesis, inflammation, and angiogenesis has prompted investigators to develop a target therapy based on antiangiogenic agents, metalloproteinase, and inhibitors of cytokine signaling. This therapy may be an effective strategy for patients with epidemic KS that progressed despite chemotherapy and/or HAART. Irinotecan (CPT-11), a semisynthetic camptothecin derivative converted by decarboxylation into a biologically active form SN-38 (7-ethyl-10-hydroxycamptothecin), belongs to a recently established class of anticancer agents with a cytotoxic mechanism targeting the cellular enzyme DNA topoisomerase I. The model of fibroblast growth factor-β–induced angiogenesis in mouse cornea suggests that irinotecan may be active also in KS. Data from a GICAT (Gruppo Italiano Cooperativo AIDS e Tumori) Phase II study show that intravenous CPT-11 (150 mg/m^2 day 1; 10 mg/m^2 every 21 days) plus HAART including protease inhibitors is active and well tolerated in HIV-infected patients with KS relapse or progression during HAART.[113]

Matrix metalloproteinases (MMPs), constitutively over-expressed in KS cells, are a family of zinc-dependent endopeptidases involved in the degradation of collagen IV, the major component of basement membranes, that facilitate tumor invasion and metastases. Phase II trial data have shown that 50 mg COL-3, an MMP inhibitor that blocks *in vitro* activated neutrophil gelatinase and the expression of MMPs in human colon and breast cancer cell lines in a dose-dependent manner, administered orally once daily, produces a significant decline in MMPs levels. The ORR is 41%, with median duration of response of 52 weeks.[114] Thalidomide (100 mg/day for 12 months) has been shown to block TNF-α production and to 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 transcription factor SP1, which is involved in the extracellular matrix gene expression and moderate inhibition of nuclear factor-κB activation in nuclear extracts.[115] IL-12, a cytochine that enhances type 1 immunity, can down-regulate a constitutively active G protei-coupled receptor that is encoded by HHV-8. According to the preliminary results from a Phase I study on the combination of IL-12 plus liposomal doxorubicin and HAART, remission was obtained in a substantial percentage of patients with advanced KS.[116] Oral imatinib mesylate (300 mg twice daily) inhibited activation of the platelet-derived growth factor and *c-kit*

receptors, important targets in mediating the growth of AIDS-related KS.[117]

Conclusions

In the latest decades, the pathogenesis of KS has been greatly elucidated and new etiologic factors have been described, which has facilitated the development of more effective therapeutic approaches. Many aspects of KS still remain unsolved, and further studies are needed on the matter.

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