Expert Opinion

Pharmacological management of Kaposi's sarcoma

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Introduction: Kaposi's sarcoma (KS) is an angioproliferative disease that occurs in four clinical-epidemiological forms sharing the same immunological and histopathological features, suggesting common etiological and pathogenic factors. Infection with the human herpesvirus 8, cytokine- and angiogenic factor-induced growth together with an immuno-dysregulated state represent fundamental conditions for the development of this tumor. Despite the recent improvements in KS management, it remains an incurable disease.
Areas covered: The growing knowledge of KS biology provides multiple opportunities for the development of rational, molecularly targeted therapies. The present review summarizes the current management of KS, including local and systemic conventional therapies, and thoroughly describes the results obtained with new pathogenesis-based anti-KS treatments.
Expert opinion: Kaposi's sarcoma represents a paradigm of how the elucidation of disease pathogenesis can drive the development of molecularly targeted treatments. The multifactorial pathogenesis of KS has led to the evaluation of many experimental agents targeting one or more specific factors or pathways involved in the development or progression of the disease. Although targeted therapy so far represents investigational treatment, clinical evaluation of several of these agents is yielding promising results.

Keywords: clinical trials, conventional treatment, Kaposi's sarcoma, pathogenetic/targeted therapies

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1. Introduction

Kaposi's sarcoma (KS) is a tumor of vascular origin arising with multiple independent cutaneous lesions in the form of purple maculae or plaques more frequently localized on the skin of the extremities which, in time, can progress towards a nodular-tumoral form and can coalesce to form large cutaneous tumors. In late-stage disease, mucous membranes, lymph nodes, lungs and gastrointestinal tract can be involved (reviewed in [1]). The main clinical and biological features of the disease are briefly described in the following subsections (additional details and specific literature can be found in the cited references).

1.1 Clinical and epidemiological forms of Kaposi's sarcoma

KS can affect patients of all ages, but occurs most commonly in adults, with a general predilection for men. Four clinical and epidemiological forms of KS are recognized, all associated with infection by the human herpesvirus 8 (HHV-8): classical (or Mediterranean), African (or endemic), iatrogenic and AIDS-associated (or epidemic) KS [1]. Classical KS (CKS) is a rare and clinically mild tumor that occurs in elderly people of Mediterranean, Eastern European and Middle Eastern heritage. Patients typically have one or more lesions on the legs, ankles or soles of the feet. CKS has a long indolent course and rarely involves other organs, although it may sometimes show a rapid progressive evolution and dissemination to visceral organs. Endemic or African KS (AKS) is frequent in subequatorial Africa and is

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Article highlights.

- The recent advances made in the understanding of the mechanisms underlying Kaposi's sarcoma (KS) pathogenesis represent a great opportunity for the design and use of rational targeted therapies for a disease that, despite recent improvements, continues to be an incurable disease, even though long-term remission can be seen in highly active antiretroviral therapy (HAART)-treated AIDS-KS patients.
- Although non-HIV-associated KS clinical variants have relatively low incidence rates in the general population of the western world, AIDS-KS remains the most frequent tumor in HIV-infected patients worldwide, even in the HAART era, and it has become the most common cancer among males of sub-Saharan Africa after the spread of HIV infection.
- Agents inhibiting angiogenesis and/or multiple cellular pathways have been recently evaluated or are under evaluation at present. In particular, IL-12 alone or associated with chemotherapy has yielded promising results, although randomized studies would be needed to define better its activity.
- Interesting results might be obtained with drugs that showed to be very effective in other tumor settings and that are now under evaluation in KS treatment, including the antiangiogenic agent bevacizumab, tyrosine kinase inhibitors, such as sunitinib, imatinib or sorafenib, or the proteasome inhibitor bortezomib.
- Given the role attributed to human herpesvirus (HHV) 8 in KS development, there has been great optimism that agents directly targeting HHV-8 may be effective in KS treatment, but clinical response to herpesvirus DNA inhibitors were limited and inconsistent.
- Antiretroviral drugs included in HAART such as HIV protease inhibitors, which have been shown to block angiogenesis and tumor cell invasion and to induce tumor cell apoptosis and growth arrest, are now under evaluation alone or associated with chemotherapy in KS and other tumors, in HIV-infected or seronegative patients.

This box summarizes key points contained in the article.

characterized by a more aggressive course, with involvement of visceral organs, infiltrative cutaneous lesions and high morbidity. A form with massive involvement of the lymph nodes is often seen in African children and young adults and has a rapid and fatal course. An iatrogenic form of KS develops in patients treated with chronic immunosuppressive therapy, especially in organ transplant recipients (posttransplant KS). Posttransplant KS can lead to multifocal, progressive (florid) lesions with frequent primary involvement of the oral mucosa and dissemination to the viscera. A fourth and very aggressive form of KS has been described in association with HIV infection (AIDS-KS). In contrast to CKS, this form does not have a preferential pattern of localization, even though the clinical presentation may differ in Africa as compared to the western world, where large exophytic and fungating tumors are more frequent and a higher incidence among women and children has been documented [2]. It is characterized by widely disseminated cutaneous disease, with advanced cases involving the oral mucosa and viscera (lung, liver, spleen, gastrointestinal tract). Since the beginning of the epidemic, KS represented the most frequent tumor of HIV-infected individuals, particularly homo- and bisexual men. Its incidence has declined since the late 1990s following the introduction of highly active antiretroviral therapy (HAART) [3]. Nonetheless, the disease continues to be diagnosed even among individuals with effective HIV suppression and relatively high $CD4^+$ T cell numbers, and its incidence ratio remains higher in HIV-infected subjects than in the general population. AIDS-KS together with non-Hodgkin's lymphomas (NHL) remains the most frequent tumor in HIV-infected patients worldwide [3]. Even though the pattern of cancer incidence varies across Africa and between genders, after the spread of HIV and in Africa as a whole KS represents the third most common cancer after cervix and breast in females (5.1% of all cancers) and the most common cancer in males (12.9% of all cancers) [4], accounting for up to 50% of tumors reported in men in some countries, where financial constraints make the access to HAART or specific therapies very limited [5].

1.2 Histopathology of Kaposi's sarcoma

Although these four clinical-epidemiological forms of KS have a different geographical distribution and clinical course, they share indistinguishable histologic features. KS lesions are composed of a diverse mixture of ectatic, irregularly shaped capillary and slit-like endothelium-lined vascular spaces and spindle-shaped cells, which are considered to be the neoplastic cells of KS, with red blood cell extravasation and hemosiderin pigments [1]. Sometimes the earliest patch and plaque stage lesions are difficult to distinguish from granulation tissue because of the presence of a varied inflammatory mononuclear cell infiltrate. The spindle cells eventually become the predominant cell population, forming fascicles that compress the vascular slits, and the lesions become progressively nodular [1].

The histogenesis of KS spindle cell has not been easy to trace. Although KS cells stain for certain vascular endothelial cell markers such as CD34 and factor VIII, some studies show that they express proteins similar to dendritic cells, macrophages or smooth muscle cells [1,6-7]. More recent studies have indicated that at least part of spindle cells may be of lymphatic endothelial cell origin [8], but is not clear whether these cells are of vascular or lymphatic origin, since other studies have suggested that latent infection of blood endothelial cells by HHV-8 (see below) drives their differentiation to a lymphatic phenotype [9]. Interestingly, HHV-8-infected spindle-shaped cells expressing markers of KS spindle cells are also cultured from blood of patients with KS or at risk for KS and they may represent circulating KS cell progenitors, possibly explaining the multifocal nature of KS [10-12].

Clinical and experimental data indicate that, at least in early-stage disease, KS may not be a true sarcoma but starts

as a reactive process [1,13]. In early KS lesions there are few spindle cells compared with the inflammatory component. Furthermore, KS cells in culture are dependent on exogenous growth factors and, when implanted into nude mice, can induce an inflammatory and angiogenic reaction closely resembling early KS lesions, but do not induce tumors as would fully transformed cells [1,14-15]. Moreover, regression of KS can happen spontaneously or when immunosuppression is corrected. Such characteristics, along with the multifocality of KS lesions, lend to the argument that KS is primarily a reactive disease mediated by inflammatory cytokines and angiogenic factors, whose production is triggered or enhanced by HHV-8 infection [1,15]. Indeed, the disease onset of all epidemiological forms of KS is associated with a disturbance of the immune system (reviewed in [1]). In particular, patients with all forms of KS and individuals at risk of KS, including homosexual men, HIV-1-infected individuals or elderly people of Mediterranean origin, show $CD8^+$ T-cell and Th-1-type activation and increased serum concentrations of inflammatory cytokines, particularly interferon (IFN)-γ, interleukin (IL)-1-β and tumor necrosis factor (TNF)-α, or show $CD8^+$ T-cell activation [1]. African subjects are also immunoactivated and also show a Th-1-type activation, probably due to the frequent exposure to different infections [1]. Despite iatrogenic immunosuppression, in posttransplant patients, allograft allogeneic stimulation may result in the emergence of local foci of activated immune cells [1]. In addition, KS can occur in the absence of HIV-infection or before overt immunosuppression, respectively, and AKS development is not associated with a deficient immunity [1]. Moreover, immunoactivation and production of inflammatory cytokines also leads to reactivation of HHV-8 infection (see below) [1]. Thus immunoactivation is key to KS development, as also indicated by the worsening of KS or KS onset in patients treated with TNF-α or IFN-γ [16,17], at the site of surgical wounds where an inflammatory reaction occurs [18,19], or in HIV-infected HAART-treated patients that develop an immune reconstitution inflammatory syndrome (IRIS) [20]. In the context of this immunoactivation, the inflammatory cytokines activate endothelial cells to acquire the typical spindle-shaped phenotype and to produce chemokines and angiogenic factors, such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). The concerted action of all these factors, which have also been detected in sera and lesions from KS patients [1], mediates the recruitment of circulating cells into tissues, the appearance of KS spindle cells, angiogenesis and edema, and induces in mice the development of angioproliferative lesions closely resembling primary KS lesions in humans [1,10,11,21]. However, given time, reactive KS may progress to a true sarcoma as indicated by studies that have shown varying monoclonality, oligoclonality and polyclonality from lesions of different patients [1,22-23], suggesting, indeed, that KS starts as a hyperplastic polyclonal lesion that later can give rise to a clonal cell population only under specific circumstances, such as immunosuppression and the deregulated expression of cellular and HHV-8 proto-oncogenes and/or onco-suppressor genes, including c-myc, bcl-2 and p53 (see below), leading to transformation of KS cells, which can be tumorigenic in severe combined immunodeficiency (SCID) mice [1]. Finally, KS progression is also associated with the increase in patient sera and lesions of matrix metalloproteinases (MMPs), enzymes that degrade extracellular matrix and basement membrane molecules [24]. They mediate tissue remodeling and are required for embryogenesis, wound healing and angiogenesis [24]. Among these enzymes, MMP-2 plays a major role in angiogenesis and KS pathogenesis [1]. In particular, KS cells express high levels of MMP-2, which mediates KS cell invasion of the basement membrane and contributes to KS-associated angiogenesis and vascular permeability [1,24]. All KS initiating and progression factors described above, including the Tat protein of HIV-1 (see below), are all capable of increasing MMP-2 expression, release and activation [1,25].

1.3 Viral factors associated with Kaposi's sarcoma development and/or progression

Molecular and epidemiological studies indicate that the development of KS is associated with infection by HHV-8, which is considered the etiologic agent of KS. In fact, HHV-8 can be detected in virtually all KS lesions, and seropositivity for HHV-8 is strongly associated with a high risk for developing KS (reviewed in [26]) [27-31]. However, several pieces of evidence indicate that infection with HHV-8 is necessary but not sufficient for the development of KS, since only a minor fraction of HHV-8 seropositive individuals develop KS [26]. Indeed, a dysregulation of the immune system detectable in all KS clinical forms and, for epidemic KS, HIV coinfection (see below) significantly increase the risk of KS [13,26-27]. Moreover, although nearly all KS spindle-shaped tumor cells are infected by HHV-8, most of them and the endothelial cells within KS lesions are latently infected by the virus, suggesting a prevalent role of HHV-8 in KS progression [28,32]. A small subpopulation, however, supports lytic viral growth [33], as do monocytes and lymphocytes infiltrating the lesions [26,27]. By the expression of several viral homologs of human cellular proteins, the virus drives the modulation of pathways involved in cell cycle, cell proliferation, apoptosis, angiogenesis, oncogenic transformation and immune regulation. These viral genes, which are differently expressed according to the latent or lytic virus infection cycle, include homologs of cyclin D (v-cyc) [34], bcl-2 [35] and G protein-coupled receptor (vGPCR) [36], a viral FLICE inhibitor protein (vFLIP) [37] and an interferon regulatory factor (vIRF) [38] (see also below for more details on these viral genes; reviewed in [13,26-27]).

All factors described above including HHV-8 are present in all forms of KS. However, AIDS-KS is more frequent and has a more aggressive course than the other KS forms, including AKS, which acquires the most aggressive course after HIV-1 infection. This suggests that HIV-1 itself may play a role in

KS development. Several studies indicate that the Tat protein of HIV may be responsible for the aggressive nature of AIDS-KS [39,40]. In this context, experimental evidence indicate that Tat, an activator of viral gene expression and replication, acts as a progression factor for AIDS-KS, thus explaining the higher frequency and aggressiveness of the disease in the setting of HIV-1 infection. Specifically, upon its release by HIV-infected cells, Tat promotes the invasion and proliferation of KS cells and activated endothelial cells [1]. This is due to Tat capability of mimicking and/or enhancing the effects of extracellular matrix molecules, which regulate and enhance the effects of angiogenic growth factors on endothelial cell growth and locomotion [1].

The recent advances made in the understanding of the mechanisms underlying KS pathogenesis have provided multiple opportunities for the design and use of rational targeted therapies. The aim of this article is to give an up-to-date review of the current status of KS treatment and to present the results with new approaches based on pathogenetic therapies published so far as well as the experimental treatments now under evaluation.

2. Treatment of Kaposi's sarcoma

Among and within the different epidemiological forms of KS, a variable clinical course ranging from very indolent forms with limited extension to a rapidly progressive disease can be observed. Thus, treatment decisions must take into consideration the extent and the rate of tumor growth, patient symptoms, age and general conditions, extent of immunodeficiency, and, in AIDS-KS patients, concurrent HIV-related complications. At present, no definitive cure has been established for KS and all the conventional therapies are palliative and in most cases have only temporary efficacy. In fact, the disease generally reoccurs and progresses, seriously hampering patients' quality of life, and can also become fatal, particularly in the presence of pulmonary lesions. In addition, therapeutic interventions are neither well established nor standardized and there no uniformity of treatment for KS or a consensus as to the best treatment, particularly for non-HIV-associated forms of KS.

In current practice, patients with limited, indolent, early-stage non-HIV-associated KS are generally treated by surgical removal or topical/intralesional therapy, while HAART represents a first-line treatment for patients with early AIDS-KS (**Table 1**). Patients with progressing, extensive or recurrent disease can instead be treated with a combination of surgery, systemic chemotherapy, radiation, or with immunomodulators such as IFN-α (**Table 1**). In patients with iatrogenic KS, the first approach is to reduce immunosuppressive regimens to the lowest possible level. This is particularly important in posttransplant KS in order to keep the allograft functional, which is vital in case of liver or heart transplantation, with the objective of controlling disease progression and to relieve symptoms, as opposed to achieving complete tumor remission [41]. In this clinical setting, the switching of calcineurin inhibitor-based immunosuppression to sirolimus or one of its analogs (see below) is considered the first-line treatment. Less frequently, systemic treatment modalities, such as chemotherapy, can be used [41].

The molecular basis and the main clinical results of the different approaches to KS treatment are briefly described in the following subsections. Additional details can be found in the cited references.

2.1 Local therapy

Local therapy may be useful for patients with stable, limited and accessible lesions or for cosmetic reasons. It has the advantages of being provided in the ambulatory care setting, well tolerated and less costly than systemic therapeutic approaches, although they are rarely employed in the setting of AIDS-KS since the introduction of effective HAART. In addition to more conventional approaches, a number of other experimental agents has been tested or are under investigation for the local treatment of KS (**Table 2**).

2.1.1 Conventional local treatments

Conventional local treatments include: surgery, laser or cryotherapy, intralesional chemotherapy, radiation therapy and alitretinoin topical treatment (**Table 2**).

Surgical treatment is limited to excisional biopsies for diagnosis and palliative removal of small tumors in cosmetically disturbing areas in slowly progressing disease. When used as a primary treatment, no recurrences have been reported in 56% of CKS patients for a median time of 15 months of follow-up [42]. However, the possibility of the appearance of the 'Koebner phenomenon' (skin lesions developing on lines of trauma) at the surgical wound, which has been described either in HIV-positive patients and in seronegative individuals [18,19], should be taken into consideration.

Laser therapies, including argon laser, carbon dioxide laser and pulsed-dye laser, can also be quite effective in controlling skin or oral KS lesion growth [43-45]. Cryotherapy with topical liquid nitrogen leads to > 70% cosmetic improvement because of camouflaging by superficial scaring [46]. However, it can cause pain and hypopigmentation and can only be used for small lesions.

KS lesions are highly radiosensitive and thus radiation therapy can effectively palliate symptomatic disease that is too extensive to be treated with intralesional chemotherapy but not extensive enough to warrant systemic therapy. Administered according to a different fractionated schedule and total doses, radiotherapy is well tolerated and temporarily controls large localized lesions, with response rates (partial + complete responses) for CKS > 80% [42,47-48]. A response rate of up to 91% has also been reported in a series of AIDS-KS patients with lower limb lesions [49]. Toxicity can be observed in up to 7% of patients, but is usually limited to low-grade dermatitis that usually resolves within 2 weeks of treatment completion [42,47-48]. However, poor wound

Table 1. First-line and alternative treatments for the different clinical forms of Kaposi's sarcoma.

KS clinical form	Disease stage	First-line treatments	Alternative treatments
Classical KS	Early/local	Clinical monitoring; local therapies (i.l. VCR; radiation therapy)	i.l. vinblastine, bleomycin; local laser or cryotherapy
	Advanced/disseminated	BV; PLD	Paclitaxel, etoposide, gemcitabine, ABV, IFN-α
African KS*	Early/local	Local therapies (i.l. VCR; radiation therapy)	Local laser- or cryo-therapy; i.l. vinblastine
	Advanced/disseminated	ABV, BV, etoposide	Liposomal anthracyclines, taxanes‡
Iatrogenic KS	Early/local	Sirolimus/CNI withdrawal, reduction of immunosuppressive therapy	Local therapies (laser- or cryo-therapy, i.l. chemotherapy
	Advanced/disseminated	Sirolimus/CNI withdrawal, reduction of immunosuppressive therapy	Liposomal anthracyclines, taxanes, gemcitabine
AIDS-KS§	Early/local	HAART	Radiation therapy, alitretinoin
	Advanced/disseminated	PLD	Liposomal daunorubicin, paclitaxel, irinotecan, ABV

*Resource constrains limit the therapeutic approaches to African KS.

‡Not routinely available.

§HAART is always present in all first- and second-line treatments, and as maintenance therapy.

ABV: Doxorubicin (adriamycin), bleomycin, vinblastine; BV: Bleomycin, vinblastine; CNI: Calcineurin inhibitors; HAART: Highly active antiretroviral therapy; IFN: Interferon; i.l.: Intralesional; PLD: Pegylated liposomal doxorubicin; VCR: Vincristine.

Table 2. Local approaches to the treatment of Kaposi's sarcoma.

Local therapies	Dose/schedule*
Surgery	
Lasers (argon, carbon, dioxide or pulsed-dye lasers)	
Cryotherapy	
Radiation	Up to 30 Gy, with diverse fractionated schedules
Intralesional chemotherapy	
Vinblastine	0.1 mg
Vincristine	0.1 – 0.2 mg
Bleomycin	1.5 mg
Alitretinoin	0.1% w/w gel, twice daily
Experimental treatments	
hCG	250 – 2000 IU intralesionally, 3 times/week
IFN-α	1 – 3 million IU, 3 times/week
Imiquimod	5% cream, lesion occlusion 3 times/week
Halofuginone	0.01% w/w ointment, once/day
Transdermal nicotine patches	1.75 – 7 mg/patch, lesion occlusion 3 times/week
Bevacizumab	5 mg/cm^2 intralesionally, every 2 weeks

*Doses and schedules are indicative and may vary among different studies/protocols and Kaposi's sarcoma clinical variants.

Gy: Gray; hCG: Human chorionic gonadotropin; IFN: Interferon; IU: international unit.

healing and induration/fibrosis have been also described, which may be problematic for patients with large lesions or KS-associated lymphedema.

Intralesional chemotherapy, which avoids many of the side effects normally seen with systemic chemotherapy, is based on bleomycin, vincristine or, more commonly, vinblastine administration. The majority of the data reported in the literature concern CKS patients, but reports of its use in AIDS-KS in the pre-HAART era are also found [50]. In CKS, response rates of 60 – 98% are reported [51-53]. Disadvantages of intralesional chemotherapy include pain at injection site, hyperpigmentiation, flu-like symptoms, perilesional edema and cellulitis.

Alitretinoin (9-cis retinoic acid) is a retinoid-receptor pan-agonist binding both nuclear retinoic acid receptors (RAR) and retinoid X receptors (RXR), and this wide receptor binding profile probably gives alitretionin its efficacy for the topical treatment of KS. Retinoic acids mediate numerous biological activities by regulating cellular pathways such as modulation of cell growth and differentiation, induction of

apoptosis and inhibition of angiogenesis and tumor growth [54,55]. Alitretinoin is approved for the topical treatment of cutaneous lesions in patients with AIDS-KS. In two large, double-blind, randomized trials with alitretinoin, conducted in AIDS-KS patients undergoing or not antiretroviral therapy, response rates of 34 and 37% have been observed versus 7 – 18% in the placebo group [56,57]. Toxicity consisted of local skin reaction. Literature records on its use in CKS are limited to a few case reports, which are discordant on its clinical activity [58,59].

2.1.2 *Experimental local treatments*

Several biological agents have been tested for the local treatment of KS, including IFN-α and human chorionic gonadotropin (hCG; **Table 2**). Although these agents have been reported to affect KS lesion growth, experience with them is largely anecdotal or limited to experimental clinical investigation. For example, non-HAART-treated AIDS-KS patients have been treated with some success with intralesional hCG [60], based on the long-standing clinical observations that all forms of KS are more common in men than in women and the experimental observation that KS could not be established in immunodeficient mice during pregnancy or after hCG treatment. However, the effects reported could not be reproduced when highly purified hCG was administered parenterally in non-HAART-treated AIDS-KS patients, suggesting that a co-purified molecule or degraded hCG products may be responsible for the reported anti-KS activity [61,62].

Anecdotal or limited case reports indicate that IFN-α (see below) may be effective also upon intralesional administration in both HAART-treated HIV-positive and seronegative KS patients [63,64]. In another study using lower doses, IFN-α failed to demonstrate superior efficacy over placebo in AIDS-KS patients treated with zidovudine [65].

More recently additional immunomodulators have been evaluated by topical administration. Imiquimod is a member of the imidazoquinoline molecule family that has been approved for the treatment of actinic keratosis, basal cell carcinoma and papillomavirus-induced warts. It has been demonstrated to have immunomodulating properties by triggering a cell-mediated immune response through toll-like receptors that are predominately expressed on dendritic cells and monocytes [66]. Because of this activity, it may promote the local immune recognition of KS cells. Imiquimod also has antiangiogenic activity mediated by the induction of cytokines that themselves inhibit angiogenesis (IFNs, IL-10, IL-12), local upregulation of endogenous angiogenesis inhibitors (tissue inhibitor of metalloproteinase, TIMP; thrombospondin, TSP-1), local downregulation of proangiogenic factors (bFGF, MMP-9), and the induction of endothelial cell apoptosis [67]. Anti-KS activity of topical imiquimod has been evaluated in a Phase II study in seronegative patients, in which an overall response rate of 47% has been observed [68]. It was well tolerated, and the most frequent side effects were local itching and erythema. Two recent case reports indicate that it may be active and well tolerated (local mild to moderate irritation and erythema reported) also in posttransplant KS and non-HAART-treated AIDS-KS with limited extension [69,70].

Halofuginone is a plant-derived anticoccidial with antifibrotic and potential antineoplastic activities [71]. Halofuginone specifically inhibits collagen type I gene expression and MMP-2 expression, which may result in angiogenesis and tumor growth inhibition [71]. This compound has been recently evaluated by topical administration in a blinded intra-patient vehicle-controlled Phase II trial conducted in either HAART-treated and naive AIDS-KS patients. The treatment was generally well tolerated and the most frequent side effects reported were local reactions, but the small number of subjects whose response could be evaluated precluded definitive assessment of halofuginone efficacy [72]. It is of note that a significant decrease in type I collagen was observed only in halofuginone-treated lesions, but no effect on MMP-2 [72].

Based on nicotine immunologic and vascular effects, and since smoking is associated with a low risk of KS [73,74], a Phase II double-blind study of transdermal nicotine patches has been recently conducted in CKS patients. However, although well tolerated (skin irritation reported in 29% of patients), this approach was not associated with significant or consistent changes in KS lesions. HHV-8 viral load or antibodies [74].

Finally, bevacizumab, a recombinant humanized monoclonal antibody directed against VEGF (see below) [75], is now being evaluated in a Phase II trial to compare its effectiveness by intralesional administration in combination with HAART versus HAART alone in HIV-infected patients with KS lesions localized to the airway (www.clinicaltrials.gov; **Tables 2** and **3**).

2.2 Conventional systemic treatments

For patients with more widely disseminated, progressive or symptomatic disease, a systemic approach based on cytotoxic chemotherapy, IFN-α (**Table 4**), and/or, in HIV-infected patients, HAART, is generally warranted. As a general rule, the same treatment modalities apply to all different forms of KS, while response rates and their duration may vary.

2.2.1 *Cytotoxic agents*

The cytotoxic drugs with activity against CKS and posttransplant KS are also active against epidemic KS, though in the pre-HAART era they were generally associated with lower response rates, shorter responses and non-negligible side effects. Of note, although the improvement of clinical conditions observed in the HAART era has allowed the use of more toxic/myelosuppressive polychemotherapy regimens in AIDS-KS patients, this has however increased the chance of cross-toxicity and pharmacokinetic interactions between antineoplastic drugs and antiretroviral drugs included in HAART regimens [76]. Indeed, antiretrovirals such as HIV protease

Table 3. Active (recruiting, not recruiting or not yet recruiting) clinical trials for Kaposi's sarcoma treatment posted on the ClinicalTrials.gov registry.

ClinicalTrials.gov identifier	Phase	Condition	Intervention	Anti-KS mechanism/Agent	Country
NCT00427414	II	AIDS-KS	Liposomal daunorubicin	Cytotoxic agents	USA, Brazil
NCT00923936	II	All KS forms	PLD + bevacizumab in advanced disease	Cytotoxic agent + angiogenesis inhibitor (anti-VEGF MoAb)	USA
NCT00521092	II	African KS/AIDS-KS	Sunitinib malate	Angiogenesis inhibition (TK inhibitor)	Uganda, Kenya
NCT01296815	II	AIDS-KS	Bevacizumab (intralesional)	Angiogenesis inhibitor	Mexico
NCT00686842	I/II	AIDS-KS	PTC299	Angiogenesis inhibition (VEGF inhibition)	USA
NCT01057121	I/II	AIDS-KS	Lenalidomide	Immunomodulation, angiogenesis inhibition	USA
NCT01282047	II	AIDS-KS	Lenalidomide	Immunomodulation, angiogenesis inhibition	France
NCT01016730	I	AIDS-KS	Bortezomib in advanced disease	Proteasome inhibitor	USA
NCT00304122	I	CKS/AIDS-KS	Sorafenib	Multi-kinase inhibitor	USA
NCT00450320	I	AIDS-KS	Sirolimus	mTOR inhibitor	USA
NCT01067690	II	CKS	HIV-PI IDV + VLB ± Bleo in advanced disease	Antiretroviral + cytotoxic agents	Italy
NCT00003419	II	AIDS-KS	2 NRTI ± 2 HIV-PI HAART in slowly progressing disease	Antiretroviral agents	Italy
NCT00834457	II/III	AIDS-KS	NNRTI (ABC/3TC/AZT) ± HIV-PI (LPV/RTV) HAART	Antiretroviral agents	Zimbabwe
NCT00444379	IV	AIDS-KS	HIV-PI-based (LPV/RTV + FTC/TFV) vs NNRTI-based (EFV+ FTC/TFV) HAART in naive patients	Antiretroviral agents	Uganda
NCT01276236	I	AIDS-KS	Maraviroc (as intensification of current HAART)	Antiretroviral agent	USA

3TC: Lamivudine; ABC: Abacavir; AIDS-KS: Acquired immunodeficiency syndrome-associated KS; AZT: Zidovudine; Bleo: Bleomycin; CKS: Classical KS; EFV: Efavirenz; FTC: Emtricitabine; HAART: Highly active antiretroviral therapy; HIV-PI: HIV protease inhibitor; IDV: Indinavir; KS: Kaposi's sarcoma; LPV: Lopinavir; mTOR: Mammalian target of rapamycin; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: Nucleoside reverse transcriptase inhibitor; PLD: Pegylated liposomal doxorubicin; RTV: Ritonavir; TFV: Tenofovir; TK: Tyrosine kinase; VEGF: Vascular endothelial growth factor; VLB: Vinblastine.

Table 4. Conventional systemic therapies.

Agent(s)	Dose/schedule*
Cytotoxic agents	
Vincristine	1.4 mg/m^2 i.v., every 2 weeks
Vinorebline	30 mg/m^2 i.v., every 2 weeks
Vinblastine	6 mg/m^2 i.v., weekly
Bleomycin	4 – 5 mg/day i.m. for 3 – 4 days, every 2 – 4 weeks, or 6 – 20 mg/m^2/day i.v. for 3 – 4 days, every 3 – 4 weeks
Etoposide	20 mg/m^2 p.o. every 8 h for 7 days, every 3 weeks
Gemcitabine	1.2 g/week i.v. for 2 weeks, every 3rd week
Irinotecan	150 mg/m^2 i.v. on days 1 and 10, every 3 weeks
Mitoxantrone	Not available
ABV	Doxorubicin 10 – 20 mg/m^2 + bleomycin 10 – 15 U/m^2 + vincristine 1 – 2 mg i.v., every 2 weeks
BV	Bleomycin 10 – 15 U/m^2 + vincristine 1 – 2 mg i.v., every 2 weeks, or bleomycin 15 mg i.m. + vincristine 4 – 10 mg i.v., every 3 weeks
Pegylated liposomal doxorubicin	20 mg/m^2 i.v., every 2 – 3 weeks
Liposomal daunorubicin	40 mg/m^2 i.v., every 2 – 3 weeks
Paclitaxel	100 – 175 mg/m^2 i.v., every 2 – 3 weeks
Docetaxel	25 mg/m^2 i.v., every week, or 60 mg/m^2 i.v., every 3 weeks
Immunomodulating agents	
IFN-α	5 – 20 million Units/day s.c.
Pegylated-IFN-α	140 – 180 μg/week s.c.

*Doses and schedules are indicative and may vary among different studies/protocols and Kaposi's sarcoma clinical variants.
ABV: Doxorubicin (adriamycin), bleomycin, vinblastine; BV: Bleomycin, vinblastine; IFN: Interferon; i.m.: Intramuscular; IU: International unit; i.v.: Intravenous; p.o.: Orally; s.c.: Subcutaneous.

inhibitors (HIV-PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are substrates and potent inhibitors or inducers of the cytochrome P450 (CYP) system [76]. Since many antineoplastic drugs are also metabolized by the CYP system, coadministration with HAART could result either in drug accumulation and possible toxicity or in decreased efficacy of one or both classes of drugs (for a review see [76]).

The most active cytotoxic drugs include vinca alkaloids, bleomycin, etoposide, liposomal anthracyclines and taxanes, which have been used as single agents or in combination regimens (**Table 4**).

Among the vinca alkaloids used as single agents, vincristine is the most active in non-HAART-treated AIDS-KS patients followed by vinorebline and vinblastine, with response rates of 61, 43 and 26%, respectively, and duration of responses as short as 4 months [77-79]. The most frequent side effects were neurotoxicity, particularly for vincristine or vinorelbine, and myelosuppression. The antineoplastic antibiotic bleomycin has also been studied as a single agent in non-HAART-treated AIDS-KS. Two studies with either intramuscular administration or continuous infusion of the drug showed partial remission of the disease in 48 and 65%, respectively, although the median duration of response was only 3 months [80,81]. Oral etoposide, a topoisomerase II inhibitor inducing double-strand DNA breaks and apoptosis, has also shown efficacy in HAART-treated advanced AIDS-KS with a response rate of 83% and reduced myelotoxicity compared with vinblastine [82]. CKS seems to be generally more responsive to these chemotherapeutic drugs even if used at slightly lower doses. In particular, in this clinical variant response rates of about 60 and 70% have been observed with vinblastine or etoposide, respectively [83].

Several regimens employing various combinations of the anthracycline antibiotic doxorubicin (adriamycin) with bleomycin, and/or vinblastine (ABV and BV regimens) have shown promising results, even in extensive cutaneous/visceral disease and in HAART-naive AIDS-KS patients with severely compromised immune function. Reported response rates to ABV and BV range from 25 to 88% and from 23 to 72%, respectively [84,85]. The association of vinblastine and bleomycin has been recently shown to promote a 97% response rate and limited toxicity in CKS patients [86].

Other cytotoxic drugs have been recently tested as anti-KS agents (**Table 2**). Among these, the deoxynucleoside analog gemcitabine was shown to be effective in CKS patients, with response rates of > 90% and mild myelo- or hepatic toxicity [87]. Some effects have also been reported in African HAART-treated AIDS-KS patients [88]. A Phase II study conducted in AIDS-KS patients investigated the effects of irinotecan (CPT-11), a new cytotoxic agent that acts by inhibiting DNA topoisomerase I, resulting in DNA breaks and apoptotic cell death. Irinotecan has been recently marketed for the treatment of colorectal cancer and has shown clinical activity against several other malignancies. It was also demonstrated that irinotecan has antiangiogenic activity, suggesting that it might be effective also in KS. Data from a Phase II study showed that irinotecan is active and well tolerated also in HAART-treated AIDS-KS patients, with an overall response

rate of 75% [89]. Of note, it has been recently shown that the antiretroviral lopinavir-ritonavir dramatically affects the pharmacokinetics of irinotecan in HIV patients with Kaposi's sarcoma [90]. Another Phase II dose-comparison study has also evaluated the toxicity and efficacy of the antineoplastic antibiotic mitoxantrone, another inhibitor of topoisomerase II, in AIDS-KS (www.clinicaltrials.gov), but the results of this study have not yet been published. Of note, in a case report the rapid complete regression of KS lesion in a HIV seronegative patient affected by acute myelocytic leukemia has been ascribed to the use of mitoxantrone [91].

Though all these cytotoxic agents have been shown to have some effectiveness in AIDS-KS, three other drugs are approved at present for this indication based on clinical effectiveness and a reasonable side-effect profile. They include the two liposomal anthracyclines (pegylated liposomal doxorubicin and liposomal daunorubicin) and the taxane paclitaxel (**Table 4**).

At present, liposomal anthracyclines are considered the standard first-line chemotherapy for advanced AIDS-KS patients. Liposomal encapsulation alters anthracycline kinetics, resulting in prolonged half-life and reduced toxicity as compared with the non-encapsulated drug. The formulation of the anthracycline antibiotic doxorubicin in pegylated liposomes (PLD) results in better tumor localization, efficacy, pharmacokinetic and toxicity profile in non-HAART-treated AIDS-KS patients [92,93]. Peripheral neuropathy occurs infrequently and cardiotoxicity is rare, while myelosuppression remains the most important dose-limiting toxicity of these drugs. In randomized, multicenter trials, each of these liposomal agents proved superior to conventional polychemotherapy also regarding response rates. In two pre-HAART randomized studies, PLD showed activity superior to ABV or BV with response rates of 46 – 59% [93,94]. The liposomal formulation of another anthracycline, daunorubicin, was associated with a response rate of 25 – 73% in non-HAART-treated AIDS-KS patients [95,96]. Thus, the efficacy and toxicity profiles of liposomal anthracyclins make them a gold standard for the treatment of rapidly proliferating or visceral AIDS-KS. In this regard, a double-blind, multicenter study comparing PLD and liposomal daunorubicin in AIDS-KS patients under stable HAART showed that response rates and toxicity were similar between the two arms. Thus, the decision to use one agent over the other relies more on local access to the drugs and costs [97]. Interestingly, a new pharmacodynamics study is now ongoing to determine the effect of liposomal daunorubicin on HHV-8 viral gene expression in lesions of HAART-treated AIDS-KS patients (www.clinicaltrials.gov).

PLD was shown to be very effective and well tolerated also in pretreated progressing CKS patients [98]. Recently, an international multicenter retrospective analysis evaluated the activity and safety of PLD in patients with CKS who had not received previous systemic chemotherapy. The overall response rate was 71%, with higher responses in early-stage, limited disease [98]. The most frequent treatment-related toxicity was hematological, without cardiac side effects, but, more interestingly, the study demonstrated that PLD can control disease for more than 2 years [98]. These data make PLD a very promising agent for first- and second-line CKS treatment, although more studies comparing this drug with active and well-tolerated strategies (such as vinblastine alone or in combination with bleomycin, or taxanes) are needed.

The taxane paclitaxel is a microtubule-stabilizing agent with strong cytotoxic and antitumor effects. Recent experimental data have shown that paclitaxel also has antiangiogenic effects, causes regression of experimental KS lesions *in vivo*, blocks the growth, migration and invasion of experimental KS cells *in vitro*, and promotes cell apoptosis by downregulating Bcl-2 expression both *in vitro* and *in vivo* [99].

Paclitaxel has proved to be highly effective in the treatment of anthracycline-resistant naive or HAART-treated AIDS-KS with response rates of 59 – 71% [100,101]. A randomized trial comparing the efficacy and toxicity of paclitaxel and PLD conducted in either naive or HAART-treated AIDS-KS patients revealed comparable response rates between the two treatments, but a worse toxicity profile for paclitaxel [102], making it a less favored option than liposomal anthracyclines as initial therapy for advanced KS. The clinical response and tolerability of standardized paclitaxel treatment was also evaluated in advanced and refractory CKS or posttransplant KS, showing that paclitaxel is effective and well tolerated also in these settings [103-105].

Clinical experience with another taxane, docetaxel, is more limited than that with paclitaxel. Some clinical effectiveness has been shown for docetaxel in either HIV-negative KS and HAART-treated AIDS-KS patients; however, severe neutropenias were common, even for relatively modest drug doses [106,107].

2.2.2 Immunomodulatory agents

IFN-α is a pleiotropic cytokine with multiple effects on the immune system, proliferation, apoptosis and angiogenesis [108]. It also has antiviral effects that may be important for KS control. In this context, it was shown to reduce HIV replication [109] and HHV-8 lytic viral reactivation *in vitro* [110], or HHV-8 viral load in mononuclear cells from KS patients [111]. In addition, IFN-α increases natural killer cell and monocyte-mediated cytotoxicity against KS-derived targets [112,113], and inhibits the expression of factors involved in KS pathogenesis, such as bFGF and MMP-9 [114,115].

IFN-α was among the first agents studied for the treatment of both classic and epidemic KS, and was the first drug to receive FDA approval for the treatment of AIDS-KS (**Table 4**). It is not recommended after organ transplantation because of rejection risks [116].

Most of the published experience refers to patients of the pre-HAART era, treated with IFN-α alone or in association with single antiretrovirals [117]. Higher response rates were observed in patients with a more conserved immune

system [117]. It was shown that the combination of IFN-α with combined antiretroviral drugs synergistically suppresses AIDS-KS, probably by decreasing HIV and its associated proinflammatory cytokines, thus allowing a reduction of IFN-α doses and decreasing side effects [118,119]. Response rates between 30 and 50% and side effects such as myelosuppression, hepatic toxicity, neuropathy, flu-like symptoms, confusion and depression have been reported [118,119].

The need for the frequent (daily) self injections coupled with the IFN-related side effects has recently limited IFN-α use now that other active therapeutic options such as liposomal anthracyclins and paclitaxel can be given with fewer side effects. However, this inconvenience could potentially be overcome by the use of longer-acting IFN-α formulations such as pegylated IFN-α (PEG-IFN), which in viral diseases such as hepatitis B and C has shown superior activity and a prolonged half-life compared with IFN-α. Interestingly, weekly PEG-IFN administration has been recently tested in two virally suppressed HIV-infected patients with refractory aggressive AIDS-KS. PEG-IFN, promoted a complete tumor response in both patients, with suppression of HHV-8 viral load [120]. An additional therapeutic option could be represented by albinterferon α-2b (alb-IFN), a recombinant polypeptide composed of IFN-α-2b genetically fused to human albumin having an extended half-life that allows dosing at 2- or 4-week intervals in chronic hepatitis C [121].

IFN-α was shown to be very effective in CKS. Major clinical improvements and complete regression by low-dose IFN-α have been reported in these patients. Toxicity was limited and recurrences resulted responsive to retreatment in a high proportion of patients [122-124]. However, low-dose IFN-α has been recently compared with PLD in CKS patients and found to be less tolerated and less effective than PLD (19 vs 91% responses, respectively) [125].

2.3 Experimental systemic treatments

Progress recently made in the knowledge of KS biology and pathogenesis led to the evaluation of various systemically administered experimental agents targeting specific factors or pathways involved in the development or progression of the disease (**Tables 3** and **5**). As detailed below, some of these new approaches have shown limited activity, while other more promising agents will need further clinical evaluation to assess better their use in KS treatment, alone or associated with conventional therapies.

2.3.1 Immunomodulatory/multifunctional agents

IL-12 is a multifunctional heterodimeric glycoprotein produced by activated monocytes and antigen-presenting cells that targets mainly T and natural killer cells, promoting their proliferation, cytotoxic activity and production of IFN-γ [126]. It was also shown that IL-12, through the induction of IFN-γ and subsequent induction of the antiangiogenic and antitumor chemokines CXL10 (IP-10) and CXCL9 (Mig), blocks tumor growth and angiogenesis [127,128]. In addition to this, since CXL10 is a known negative regulator of vGPCR, which has been associated with HHV-8 oncogenic transformation [129], IL-12 may inhibit vGPCR signal transduction through this mechanism. Based on these properties, IL-12 has been investigated as a potential treatment for KS.

In a Phase I exploratory study preliminary evidence established that IL-12 has substantial activity against HAART-treated AIDS-KS patients. IL-12 was found to promote major responses in 70% of patients [130]. The principal toxicities observed were flu-like symptoms, transaminase or bilirubin elevations, neutropenia, hemolytic anemia and depression. Interestingly, IL-12 treatment was associated with increase of serum IL-12, IFN-γ and CXCL10. Since with this regimen tumor responses often took several months, limiting its utility in advanced disease, in a following Phase II study conducted in HAART-treated AIDS-KS patients, IL-12 was combined with PLD, followed by IL-12 alone. This regimen of IL-12 plus liposomal doxorubicin yielded rapid tumor responses and a high response rate (83.3% major responses); responses were maintained, and sometimes improved, with continued IL-12 alone maintenance therapy [131]. Altogether, these studies indicated that IL-12 has an anti-KS effect; however, a randomized trial will be needed to define this activity better.

As the agents described above, thalidomide shows a range of activities that could influence the growth of KS lesions. It inhibits monocyte production of TNF-α and thus has emerged as a useful treatment option for many refractory dermatologic, infectious and autoimmune disorders [108,132]. Thalidomide also inhibits HIV proliferation *in vitro*, acts as a co-stimulator of human T cells and increases production of T-helper type 1 cytokines, including IFN-γ and IL-12 and, importantly, it has been shown to inhibit both bFGF- and VEGF-induced angiogenesis, and to reduce transcription of $\alpha_v\beta_3$ integrin [108], key molecules for angiogenesis and KS development [26]. Since the mid-1990s, the discovery of these antiangiogenic effects has led to renewed interest for this drug, especially in oncology. In this context, thalidomide has been shown to be an active and promising antitumor drug, as a single agent or in combination with dexamethasone, in hematological malignancies, such as multiple myeloma, myelodysplasia or acute myeloid leukemia. The overall clinical experience of thalidomide in KS is limited. Thalidomide was first studied in naive or HAART-treated HIV-associated KS with response rates ranging between 34 and 47% [133,134]. Toxicity included neutropenia, rash, fever, myositis, sedation and depression, especially at the higher doses. HHV-8 viral load was reduced only in a subset of responding cases and treatment was not associated with measurable changes in serum bFGF, VEGF or IL-6 levels [133,134]. The effect of low-dose thalidomide has been also assessed in non-HIV KS (iatrogenic or classic); however, the overall response rate was quite similar to AIDS-KS, and in any case lower than the response rates obtained with other systemic therapies [135,136].

With the recent 'rediscovery' of thalidomide, several structural analogs have been developed in an attempt to find

Table 5. Experimental systemic treatments.

Agent	Dose/schedule*
Immunomodulating/multifunctional agents	
IL-12	300 – 500 ng/kg s.c. b.i.d.
Thalidomide	100 – 1000 mg/day p.o.
Lenalidomide	Not available
Angiogenesis/multiple pathway inhibitors	
COL-3	25 – 70 mg/m^2/day p.o.
Rebimastat	1200 mg once/day p.o.
Bevacizumab	15 mg/kg i.v., every 3 weeks
PTC299	Not available
SU5416	145 mg/m^2 i.v., twice/week
VEGF-AS	200 mg/m^2/day i.v., for 5 days, every 2 weeks
Tecogalan	125 – 500 mg/m^2, every 3 weeks
Pentosan	25 mg/m^2 i.v. every 6 h (day 1), then s.c. b.i.d., every day
TNP-460	10 – 70 mg/m^2 i.v., every week
Alitretinoin	60 – 140 mg/m^2/day p.o.
Tretinoin	45 mg/m^2/day p.o
Isotretinoin	1 mg/kg/day p.o.
Bexarotene	Not available
Sunitinib	50 mg/day p.o. for 4 weeks, every 6 weeks
Imatinib	300 mg b.i.d. p.o.
Sorafenib	400 mg b.i.d. p.o.
IM862	5 mg every other day i.n.
Cilengitide	Not available
Agents targeting HHV-8	
Ganciclovir	4.5 g/day p.o., or 10 g/day i.v.
Valganciclovir	900 – 1800 mg/day p.o.
Foscarnet	90 – 180 mg/kg/day i.v.
Cidofovir	5 mg/kg i.v., every 1 – 2 weeks
Valproic acid	250 – 1000 mg b.i.d. p.o.
Bortezomib	Not available
Sirolimus	0.0015 – 0.05 mg/kg/day p.o.
Antiretrovirals	HIV-PI/NNRTI/CCR5 antagonist p.o., same dosing used in HAART

*Total daily doses are indicated, unless specified. Doses and schedules are indicative and may vary among different studies/protocols and Kaposi's sarcoma clinical variants.

HAART: Highly active antiretroviral therapy; HHV-8: Human herpesvirus 8; HIV-PI: HIV protease inhibitor; i.n.: Intranasal; i.v.: Intravenous; p.o.: Orally; s.c.: Subcutaneous.

compounds with thalidomide's properties without the associated side effects. In particular, lenalidomide, a second-generation thalidomide derivative identified as more potent than thalidomide and devoid of adverse reactions associated with thalidomide administration, has been extensively studied in patients with several hematological disorders and is now approved for the treatment of myelodisplastic syndromes [137]. Lenalidomide is going to be evaluated in two different Phase I/II clinical trials in HAART-treated AIDS-KS patients (www.clinicaltrials.gov; **Table 3**).

2.3.2 Agents inhibiting angiogenesis and/or multiple cellular pathways

Angiogenesis is the process of capillary sprouting from pre-existing blood vessels. Endothelial cell activation, migration and proliferation are major cellular events in this process. Angiogenesis is necessary for all tumors to grow, but KS may be particularly vulnerable to agents that inhibit angiogenesis because vascular cells are the main component of KS lesions, particularly in the early stages. Indeed, many agents targeting one or more of the different steps of the angiogenic process have been evaluated or are under investigation, including MMP, VEGF, bFGF and kinase inhibitors (**Tables 3** and **5**).

The potential of MMP inhibitors as therapeutic agents for cancer has been investigated for more than 20 years, leading to the development of synthetic compounds that mimic the cleavage sites of MMP substrates or block MMP active site [138]. However, early-generation MMP inhibitors, such as marimastat and batimastat, demonstrated modest antitumor activity, poor oral bioavailability and dose-limiting polyarthritis that limited their clinical usefulness [138].

A Phase I, dose-finding trial with the second-generation MMP-2 and -9 inhibitor COL-3 (metastat), an orally bioavailable tetracycline, was conducted in refractory naive or HAART-treated AIDS-KS patients, with an overall response

rate of 44% [139]. The drug was well tolerated: photosensitivity, rash, and headache were among the adverse reactions reported. Interestingly, there was a significant difference between responders and nonresponders with respect to the change in MMP-2 serum concentrations from baseline to minimum value on treatment. A similar response rate was observed in a subsequent Phase II trial with COL-3, but, although plasma concentrations of MMP-2 and -9 declined overall, the decrease did not correlate with KS response status, indicating that other factors/mechanisms may be involved [140].

Rebimastat (BMS-275291) is another orally bioavailable, non-peptidomimetic MMP inhibitor targeting MMP-1, -2, -7, -9, -13 and -14 that was shown to have antiangiogenic and antitumor activity in preclinical and Phase I/II clinical studies with limited toxicity [141]. It has been tested in a Phase I trial conducted in naive or HAART-treated AIDS-KS patients, but the study was closed prematurely because of the low tumor response at well-tolerated doses [141]. The most frequent side effects included fatigue, allergic reactions and arthralgias [141].

The limited results obtained with MMP inhibitors in the treatment of tumors, including KS, led to renewed efforts in the identification of specific MMPs, which might be considered as validated tumor targets rather than anti-targets – that is molecules that must be therapeutically avoided to prevent worsening of disease or the onset of severe adverse side effects [138]. Accordingly, third-generation MMP inhibitors should be selective against validated MMP targets, which include MMP-1, -2 and -3, but should spare MMP validated anti-targets (namely MMP-3, -8 and -9). In this context, the HIV-PIs indinavir and saquinavir (see below) have been shown to target MMP-2 and -7 but not the anti-target MMP-9, which can be considered either target or anti-target depending on the tumor type [142].

Bevacizumab, the first antiangiogenic treatment designed to inhibit angiogenesis, is a recombinant humanized monoclonal antibody directed against VEGF. It was demonstrated to improve the disease-free and overall survival of several solid tumors when used alone or in combination with chemotherapy or IFN-α and it is now approved for the treatment of colon, lung, renal and breast tumors [75]. Bevacizumab has been evaluated in a Phase II trial in HIV-infected HAART-treated or seronegative KS patients, but results are not available yet (www.clinicaltrials.gov). Another study with this agent in combination with PLD is ongoing in the same clinical setting (www.clinicaltrials.gov; **Table 3**).

PTC299 is a new, orally administered, small molecule designed specifically to inhibit the production of hypoxia-induced VEGF by targeting the post-transcriptional processes that regulate VEGF synthesis, and other angiogenic cytokines (see PTC Therapeutics, Inc. website at: http://www.ptcbio.com/3.1.2_oncology.aspx). PTC299 also induces a parallel interruption of tumor cell division at the G1/S phase of the cell cycle, and inhibits serum and tumor VEGF levels, tumor-angiogenesis and growth in animal models of human cancer, including breast tumor and fibrosarcoma. It is now being tested in Phase I/II studies in patients with neurofibromatosis or advanced solid tumors. In addition, a Phase I/II dose-finding trial with PTC299 in HAART-treated AIDS-KS patients is now ongoing (www.clinicaltrials.gov; **Table 3**).

Despite preliminary evidence that SU5416 (semaxinib), a synthetic low molecular-weight inhibitor of the VEGF-receptor 2 tyrosine kinase domain, had some biological activity and no dose-limiting toxicity in KS patients, further investigations of SU5416 on KS patients were halted after two HAART-treated AIDS-KS subjects died after developing thrombocytopenia and renal failure, suggestive of thrombotic thrombocytopenic purpura [143], and after the development of other tyrosine kinase inhibitors (TKIs) such as sunitinib with improved pharmacologic properties and efficacy (see below).

An antisense oligonucleotide to VEGF (VEGF-AS) targeting the coding region of VEGF common to all isoforms of VEGF-A has been evaluated in a Phase I dose-finding study for the treatment of patients with advanced malignancies, including AIDS-KS [144]. VEGF-AS treatment was associated with strong decreases in VEGF plasma concentrations and a complete remission has been documented in one KS patient. However, very limited effects have been observed in the other malignancies evaluated and dose-limiting toxicities were common [144]. To our knowledge, this compound has not been investigated further.

Tecogalan (DS-4152) is a bacteria-derived polysaccharide with antiangiogenic and antineoplastic properties because of its capability of preventing bFGF from binding to its receptors [145]. Disruption of this receptor binding results in the inhibition of bFGF-stimulated endothelial cell growth, proliferation and migration. This compound, however, did not promote any objective clinical responses in two preliminary Phase I studies conducted in refractory malignancies, including naive AIDS-KS patients, although adverse events were limited and reversible [145,146]. Additional clinical evaluation has been dropped.

Pentosan polysulfate sodium is a semi-synthetic, heparin-like glucosaminoglycan with anticoagulant and fibrinolytic properties approved for the oral treatment of interstitial cystitis which has been shown to inhibit bFGF- and FGF-like dependent tumor growth both *in vitro* and *in vivo* and the growth of KS-derived spindle cells *in vitro* [147,148]. Based on these observations, pentosan polysulfate was evaluated in two early-phase trials conducted in the pre-HAART era on AIDS-KS patients. Although well tolerated, this agent showed limited objective responses in both trials [147,148] and has not been explored further in KS treatment.

IM862 (oglufanide) is a naturally occurring dipeptide with antiangiogenic properties. Although its exact mechanism of action remains unclear, IM862 was shown to inhibit bFGF- and VEGF-induced angiogenesis *in vitro* and tumor growth in *in vivo* preclinical models [149]. It is being evaluated at

present in ovarian and colorectal carcinoma patients. In a first Phase I/II study in HAART-treated AIDS-KS patients IM862 showed low toxicity upon intranasal administration and a response rate of 36% [150]. However, the following Phase III randomized, double-blind, placebo-controlled trial conducted in HAART-treated patients failed to show significant antitumor activity [149]. HAART alone was associated with a substantial rate of sustained tumor response and may have contributed to previous estimates of IM862 response [149].

TNP-470 (AGM-1470) is a synthetic analog of fumagillin, an antimicrobial agent isolated from the microbial organism *Aspergillus fumigatus*, that binds to and irreversibly inactivates methionine animopeptidase-2, resulting in endothelial cell cycle arrest in late G1 phase and inhibition of tumor angiogenesis. This agent may also induce the p53 pathway, thereby stimulating the production of cyclin-dependent kinase inhibitor p21 and inhibiting proliferation and angiogenesis. TNP-470 was one of the first inhibitors of angiogenesis to be investigated in tumor treatment. TNP-470 was tested in a dose-finding Phase I trial in patients with AIDS-KS. A clinical response (partial response) was observed in 18% of treated patients. This study was done before the introduction of HAART, and patients generally had advanced HIV infection, which may have adversely influenced the response rate and duration [151]. Additional clinical development of TNP-470 has been dropped, however, because of poor pharmacokinetics and dose-limiting toxicity. Other derivatives with better potency and less toxicity compared with TNP-470 such as CKD-732 are now undergoing clinical evaluation for advanced tumor treatment, which might also be evaluated in KS treatment.

Given the antiangiogenic and antitumor effects of retinoids [54,55], and the anti-KS activity of the topical formulation of alitretinoin (see above), this class of compounds has also been studied upon systemic administration in KS patients. In particular, an oral formulation of alitretinoin (9-cis-retinoic acid) was evaluated for the treatment of HAART-treated AIDS-KS in two large Phase II studies. Moderate activity with response rates of 20 – 37% was reported [152,153]. Skin and constitutional toxicity were the most frequent side effects observed [152,153]. Other attempts to treat AIDS-KS patients undergoing or not HAART with other oral retinoic acid derivatives such as tretinoin (all-trans retinoic acid) and isotretinoin (13-cis-retinoic acid) resulted variable results and in excessive toxicity [154-156]. Recently, an oral formulation of bexarotene, a new retinoid specific for RXR subtypes approved for the treatment of cutaneous T-cell lymphoma, has been evaluated in a Phase II trial in AIDS-KS patients (www.clinicaltrials.gov), but results have not yet been published.

The new compound sunitinib malate (SU11248) is an orally bioavailable ATP-competitive TKI targeting multiple tyrosine kinase receptors such as platelet-derived growth factor (PDGF) receptors α and β, VEGF receptors 1 and 2, the stem-cell factor receptor c-kit, FMS-like TK-3 receptor (FLT-3), and the glial cell-line derived neurotrophic factor receptor (RET) [157]. These tyrosine kinase receptors are important in signal transduction and growth of a number of solid tumors [157]. Inhibition of these tyrosine kinases blocks signal transduction, thereby affecting many of the processes involved in tumor growth, progression, metastasis and angiogenesis. Sunitinib has antitumor activity in patients with metastatic breast, colon and neuroendocrine cancer and has been approved for the treatment of advanced renal cell carcinoma and gastrointestinal stromal tumor [157,158]. A Phase II pilot study was planned to start to evaluate the effects of oral sunitinib in African HIV-seropositive or -seronegative KS patients, which, however, has been recently suspended owing to administrative reasons (www.clinicaltrials.gov; **Table 3**).

Imatinib is another orally bioavailable ATP-competitive TKI targeting the PDGF receptor and c-Kit, both implicated in KS formation [159]. This agent is mostly known because of its clinical effects in Philadelphia-positive (Ph^+) hematological malignancies and approved for the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumor [159]. In a pilot study of HAART-treated AIDS-KS patients, imatinib was well tolerated (diarrhea and leucopenia were the most common adverse events) and promoted a 50% response rate, with reduced lesional expression of PDGF receptor and its downstream effectors, extracellular receptor kinase (ERK) [159]. It has since been evaluated in a multicentric Phase II trial in HAART-treated AIDS-KS patients (www.clinicaltrials.gov), but results are not yet available.

Sorafenib is a synthetic oral multikinase inhibitor targeting growth signaling and angiogenesis. Sorafenib blocks the enzyme RAF kinase, a critical component of the RAF/MEK/ERK signaling pathway that controls cell division and proliferation; in addition, sorafenib inhibits the VEGF receptor 2/PDGF receptor β, c-Kit and FLT-3 signaling cascade, thereby blocking tumor angiogenesis [160]. This agent is approved for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma and is being also evaluated for the treatment of other tumors, including thyroid, breast and lung tumors. Interestingly, it was recently shown to prevent brain metastasis progression in a seronegative patient with renal cell carcinoma and the complete remission of a concomitant KS [161]. A Phase I dose-finding trial is ongoing with sorafenib in HAART-treated HIV-infected or uninfected KS patients (www.clinicaltrials.gov; **Table 3**).

Cilengitide (EMD 121974) is a cyclic Arg-Gly-Asp peptide that specifically inhibits the activities of the $\alpha v\beta 3$ and $\alpha v\beta 5$ integrins, thereby inhibiting endothelial cell–extracellular matrix interactions and angiogenesis. In particular, it blocks bFGF- and VEGF-mediated angiogenesis and tumor growth in various preclinical models [162]. Of note, cilengitide has shown very promising results with minimal side effects in glioblastoma patients included in Phase II/III trials, and is being tested in Phase II trials in patients with lung and prostate cancer [162]. Cilengitide has been recently evaluated

in a Phase I dose-escalating trial in HAART-treated AIDS-KS patients (www.clinicaltrials.gov); these results are not yet available.

2.3.3 Agents targeting HHV-8 or HHV-8-activated pathways

Given the role attributed to HHV-8 in KS development, there has been great optimism that agents directly targeting HHV-8 may be effective in KS treatment. Unfortunately no such treatments are available at present.

In this regard, *in vitro* studies conducted with herpesvirus DNA synthesis inhibitors have shown that HHV-8 is very sensitive to cidofovir, moderately sensitive to ganciclovir and foscarnet, and only weakly sensitive or ineffective to acyclovir [163]. However, although the use of foscarnet or ganciclovir, was associated with a reduced risk of KS development in HIV-1-infected individuals [164,165], KS regression upon treatment with these drugs has been reported rarely [166,167]. Interestingly, a pilot study with the valine-ester of valganciclovir, a prodrug for ganciclovir, that after oral administration is rapidly converted to ganciclovir by intestinal and hepatic esterases, has been recently conducted in CKS, but results are not available yet (www.clinicaltrials.gov). Clinical responses to cidofovir were also limited or inconsistent [133,167]. These results are in contrast to reports of clinical improvements observed in patients with other HHV-8-associated diseases such as multicentric Castleman disease or primary effusion lymphoma treated with ganciclovir with or without cidofovir [168]. The reason for this variable activity of antiviral agents among HHV-8-associated diseases is unclear, but probably lies in the different proportion of lytic-phase virus present in each disease. Indeed, drugs of this class target only the lytic viral replicative cycle and are unlikely to influence the latent infection that characterizes most KS cells.

This problem might be overcome by using agents capable of activating *in vitro* lytic gene infection in latently infected cells, such as histone deacetylase (HDAC) or proteasome inhibitors, thereby 'sensitizing' the tumor to antiviral therapy [169,170]. In this context, activation of lytic viral genes might also lead to direct killing of KS cells, or to the expression of viral antigens commonly targeted by the immune system. These observations led to the clinical evaluation of the HDAC inhibitor valproic acid, an agent used to treat seizure and mood disorders, in HAART-treated AIDS-KS patients. Valproic acid treatment was associated with minimal toxicity but KS clinical response and HHV-8 lytic induction rates were not sufficiently high to meet predefined criteria for efficacy [171]. However, since valproic acid plasmatic levels correlated positively with expression of lytic viral mRNAs [171], these findings support further investigation with more potent HDAC inhibitors or alternative lytic activation strategies, such proteasome inhibition. In this context, bortezomib is a synthetic tripeptide that reversibly inhibits the 26S proteasome [172]. By blocking the nuclear factor (NF)-κB, a protein that is constitutively activated in some cancers, bortezomib interferes with NF-κB-mediated cell survival, tumor growth and angiogenesis [172]. Approved for the treatment of relapsed multiple myeloma and mantle cell lymphoma, bortezomib is now being evaluated for the treatment of refractory HAART-treated AIDS-KS patients in a dose-finding pilot trial (www.clinicaltrials.gov; **Table 3**).

Recent experimental evidence indicates that downstream signaling pathways upregulated by HHV-8-encoded homologs of human proteins may represent promising therapeutic targets in KS. In particular, it has been shown that one of these homologs, the vGPCR, may contribute to oncogenesis by the activation of several signaling pathways in a constitutive (agonist-independent) way [36,173]. In this context, one of the most important signaling pathways is the phosphatidylinositol 3-kinase (PI3K) pathway. PI3K is a lipid kinase that activates Akt, a serine-threonine kinase that modulates a number of downstream signaling effector molecules, including the mammalian target of rapamycin (mTOR), involved in cell proliferation and survival, angiogenesis and invasion [174]. Importantly, immunohistochemical analysis of posttransplant KS lesions showed increased levels of phosphorylated Akt and mTOR downstream effectors [175]. The importance of the PI3K/Akt/mTOR pathway in KS growth has been suggested by numerous recent reports that described KS lesion regression in kidney-transplant recipients that switched from an immunosuppressive regimen based on calcineurin inhibitors to the mTOR inhibitor sirolimus or its derivative everolimus (reviewed in [41]). In order to evaluate the anti-KS activity of mTOR inhibitors, a pilot study with sirolimus is now ongoing in HAART-treated AIDS-KS patients (www.clinicaltrials.gov; **Table 3**). Interestingly, everolimus and another derivative, temsirolimus, which have been approved for the treatment of renal cell carcinoma, are now being evaluated for the treatment of patients affected by other solid tumors (www.clinicaltrials.gov), and, thus, these agents may be worthy of future clinical evaluation in KS patients as well.

2.3.4 Antiretroviral drugs

The advent of HAART has dramatically reduced the incidence of NHL, cervical cancer and AIDS-KS, which is now five times lower in patients who have received HAART compared with those who have not [3,168]. Regression of established AIDS-KS lesions has been also reported, particularly in regimens including HIV-PIs [176,177]. Because of this, the optimal treatment of AIDS-KS requires the commencement of lifelong effective HAART. Indeed, HAART now represents the first treatment step for early-stage and slowly progressive AIDS-KS with an overall response rate of 66 – 86% [178]. Chemotherapy plus HAART is indicated for visceral and/or rapidly progressive disease, whereas it may be an effective anti-KS measure when used after debulking chemotherapy [178].

There remains controversy about the relative contributions of direct effects of antiretroviral agents on tumor growth versus more general stimulation by HAART of immune

system-mediated mechanisms of KS regression and inhibition of Tat- and cytokine-mediated stimulation of KS growth [177]. Still, recently published studies have provided insights into potentially relevant effects of antiretrovirals beyond immune reconstitution that may have implication for therapy of all subtypes of KS and tumors in general. In particular, NNRTIs, one of the classes of antiretroviral drugs included in HAART, have been shown to inhibit tumor growth and aggressiveness by blocking endogenous reverse transcriptases involved in cell proliferation and differentiation [179]. On the other hand, HIV-PIs block angiogenesis and tumor cell invasion, inhibit endothelial cell and tumor cell growth, induce endoplasmic reticulum stress, autophagy and tumor cell apoptosis [177,180-182]. In particular it has been shown in *in vivo* experimental models that systemic administration of the HIV-PIs saquinavir and indinavir blocks the development of KS-like lesions promoted by human primary KS cells or angiogenic factors, and of highly prevalent human tumors, such as lung, breast, colon and hepatic adenocarcinomas [180,142]. These drugs were also found to block bFGF- or VEGF-induced angiogenesis in a chorioallantoic membrane assay with a potency similar to paclitaxel. These antiangiogenic and anti-KS effects of HIV-PIs are mediated by the inhibition of endothelial, KS and tumor cell invasion and of MMP-2 proteolytic activation, and occurs at the same drug concentrations present in plasma of treated individuals [180,142]. Moreover, HIV-PIs may affect tumor growth by modulating inflammation and T-cell-mediated cytotoxic responses (reviewed in [177]. These antitumor effects of HIV-PI have been related to a few mechanism(s) of action that have been observed at different drug concentrations. In particular, at low concentrations, similar to the steady-state (C_{min}) drug plasma concentration present in HIV-infected patients treated with HAART, HIV-PIs inhibit activation of MMP-2 and production of MMP-7, which are both required for angiogenesis and/or tumor invasion and growth [142,176,177,180]. By contrast, at high concentrations, similar to or above the peak drug plasma concentration (C_{max}), HIV-PIs inhibit the proteasome, causing tumor cell growth arrest and apoptosis (reviewed in [145]). In addition, HIV-PIs modulate cellular signaling pathways, including the signal transducer and activator of transcription 3 (STAT-3) and the Akt pathways (specific references in [142]). They also increase the effectiveness of radiotherapy or chemotherapy in several tumor models, including lung, glioblastoma, prostate, head and neck cancers, by blocking PI3-kinase/Akt signaling and downregulating hypoxia-inducible factor (HIF)-1α and VEGF expression (specific references in [142]). Finally, when used in combination with cytotoxic agents, they enhance their bioavailability by inhibiting the cytochrome P450 (CYP) 3A4 metabolic enzyme, thus increasing the systemic exposure to the cytotoxic agents in treated patients [183]. Interestingly, as a final remark, no direct effect of HIV-PIs on HHV-8 latent infection or reactivation has been observed [176].

Based on these data, several trials with HIV-PIs alone or associated with chemotherapy have been conducted or are currently ongoing in HIV-infected or seronegative KS patients (www.clinicaltrials.gov; **Table 3**). So far, results are available only from a Phase II proof-of-concept study for the treatment of HIV-negative CKS patients with the HIV-PI indinavir [184]. In this trial, indinavir was well tolerated and induced KS regression/improvement in early-stage disease, and prolonged stabilization in late-stage KS. Response required high plasma drug concentrations indicating a 'therapeutic' drug threshold and was associated with a decrease of angiogenesis markers (bFGF and MMP-2 plasma levels, and circulating endothelial cell) [184]. Since large, confluent tumor masses were generally not responsive, a new Phase II trial to evaluate the effectiveness of indinavir associated with conventional chemotherapy has been started for the treatment of late-stage CKS patients (www.clinicaltrials.gov; **Table 3**).

Notably, HIV-PI antitumor effects are also being evaluated in other cancers. More than 15 trials are ongoing at present for their use alone or in combination with radiotherapy/chemotherapy in several types of poor prognosis tumors, including advanced pancreatic adenocarcinoma, non-small cell lung carcinoma and gliomas (www.clinicaltrials.gov). Recent results of one of these studies have indicated that the combination of the HIV-PI nelfinavir and chemoradiotherapy has acceptable toxicity and promising activity in patients with pancreatic cancer [185]. In addition, a Phase II trial evaluated the effects of the HIV-PI lopinavir boosted by ritonavir in patients with heavily pretreated refractory high-grade gliomas. Interestingly, although the study did not meet its efficacy end point (6 months progression free survival), 22% of patients showed a clinical benefit (complete and partial responses plus stable disease) to lopinavir/ritonavir, two HIV-PIs that penetrate the blood–brain barrier poorly [186].

Overall, these data are very promising and form the basis for the further development of HIV-PIs in treatment of KS and other tumors in both HIV-infected and seronegative patients.

As a final remark, new classes of antiretroviral have recently been introduced in the treatment of HIV-infected patients, such as fusion inhibitors, integrase inhibitors and CCR5 antagonists, but there are no preclinical or clinical data available yet about their effects on KS. Interestingly, in this context, a new pilot study has just been started to determine whether maraviroc, the new antiretroviral antagonist of the HIV co-receptor CCR5, is effective in the treatment of AIDS-KS, when this does not remit with standard antiretroviral drug therapy (www.clinicaltrials.gov; **Table 3**).

3. Conclusions

KS is a disease with multifactorial pathogenesis, occurring in an abnormal milieu of inflammatory cytokines and angiogenic molecules, within the setting of HHV-8 infection and immune system dysregulation. Overall, the pharmacological

management of KS must take into consideration the extent and the rate of tumor growth, patient symptoms, age and general conditions, extent of immunodeficiency, and, in AIDS-KS patients, concurrent HIV-related complications. While various traditional chemotherapeutic approaches may be effective in patients with disseminated KS, response duration is short and the disease is not curable. Moreover, at present there is no uniformity of treatment for KS or a consensus as to the best treatment, particularly for non-HIV-associated forms of KS and in resource-poor settings. Continued efforts remain essential in determining the optimal treatment for KS which will minimize toxicity and enhance patient quality and quantity of life. The growing knowledge of KS biology has provided in recent years multiple opportunities for the evaluation of alternative rational targeted therapies directed at the molecular pathways that lead to tumor growth and new vessel formation. Although targeted therapy represents so far investigational treatment, clinical evaluation of several of these agents is yielding promising results that might also be translated to the treatment of other tumors in both HIV-infected and seronegative patients.

4. Expert opinion

KS represents a paradigm of how the elucidation of its pathogenesis can drive the development of molecularly targeted treatments. The multifactorial pathogenesis of KS led to the evaluation of many experimental agents targeting one or more specific factors or pathways involved in the development or progression of the disease. In this regard, while only a small number of the many agents with the potential to inhibit factors known to stimulate KS growth have been evaluated clinically, most of the anti-KS experimental agents so far tested will need further clinical evaluation to assess in more detail their use in KS treatment. In addition, there are great expectations on the many proof-of-concept studies with compounds used for the first time in KS patients which are still ongoing and which might result in effective anti-KS approaches. Indeed, as described above, several of these agents, such as IL-12, the TKI imatinib and some antiangiogenic agents showed promising results in early clinical trials, while others, which were very effective in other tumor settings, such as mTOR inhibitors, other TKIs and the proteasome inhibitor bortezomib, are being evaluated.

Other approaches showed limited activity. However, several of them have been investigated only in the setting of AIDS-KS and not in other epidemiological forms of KS with lower incidence, and at a time when antiretroviral treatment was relatively ineffective. These limitations might have affected the results obtained. In addition, the limited anti-KS effects of some of these agents may not mean that they lack for a relevant biologic effect, but that the inhibition of a single factor/pathway may be insufficient to achieve regression in a multifactorial tumor like KS that is modulated by a broad array of growth factors/pathways. Thus, it is likely that drug combinations that target several pathogenetic mechanisms will be more effective than single drugs in suppressing KS growth. Moreover, some of these targeted agents showed activity in a proportion of patients, and thus would be crucial to identify markers of response or develop assays to measure specific biologic effects on the specific target, to identify more clearly potentially active approaches or to determine the subset of patients potentially responding to the experimental treatment. Finally, additional studies on new formulations, doses or associations of agents might result in improved activity.

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