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Review paper

Treatment of Kaposi's sarcoma—an update

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Kaposi's sarcoma (KS) is an angioproliferative disease of multifactorial origin arising in different clinic-epidemiologic forms, which show the same histopathological features. It generally starts as a hyperplastic reactive-inflammatory and angiogenic process, which may evolve into monomorphic nodules of KS cells that can be clonal (late-stage lesions) and resemble a true sarcoma. 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. Several local therapies are used to eradicate early and confined skin lesions, whereas widely disseminated, progressive or symptomatic disease requires a more aggressive treatment. Although different chemotherapeutic agents have been used to treat aggressive KS, the growing understanding of the pathogenetic factors participating in KS development has provided a strong rationale for using less- or non-cytotoxic agents that block the mechanisms involved in KS pathogenesis. The angiogenic nature of KS makes it particularly suitable for using therapies based on anti-angiogenic agents. Of note on this goal, recent studies indicate that the highly active anti-retroviral therapy, including at least one human immunodeficiency virus (HIV) protease inhibitor (PI), is associated with a dramatic decrease in the incidence of AIDS-KS and with a regression of KS in treated individuals. Consistent with this, results from preclinical studies indicate that PIs have potent and direct anti-angiogenic and anti-KS activities, suggesting that they should be further investigated, alone or combined with other therapies, as a novel treatment for KS in both HIV seropositive or seronegative individuals. [© 2002 Lippincott Williams & Wilkins.]

Key words: AIDS, anti-angiogenic therapy, anti-tumor therapy, HIV protease inhibitors, human herpesvirus 8, Kaposi's sarcoma.

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Introduction

Kaposi's sarcoma (KS) is an angiogenic-inflammatory proliferative disease arising on the skin of the extremities, but often involving also mucosas and visceral organs. Lesions evolve from flat discolorations or patches (early/patch stage) to plaques (plaque stage) and then to nodules that can coalesce (late/nodular stage).

Different clinical and epidemiological forms of KS have been recognized. Classical KS (CKS) was the first clinically identified form.[1] It is an indolent form found in elderly men of Mediterranean, Eastern Europe or Jewish heritage, usually arising at the lower extremities and sometimes involving visceral organs.[2,3] CKS has a chronic course and rarely involves other organs, although it may be complicated by lymphoedema and/or hyperkeratosis. Post-transplant KS (PKS) is found in transplanted individuals after therapy with cyclosporin and corticosteroids, particularly in patients from Italy and Saudi Arabia or in certain ethnic groups of Ashkenazi or Shepardnazi Jewish descent.[2,4,5] In about half of the patients this type of KS has a mild clinical course; in others it can be more severe. An endemic and aggressive form of KS involving visceral and/or lymphatic organs occurs in young adults and children of sub-Equatorial Africa [African KS (AKS)].[2,6,7] With the outbreak of AIDS, an important increase in the incidence of KS has been observed in Central Africa, where KS now accounts for 50% of tumors reported in men. However, the most aggressive and fatal form of KS is found in human immunodeficiency virus (HIV)-1-infected homo-bisexual men regardless of their ethnical or geographical provenance [acquired immunodeficiency syndrome-associated KS (AIDS-KS)]. This form of KS is generalized and disseminated localizing in skin and visceral organs including the

gastrointestinal tract and lungs.[2,8] Despite these different clinic-epidemiologic forms, all types of KS show the same histological features characterized by an inflammatory cell infiltrate, angiogenesis, edema, and perivascular and interstitial spindle cells that are considered to be the neoplastic cells of KS.[2] In addition, molecular and epidemiological studies indicate that the development of KS is tightly associated with infection by human herpesvirus 8 (HHV8). In fact, HHV8 can be detected by polymerase chain reaction in approximately 95% of all KS tissue samples[9,10] and seropositivity for HHV8 is strongly associated with a high risk for developing KS. The virus encodes homologs of human cellular proteins involved in cell cycle regulation, cell proliferation, apoptosis, angiogenesis and immune regulation, which are differently expressed according to the latent or lytic virus infection cycle.[9,10] Most of the spindle-shaped tumor cells and endothelial cells (ECs) within KS lesions are latently infected by the virus, suggesting a prevalent role of HHV8 in KS progression (see below).[9,10] A small subpopulation, however, supports lytic viral growth, as do monocytes and lymphocytes infiltrating the lesions.[2,9,10]

In vitro and *in vivo* experimental data and clinical observations suggest that, at least in the early stages, KS is not a true sarcoma but rather a hyperplastic reactive–inflammatory–angiogenic process. In fact, KS lesions can simultaneously appear at different sites of the body with symmetrical or dermatome distribution and can regress spontaneously or following therapy.[11–14] KS onset is associated with a disturbance of the immune system leading to activation of $CD8^+$ T cells and increased expression T helper type 1 (T_h1) inflammatory cytokines (ICs) with a high level production of interferon (IFN)-γ. ICs [particularly IFN-γ, interleukin (IL)-1β and tumor necrosis factor (TNF)-α] promote key events in KS initiation, including the activation of the vascular system and the reactivation of HHV8 infection.[15–17] In fact, they activate ECs 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 mediates the recruitment of circulating cells into tissues, the appearance of KS spindle cells, angiogenesis and edema.[15,18–24] High levels of both bFGF and VEGF have also been detected in sera from patients with KS or at risk of KS, and both factors are highly expressed in KS lesions.[20,22,25,26] These angiogenic molecules, in turn, mediate KS and endothelial cell growth and locomotion, and induce in mice the development of angioproliferative lesions closely resembling primary KS lesions in humans.[20,23,24,27,28]

Although early stage KS is polyclonal, late-stage KS can be transformed and evolve into a monoclonal tumor. The long-term expression of HHV8 latency genes [latent nuclear antigen (LANA), viral cyclin D (v-cyc D), viral flice inhibitory protein (v-FLIP), Kaposin] associated with the deregulated expression of oncogenes or oncosuppressor genes such as c-*myc*, Bcl-2, and p53 that is found in late-stage KS, may play a key role in the transformation of KS into a true sarcoma.[2,9,10] In addition, the HIV-1 Tat protein acts as a progression factor for AIDS-KS by stimulating KSC growth and angiogenesis.[18,21,29–32] In fact, Tat promotes KS cells and IC-activated EC growth, migration and invasion

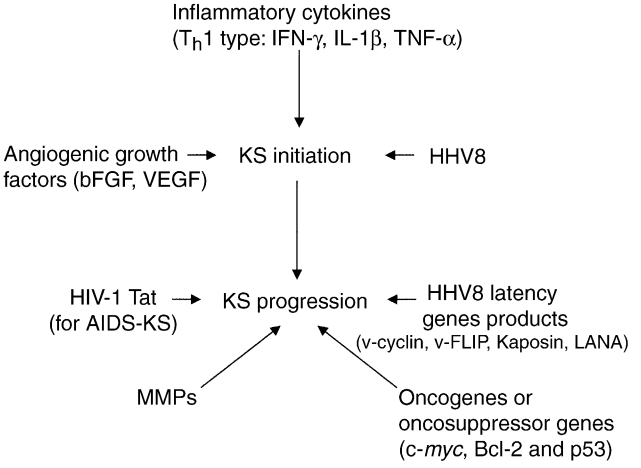

Figure 1. KS pathogenesis. Several factors, such as HHV8, inflammatory cytokines, bFGF, VEGF, the HIV-1 Tat protein (for AIDS-KS), the proteins encoded by the HHV8 latency genes, MMPs and oncogenes or oncosuppressor gene are involved in the initiation and/or progression of KS, as described in the text.

by a molecular mimicry of extracellular matrix (ECM) proteins and by retrieving in a soluble form bFGF bound to the ECM or to the cell membrane-associated heparan sulfate proteoglycans (HPSG).[15,18–21,23,24,30–33] Furthermore, Tat, alone or in combination with bFGF, induces the expression of cytokines, adhesion molecules and matrix metalloproteinases (MMPs) that play a key role in KS reactive processes or progression.[28,34–37] Evidence also indicates that a profound immunodeficiency may be required for progression of KS to a real sarcoma, that may be more common in AIDS-KS patients particularly from Africa, as also suggested by the microsatellite instability detected in AIDS-KS, but not in CKS (Figure 1).[38]

No definitive cure is known for KS. Excision, cryo- and radiotherapy, photodynamic therapy, and intralesional chemotherapy are applicable to single lesions or to locoregional disease of limited extent. However, patients with widespread or recurrent KS might require extensive treatments such as radiotherapy, cytotoxic chemotherapy and some therapies based on biomodulators such as IFN. More recently, a great interest is also arising in non-cytotoxic drugs that target the mechanisms believed to be involved in KS pathogenesis.

This review will briefly describe current and novel approaches to the treatment of KS.

Local treatments

Treatment of KS must be individualized according to the patient status and to his/her overall disease. However, despite KS form, local therapies are generally indicated for patients with early disease that is confined to the skin (Table 1). These therapies are easy to perform, relatively safe and often sufficient especially for certain mild CKS, and are based on the induction of an inflammatory response leading to tumor flattening or disappearance. Nevertheless, recurrences are frequent.

Table 1. Local and systemic treatments currently available for KS

Local	Surgical, laser, cryotherapy, radiotherapy, intralesional injection and topical treatments (vinca alkaloids, alitretinoin, hCG, GM-CSF)
Systemic	Cytotoxic chemotherapy: vinca alkaloids (vinblastine, vincristine, vinorebline), etoposide, bleomycin Liposomal anthracyclines Paclitaxel

Surgical, laser and cryotherapy

For patients with single lesions, excisional biopsy often provides adequate treatment, especially in CKS. Of 52 patients who underwent surgery as the primary treatment, 29 (56%) had no recurrence for 1–162 months.[39]

Laser therapies including argon lasers, carbon dioxide lasers and pulsed-dye lasers have been successfully used to treat large oral lesions or cutaneous macular lesions.[40–42]

Topical liquid nitrogen for cutaneous lesions has also proven successful. In fact, cryotherapy leads to more than 70% cosmetic improvement because of camouflaging by superficial scaring. However, it can cause hypopigmentation and can be used for small lesions only.[40,43]

Intralesional and topical chemotherapy

Intralesional cytotoxic chemotherapy with vinblastine or vincristine gives complete or partial clinical response rates of 60–92% in the treatment of both cutaneous and oral lesions.[44,45] Local bleomycin treatment of the lesions of AIDS-KS patients determined complete responses in 43% and partial responses in 44%.[46] In recent studies, topical alitretinoin (9-*cis*-retinoic acid) gel has been used for the treatment of cutaneous KS. Two large double-blind, multicenter, randomized trials have demonstrated partial response (greater than 50% reduction in surface area) in 46 (34%) and 23 (37%) patients, respectively, in the alitretinoin arm, with the median time to response being 63 days.[43] Another open-label multicenter trial enrolling 115 patients showed a significant clinical response in 27% of the patients.[43]

Radiotherapy

The efficacy of radiotherapy in controlling non-AIDS-KS has been well documented, achieving response rates greater than 80%.[47,48] KS lesions are highly radiosensitive, and the treatment is well tolerated and temporarily controls large localized lesions. Radiation to the oral cavity still represents the mainstay of oral KS treatment. Recent studies on AIDS-KS summarize the results of radiotherapy in 594 lesions in 65 patients and 5015 lesions in 435 patients.[40] Complete remission was achieved in more than 85% of the lesions with 15–30 Gy of radiation. However, severe mucositis is a frequent complication

in oro-pharyngeal irradiation and fractionated, reduced doses of 1–5 Gy (to a total dose of 15 Gy) were found to decrease the risk of this side effect.[49,50]

Experimental local therapies

Following on the long-standing clinical observation 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 treatment with human chorionic gonadotrophin (hCG), this hormone was injected directly into cutaneous tumor nodules of patients with AIDS-KS. The findings have been shown a dose-dependent regression and apoptotic cell death of KS as well as a decline in serum levels of follicle-stimulating and luteinizing hormones.[51] However, other investigators were unable to confirm these results.[52,53] Both AIDS-KS and CKS have been intralesionally treated with recombinant granulocyte macrophage colony stimulating factor (GM-CSF).[54] This treatment has only a local effect and it may act by inducing inflammation and necrosis.

A promising therapy is the intralesional injection of IFN-α that gave encouraging results for the treatment of both AIDS-KS and CKS.[40,55]

Systemic treatments

For patients with more widely disseminated, progressive or symptomatic disease, systemic therapy with cytotoxic chemotherapy is generally warranted (Table 1). As a general rule, the same treatment modalities apply to all different forms of KS, while response rates and their duration may vary. The most active cytotoxic drugs include vinca alkaloids (vinblastine and vincristine), bleomycin, ectoposide, liposomal anthracyclines and paclitaxel.

Cytotoxic therapy

The cytotoxic drugs with activity against CKS and PKS are also active against epidemic KS,[56–61] but are generally associated with lower response rates, shorter responses and not negligible side effects.

The vinca alkaloids which have been evaluated include vinblastine, vincristine and vinorebline. Vinblastine have been associated with responses in 25% of AIDS-KS patients, with responses lasting approximately 4 months.[59] The major side effect of vinblastine is myelosuppression. Vincristine is also effective as a single agent and is significantly less toxic to the marrow[60] even if it causes neurotoxicity. To compensate the toxicity profiles of these two agents, a regimen of alternating weekly vincristine and vinblastine has been studied, with a response rate of 43%.[62] Encouraging results have also been obtained by treating AIDS-KS patients with vinorebline with a response rate of 43%. It also induces responses in patients who had become resistant to regimens that included other vinca alkaloids. It was well tolerated, and toxicity was mild and reversible.[61] Bleomycin has also been studied as a single agent in 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,[63] although the median duration of response was only 3 months.

Oral etoposide has also shown some efficacy in patients with advanced AIDS-KS and severe CKS with reduced myelotoxicity when compared with vinblastine.[56]

Several regimens employing various combinations of adriamycin, bleomycin and vinca alkaloids (ABV and BV) have shown promising results, even in extensive cutaneous and visceral disease, and in patients with severely compromised immune function. Rates of response to ABV and BV range from 25 to 88% and 23 to 72%, respectively.[43,63]

Liposomal anthracyclines

Liposomal anthracyclines are effective against KS and are less toxic than non-liposomal anthracyclines. Liposomally encapsulated daunorubicin and doxorubicin have been studied extensively in the treatment of AIDS-KS.[64,65] Pegylated (PEG) liposomes have been developed to stabilize liposomes in plasma, to prolong their circulation time and to optimize their size (85 nm) to increase preferential extravasation in the tumor vasculature. The extravasation of PEG-liposomes appears to occur through endothelial gaps, characteristic of the neovascularization associated with KS lesions.[66] Following promising studies with PEG-conjugated liposomal doxorubicin as monotherapy, comparative studies on different chemotherapeutics in advanced AIDS-KS have been performed showing a superior outcome of monotherapy with liposomal anthracyclines when compared with combination therapy including ABV or BV.[43] In two independent phase III studies in KS, both PEG liposomal daunorubicin and doxorubicin

as single agents had a significantly higher response rate when compared to combinations of ABV or BV. Furthermore, the toxicity of liposomal anthracyclines are substantially reduced when compared with the combination chemotherapy.[43,64]

Paclitaxel

Paclitaxel shows strong anti-tumor effects which are exerted by several mechanisms. In fact, it is able to stabilize microtubules, to inhibit cell division and to induce cell death.

Recent experimental data have been shown that paclitaxel has also anti-angiogenic effects[67] and causes regression of experimental KS lesions *in vivo*.[68] In addition, it is able to block the growth, migration and invasion of experimental KS cells *in vitro*, and promotes cell apoptosis by down-regulating Bcl-2 expression both *in vitro* and *in vivo*.[68] In two studies of a total of 105 AIDS-KS patients who were treated with paclitaxel, response rates ranged from 49 to 71%.[69] The efficacy of paclitaxel with low toxicity has also been demonstrated in post-transplant KS and in CKS.[70]

Pathogenesis-based therapies

KS starts in a context of immune dysregulation characterized by $CD8^+$ T cell activation and by the production of T_h1-type cytokines in response to (or amplified by) infection with HHV8. These ICs, in turn, induce production of angiogenic and chemotactic factors, which create a microenvironment that mediates lesion formation and leads to the appearance of KS spindle cells.[9] Thus, most of these factors, by playing a key role in the pathogenesis of the disease, are potential targets for therapeutic approaches with various agents (Table 2).

Angiogenesis inhibitors

Angiogenesis is the process by which new vessels emerge from existing endothelial lined vessels. It is an invasive process that requires proteolysis of the extracellular matrix, and proliferation and migration of activated ECs, as well as the synthesis of new matrix components. Angiogenesis is a prerequisite for tumor growth and metastasis formation and a prominent feature of KS. Several different cytokines, angiogenic growth factors (bFGF and VEGF), chemokines, and MMPs appear to mediate these phenomena and have been targeted for therapeutic development.

Thalidomide

Like IFN, thalidomide shows a range of activities that could influence the growth of KS lesions. It inhibits monocyte production of TNF-α *in vitro* without affecting TNF-α production by T cells.[71] Thalidomide also acts as a co-stimulator of human T cells *in vitro* and increases production of T_h1-type cytokines, including IFN-γ and IL-12, and, importantly, it has been shown to inhibit both bFGF- and VEGF-induced angiogenesis.[71] Studies of oral thalidomide (100 mg per day for 8 weeks) showed that the drug has clinical activity (partial response in 35%) in a phase II study with 17 AIDS-KS patients on anti-retroviral therapy. In addition, peripheral blood titers of HHV8 declined to undetectable levels in three out of five responding patients whose virologic response could be assessed.[72] Preliminary results of a study with thalidomide starting at a dose of 200 mg/day with dose escalation to 1000 mg/day have also been reported. Up to 40% of the patients showed a partial response with the mean time to disease progression being 4 months.[73] Toxicity includes somnolence, neutropenia, rash, fever, myositis and depression, especially at the higher doses.[73]

Antisense (AS) oligonucleotides directed against angiogenic growth factors

Our experimental and preclinical data have demonstrated that phosphorothioate AS oligonucleotides directed against bFGF mRNA (ASbFGF) inhibit both the growth of AIDS-KS cells derived from different

Table 2. Pathogenesis-based treatments currently available or on study for KS

Thalidomide, ASbFGF, ASVEGF, SU5416, IM862, TNP-470 (inhibitors of angiogenesis)
COL-3 (inhibitor of angiogenesis and of tumor cell invasion)
HIV-1 PIs (inhibitors of angiogenesis, inhibitors of tumor cell invasion and anti-inflammatory)
Retinoic acids (modulators of cellular genes, including mediators of the immune response)
IFN-α (immunomodulator, inhibitor of angiogenesis and antiviral)
Anti-HHV8 therapy

patients and the angiogenic activity associated with these cells, including the induction of KS-like lesions in nude mice.[27] A similar effect was also shown by AS oligodeoxynucleotide directed against VEGF (ASVEGF) mRNA.[74] ASbFGF and ASVEGF synergize in both *in vivo* and *in vitro* models of experimental KS.[20] Therefore, these compounds can represent potential therapeutic agents for the cure of KS.

SU5416, IM862 and TNP-470

SU5416 is a small synthetic inhibitor of the Flt kinase, designed to block signal transduction by Flt11/KDR, one of the VEGF receptors. It inhibits the VEGF-dependent phosphorylation on the Flt-1 receptor leading to reduced tumor vascularization and is currently in advanced clinical trials for the treatment of AIDS-KS.[75,76]

Other compounds, such as IM862, a naturally occurring peptide with anti-angiogenic properties, and TNP-470 (an analog of fumagillin) are now being evaluated in clinical trials in KS. In particular, IM862, administered as intranasal drops, showed major responses in 36% of the treated patients.[77] The drug was well tolerated, with adverse effects limited to mild and transient headache, fatigue, tingling and nausea.

Cellular protease inhibitor

MMPs contribute in a multiple way to the angiogenic processes and to the vascular permeability characterizing KS.[28,37,78,79] Given that many of them are expressed by KS,[80] inhibitors of these enzymes, either alone or in combination with other agents, may represent a particularly effective therapeutic approach for KS. Recently, a phase II trial was initiated assessing the effect of the MMP inhibitor COL-3 in 18 patients. The study showed one complete response and seven partial responses, with an overall rate of 44%. COL-3 was reasonably well tolerated and showed a dose-related photosensitivity as an adverse event.[81]

HIV protease inhibitors (PIs)

Recent reports have described a reduced incidence or the regression of AIDS-KS in patients treated with the highly active anti-retroviral therapy (HAART) that includes at least one HIV PI such as indinavir or saquinavir.[82–85] In addition to their principal action against the catalytic site of the HIV protease,[85] these drugs have also been shown to affect the cell metabolism, to interfere with host and fungal proteases, and to block T cell activation and dendritic cell function.[86–93] These effects, together with the fact that proteases are essential for angiogenic and inflammatory processes and tumor growth, suggested to us that the lower incidence and regression of KS observed in PI-treated patients could be due to direct anti-KS and/or anti-angiogenic effects of these drugs. To test this hypothesis we performed a preclinical study, which showed that the administration of indinavir or saquinavir to nude mice blocked the development and induced regression of angioproliferative KS-like lesions promoted either by primary human KS cells inoculation or by injection with growth factors.[94] In addition, indinavir or saquinavir also blocked bFGF- and VEGF-induced angiogenesis in the chorioallantonic membrane assay.[94] These effects were mediated by the inhibition of EC and KS cell invasion, and of MMP-2 proteolytic activation by PIs at concentrations present in plasma of treated individuals.[94] Thus, our results indicate that PIs are promising anti-angiogenic and anti-tumor drugs, and, in addition to AIDS-KS patients or at risk of KS, they should also be used, alone or combined with other treatments, for the therapy of KS in seronegative individuals. Based on these results, an Italian multi-centric clinical trial with indinavir for the treatment of KS developing in HIV-negative patients is in the process to start.

Retinoic acids (RAs)

RAs and their synthetic analogs mediate numerous biological activities by regulating cellular genes, including mediators of the immune response, such as IL-6 and the IL-6 receptor. RAs have been studied in KS, and have shown activity in both preclinical and clinical studies. They act as anti-proliferative agents by inhibiting mRNA and protein levels of IL-6, which is an autocrine growth factor for KS cells.[95]

Several retinoid compounds have been tested in clinical trials for KS. Oral treatment of 27 AIDS-KS patients with all-*trans*-retinoic acid showed a partial response in 17% after 12–28 weeks of therapy.[96] Two more studies of 66 and 57 patients, respectively, treated with oral 9-*cis*-retinoic acid gave a major response in 37%.[63] However, in both these two trials patients received also anti-retroviral therapy, including protease inhibitors, thus influencing the

study results. Major side effects included headache, fatigue, alopecia, dry skin and elevation of triglycerides.

IFN-α

Type I (α and β) IFNs have multiple effects on cell proliferation, angiogenesis, immune function and gene expression, as well as anti-viral effects that may be important for KS control. Interferons have long been known to inhibit HIV replication *in vitro*.[97] More recently IFN-α was also shown to inhibit HHV8 lytic viral reactivation in the latently infected body cavity based lymphoma-1 cell line[98,99] and to reduce the HHV8 viral load in cultured peripheral blood mononuclear cells from KS patients.[99] IFNs have also been shown *in vitro* to increase natural killer cell and monocyte-mediated cytotoxicity against KS-derived targets.[71] Moreover, IFN-α induced a decrease of bFGF and MMP-9 gene expression that are involved in KS pathogenesis.[71]

Many trials of IFN-α for KS have been conducted since the beginning of the AIDS epidemic. Tumor regression was shown in various studies, which documented a dose-dependent tumor reduction in up to 30% of patients with doses higher than $20 \times 10^6 U/m^2$ body surface area.[71,100,101] These studies also documented superior response rates among patients with CD4 counts greater than 200/μl and no previous AIDS-defining opportunistic infections or lymphoma-like 'B' symptoms. The combination of IFN-α with different anti-retroviral drugs determined a synergistic suppression of KS, probably by decreasing HIV and its associated pro-inflammatory cytokines. However, since this therapy showed dose-dependent side effects a gradual dose escalation was necessary to reduce the immediate toxicity (chills, fever and malaise).[71] Pegylated IFN-α2b has been recently introduced as a new therapeutic tool in the AIDS-KS treatment. This drug shows improved pharmacokinetic properties and a median elimination half-life of more than 30 h.[102] Clinical trials of pegylated IFN-α2b for the treatment of KS are currently ongoing.

Anti-HHV8 therapy

Inhibition of HHV8 may be useful for both treatment or prophylaxis of KS (AIDS-KS). In this regard, *in vitro* assays show that HHV8 is very sensitive to cidofovir, moderately sensitive to ganciclovir and foscarnet and weakly sensitive to acyclovir.[103,104] A recent retrospective study of patients with previously diagnosed KS who received foscarnet or ganciclovir for cytomegalovirus (CMV) infection showed a longer time to KS progression in patients receiving foscarnet than in patients receiving ganciclovir.[105] On the contrary, patients with CMV retinitis receiving oral ganciclovir had a decreased risk of developing KS, suggesting a prophylactic effect.[105,106] In several other studies, however, no correlation was found between anti-herpesvirus chemotherapy and a decreased risk of KS development.[107–109] Furthermore, although KS regression upon HAART or systemic administration of IFN-α has been shown to be associated with a decreased HHV8 load in blood and tissues,[13,110] this was not confirmed in AIDS-KS patients treated with liposomal doxorubicin.[111] Thus, it is at present unclear whether inhibition of HHV8 infection may have beneficial effects in blocking the development of the disease.

Conclusions

KS is a tumor of vascular origin, whose pathogenesis is multifactorial, including HHV8 infection and underlying immunosuppression, occurring within the setting of an abnormal milieu of inflammatory cytokines and angiogenic factors. Care for KS patients must take into account the type of KS, the extent of the tumor and the organs involved. Although various traditional therapies may be effective in patients with local or extensive disseminated KS, further advancing in understanding of the pathogenesis of KS may lead to target factors involved in the initiation and progression of the disease. Anti-angiogenic compounds designed to control or to inhibit vascular activation and proliferation demonstrated to be useful in the therapy of AIDS-related KS, and specific approaches aimed at HHV8 itself are currently under study. These therapies have several advantages compared to traditional cytotoxic agents. They are typically less toxic, produce less debilitating side effects and, combined with cytostatic agents that reduce the bulk tumor, prevent tumor regrowth. Notably, the use of HAART with at least one protease inhibitor aimed at the underlying HIV-induced immunosuppression, has been associated with a dramatic decrease in the incidence of AIDS-KS. In this regard, *in vivo* and *in vitro* preclinical studies showed that PIs are able to block directly angiogenesis, KS lesion formation and tumor growth, thus representing promising anti-angiogenic and anti-tumor compounds.

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