European Review for Medical and Pharmacological Sciences 2019; 23: 7488-7497

The treatment of Kaposi's sarcoma: present and future options, a review of the literature

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Abstract. – Kaposi's Sarcoma (KS) is an angiogenic tumor involving skin, mucosa and splanchnic organs. It is caused by Human Herpes Virus 8 (HHV8), when in the presence of other cofactors, such as an immune dysregulation. KS is particularly frequent in HIV-infected individuals. The major goals of treatment are to prevent disease progression, to reduce tumor and edema, to avoid organ compromise, and to relieve psychological stress. The importance and the high cancer risk offered by this co-infection, together with the spread of both these viruses, and the fact that angiogenesis is such an important characteristic of KS led to a lively interest in finding a definitive therapy. Most of the ongoing studies are focused on finding an application of old drugs in KS. Unfortunately, given the number of studies with different targets, it seems we are still far from completely understanding this disease and obtaining a "cure" which could be effective and safe for everyone. Further studies will hopefully offer new and definitive solutions.

Key Words:
Kaposi's Sarcoma, Human herpesvirus 8, HIV, PLWH, Angiogenesis, Treatment.

Introduction

The introduction of the combined antiretroviral therapy (cART) against the Human Immunodeficiency Virus (HIV) was followed by both positive and negative effects. A decrease of the comorbidities linked to the HIV-disease and an increase of the life expectancy for People Living With HIV (PLWH) was, as a matter of fact, accompanied by a relative increase in comorbidities linked to ageing[1-21]. Moreover, due to the increase of the life expectancy, cancer has become the first cause of death in PLWH[7]. Among the AIDS-related comorbidities, we assisted to a decrease of the so-called AIDS-defining cancers (ADCs). However, during the last few years, the increase in the numbers of late-presenters halted this positive trend, causing a recrudescence of pathologies such as the Kaposi's Sarcoma (KS)[22]. KS is an angiogenic tumor involving skin, mucosa and splanchnic organs. It is caused by Human Herpes Virus 8 (HHV8), when in presence of other cofactors, such as an immune deregulation. Its lesions are characterized by a chronic inflammatory infiltrate, and the infection with HHV8 leads to activation of cell pathways producing angiogenetic and pro-inflammatory chemokines, and it also produces proteins having a cytokine-like action. As effect or a cause of this association with immune deregulation, KS is observed almost exclusively in immune depressed hosts, with the principal sub-population involved being represented by PLWH[2,23-27]. On March 31st, 2019 we performed a systematic review of the literature regarding the link existing between angiogenesis and Kaposi's sarcoma in PLWH. We searched PubMed and Scopus applying "(angiogenesis) and (Kaposi's sarcoma)" as search terms. References of the articles retrieved were also reviewed. We limited the inclusion only to articles written in English. No age-related exclusion was performed. We identified 1314 records and, after duplicates were removed, we screened 983 of them. We excluded 689 articles by title and abstract, because they reported just one out of the two queries, and we assessed 294 full-texts for eligibility. After

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assessment, we excluded 224 full-text articles because they reported about findings that were not confirmed in more recent research. At the end of the assessment, we included in our review 70 full-text articles reporting about the importance of angiogenesis in Kaposi's sarcoma in PLWH and the treatment available targeting this stage of the cancer. The aim of this paper is to review the available literature on KS and shed light on the role of antiangiogenetic agents in PLWH.

Epidemiology

Moritz Kaposi first described the KS in 1872 as an angio-proliferative tumor of the elder, characterized by a survival not longer than 5 years[28-30]. Before the AIDS-era, it was particularly spread in Central Africa, Eastern Europe, Central Europe and Mediterranean regions[28-31].

Its distribution is similar to that of Human Herpes Virus 8 (HHV8), a gamma-herpesvirus discovered in 1994, also called Kaposi Sarcoma Herpes Virus (KSHV) to highlight its causal relationship with KS[28-32].

Since its discovery, it has become apparent that HHV8 infection prevalence is high in the general population, with child-to-child transmission being the most frequent transmission[33]. However, in PLWH, and in particular among men who have sex with men (MSM), the transmission is mainly sexual, because of the use of saliva for lubrication during sexual intercourses[28,29,31,32]. Another way of transmission, less frequent, is via blood transfusion and organ transplant. This iatrogenic transmission accounts for less than 3%, even where the seroprevalence is high[28,29]. On the other hand, the transmission via organ transplant, though infrequent, is important because of the possible onset of iatrogenic KS[28,29].

KS is a burden in PLWH. In 1997 it was estimated that PLWH were 20,000 more likely to develop KS than the general population, and this estimate was confirmed to be true in 2010, highlighting HIV as the most important cofactor in developing KS[29,32]. As a matter of fact, almost 50% of PLWH acquiring a HHV8 infection after a HIV infection develop KS.

Pathogenesis

KS, caused by HHV8, a B lymphotropic herpesvirus, with a latency/lytic reactivation lifecycle, is characterized by an intense angiogenesis[34,35].

Most of the proteins encoded by HHV8 genome are, as a matter of fact, involved in the promotion of the host cell survival and proliferation and in the upregulation of angiogenesis. Viral FLICE inhibitory protein (v-FLIP), viral cyclin (v-cyclin), the latency-associated nuclear antigen (LANA) together with non-structural HHV8 membrane proteins, such as vGPCR, K1 and K15 are only a few of the viral products that variously interact with the host[34-36]. In particular, vFLIP increases uncontrolled angiogenesis by downregulating the Sin3A Associated Protein 18/Histone Deacetylase 1 (SAP18/HDAC1) complex. SAP18/HDAC1 action is mediated by the nuclear factor kappa-light-chain of activated B cells (NF-kB) and apoptosis activation[34-36].

HHV8 genome also includes 12 MicroRNA precursor (pre-miRNA), which encode 25 microRNAs (miRNA)[35]. It has been demonstrated that miRNA, and especially miRNA-K3 and miRNA-K6-5p, interact with the host upregulating the expression of different growth factors, cytokines and pathways. Among them: Platelet-Derived Growth Factor (PDGF), Epidermal Growth Factor-like domain 7 (EGFL7), Vascular Endothelial Growth Factor (VEGF), Angiopoietin-2 (Ang-2), rapamycin (mTOR) and c-kit signaling. All these elements are involved in angiogenesis upregulation[37,38]. Upregulation of angiogenesis is important in the setting of KS and constitutes one of the fundamentals of this disease[39].

As a matter of fact, as previously hinted, KSHV interacts with the host in a number of ways, all converging in increasing the cell turnover and angiogenesis.

KS in PLWH

KS is particularly frequent in HIV-infected individuals. It is common knowledge that PLWH are affected by an increase in aberrant alternative splicing. This leads to an abnormal production of proteins and a dysregulation of the cell cycle[40].

Moreover, HIV and HHV8 variously interact, enhancing each other pathogenicity, and this is the main reason why KS incidence is so important in PLWH.

It has been demonstrated that HIV Viral Protein R (Vpr) inhibits HHV8 lytic cycle by upregulating a cellular miRNA which activates the NF-kB signaling[41]. Also HIV-Tat and HIV-Nef have been recognized to interact with HHV8 as promoters of angiogenesis and tumorigenesis[42].

The importance and the high cancer risk offered by this co-infection, together with the spread of both these viruses, and the fact that angiogenesis is such an important characteristic of KS led to a lively interest in finding a definitive therapy.

Diagnosis

KS diagnosis is mainly clinical, especially in PLWH. The patient presents with various symptoms, but their principal complains are about red-violet cutaneous lesions in the lower extremities, face, and genitalia. These lesions are typically multifocal, with the appearance of papules, patches, plaques, or nodules[30].

However, KS can also have a visceral expression, for the diagnosis of which different techniques were studied. During the first decade of the 2000 it was demonstrated that a combination of thermography, laser Doppler imaging and near-infrared spectroscopy could be useful in diagnosis, staging and follow up of KS lesions[43].

Treatment

As for other herpes viruses, an eradicating treatment for HHV-8 does not exist. This fact makes scientists question whether it is possible to cure any form of KS. So, the major goals of treatment are to prevent disease progression, to reduce tumor and edema, to avoid organ impairment, and to relieve psychological stress.

Despite KS pathogenesis and treatment have been the object of many prospective randomized trials, they did not have any effect on the management of the disease over the last 20 years[44]. cART is the pillar of KS treatment. Local therapy, radiotherapy and chemotherapy are applied on a case-severity basis. The choice is based on the rapidity of tumor growth, the extension and the number of the lesions, HIV viral load and $CD4^+$ T-cell count, the general conditions of the patient and the existence of possible drug to drug interactions[45].

Since its introduction, cART dramatically changed the KS natural history[25,46,47]. The observed decrease in incidence rates, progression of illness, visceral involvement and related mortality is likely due to an improved immune control in comparison with a pre-cART era.

cART seems to be so important that even when it is not completely successful in controlling HIV, its benefits among patients with KS are clear and independent from $CD4^+$ T-cell count and HIV-RNA plasmatic viral load[47].

Several studies tried to demonstrate a direct effect of specific antiretroviral drugs in KS. A study conducted by Pati et al[48] showed the *in vitro* effects of ritonavir (RTV), a drug belonging to the Protease Inhibitors (PIs) class. RTV inhibits the production and secretion of several inflammatory cytokines and chemokines from the endothelial cells, leading to a decreased proliferation and a stimulated apoptosis in KS cells. A similar study about PIs, performed *in vivo* on mice by Monini et al[49], showed that saquinavir and indinavir inhibits the secretion of basic fibroblast growth factor (bFGF) and VEGF. Despite these brilliant results *in vitro*, regimens containing PIs do not show superiority when compared to non-PI ones in observational studies in PLWH[50,51].

As a consequence, the onset of KS does not represent a reason for a cART regimen modification. Moreover, PI-containing regimens have the same effect on preventing KS compared to non-PI regimens[46].

Local Therapy

When a systemic treatment is not required for the severity of the disease, some options for a local treatment are available.

Vinblastine (VNB) is a natural Vinca alkaloid. It shows an antimitotic cytotoxic effect and antiangiogenetic activity even at low concentrations[52]. Typically, lesions treated with VNB regress but not resolve completely[53-55]. A different number of doses are required, according to the surface area of the lesions. For lesions larger than 0.5 cm^2, a second treatment cycle after a month is often required[53-55].

When the area affected is wide, treatment with VNB is not possible. However, before resorting to systemic therapy, a cycle of radiation therapy can represent a valid option[56-57].

Alitretinoin application is a second line option for local therapy. It showed a response *vs.* placebo of 35-37% *vs.* 7-8%[58,59].

Chemotherapy

Systemic chemotherapy should be added to cART whenever there is a progression of KS, presence of an extensive edema, massive skin involvement or symptomatic visceral involvement. Chemotherapy is also required in case of immune reconstitution inflammatory syndrome (IRIS).

Pegylated liposomal doxorubicin and liposomal daunorubicin represent the first line chemotherapeutic drugs in KS. Other agents are vinblastine, bleomycin, paclitaxel, vincristine and etoposide[60]. Most of these drugs are currently under investigation in clinical trials, in various combinations between them (Table I).

First Line

Pegylated liposomal doxorubicin and liposomal daunorubicin represent the first choice in

Table I. Current Clinical Trials for Kaposi's Sarcoma.

Study title	Status	Study phase	NCT ID	Drugs
Pomalidomide in Combination With Liposomal Doxorubicin in People With Advanced or Refractory Kaposi Sarcoma	Recruiting	Phase 1	NCT02659930	Liposomal doxorubicin/ pomalidomide
sEphB4-HSA in Treating Patients With Kaposi Sarcoma	Recruiting	Phase 2	NCT02799485	Recombinant EphB4-HSA Fusion Protein
Nivolumab and Ipilimumab in Classical Kaposi Sarcoma (CKS)	Recruiting	Phase 2	NCT03219671	Nivolumab/Ipilimumab
An Evaluation of Tc 99m Tilmanocept by Intravenous (IV) and Subcutaneous (SC) Injection in Kaposi Sarcoma (KS)	Recruiting	Phase 1	NCT03157167	Tc99m-tilmanocept
Nelfinavir Mesylate in Treating Patients With Kaposi Sarcoma	Recruiting	Phase 2	NCT03077451	Nelfinavir Mesylate
Pomalidomide for Kaposi Sarcoma in People With or Without HIV	Active, not recruiting	Phase 1/ Phase 2	NCT01495598	Pomalidomide
Investigating Chemotherapy Treatments, Response and Subsets of HIV-associated Kaposi Sarcoma in Malawi	Recruiting		NCT03160183	ART (different regimens)
Evaluating Quality of Life in Patients With AIDS-Associated Kaposi Sarcoma Treated With Bleomycin and Vincristine	Recruiting	Phase 1	NCT03596918	Bleomycin Sulfate/Vincristine Sulfate
Compression Therapy for Leg Ulcers and Kaposi Sarcoma in Western Kenya	Recruiting	Not Applicable	NCT03404297	
Intra-lesional Nivolumab Therapy for Limited Cutaneous Kaposi Sarcoma	Recruiting	Early Phase 1	NCT03316274	Intra-lesional injection of nivolumab
Valganciclovir Four Weeks Prior to cART Initiation Compared to Standard Therapy for Disseminated Kaposi Sarcoma	Active, not recruiting	Phase 2	NCT03296553	Valganciclovir/ART
Phase II Multicentric Study of Pembrolizumab in Classic or Endemic Kaposi's Sarcoma	Recruiting	Phase 2	NCT03469804	Pembrolizumab
Antiretroviral Therapy (ART) Alone or With Delayed Chemo Versus ART With Immediate Chemo for Limited AIDS-related Kaposi's Sarcoma	Active, not recruiting	Phase 3	NCT01352117	Etoposide and efavirenz/emtricitabine/ tenofovir disoproxil fumarate
Tocilizumab for KSHV-Associated Multicentric Castleman Disease	Recruiting	Phase 2	NCT01441063	Zidovudine/Tocilizumab/Valganciclovir
History of the KSHV Inflammatory Cytokine Syndrome (KICS)	Recruiting	Phase 2	NCT01419561	Zidovudine/Liposomal Doxorubicin/ Valganciclovir/Rituximab
Virotherapy and Natural History Study of KHSV-Associated Multricentric Castleman s Disease With Correlates of Disease Activity	Recruiting	Phase 2	NCT00092222	Etoposide/Interferon-alpha/Rituximab/ Zidovudine/Liposomal Doxorubicin/ Bortezomib/Valganciclovir/Vincristine/ Cyclophosphamide/Filgrastim (G-CSF)/ Prednisone/Sirolimus
Nivolumab and Ipilimumab in Treating Patients With HIV Associated Relapsed or Refractory Classical Hodgkin Lymphoma or Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery	Recruiting	Phase 1	NCT02408861	Ipilimumab/Nivolumab
Pembrolizumab in Treating Patients With HIV and Relapsed, Refractory, or Disseminated Malignant Neoplasms	Recruiting	Phase 1	NCT02595866	Pembrolizumab
Nivolumab With or Without Varlilumab in Treating Patients With Relapsed or Refractory Aggressive B-cell Lymphomas	Recruiting	Phase 2	NCT03038672	Nivolumab/Varlilumab
Phase II Multicentric Study of Digoxin Per os in Classic or Endemic Kaposi' s Sarcoma	Recruiting	Phase 2	NCT02212639	Digoxin
Alpha Radiation Emitters Device for the Treatment of Cutaneous, Mucosal or Superficial Soft Tissue Neoplasia (DaRT)	Recruiting	Not Applicable	NCT03737734	Radiation: Diffusing Alpha Radiation Emitters Therapy (DaRT)
Study to Evaluate Safety and Tolerability of XmAb13676 in Patients With CD20-expressing Hematologic Malignancies	Recruiting	Phase 1	NCT02924402	XmAb13676

case of systemic chemotherapy. Both achieve the goal of decreasing edema and cancer volume. Moreover, they improve the typical KS hyperpigmentation with a response rate of 30-60%[61-64].

In a double-blind comparison between these two liposomal anthracyclines both tumor responses and clinical benefits were better in the doxorubicin arm[65]. Side effects are usually mild in comparison with conventional combination chemotherapy regimens[64,66].

Taxanes are a family of chemotherapeutic agents, which act disrupting the microtubule function and cellular division. They showed promising results in KS.

In particular, paclitaxel demonstrated a great efficacy in KS. Compared to other drugs of the same family, paclitaxel is able to downregulate angiogenesis acting on different pathways. Its first effect on the microtubules leads to a decrease of cell proliferation, motility and migration. Paclitaxel also downregulates both VEGF and Angiopoietin-1 (Ang-1), and upregulates thrombospondin-1 (TSP-1)[67]. Thus, paclitaxel is a valid second line alternative to liposomal anthracyclines or even the first choice in selected cases[68-71]. However, paclitaxel high toxicity limits its use[68-71].

Docetaxel and cabazitaxel are other taxane drugs able to downregulate angiogenesis. However, their most common adverse effect is severe neutropenia and their use is not suggested in PLWH suffering from KS. Two important limitations in taxanes use are the necessity of premedication with glucocorticoids (not ideal for already immunosuppressed patients) and their metabolization through cytochrome P450.

Second Line

In case of failure of a first line treatment or when drug-drug interactions make their use difficult (i.e. paclitaxel and ritonavir) few second line options are available. Among them, the most used are etoposide[72,73] (once daily and oral dose), vinorelbine[74,75] (active even after first line treatment failure) and interferon-alfa[76] that has been tested in association with zidovudine[77].

Other Targets

Angiogenesis

Inhibitors of mTOR pathway, such as temsirolimus and rapamycin have been studied in the last years for the treatment of KS[38,78-81]. Following the observation that patients who experienced KS after transplant and have been treated successfully with rapamycin, this drug was applied in HIV-related KS obtaining only a partial success[82-83].

VEGF could be a target for KS treatment[84,85]. Bevacizumab, a monoclonal antibody against VEGF, showed a complete or partial response in 29% of the cases in a phase II study. Moreover, it results in stable disease in 64% of the cases[86]. Anti-VEGF/VEGFR therapy is not currently used in KS.

Imatinib, an inhibitor of the PDGF and c-kit receptors, has been studied in a multicenter phase II trial[37-87]. It showed a partial response in 33 %, with an acceptable toxicity profile[87].

Fumagillin and thalidomide were studied in KS setting because of their known action on angiogenesis. However, their toxicities and lack of prolonged controls put them on the back burner[88-92].

Sorafenib, a VEGF, angiogenesis and tyrosine kinase inhibitor, has been studied in a phase Ib trial (NCT00287495). The importance of this study was in pointing out that most of the anti-angiogenic drugs were CYP3A4 inhibitors, with negative drug-drug interactions with cART[93].

PTC299 is an inhibitor of VEGFA mRNA translation showing promising results in a phase Ib trial (NCT00686842)[94]. In three patients a partial response was observed and in eleven the disease did not progress. Notably, no differences by cART regimen were observed and the patients did not experience the typical VEGF-inhibitors adverse effects (bleeding, renal vascular injury, hypertension). Unfortunately, the redundancies in the VEGF feedback pathway implicates that PTC299 should be combined with other antiangiogenetic agents to be effective.

HHV-8

Even if HHV-8 has been clearly identified as the etiologic agent of KS, there is no drug capable of its complete eradication.

Drugs used for the management of infections caused by other herpes viruses, like *ganciclovir* (and its prodrug *valganciclovir*), *foscarnet* and *acyclovir*, have been evaluated in HIV patients with KS[95-97]. All of them showed anti-HHV-8 activity, except for acyclovir. However, all these studies were carried out on patients treated with different cART regimens and under treatment for other HIV-related infections or complications.

The most robust data in our opinion are the ones on ganciclovir, which showed to reduce the risk of KS by 75-93% when compared with placebo[97].

Conclusions

Given the suboptimal results obtained so far with targeted therapies, a future combined approach should be considered. Table I resumes the currently active clinical trials. It is clear, from what we stated before and what is shown in the table, that targeting just one pathway of angiogenesis is not the right choice. As a matter of fact, the research is currently focused on finding the most effective combination of antiretrovirals, anti-HHV8 drugs and chemotherapeutic agents with the smallest burden in terms of toxicity for the patient.

Most of the ongoing studies are focused on finding an application of old drugs in KS. We can see how the efforts rotate around evaluating the efficacy of classic chemotherapeutic agents such as doxorubicin and bleomycin, two antimicrobials, and etoposide, a Topoisomerase II inhibitor, in new therapeutic combinations with antiretrovirals of every class (nelfinavir, efavirenz/emtricitabine/tenofovir disoproxil fumarate, zidovudine).

The interest in monoclonal antibodies is also definitively high. These drugs can effectively target specific pathways, leading to a combined block of an aberrant function. A lot of drugs are already available on the market and are currently been tested for their efficacy in the KS landscape.

A particular attention should be given to the studies regarding pomalidomide, a thalidomide derivative with an anti-angiogenic activity, bortezomib, a proteasome inhibitor, also with an anti-angiogenic activity, and sirolimus, or rapamycin, an antimicrobial with known effectiveness in Castleman's Disease, a hematologic disease also related to HHV8.

Unfortunately, given the number of studies with different targets, it seems we are still far from completely understanding this disease, obtaining a "cure" which could be effective and safe for everyone. Further studies will hopefully offer new and definitive solutions.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

The authors did not receive funds for this research.

Authors' Contribution

MC, AF and EVR searched the literature; MC, AF, MB, GFP, GN and EVR independently assessed the full-text articles; MC, AF and EVR wrote the article; GN and EVR reviewed the manuscript. All the authors read and accepted the final manuscript.

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