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HIV-Associated Kaposi's Sarcoma

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Summary
Kaposi's sarcoma (KS) is still one of the most common malignancies in patients with human immunodeficiency virus (HIV) infection. Large randomized clinical trials have shown a protective effect of combination antiretroviral therapy (cART) against the development of KS, even in patients with a relatively preserved immune system. In patients with sufficient cART, KS has become a rarity. In most patients with HIV-associated KS who initiate cART, the KS lesions stabilize with decreasing HIV plasma viremia and immune reconstitution, or even resolve completely without any specific treatment. In patients with advanced or rapidly progressive disease, especially in the setting of an immune reconstitution syndrome, cART should be combined with cytotoxic chemotherapies. With regard to the KS pathogenesis, several new therapies have been suggested, such as antiviral agents, cytokines, and inhibitors of angiogenesis.

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Introduction

Kaposi's sarcoma (KS) is still one of the most common malignancies in patients with human immunodeficiency virus (HIV) infection. In 1981, the simultaneous occurrence with *Pneumocystis* pneumonias in young men who have sex with men (MSM) led to the first descriptions of the acquired immunodeficiency syndrome (AIDS). This entity is named after the Hungarian dermatologist Moritz Kaposi who first described the 'classical' KS in 1872. In contrast to the classical KS, the HIV-associated KS may affect the whole skin and mucous membranes. Lymph nodes and internal organs such as stomach, gut, lung, or liver may also be involved. The progression of the disease is highly variable and reaches from small lesions that remain stable for many years to extremely aggressive courses, in which progression may lead to death within a few months.

Compared to the 1980s and early 1990s, the KS incidence in Western countries has seen a sharp decline to less than a tenth of what it was. Measured at 5 years after AIDS onset, the cumulative incidence of KS in the USA declined from 14.3% in 1980–1989, to 6.7% in 1990–1995, and to 1.8% in 1996–2006 [1]. Similar trends were seen in Europe [2]. With the introduction of combination antiretroviral therapies (cARTs), the clinical course of KS has also markedly changed. Refractory variants with an aggressive, devastating and often fatal course, which were frequently seen in the pre-cART era, have become a rarity today. However, some very aggressive cases still occur, typically as an immune reconstitution inflammatory syndrome (IRIS) only a few weeks or months after cART initiation. This IRIS-associated KS often comes with rapid visceral lesions and high mortality and seems to occur mainly in patients with high human herpesvirus (HHV)-8 and high HIV viremia [3].

Pathogenesis and the Role of HHV-8

KS is characterized by abnormal neoangiogenesis, inflammation, and the proliferation of tumor cells that are now known to be of endothelial cell origin, phenotypically most similar to lymphatic endothelial cells, but poorly differentiated (for a review, see [4]). It is well known that KS is induced by infection with HHV-8, also known as KS-associated herpesvirus (KSHV). This human γ-herpesvirus was discovered in 1994 by Yuan Chang and Patrick Moore [5]. HHV-8 can always be detected in the tumor tissue. The exact role of HHV-8 in the pathogenesis of KS is not fully understood, and infection with HHV-8 does not inevitably lead to KS.

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Through manipulation of endothelial cell-specific transcriptional regulators, HHV-8 infection may contribute to viral persistence and the genesis of KS.

Transmission of HHV-8 occurs predominantly via saliva, but also sexually, vertically and via blood products [6]. In some regions, particularly in Italy and Central Africa, HHV-8 can be found in up to 50% of the general population. Among the HIV-infected population in Western countries, men who have sex with men (MSM) are almost the only ones affected by KS; in HIV-infected women, children, or hemophiliacs in Europe or the USA, KS is a rare disease. Immune defects, immunosuppression, and/or low CD4 T cell counts promote the emergence and growth of KS. However, severe immunodeficiency is not a prerequisite for KS development. It is one of the few AIDS illnesses occurring in patients with a relatively preserved immune status. Approximately 29% of all patients who participated in KS studies in the USA in the years 1996–2007 had more than 300 CD4 T cells/μl and an HIV plasma viremia below detection [7]. Of note, HHV-8 viremia is prevalent only in a subset of cases. In an analysis of 335 patients with HIV-associated KS, only 130 (39%) were viremic and the mean HHV-8 viral load was only moderate with 6,630 DNA copies/ml, which was markedly lower than in patients with multicentric Castleman disease [8].

Symptoms, Diagnosis, and Staging

HIV-associated KS does not have a preferential pattern of localization. The disease can begin on any area of the skin, but may also appear on oral, genital, or ocular mucous membranes. Typical findings at manifestation are a few asymptomatic purple macules or nodules. These lesions have a predilection for distribution along relaxed skin tension lines. As mentioned above, the disease progression is highly variable: The tumors can remain unchanged for months or years, or they may grow rapidly within a few weeks and disseminate. Rapid growth can lead to localized pain and a yellow-green discoloration of the area around the tumor as a result of hemorrhage. Further progression of the tumor can lead to central necrosis and ulceration. The tumors may bleed easily. Plaque-like and nodular KS lesions often become confluent and can be accompanied by massive lymphedema. In the oral cavity, the hard palate is frequently affected. Lesions begin with purplish erythema and progress to plaques and nodules that ulcerate easily. KS lesions may also involve the external genitalia including the foreskin and glans penis.

Regression of KS during treatment is not only indicated by a reduction in lesion size but also by changes in color from dark to bright red. However, some lesions may persist for life. These often dirty-grey-brown to light brown hyperpigmentations are the result of hemosiderin and/or melanin deposits, which are caused by increased stimulation of melanocytes due to inflammation. Lymphedema can also persist for years and may lead to chronic complications.

The diagnosis of cutaneous KS is usually based on visible clinical findings. However, in all questionable cases, a histologic diagnosis is recommended. Differential diagnosis includes other neoplasias such as cutaneous lymphomas or angiosarcoma, but also infectious diseases such as syphilis and bacillary angiomatosis and dermatological diseases like erythema elevatum et diutinum. Histological findings in KS include spindle-shaped cells with vascular channels lined by abnormal endothelial cells assembled like a catch of fish. Extravasated erythrocytes, hemosiderin, and fibrosis can often be seen.

In all cases of KS, clinical staging procedures should be considered. Staging of KS include a complete inspection including oral and genital mucous membranes, an abdominal ultrasound, and a chest radiography (exclusion of a pulmonary KS). Gastroduodenoscopy and colonoscopy should be considered when mucous membranes are involved. Measuring the plasma levels of HHV-8 as a biomarker in KS has a very limited value in either diagnosis or prognostication [8].

There is no widely accepted staging system. The AIDS Clinical Trial Group (ACTG) staging system for AIDS-related KS, which was developed in the pre-cART era to predict survival, includes tumor-related criteria, the host immunologic status, and the presence of systemic illness. This ACTG staging system is no longer valid as prognostic tool for KS patients because the resulting grades are usually good in cART-treated patients. For example, in a large study from the UK, only 15 of 469 HIV-infected patients who were diagnosed for the first time with KS since 1998 died as a result of KS [9]. In our own retrospective cohort of 230 KS cases diagnosed between 2000 and 2014 in 3 German HIV centers, only 5 deaths could be attributed to KS [10]. Recently, T staging has been proposed as the basis for treatment planning (see below). Whereas T0 represents limited disease, T1 stage disease is defined as the presence of tumor-associated edema or ulceration, or extensive oral or gastrointestinal (GI) KS or other non-nodal visceral KS [9].

KS and cART

Large randomized clinical trials have shown a protective effect of cART against the development of KS, even in patients with a relatively preserved immune system. In the START trial, in which 4,685 HIV-positive participants with CD4 counts > 500/μl were randomized either to start cART immediately or to defer therapy until the CD4 count dropped below 350 cells/μl, the reduced risk of infection-related cancer in the immediate arm was mainly driven by a reduction in KS incidence [11]. Similar results were seen in the SMART trial, in which patients on a CD4 T cell-guided cART strategy had a higher incidence of KS lesions during treatment interruptions than patients on continuous cART [12]. Recent data from large European cohorts suggest that, in patients initiating antiretroviral therapy (ART), both the incidence and the risk factors for KS change with time since starting cART. The incidence rate per 100,000 person-years was highest 6 months after starting cART, at 953 (95% confidence interval (CI) 866–1,048), declining to 82 (95% CI 68–100) after 5–8 years. Whereas a low CD4 cell count was the dominant risk factor soon after starting ART, a detectable HIV-1 RNA viral load became an increasingly important

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Table 1. Specific and systemic therapies for KS

Therapy	Dosage	Comments
Pegylated liposomal doxorubicin (Caelyx™ or Doxil™)	20 mg/m² i.v. every 2 weeks	treatment of choice, beware of myelotoxicity, cardiotoxicity, hand-foot syndrome
Liposomal daunorubicin (DaunoXone™)	40 mg/m² i.v. every 2–3 weeks	possibly slightly less effective than Caelyx™, considered as alternative
IFN-α 2a (Roferon™)	3×10^6–6×10^6 IU s.c. or i.m. 3 times/week	considerable side effects, lower efficacy than with doxorubicin; use only when CD4 T cells are > 200/μl and limited disease
Pegylated IFN-α 2b (PegIntron™)	50 μg s.c. weekly	tolerability improved compared to conventional IFN-α (2a, 2b), but lack of data in AIDS KS, off-label use
Paclitaxel (Taxol™)	100 mg/m² i.v. every 2 weeks or 135 mg/m² i.v. every 3 weeks	beware of neutropenia, peripheral neuropathy, allergic reactions, alopecia; off-label use (!); caution with ART interactions

KS = Kaposi's sarcoma, IFN = interferon, i.v. = intravenously, IU = international unit, s.c. = subcutaneously, i.m. = intramuscularly, AIDS = acquired immunodeficiency syndrome, ART = antiretroviral therapy.

risk factor in patients who had started cART several years earlier, independently of immunodeficiency [13]. In our own cohort of 230 patients, only 10% developed KS while on current cART, among them only 4% with an HIV RNA level of less than 50 copies/ml [14]. In the prospective cohort study from the UK, the corresponding proportions were 18% and 9%, respectively [9].

If KS is newly diagnosed in an HIV-infected patient naive to ART, cART should be initiated. In patients on cART without complete suppression of HIV plasma viremia, the regimen should be optimized. With decreasing HIV plasma viremia and immune reconstitution, many KS lesions stabilize or even resolve completely without any specific treatment. The resolution with cART may take several months and generally follows the recovery of host cell-mediated immunity. Sustained complete remission of the KS lesions is achieved in the majority of the cases. Among 213 cART-naive patients with early KS stages who were treated with cART alone, the overall survival at 5 years was 95%, while the progression-free survival was 77% [9].

Animal and in vitro experiments have suggested a direct antiproliferative effect of protease inhibitors (PIs) [14]. There is some evidence that PIs may reduce oral shedding of HHV-8 [15] and that KS incidence is reduced with longer PI use [16]. However, despite some biological plausibility, other studies have suggested that non-PI-based regimens are equivalent to PI-based regimens regarding the clinical and virological outcome of antiretroviral-naive HIV-infected patients with KS [17]. The only randomized study to date on 224 patients in Uganda found no evidence that PI-containing regimens were superior to other antiretroviral regimens in terms of survival or need for chemotherapy among patients with KS who did not initially have urgent chemotherapy indications [18].

Chemotherapy and Immunotherapy

In patients with rapidly progressing disease (especially in the setting of an IRIS), with KS-related symptoms, or with visceral disease or lymphedema, cART should be combined with cytotoxic chemotherapy (table 1). Prognosis is good even in advanced disease. For 140 patients with T1 disease who were treated with cART and liposomal anthracycline chemotherapy, the 5-year overall survival was 85% [9].

Although the overall quality of evidence toward a specific chemotherapy is only moderate, most guidelines in Western countries recommend pegylated liposomal doxorubicin hydrochloride (Caelyx® or Doxil®) at a dosage of 20 mg/m² body surface every 2 or 3 weeks as the treatment of choice. Complete remission rates of up to 80% are possible [19–21]. The infusions every 2–3 weeks are feasible on an outpatient basis and are usually well tolerated. Usually 6–8 cycles are required to achieve a good clinical response. During treatment, myelotoxicity and cardiotoxicity of doxorubicin should be considered. Although the latter is rare and occurs only above cumulative doses of 450 mg/m² body surface, echocardiography is recommended at the beginning of therapy, as well as controls after 6 cycles. Data on long-term safety is limited.

Liposomal daunorubicin (DaunoXome®) is an alternative to pegylated liposomal doxorubicin. However, according to a small randomized study that was not sufficiently powered, it appears to be slightly less effective than pegylated liposomal doxorubicin [21]. Another option is paclitaxel, which has shown similar response rates in a small randomized trial on patients with advanced KS [22]. However, paclitaxel is more myelotoxic and almost always leads to complete alopecia, often during the very first cycle. It should also be mentioned that significant interactions may exist and that paclitaxel levels may increase significantly when combined with PIs. A 2-weekly regimen of vincristine 1–2 mg and bleomycin 10 IU/m² may also induce response in many patients and, despite higher toxicity rates, remains an effective treatment option in countries with limited financial resources [23].

As the widespread introduction of cART has markedly increased the rates and duration of responses to KS treatment, no large randomized trials have compared liposomal anthracyclines with other regimens such as taxanes. According to a recent Cochrane review, for patients on cART, when choosing from different chemotherapy regimens, there was no observed difference between liposomal doxorubicin, liposomal daunorubicin, and paclitaxel [24].

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Beside chemotherapy, an immunotherapy with interferons (IFNs) can be considered. IFN-α was one of the first agents to be used therapeutically in AIDS-associated KS. The mechanism of effect of IFN on KS is not fully clarified and the rates seem to be lower than with pegylated liposomal doxorubicin [25]. Apart from an immune-modulating effect, IFN probably induces apoptosis in KS cells. Effectiveness strongly depends on the immune status. In patients with > 400 CD4 T cells/μl, the remission rates achieved with IFN are at least 45%, compared with only 7% in patients with < 200 CD4 T cells/μl. There are currently no standardized IFN treatment regimens. Due to the considerable side effects of IFN, low doses of 3–6 million IU subcutaneously are usually given. After remission, dosing can be reduced to 3 times per week. Remission can be expected after 6–8 weeks of treatment. There is not sufficient data on the use of pegylated IFN in case of HIV-associated KS. It is not licensed for KS and the optimal dosage is unknown. However, there are some promising case reports on AIDS patients [26].

Local Therapy for KS

Local therapy is usually well tolerated and less costly. Many different methods are used depending on the size and location of the tumors: cosmetic camouflage, cryosurgery, intralesional injections of *Vinca* alkaloids or IFNs, soft X-ray radiation, electron beam therapy, cobalt radiation (fractionated), alitretinoin gel, or imiquimod [27]. Compressive therapy with elastic stockings may be an important strategy in the treatment of KS-associated lymphedema [28].

As KS is a multifocal systemic disease, surgical treatment is limited to excisional biopsies for diagnosis and palliative removal of small tumors in cosmetically or functionally disturbing areas. Since tumors often extend further into the surroundings than is clinically visible and local trauma can lead to new tumors (the Koebner phenomenon); local and regional recurrences can be expected. These can be prevented by radiation therapy: In order to reach the tumor cells spreading along the vascular channels, the field of radiation should be extended 0.5–1.0 cm beyond the edges of the tumor. KS is a strikingly radiosensitive tumor [29]. Superficial macular or plaque-like KS lesions respond well to daily doses of 4–5 Gy (total dose 20–30 Gy, fractionated 3 times/week) of soft X-ray radiation. In the case of large KS lesions with lymphedema, radiation with fast electron beams can be considered and manual compression lymphatic massage should be initiated as soon as possible.

New Therapeutic Approaches

A large number of new targeted therapies for KS are under investigation. With regard to the KS pathogenesis, several new therapies have been suggested, such as virustatic agents, cytokines, and inhibitors of angiogenesis. The most promising virustatic agent is valganciclovir, which significantly reduces HHV-8 replication, as shown in a randomized trial [30]. However, there are no data on its clinical efficacy in AIDS-related KS published to date. As HHV-8 is involved in the early steps of KS pathogenesis, it is questionable if valganciclovir has any effect on manifest lesions. In patients with classical KS, the drug remained inefficient [31]. For lenalidomide, an immunomodulatory drug with antiangiogenic effects, a number of encouraging case reports exist [32, 33]. There is an ongoing US phase I/II trial to evaluate the efficacy and tolerance of lenalidomide in HIV-related KS with and without visceral involvement. Sirolimus and everolimus may inhibit tumor angiogenesis through impaired vascular endothelial growth factor (VEGF) production. Good response rates were seen in uncontrolled studies on HIV-negative renal transplant recipients with KS [34]. As VEGF-A contributes to KS pathogenesis, the humanized anti-VEGF-A monoclonal antibody, bevacizumab, was evaluated in patients with HIV-KS. In an early study, moderate response rates were seen in 31% of 17 HIV-positive patients with KS progression on cART [35]. A study of combination with liposomal doxorubicin is ongoing. Further encouraging data from phase II studies exist for imatinib and for topical halofuginone [36, 37].

Disclosure Statement

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