Kaposi's Sarcoma Epidemiology, Risk Factors, Staging and Treatment: AN OVERVIEW

Kaposi Sarkoma Epidemiyolojisi, Risk Faktörleri, Evrelemesi ve Tedavi Seçenekleri: DERLEME.

Yusuf Karakaş[1], Sercan Aksoy[1], H. İbrahim Güllü[1]

Hacettepe Üniversitesi Onkoloji Enstitüsü, Medikal Onkoloji Bilim Dalı, Ankara

ÖZET

Kaposi sarkomu immun disfonksiyon ve muhtemel viral etiyolojiye bağlı oluşan anjioproliferatif bir hastalıktır. Kaposi sarkomu etiyolojilerine göre 4 alt tipe ayrılır. Hastalığın tedavi seçenekleri ve klinik seyri açısından alt tipler bizlere fikir verir. Ülkemizde ve dünyada nadir görülen bir hastalık olması nedeniyle şu an için randomize kontrollü çalışmaları bulunmamaktadır. Kaposi sarkomundaki bilgilerimiz genelde retrospektif ve faz II çalışmalara dayanmaktadır. Bu derlememiz kaposi sarkomunun epidemiyolojisi, risk faktörleri ve son tedavi stratejileriini içermektedir.

Anahtar Kelimeler: Kaposi sarkomu, risk faktörleri, tedavi

ABSTRACT

Kaposi's sarcoma (KS) is an angioproliferative disease, with a viral etiology and a multifactorial pathogenesis that depends on an immune dysfunction. It is divided into four types according to the aetiology. There was no randomized controlled trials due to very rare disease. Thus clinical guidelines has not been established properly. This review summarized epidemiology, risk factor, and recent treatment strategies in Kaposi sarcoma patients.

Keywords: Kaposi sarkoma, risk factors, treatment

History and Classification

Moritz Kaposi (1827-1902), a Hungarian dermatologist, gave his name to disease who described three fatal cases of multiple idiopathic pigmented hemangiosarcoma in old men at the University of Vienna in 1872 . KS is rare disease. The most of the cases seen in Europe, North America, African young – children, renal allograft recipients, receiving other immunosuppressive agents, and HIV infected patients[1].

Kaposi Sarcoma Classification: After the definition provided be Dr. Kaposi, clinicians have defined four different types.

Classic Type: This type originally described by Kaposi, is typically found in old Mediterranean men, it has been diagnosed worldwide and usually follows a benign course.

Endemic Form (African): Occurs more often among african men aged 25 to 40 years and children of both sexes, the mean age of the affected children is 3 years [2].

Iatrogenic type: This is associated with immunosuppression such as organ transplant recipients, long time corticosteroid using for various disorder, and patients immunosupressed as a result of any therapeutic regimens, including chemotherapy [3, 4].

Epidemic type (HIV-associated): An epidemic of KS appeared among young men who had sex with men in developed countries. Also heterosexual men and women may have KS in Africa[5].

The different epidemiologic and clinical aspects of these four types are summarized in the table 1.

Table 1: Clinical aspects of Kaposi sarcoma types.

Type	Predominant risk groups	Cutaneous presentation	Visseral involvement	Clinical course
Classic (sporadic)	3:1 male:female ratio Age>60 years Mediterranean, Eastern European or Middle East	Distal lower extremities	Uncommon	Usually indolent, Rarely aggressive or disseminated
Endemic (African)	Male adults, Children both sexes Equatorial Africa	Various: may be similar to classic or more locally aggresive, lower extremity lymphedema in adults. Cutaneous disease often absent in clildren	Internal organs involved in a subset of adults. But common in children especially lymp nodes and viscera.	Indolent to locally invasive in adults Occasional rapid progression with visceral disease in adults Aggresive in children
Iatrogenic	Exogenous immunosuppression, solid organ transplantation, steroid using Older age>50 years	Distal lower extremities, may be disseminated	Relatively common	May regress with modification of immunosuppression May be aggresive
Epidemic (AIDS-associated)	Men who have sex with men (developed countries) heterosexual men and female in Africa	Localized or disseminated	Common with poor HIV control	Aggresive or indolent May regress with effective HIV treatment

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Risk Factors:

Human Herpes Virus 8 (HHV-8): Is a gamma herpes virus associated with Kaposi sarcoma, multicentric Castleman disease, and primary effusion lymphoma, lymphoproliferative disease that are most commonly observed in immuncompromised individuals [6]. HHV-8 has been detected more than 95% of patients for all types of KS [7]. HHV-8 found in body secretions such as saliva and semen, may spread through kissing or sexual intercourse, similarly with other herpesviruses [8]. HHV-8 is a oncogenic DNA viruses, expresses viral genes that perturb p53 protein function and thereby mediate viral oncogenesis[9].

Also anti- HHV antibodies and viremia may be important for KS. A comparison of age and sex-matched HHV-8 infected Italians with and without Classic KS showed that HHV-8 DNA detection in peripheral blood mononuclear cells and high HHV-8 lytic and latent antibody titers were significantly associated with development of classic KS [10]. More recently, it has been suggested that a certain subtype of HHV-8, strain A, may be associated with higher blood viral loads and more aggressive disease behavior than strain C, which was associated with slowly progressive disease [11].

But not all infected persons develop the disease. For example, in the Mediterranean area, Classic KS develops annually in only 0,03% of HHV-8 infected men and only 0,01% of HHV-8 infected women over age 50 [12].

Other findings suggest that host genetic factors may affect the risk of Classic KS at least in part by influencing the ability to develop antibodies to HHV-8 and ultimately, control HHV-8 infection [13]. In the recent data, all types of KS have a common etiology in HHV-8 infection but all HHV-8 infected persons do not have disease due to different genetic, immunologic and environmental factors [14].

Immune Deficiency: The role of immunosuppression is well defined in iatrogenic and HIV-associated types. KS prevalence is higher in post-transplant and AIDS patients, being 500 times and 20.000 times, respectively, greater than in the general population [14]. However, there is evidence that more subtle degrees of immune suppression may be present in people with Classic KS. The significant decrease in the number of total and B-lymphocytes has been linked to progression of Classical KS from early stages to more advanced disease [15]. Also an increased risk of Classic KS has been reported among individuals with history of topical corticosteroid use (OR 2,73, 95% Cl 1,35-5,51)[13]. This suggests that local perturbations in cutaneous immune function may be an important predisposing factor for Classic KS.

Local immunodeficiency is another cause of KS. In endemic KS, there is relationship between KS and podoconiosis (non-filarial elephantiasis) [16]. Also a body region where there is chronic lymph stasis leads to an immune stasis. The link between the impairment of lymph circulation and regional immune dysfunction in classical KS was first proven in 1984 [17].

Environmental factors: Related to skin hygiene or skin disease may influence the development of KS. Also in endemic KS, walking barefoot on volcanic soils exposes pores and sweat glands in bare feet permitting abrasions and allowing alumino silicates and possibly iron oxides to be taken up by lymphatics. The silicates can cause an obstacle to lymph flow, inflammation of regional lymph nodes, and disruption of the immune control in the feet and legs [16].

Miscellaneous: There is a statistically significant reduction in KS risk among smokers [18], particularly those with more intensive (more packs per day) and more cumulative (more pack-years) history of tobacco abuse [18-20]. It has been suggested that the protective effect of smoking may be mediated by a decrease in the production of inflammatory cytokines [13, 16, 17].

A case control study documented a 3.65-fold increased risk of Classic KS among patients with chronic edema of lower extremities, and among those with diabetes mellitus (OR 4,73) [19].

CLINICAL FEATURES

Cutaneous KS: Although KS can involve any site in the body, cutaneous disease is most common and is the usual initial presentation of KS. Lesions of KS appear most often on the lower extremities, face (especially the nose), oral mucosa, and genitelia. The dermatology literature contains reference to at least 10 different morphologic variants of the cutaneous lesions of KS [21]. KS is characterized by the appearance of purplish, reddish blue or dark brown-black macules, plaques and nodules on the skin. Noduler lesions may ulcerate and bleed easily. The lesions are not painful or pruritic and usually do not produce necrosis of overlying skin or underlying structures. The skin lesions range in size from very small to several centimeters in diameter, and they can remain unchanged for months to years, or grow rapidly within a few weeks and disseminate.

Visceral KS: KS involvement has been observed in almost all visceral sites, including lymph nodes, the liver, pancreas, heart, the testes, bone marrow, bone and skeletal muscle [22, 23]. The most frequent sites of non-cutaneous disease are the oral cavity, gastrointestinal tract, and respiratory system. However, visceral involvement as the initial manifestation of KS is relatively uncommon. Also, now visceral disease appears to be much less frequent in HIV-associated KS that receive anti-retroviral therapy [24].

Oral cavity involvement occurs in KS. The intraoral site most commonly affected is the palate and gingiva [25]. Intraoral lesions are easily injured which can result in pain, bleeding, ulceration, or secondary infection.

Gastrointestinal tract involvement may be asymptomatic or may cause weight loss, abdominal pain, gastrointestinal bleeding, and diarrhea [26, 27]. Gastrointestinal KS lesions are typically hemorrhagic nodules and they may occur in any portion of the gastrointestinal tract [22]. However biopsies may not demonstrate KS because the lesions tend to be submucosal.

Pulmonary involvement is common in epidemic (AIDS-associated) KS. The affected patients may have the symptoms of dyspnea, fever, cough, hemoptysis, chest pain or may be asymptomatic. The radiological findings are variable and can include nodular lesion, interstitial infiltrates, pleural effusion, hilar and mediastinal adenopathy.

Diagnosis: Presumptive diagnosis of KS can often be made based upon the characteristic appearance of, purplish, reddish blue, dark brown patches, plaques or nodules. This should be confirmed by a biopsy whenever possible. The microscopic features of all four different types of Kaposi sarcoma do not differ. All forms show evidence of angiogenesis, inflammation and spindle cell proliferation. In addition to observing typical histological features on standard microscopy, PCR (polymerase chain reaction) can be performed on the skin lesions to detect amplified HHV-8 DNA sequences, and immunohistochemical staining of biopsy specimens can also be performed to detect the presence of HHV-8 latency-associated nuclear antigen (LANA-1) within the spindle cells, thus confirming the diagnosis [28].

Staging: There is no commonly used or universally agreed upon staging system for KS. The American Joint Committee on Cancer TNM staging system, which is the standard staging for all cancer types, does not include KS. But in contrast to HIV associated KS, the most commonly utilized staging system for HIV associated KS was developed by the AIDS Clinical Trial Group (ACTG) of the National Institute of Health [29] and summarized in Table 2.

Table 2: Utilized staging system for AIDS- associated epidemic KS:

T (Extent of tumor)	T0 Disease limited to the skin or with minimal involvement of the oral cavity	T1 More extensive oral cavity involvement, other visceral disease
I (Immune status)	I0 CD4 >200 cells/microL	I1 CD4 <200 cells/microL
S (severity of systemic illness)	S0 No history of opportunistic infections or thrush No "B" symptoms- unexplained fever, night sweats, <10 percent involuntary weight loss, or diarrhea persisting more than two weeks. Karnofsky performance status >70	S1 History of opportunistic infections or thrush B symptoms Karnofsky performance status <70 Other HIV-related illness (neurologic disease, lymphoma)

AIDS Clinical Trials Group Oncology committee[29].

A proposed staging system for Classic Kaposi's sarcoma is:

Stage I (Macronodular Stage) - Small lesions (macules) confined to the lower extremities

Stage II (Infiltrative Stage) - Larger lesions (plaques) confined to the lower extremities

Stage III (Florid Stage) – Multiple larger lesions (plaques and nodules) confined to the lower extremities

Stage IV (Disseminated Stage) – Multiple large lesions extending beyond the lower extremities

The stages I or II disease had a slower rate of progression, fewer complication and lower occurrence of gastrointestinal/visceral involvement. However, stage III or IV disease had more rapid disease progression and more frequent gastrointestinal, visceral involvement.

Patient evaluation: The initial evaluation of KS patients consists of physical examination and special attention to affected areas.

Asymptomatic patients with classic KS rarely require radiologic evaluation because of the chronic and indolent course. Screening for distant organ involvement is not needed due to the low frequency of radiological evident disease. If mucosal involvemet of the gastrointestinal tract is present, it cannot be visible in radiologic studies. Evaluation of visceral involvement is guided by symptomatology and basic laboratory testing. Testing the stool for occult blood is the simplest way to screen for gastrointestinal involvement. Endoscopy is usually reserved for patients who detected occult blood in stool or have gastrointestinal symptoms. Also chest X-ray is useful to screen for pulmonary lesions. Bronchoscopy should be reserved for those with an abnormal radiograph and persistent respiratory symptoms. CT scanning of the chest, abdomen, and, pelvis is typically not necessary.

Treatments: There are no any prospective randomized trials to investigate treatment options for KS. The relative scarcity of the disease and advanced age of the affected individuals who had many comorbidities limit treatment options and the ability to participate in clinical trials.

The goal of KS specific therapy in all patients with KS is symptom palliation and improved quality of life. In patients with limited KS and either no immune dysfunction or post-transplant history, observation is reasonable. Indications to administer specific systemic KS therapy includes cutaneous disease which is rapidly progressive, bulky, causes pain or lymphedema, impairs function or causes psychological distress. Visceral disease generally requires KS specific therapy [30].

Observation without specific treatment is an option for patients who have a limited number of asymptomatic lesions that do not impair function. However disease progression eventually occurs in most patients [31]. Symptoms related to limited lower extremity edema can be alleviated in many patients with elastic compression stocking [32].

Local treatment:

Surgery: If there is a single symptomatic lesion, excision alone may provide sustained local control [31, 33, 34], but new lesions commonly develop at other sites.

Radiation therapy: All forms of KS are very sensitive to radiotherapy. Durable local lesion control and symptom relief can be achieved in over 90 percent of cases. Excellent palliation has been obtained with doses at 20 Gy or slightly higher. However, because of the multifocal disease involvement and the tendency for new lesions to develop in non-irradiated areas, it raises questions about the place of radiation therapy. Therefore there is no consensus in radiotherapy.

Cryotherapy: Liquid nitrogen cryotherapy is sometimes used for local control of small Classic KS lesions [35]. There is no information about local cryotherapy on long term diseaes control. The main effect is cosmetic improvement and it is often used by dermatologists.

Intralesional therapy: Intralesional injection of chemotherapy such as low dose vinblastin (0, 1 mL of 0,1mg/mL) leads to local regression of cutaneous KS [36].

Also intralesional injection of interferon alfa has been reported to induce regression of classical KS lesions [37]. IFN-alfa was used in these studies; two or three times per week therefore interferon is not suitable for use in patients with multiple cutaneous lesions.

Topical therapy: Topical imiquimod demonstrated an objective response in patients with KS [38, 39].Topical 9-*cis*-retinoic acid is approved by the FDA for KS, and is associated with up to a 45% response in treated lesions [40].

9-*cis*-retinoic acid gel (0,1%) is an FDA-approved topical treatment for cutaneous KS. A single case report of an elderly patient with classic KS noted a good local control of multiple treated cutaneous lesions. However the patient continued to develop new lesions in untreated skin [40].

Electrochemotherapy: Is another viable option that is a type of chemotherapy approach aimed at treatment of cutaneous and subcutaneous tumor nodules of different histologies. Electrochemotherapy, via cell membrane permeabilising electric pulses, potentiates the cytotoxicity of non-permeant or poorly permeant anticancer drugs with high intrinsic cytotoxicity, such as bleomycin or cisplatin, at the site of electric pulse application[41-43].

Systemic treatments: Systemic therapies are often required for patients with widespread, bulky or rapidly progressive lesions, moderate

to severe symptomatic edema or visceral organ involvement [44, 45].

Chemotherapy: It is difficult to make recommendations for preferred treatments on basis of response rates, duration benefits, or adverse effects because of absence randomized trials [46].

Most clinicians consider pegylated liposomal doxorubicin to be a first line therapy unless there is a cardiac contraindication despite the lack of randomized trials demonstrating superiority. The benefit of first line pegylated liposomal doxorubicin, 20 mg/m^2, every three weeks, was addressed in a retrospective analysis with classic KS patients [47]. Liposomal anthracyclines have a longer plasma half-life than non-liposomal formulations. Liposomal formulations have less toxicity in non-target organs than conventional anthracyclines. Liposomal anthracyclines can reliably shrink tumors, lessen edema, and cause the color of lesions to fade. Also response rates range from 30 to 60 percent [48-50].

The efficacy of taxanes (paclitaxel or docetaxel), as agents with antiangiogenic properties and interference with normal breakdown of microtubules, has been described previously in the treatment of KS. Although paclitaxel is potentially more toxic than the liposomal anthracyclines, it has efficacy as a second-line treatment for KS [51-55], and may be an alternative for initial therapy of patients with advanced, symptomatic KS. Paclitaxel and dosetaxel can be associated with significant and severe toxicities. Albumin-bound paclitaxel (nab-paclitaxel) a novel solvent-free taxane, has demonstrated higher response rates and improved tolerability[56]. As known, classic KS predominantly affects elderly people, many of whom do not tolerate aggressive chemotherapy regimes. Therefore nab-paclitaxel may has a good and rapid efficacy with lower toxicities in these patients.

Several authors have used single agent vinblastine given as a weekly dose of 0.1 mg/kg and doses of vinblastine were titrated in patients according to white blood count. The most patients usually had good response and they required prolonged courses of therapy.

In a cohort study, aldoxorubicin that is a novel prodrug of doxorubicin that binds to albumin and released in the asidic environment associated with solid tumors. Aldoxorubicin was well tolerated and therapeutically active,

including reductions in both pathological and radiographic disease with nine HIV-associated advanced KS patients. Aldoxorubicin may offer an alternative to current therapy for KS[57].

Etoposide is an another drug may be effective in KS. The single-arm study including 30 patients with non-metastatic, local advanced showed that overall response rate was 87%. Treatment was well tolerated but haematological toxicity was the principal dose limiting side effect[58].

Immunomodulators: IFN-alfa (interferon-alfa) is approved for treatment of HIV-associated KS in the US. However anti-tumor activity of IFN-alfa is not known in KS. The benefit of IFN-alfa may involve direct antiproliferative effects, antiviral effects, inhibition of angiogenesis, and modulation of host immune responses [59]. But there is no consensus on IFN-alfa dosage, frequency and duration.

Thalidomide has anti-angiogenetic, anti-tumor and immunomodulatory effects, and the drug is active in epidemic HIV-associated KS and was shown to have a 35%-47% overall response rate, but thalidomide can be associated with neurologic side effects [60, 61]. Second and third generation immunomodulatory derivatives of thalidomide, lenalidomide, and pomalidomide are currently being evaluated for the treatment of KS.

Iatrogenic type KS (organ transplantation, chronic steroid using) may respond to reduction or discontinuation of the immunsuppressive regimen. This should be the first therapeutic maneuver in iatrogenic KS. The decreasing immunosuppressive therapy was associated with the disappearance of mucocutaneous disease and visceral involvement in some patients [62, 63]. In addition, the substitution of sirolimus for cyclosporin in renal transplant recipients has been associated with regression of KS lesions [64, 65].

Everolimus is the derivative of sirolumus and works similarly to sirolimus as an inhibitor of mammalian target of rapamycin (mTOR). Clinical response and tolerance to everolimus was evaluated in phase II trial. But everolimus did not demonstrate any advantage in KS [66].

Interleukin-12 (IL 12) is identified and cloned from Epstein-Barr virus-transformed B-cell lines. Although originally defined as an natural killer stimulating factor. IL 12 acted early in immunity to promote T-helper cell development and enhance survival of cytotoxic T cell.

Efficacy in patients with HIV related KS was noted [67].

Anti-retroviral treatments:

Epidemic (HIV- associated) KS treatment is totally different from other types. Combination antiretroviral therapy (ART) is recommended for all patients with HIV associated KS [44, 45, 68, 69]. If patients do not have more advanced diseases or rapid progression, firstly we can treat HIV associated patients with ART. The introduction of ART has been associated with a substantial decrease in the incidence, severity and visceral involvement of newly diagnosed HIV associated KS [70, 71]. The beginning of treatment may worsen the patient's symptoms. This antity is called IRIS (Immune Reconstitution Inflammatory Syndrome). IRIS describes a collection of host responses that can occur following the initiation of ART and it has been associated with the progression of KS within three to six weeks after starting ART [72, 73]. Chemotherapy may be considered in addition to ART. There are two small randomized trials that have looked at the role of chemotherapy plus ART and ART alone. The overall response rate of the KS was significantly better for patient in chemotherapy plus the ART group, but there was no overall survival difference between the groups [74, 75].

Also we know that HHV-8 is an etiologic agent of virally associated tumors such as Kaposi sarcoma. Various modalities have been used to prevent and treat HHV-8 related disease. Current strategies include against HHV-8 replication, reconstituting the immune system in immune deficient patients and chemotherapy. The effect of antiviral agents on HHV-8 replication has not been extensively studied and we do not know the effect of HHV-8 treatment on KS. Several antiviral agents, including ganciclovir, cidofovir, and foscarnet have been shown to inhibit HHV-8 replication in vitro. But acyclovir does not appear to have this effect like others [76].

Anti-angiogenesis treatments:

Several approaches targeting angiogenesis and the tumor microenvironment have been evaluated prospectively in the therapy of HIV-associated KS. Matrix metalloproteinase (MMPs) are highly expressed in KS lesions and may contribute to angiogenesis via degradation of the extracellular matrix. A phase II study of the MMPs inhibitor demonstrated a 41% overal response rate [77].

Activation of c-kit and platelet-derived growth factor receptor (PDGFR) have effects on angiogenesis and growth of KS cells. Imatinib is a partial selective blocker of both PDGFR and c-kit. In a phase II study with HIV associated KS, imatinib induced partial response in one third of patients [78]. In another phase II study, the monoclonal anti-VEGF antibody, bevacizumab had an overall response rate of 31 % [79]. Angiogenesis inhibitors may have a role in combination therapy, and the combination of bevacizumab with liposomal doxorubicin is being evaluated (NCT00923936).

Sorafenib is a inhibitor of several tyrosine kinase, such as vascular endothelial growth factor receptor, PDGFR. The effects of sorafenib in Kaposi's sarcoma is being investigated in clinical trials.

There are very few randomized clinical trials due to rare incidence of Kaposi sarcoma. Therefore there has been no evidence to identify effective new therapies. The phase II/III studies have been summarized in Table 3. Novel treatment strategies in Table 3 can be administered to patients who completed conventional therapies.

Table 3: A summary of recent studies related to Kaposi sarcoma.

Trial	Phase	Patients	Treatment	Results	Side effects
Intralesional Bevacizumab in the upper airway[80]	II	HIV associated 7 patients 7 controls	ART+intralesional bevacizumab vs ART	Intralesional Bevacizumab had no impact	Well tolerated
Imatinib [78]	II	AIDS associated 30 patient	ART + imatinib	33,3% partial 20% stable 23,3% progressive response	Well tolerated
Electrochemotherapy and IV bleomycin[42]	II	18 refractory patients with isolate cutaneous lesions (no visceral disease)	Electrochemotherapy + bleomycin	66% complete response	Well tolerated
Intravenous Bevacizumab + ART[79]	II	17 HIV-infected patients who progressed under ART	Intravenous Bevacizumab + ART	19% CR 12% PR 56% stable 13% progression	Well tolerated but therapy included hypertension, neutropenia, and headache
ART vs ART+chemotherapy in therapy-naive HIV infected patients[74]	III	59:ART+chemotherapy 53:ART alone	ART+ chemotherapy (bleomysin,doxorubicin, vincristin,etoposid) vs ART	Response rate was better in combined arm p=0,005, but no survival advantage	Well tolerated
Oral etoposid as first line therapy in classic type[58]	Single arm study	30	Oral etoposid	10%CR 77% PR 13% SD	Well tolerated but haemotological toxicity was dose-limiting
Electrochemotherapy in the treatment cutaneous lesions[43]	II	23	Electrochemotherapy with unresectable, not treatable by radiotherapy or intralesional vincristine therapy	65 % CR 87% local control	Well tolerated

Adress for correspondence: Hacettepe University Department of Medical Oncology, 06000, Ankara, Turkey
e-mail: dryusufkarakas@yahoo.com

Oral valganciclovir therapy in patients with classic Kaposi sarcoma [81]	Pilot study	5	Valganciclovir doses used for cytomegalovirus infection	valganciclovir was not active against KS	Well tolerated
Treatment of HIV associated Kaposi's sarcoma with aldoxorubicin[57]	I/II	9	Aldoxorubicin	6/9 significant reduction in bothpathological and radiographic	Well tolerated
Pomalidomide in the treatment of Kaposi sarcoma in individuals with or without HIV[82]	I/II	currently recruiting participants	pomalidomide	No study results NCT01495598	
The role of everolimus (RAD001) in endemic or classic Kaposi's sarcoma[66]	II	11	Everolimus	No advantage, could be responsible for progression	Increased HHV-8 viral load
Weekly nab-paclitaxel in elderly patients with classic KS	II	6	Nab-paclitaxel	All patient improved 33% PR, 66%CR	Grade III neutropenia:50% Thrombocytopenia %17

ART: Anti-retroviral treatment
CR: Complete response
PR: Partial response
SD: Stable disease

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