European Review for Medical and Pharmacological Sciences 2017; 21: 5868-5879

Kaposi's sarcoma in HIV-infected patients in the era of new antiretrovirals

A. FACCIOLÀ[1], E. VENANZI RULLO[1], M. CECCARELLI[1], F. D'ALEO[1], M. DI ROSA[2], M.R. PINZONE[3], F. CONDORELLI[4], G. VISALLI[5], I. PICERNO[5], R. FISICHELLA[6], G. NUNNARI[1], G.F. PELLICANÒ[7]

[1]Department of Clinical and Experimental Medicine, Unit of Infectious Diseases, University of Messina, Italy
[2]Department of Biomedical and Biotechnological Sciences, Human Anatomy and Histology Section, University of Catania, Italy
[3]Department of Pathology and Laboratory Medicine, School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[4]Department of Pharmacological Sciences, Università del Piemonte Orientale "A. Avogadro", Novara, Italy
[5]Department of Biomedical and Dental Sciences and Morpho Functional Imaging, University of Messina, Italy
[6]Department of Surgery, University of Catania, Catania, Italy
[7]Department of Human Pathology of the Adult and the Developmental Age "G. Barresi", Unit of Infectious Diseases, University of Messina, Italy

Abstract. – Kaposi's Sarcoma (KS) is a multicentric angioproliferative cancer of endothelial cells (ECs) caused by Human Herpesvirus 8 (HHV8) characterized by clinical heterogeneity depending on the host immune conditions. Despite its incidence has dramatically decreased in developed countries after the introduction of Highly Active Antiretroviral Therapy (HAART), KS remains the most frequent tumor in HIV-infected patients worldwide. Clinical presentation varies from an indolent slowly progressive behavior, generally limited to the skin, to an aggressive and rapidly progressing disease. In more than 50% of cases, the skin lesions are often associated with a more or less important visceral involvement, particularly to the oral cavity and the gastrointestinal tract that are involved in 35% and 40% of cases respectively. A large number of treatments can be used both as local and as systemic therapy. Particularly, HAART represents the first treatment in patients with moderate lesions limited to skin, and it can be sufficient to reduce significantly the size of lesions and, often, the complete disappear in 35% of cases after 3-9 months of treatment. In case of a rapidly progressive disease with extensive cutaneous and/or visceral involvement systemic drugs are used such as the liposomal anthracyclines pegylated liposomal doxorubicin (PLD) and daunorubicin citrate liposome (DNX), the combined treatment adriamycin-bleomycin-vincristine (ABV) and bleomycin-vincristine (BV), Paclitaxel and Interferon-alfa. In patients with limited skin localization, the local treatment can play an important role. Local medical therapy is based on the use of alitretinoin, antineoplastic drugs vincristine, vinblastine and bleomycin and Sodium Tetradecyl Sulfate (STS). In addition to medical therapy, physical treatment, such as cryotherapy and radiotherapy, are also commonly used.

Key Words:
Kaposi's sarcoma, KS, HIV, HHV8, ART, HAART.

Introduction

The introduction of highly active antiretroviral therapy (HAART) in the treatment of Human Immunodeficiency Virus (HIV) infection has significantly modified the natural history of this infectious disease[1]. However, it is not able to eliminate the virus that remains persistent in latency[2-13]. Particularly, HAART has brought an increased survival and a reduced mortality for AIDS-related diseases. It led to enhanced morbidity and mortality caused by chronic disorders such as cardiovascular, neurological, renal and bone diseases and malignancies[7,11,12,14-46]. Despite its occurrence has dramatically decreased in developed countries, Kaposi's sarcoma (KS) is still

Corresponding Author: Giovanni Francesco Pellicanò, MD; e-mail: gpellicano@unime.it

the most frequent tumor in HIV-infected patients worldwide[47-49]. This malignancy is caused by the Human Herpesvirus 8 (HHV8), also known as Kaposi Sarcoma-associated HerpesVirus (KSHV)[50].

The aim of this paper is to review the most recent data on epidemiology, pathogenesis, clinical features and therapy of KS in HIV-infected patients.

Microbiology and Epidemiology

KSHV (HHV8) is a herpesvirus belonging to the gamma-herpesvirus family with Epstein-Barr Virus (HHV4). Like the other herpesviruses, HHV8 is able to establish persistent infections, especially in the lymphoid cells. The primary infection is often asymptomatic in an immunocompetent host. In conditions characterized by immune deficiency, such as transplant and HIV-infection, KSHV can cause lymphoproliferative disorders such as KS, Primary Effusion Lymphoma (PEL) and Multicentric Castleman Disease (MCD)[35,51]. KSHV epidemiology is different across the world. It is largely present in Sub-Saharan Africa with a prevalence >50% while is quite uncommon in Europe and in United States of America (USA), where the prevalence is around 20-30% and 1.5%-7% respectively[52]. Even in South-East Asia and Central America, the prevalence is quite low, with a percentage ranged between 1.3% and 4.4%[53,54]. In USA and Europe, men who have sex with men (MSM) and bisexual-male-AIDS-patients are the most affected[52,55-57]. The incidence of KS is 1/100,000 in the general population, whereas in HIV-infected individuals it is around 1/20. Before the introduction of HAART, it reached a prevalence of 1/3 in HIV-infected MSM. The main infection route of KSHV is the contact with infected saliva. Sexual transmission has been hypothesized considering the high prevalence in homosexual patients[58,59]. It is not yet clear if heterosexual practices are a risk factor to contract KSHV, despite some studies exclude this possibility[60,61]. Even though saliva is considered the principal transmission way, KSHV can be isolated from several other fluids and cells, including semen, cervicovaginal secretions, prostate glands and peripheral blood mononuclear cells (PBMCs)[62-64]. Where KSHV seropositivity has the highest prevalence, vertical transmission from mother to child has been hypothesized[62]. Finally, other KSHV transmission ways can be blood transfusions and solid organ transplantations (SOT)[65,66].

The majority of cases of KS occur in late phases of the HIV-infection with low CD4+ T-cell counts (< 200/ml), although it has also been observed in patients on successful long-term HAART, with well-controlled HIV-infection and a CD4+ T cell count > 200/ml[55,67]. In previous studies, a percentage of People Living with HIV (PLWH) with undetectable HIV-RNA, high CD4+ cell count and an advanced median age with a long time HIV diagnosis, developed KS[68,69]. It has been hypothesized that, in patients with a long history of HIV infection, the immune system is no longer able to control KSHV. It could represent a possible future "new" epidemiological scenery, given the growing number of PLWH well controlled HAART patients. However, in these patients, the clinical presentation is much less aggressive compared to KS of untreated individuals. There are four different epidemiological forms of KS: *classic*, *endemic, iatrogenic, epidemic or AIDS-KS*. *Classic KS* especially affects elderly men living in the Mediterranean area or Eastern European Jewish. It is characterized by a rather benign course. *Endemic KS*, the most prevalent form in Central and Eastern Africa, has an aggressive course. It is HIV-unrelated and often affects children. *Iatrogenic KS* is the most frequent form in immunosuppressed individuals, especially after SOT. *Epidemic KS (or AIDS-KS)* is a major AIDS-defining malignancy[70]. AIDS-KS has suffered a sharp decline after the introduction of HAART in developed countries. Its incidence declined from 15.2/1,000 patient-years to 4.9/1,000 patient-years[71-73]. However, KS remains the second most common HIV-associated tumor in developed countries and the first in areas where the access to HAART is still difficult[74-76].

Pathogenesis

KS is a multicentric angioproliferative cancer of endothelial cells (ECs) characterized by clinical heterogeneity depending on the host immune conditions[55]. In ECs, the virus is able to carry out two different replicative cycles: a lytic and a latent cycle. The first step of KSHV infection is the attachment of specific viral glycoproteins to the host cell receptors on circulating ECs. After this step, the virus can induce three different effects: active viral replication, viral clearance, or persistence in a transformed cell[67]. When HHV8 establishes a persistent infection, the viral DNA is transferred to the cell nucleus, where it remains as a multicopy circular episomal DNA, starting the latency phase. During this phase, there is a

little expression of viral genes and no production of new virions. In lytic cycle, newly produced virions spread to further ECs, amplify the number of transformed cells and provide paracrine regulation for KS development[70,77]. A dysregulated autocrine and paracrine angioproliferative signaling has been shown to be an important driver of KS. Particularly, during both the lytic and latent cycle, KSHV encodes a number of viral oncogenes and anti-apoptotic genes that induce infected ECs proliferation, transformation, cytokine production, immune evasion, anti-apoptosis, and angiogenesis. An increased release of proinflammatory and proangiogenic cytokines and growth factors by the infected cells, via NFkB activation, seems to be the main pathogenic mechanism on the base of the angio-proliferation. In fact, immediately after viral infection occurs NF-kB activation stimulates the expression of the cluster of latent viral genes controlled from a single latent promoter[78]. Particularly, it has been shown that AIDS-KS cell lines, stromal vessels, and spindle cells express high levels of Vascular Endothelial Growth Factor (VEGF) and VEGF receptor-1 (VEGFR-1), VEGFR-2 and VEGFR-3[79-83]. The VEGF upregulation is promoted by several KSHV genes such as viral interleukin-6 (vIL-6), K1, Latency-Associated Nuclear Antigen (LANA) and Viral G Protein-Coupled Receptor (vGPCR)[55]. Particularly, the K1 gene encodes for a transmembrane glycoprotein related to the immunoglobulin receptor family that has been associated, in mouse, with the development of plasmacytoid and sarcomatoid tumors and high levels of VEGFA in the lymph nodes[21]. Moreover, it has been shown the role of LANA in promoting the replication of the latent viral episome and altering the function of p53 and RB contributing to the transformation of KSHV-infected cells and promoting cell survival[84,85]. vGPCR promotes angiogenesis and cell transformation through the mammalian Target of Rapamycin (m-TOR) pathway[55]. Cytokines also play a key role in promoting angiogenesis and inflammatory infiltrates in KS[86]. Oncostatin M, a cytokine produced by macrophages and activated T-lymphocytes, can be a mitogen for HIV-KS derived spindle cells[87]. Finally, very recently, the expression and secretion of Matrix metalloproteinases (MMPs) such as MMP-1, MMP-2, MMP-7, MMP-9 have been shown. These molecules allow vessel destabilization and infected cells migration. Their expressions are induced by Extracellular Matrix MetalloPRoteinase Inducer (EMMPRIN), a heavily glycosylated transmembrane protein, which is a member of the immunoglobulin superfamily that is induced by LANA by direct interaction with gene promoters and or with other transcription factors, including the zinc finger transcription factor Sp1[88].

Clinical Manifestations

KS has an extremely variable clinical presentation. It could have an indolent slowly progressive behavior, generally limited to the skin, or it could behave like an aggressive and rapidly progressing disease. Lesions can have different localizations and involve skin, oral mucosa, lymph nodes and various internal organs, especially lungs and gastrointestinal tract. Typical KS skin lesions are usually pigmented (pink, red or purple), varying in size from a few millimeters to large areas of several centimeters. They may also have different aspects such as macular, papular, nodular or plaque-like. They are generally not painful[35,44]. The lesions involve large areas of the body surface, especially oral cavity, face and lower extremities that often present an important edema due to a lymphatic obstruction. In an early phase, the lesions often appear as dermal red flat lesions, named "patch lesions", containing a large infiltrate of T and B cells, monocytes, and abundant neovascularity. Afterward, in an advanced phase, the lesions converge, assuming a plaque aspect ("plaque phase") and appearing indurated, often edematous and more intensely red or violaceous. Finally, the proliferation of spindle cells determines the involvement of the deepest derma with the formation of nodules ("nodular phase") often associated with ulcerations[63]. In more than 50% of cases, the skin lesions are associated with a more or less important visceral involvement. The oral cavity and the gastrointestinal tract are involved in 35% and 40% of cases, respectively. Gastrointestinal localization may be asymptomatic or cause various symptoms such as abdominal pain, malabsorption with diarrhea or obstruction, weight loss, vomiting or bleeding. Another important KS visceral localization is in the lung, and it can represent a serious life threat. This involvement may occur in an asymptomatic way or with dyspnea, cough or hemoptysis. Chest X-ray aspect varies from nodular, interstitial or alveolar infiltrates to isolated pulmonary nodule or pleural effusion. The visceral involvement, especially the pulmonary one, is more frequent in patients with extensive cutaneous involvement and an advanced immunodepression grade. Only 15% of pulmonary involvement occurs in patients

with absence of skin lesions[44]. In the pre-HAART era, the AIDS Clinical Trials Group (ACTG) established a staging system of the patients with KS dividing them in two different groups, named "good-risk group" and "poor-risk group", on the base of three parameters: (1) Extent of the tumor (T); (2) CD4+ T-cell count (I); III) Severity of systemic illness (S). Good-risk patients (T0I0S0) have a tumor confined to skin and/or lymph nodes and/or minimal oral lesions, a CD4+ T-cell count ≥ 200 cells/μl and absence of opportunistic diseases and/or B symptoms (fever, night sweats, significant weight loss, diarrhea for more than two weeks). On the other hand, poor-risk patients (T1I1S1) have widespread KS lesions, especially a more extensive oral cavity involvement or other visceral disease and lymphoedema, a CD4+ T-cell count < 200 cells/μl and presence of opportunistic infections and/or B symptoms[89,90]. It has been shown that the tumor extent and the systemic involvement are the most important predictors of patient survival, while CD4+ cell count is not[28]. Moreover, some authors identified four prognostic factors to obtain an accurate prognostic index to manage the therapeutic choice: AIDS-defining illness, age ≥50 years, CD4+ T-cell count, and S stage. Using these parameters, they obtained a prognostic score ranging from 0 to 15. According to this prognostic index, patients with a high risk (score > 12) should be treated with HAART and systemic chemotherapy. Patients with a low risk (score < 5) should be treated with HAART alone, even if they have the T1 disease. Only those with progressive disease should be treated with chemotherapy[44,91].

Treatment

KS is not a curable disease. Thus, the principal aim of the therapy is to reach a durable remission of the tumor. Some drugs can be used both as local therapy and as systemic treatment. The bulwark of the KS therapy is surely an effective HAART. Indeed, after his introduction, HAART has dramatically improved the KS patients' survival and has reduced KS occurrence in high-income countries in percentages ranging between 33% and 95%[92]. Some studies[93,94] have shown that in HAART-naïve patients with KS, tumor regression was obtained after the administration of HAART. In KS patients, HAART is able to reduce inflammation and improve immune responses to KSHV. Particularly, previous studies focused their attention on the role of Protease Inhibitors (PIs). Especially, Sgadari et al[95] highlighted the potent anti-angiogenic effect of this class of anti-retroviral drugs. However, other studies[96,97] showed no difference with the use of non-nucleoside reverse transcriptase inhibitors (NNRTIs). HAART represents the first treatment in patients with moderate lesions limited to skin (T0 and T1 slowly progressive disease). It can even be sufficient to reduce significantly the size of the lesions and to cause the complete disappearance in 35% of cases after 3-9 months of treatment[47,55,76]. However, the initiation of anti-HIV treatment can determine a sudden appearance of KS in HIV-positive patients with initial low CD4+ T-cell count. This form is a manifestation of the so-called Immune Reconstitution Inflammatory Syndrome (IRIS)[44]. In this case, as well as for rapidly progressive presentation with extensive cutaneous and/or visceral involvement, a systemic chemotherapy has to be associated to HAART. Several drugs are used as systemic chemotherapeutic treatment of KS. The first choice is represented by liposomal anthracyclines: pegylated liposomal doxorubicin (PLD) and daunorubicin citrate liposome (DNX). The use of liposomal forms improves the pharmacokinetic characteristics and reduces the cardiotoxicity. PLD showed a response rate ranging from 46 to 59% and a median remission time of 3-5 months, while DNX has a response rate of 25% and a median remission time of 175 days. Different randomized clinical trials compared liposomal anthracyclines with the combined treatment adriamycin-bleomycin-vincristine (ABV) and bleomycin-vincristine (BV). These studies showed a better tolerability profile of the first drugs with less alopecia, gastrointestinal and neurologic impacts as side effects[98-100]. However, both liposomal anthracyclines may determine grade 3-4 myelosuppression, while DNX treatment can cause stomatitis and infusion reactions[75]. One randomized, open-label, multicenter phase II trial compared the efficacy of PLD (20 mg/m^2 every 3 weeks) combined with HAART *vs.* HAART alone showing that the combined use of PLD and HAART was more effective than HAART alone in the treatment of patients with moderate to advanced AIDS-related KS[44,101]. First-line treatment with liposomal anthracyclines is not sufficient in about one-third of patients that require a second-line therapy with paclitaxel, a cytotoxic agent that acts by polymerizing microtubules and inhibiting cell division. Two phase II trials showed that intravenous administration of paclitaxel (100 mg/m^2 given every 2 weeks as a 3-hour infusion)

was associated with a response rate of 59% with a median duration of response of 7.4 months in the first trial and 10.4 months in the second one[99,102]. This drug may determine grade 3-4 hematologic toxicity, alopecia, peripheral neuropathy and renal dysfunction as side effects[44,103,104]. Unfortunately, despite the positive effects of the systemic treatment, the disease progresses within six-seven months, and an additional treatment is often required with shorter periods of remission at each cycle[44,105].

Recently, some immunotherapeutic agents were used in the KS treatment. Among these, high-dose Interferon-alfa (IFN-α) monotherapy showed a response rate of 10-40%; similar or better responses have been found using lower doses in combination with HAART. Side effects of IFN-α are flu-like symptoms and bone marrow suppression[106].

In patients with limited skin localization or for cosmetic/palliative aims in those with advanced disease, the local treatment plays an important role. Medical therapy is based on the use of various drugs including alitretinoin (9-cis-retinoic acid), an endogenous retinoid obtained after isomerization of tretinoin. In 1999, the Food and Drug Administration (FDA) approved a 0.1% gel for the treatment of KS skin lesions. This drug binds the retinoic acid receptors (RARs) and retinoid X receptors (RXRs), modulating keratinocyte differentiation and blocking neo-angiogenesis and proliferation of KS cells in vitro. Another important function is the anti-inflammatory and immunomodulatory effect expressed through the reduction of macrophages and activated dendritic cells number (two major sources of TNF-alpha), and a decreased production of pro-inflammatory cytokines such as IL-4, IL-1beta and IL-12p40. The response rate ranges from 35% to 50%[44,107]. Other drugs used in local treatment of KS are vincristine, vinblastine, and bleomycin. Particularly, intralesional vincristine has shown a complete clinical remission in up to 76.1% of treated patients and a partial response in 18.5%; it has a good tolerability and it causes few side local but not systemic effects[108]. Compared to vincristine, vinblastine and bleomycin are less effective. They lead to a temporary regression limited to about 4 months and cause more collateral effects including pain at the injection site[44,109]. Recently, Kim et al showed the effect of intralesional injection of 3% (0.2 mg/mL) Sodium Tetradecyl Sulfate (STS) in the treatment of cutaneous KS in a HIV-negative 96-year-old woman. STS is a sclerosing agent that damages vascular endothelium and is injected directly into the KS lesions[110]. In addition to medical therapy, physical treatment, such as cryotherapy and radiotherapy, are also commonly used. Cryotherapy is often used combined with the above-mentioned alitretinoin[107]. Skin KS lesions are highly radiosensitive, and radiotherapy effectively reduces pain, bleeding, and edema. The response rate is higher than 90%, with a complete remission in 70% of cases and good tolerability. Generally, in patients with advanced skin lesions, a single dose of 8 Gray is used. With this drug, it has been reported a certain grade of cytotoxicity with pain, skin erythema, desquamation, and ulcers when using 20 Gy in 10 fractions for the treatment of KS of the feet[111]. A novel local treatment has been proposed for skin KS lesions: electrochemotherapy (ECT). This treatment combines the use of electroporation with the administration of two highly cytotoxic drugs, bleomycin, and cisplatin. Particularly, the first step of this combined method aims to form pores on the cell membrane, by using pulsed, high-intensity electric fields and, thus, increase cell membrane permeability. Antiblastic drugs can entry into cells through the obtained pores and reach high concentration, avoiding the administration of high doses of drugs. This treatment showed a good clinical result and a low toxicity profile in KS patients, with response in up to 61% of cases and a long remission duration. Because ECT had no systemic side effects and needed only mild general anesthesia to be performed, it is possible to carry out repeated cycles of therapy[105,112,113].

In patients with AIDS-related KS not responding to HAART and/or chemotherapy, it is possible to use some "target" therapies based on anti-angiogenic drugs, metalloproteinase and cytokine signaling pathway inhibitors. Irinotecan (CPT-11) is a semi-synthetic camptothecin derivative converted by decarboxylation into the biologically active form SN-38 (7-ethyl-10-hydroxycamptothecin). The target of this cytotoxic agent is represented by DNA topoisomerase I. This drug was used intravenously with PIs in a GICAT phase II study (150 mg/m^2 on day 1, 10 mg/m^2 every 21 days), in a group of HIV-infected patients with KS who had relapsed or progressed during HAART. This treatment resulted effective and well tolerated. Possible side effects are grade 3-4 myelotoxicity and diarrhea, that limited the usable doses[44]. CMT-3 or COL-3 (6-deoxy 6-dimethyl 4-dimethylamino tetracycline),

a chemically modified tetracycline, is one of the most potent matrix metalloproteinases (MMPs) inhibitors. MMPs are a class of calcium-dependent endopeptidases constantly overexpressed by KS cells. These enzymes play a key role in in the process of neo-angiogenesis, tumor invasion and metastasis. Moreover, they disaggregate the extracellular matrix favoring the migration of endothelial cells and the release of several tumor growth factors, especially vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (B-FGF). Similarly, KS cells release a high amount of gelatinases MMP-2 and MMP-9, which degrade collagen IV, the major component of basement membranes[114]. For the fundamental role played by these enzymes, CMT-3 or COL-3 were used at an oral dose of 50 mg once daily obtaining a response rate of 41% and a median duration of response of 52 weeks[44,114]. Common side effects include dose-related photosensitivity and rash. Thalidomide, an anti-angiogenic and anti-tumor drug, is used at a dose of 100 mg/day for 12 months. It blocks vascular endothelial cell proliferation, TNF production, assembly of basement membrane and intercellular adhesion molecules. Moreover, it reduces the activity of the nuclear factor SP1, a transcription factor involved in the expression of extracellular matrix genes. Possible side effects are neutropenia, depression, and fever[44,115].

A phase I study evaluated the effects of a combined therapy based on liposomal doxorubicin, HAART and IL-12, a Th1 cytokine that downregulates a constitutively active G protein coupled receptor encoded by HHV-8. The preliminary results of this therapeutic combination showed a remission in a substantial percentage of patients with advanced KS[116]. Moreover, Imatinib mesylate orally (300 mg twice daily) inhibited the activation of the platelet-derived growth factor (PDGF) and c-kit receptors, which are important targets in mediating the growth of AIDS-related KS. The most common adverse events were diarrhea and leukopenia[117].

Recently, bevacizumab, a humanized anti-VEGF-A monoclonal antibody, was used in a one-phase II study to evaluate the efficacy in patients with HIV-associated KS. VEGF-A is an important growth factor that plays a key role in the KS angiogenesis. In this study, the response was lower than that reported with liposomal anthracyclines but comparable to that seen when using other angiogenesis inhibitors such as COL-3. These results suggest that bevacizumab could be used in association with other cytotoxic agents or in patients who are approaching the maximal safe cumulative dose of anthracyclines. Moreover, bevacizumab does not interfere with the immune reconstitution, in contrast to other cytotoxic agents, and this is a crucial feature of a therapeutic regimen for HIV-associated KS[118]. Sirolimus (SRL), also known as rapamycin, is a potent immunosuppressant, anti-angiogenic and anti-proliferative drug that was used in 15 renal transplant recipients with KS obtaining a complete clinical remission of skin lesions after 3 months and histological remission after 6 months[119].

Among the anti-viral drugs, ganciclovir is able to suppress HHV-8 replication in vivo and prevent the development of KS in randomized trials. Valganciclovir, the oral pro-drug of ganciclovir, was able to reduce HHV-8 oral shedding frequency by 46% and viral load by 0.44 log copies/ml in a randomized placebo-controlled cross-over trial. Previous studies showed that even foscarnet, but not acyclovir, may prevent KS[120,121].

González-Pardo et al[122] showed that TX 527 [19-nor-14,20-bisepi-23-yne-1,25(OH)2D3], an analog of 1α,25-dihydroxyvitamin D3 [1α,25(OH)2D3, calcitriol], the most active form of vitamin D, enhanced anti-proliferative effects and pro-differentiating capacities of normal and malignant cell types and immune regulatory capacities. These therapeutic actions are linked to the TX 527 capacity to inhibit the growth of endothelial cells transformed by a viral HHV-8 protein, called vGPCR, that potently activates the NF-κB pathway. Thus, TX 527 decreases nuclear translocation of NF-κB by a mechanism that depends on Vitamin D Receptor (VDR) expression and induces a VDR-dependent up-regulation of inhibitory protein IκBα, resulting in cell cycle arrest.

Conclusions

Despite the significant improvements in the diagnosis and treatment, KS is still an important cause of morbidity and mortality in HIV infected patients. Nowadays, many local and systemic therapies are available to fight this tumor. Certainly, HAART represents the pillar of the treatment as it determines the block of the viral replication and an improvement of the immune system reducing the immunodepression that is the principal cause of KS. Many other drugs,

some of which in the experimental phase, can be used to reach a more or less durable remission of the tumor. However, further studies are still necessary to find new therapeutic strategies to improve the management of KS in HIV infected patients, in order to reach a KS-free life.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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