World Cancer Research Journal WCRJ 2014; 1 (4): e393

CURRENT STATUS AND PERSPECTIVES OF AIDS-RELATED KAPOSIS'S SARCOMA IN THE c-ART ERA

F. MARTELLOTTA[1], O. SCHIOPPA[1], B. CACOPARDO[2], R. FISICHELLA[3], U. TIRELLI[1].

[1]Department of Medical Oncology, National Cancer Institute, Aviano (PN), Italy.
[2]Division of Infectious Disease, "Garibaldi-Nesima" Hospital, University of Catania, Catania, Italy.
[3]Department of Surgery, University of Catania, Catania, Italy.

Absract: *Kaposi's sarcoma (KS) may be considered as a model of both malignancy and chronic inflammation. In Highly Active Antiretroviral Therapy (HAART) era KS remains the second most frequent tumor in HIV-infected patients worldwide and occurs in over 50% of cases with advanced HIV infection. Its development depends upon infection with a γ-herpesvirus from the Rhadinovirus genus called KS-associated herpesvirus or Human herpesvirus-8 (KSHV/HHV8). Almost 50% of individuals acquiring KSHV infection with pre-existing HIV infection develop KS. This observation suggests that an already damaged immune system may predispose to a higher KSHV load, with subsequent KS development. Considering the elevated prevalence of KSHV in men having sex with men (MSM), it was suggested that it could be transmitted sexually. KSHV transmission by blood transfusion is documented, although rare. KS lesions are comprised of both distinctive spindle cells of endothelial origin and a variable inflammatory infiltrate, which suggests that KS may result from reactive hyperproliferation induced by chronic inflammation, and therefore it is not a true neoplasm. KS has a variable clinical course ranging from very indolent forms to a rapidly progressive disease. Treatment decisions must take into consideration the extent and the rate of tumor growth, patient's symptom, immune system conditions and concurrent HIV-related complications. HAART represents the first treatment step for slowly progressive disease. HAART with concomitant chemotherapy is indicated for visceral disease and/or rapidly progressive disease, and maintenance (M)-HAART after systemic chemotherapy may be effective as anti-KS therapy after debulking CT. Systemic CT is reserved for patients who do not respond to HAART and/or have widespread, symptomatic, rapidly progressive, life-threatening disease with visceral involvement and an IRIS-associated flare. The angiogenic nature of KS makes it particularly suitable for therapies based on targeted agents such as angiogenesis inhibitors and tyrosine kinase inhibitors. The aim of this article is to provide an up-to-date review of the current status and perspectives of AIDS-related KS in the HAART era.*

KEY WORDS: *Kaposi's sarcoma, HAART, HIV infection, HHV-8.*

INTRODUCTION

The introduction of combinated Antiretroviral Therapy (c-ART) into clinical practice has significantly changed the natural history of human immunodeficiency virus (HIV) infection. However, KS remains the second most frequent tumor in HIV-infected patients worldwide. In c-ART-era the course of KS is different from that at the beginning of the epidemic. Infact KS occurs in over 50% of cases with advanced HIV infection and is characterized by an extremely aggressive clinical course. KS patients on c-ART exhibit a less aggressive presentation compared to patients who were naive to c-ART at KS diagnosis. However, in recent years have been observed a cluster of cases of HIV-related KS in subjects with CD4 cell count > 200 cells/μ1 and a controlled viral load. This phe-

Corresponding Author: Ferdinando Martellotta, MD; e-mail: fmartellotta@cro.it

nomenon may increase in frequency as HIV-infected population ages, and careful monitoring is recommended for this group of patients[1-5]. KS may be considered as a model of both malignancy and chronic inflammation. Its development depends upon infection with a γ-herpesvirus from the Rhadinovirus genus KS-associated herpesvirus or Human herpesvirus-8 (KSHV/HHV8) strongly associated with all subtypes of KS, multicentric Castleman's disease, and a rare form of B-cell lymphoma called Primary Effusion Lymphoma (PEL). In Europe the prevalence of KSHV is around 20-30%, with the lowest rates (6%-8%) in Spain and Greece and the highest in Italy (20.4%). In western countries the risk for KS in MSM is 5 to 10 times higher compared to other groups of individuals practicing other HIV-risk behaviors. The incidence of KS is 1 in 100.000 in the general population, whereas in HIV-infected individuals it is around 1 in 20, reaching the value of 1 in 3 in HIV-infected homosexual men before the introduction of HAART. Almost 50% of individuals acquiring KSHV infection with pre-existing HIV infection develop KS. This observation suggests that an already damaged immune system may predispose to a higher KSHV load, with subsequent KS development. The main route of transmission of KSHV is saliva, thus in keeping with the observation that KSHV can replicate in vitro in primary oral-derived epithelial cells. Considering the elevated prevalence of KSHV in MSM, it was suggested that it could be transmitted sexually. KSHV transmission by blood transfusion is documented, although rare. The risk of transmission can be greatly reduced by depleting blood of leucocytes (KSHV-associated cells) or by storing blood for several hours or days. Some studies suggested that injecting drug users (IDUs) were not at increased risk of KSHV infection, while others have shown an increased risk of KSHV infection in IDUs with prolonged drug abuse[3,6-8].

PATHOGENESIS

KSHV/HHV8 has two modes of replication (lytic and latent phase) that play significant roles in the pathogenesis of KS. Infact during the lytic and latent phase KSHV encodes an arsenal of gene products inducing cellular proliferation, transformation (JNK/SAPK, PLC/PKC, PL3K/Akt), cell signaling (NF-kB), cytokine production (vCCL-1, vCCL-2, vCCL3, vGPCR, Kaposin B), immune evasion (KCP, K3, K5), antiapoptosis (vFLIP, K1, Lana-1, vIRF-1, vIRF-3, K8), and angiogenesis (VEGF, IL-6, vCCLs, K1, Angiopoietin-1). Two hypotheses have been proposed: the "paracrine oncogenesis" and the "abortive lytic hypothesis". The paracrine oncogenesis is based on the presence of lytically infected cells or latently infected cells expressing early lytic genes in KS lesions. These cells express vGPCR, K1 and ORF45 that promote the production of VEGF, IL-6, PDGF which stimulate the proliferation of latently infected cells and angiogenesis in a paracrine manner. Instead the abortive lytic hypothesis is based on the presence of cells expressing the oncogenic early lytic genes can be transformed by genetic or epigenetic oncogenic alterations and switch back to less immunogenic latent forms which will be paracrinally stimulated by litically infected cells. The presence of admixed immune infiltrate in the lesions suggests that KS may be the result of reactive hyperproliferation induced by chronic inflammation, and therefore it is not a true neoplasm. The first step is KSHV infection of normal and circulating endothelial cells (ECs). Infected ECs proliferate in response to viral oncogenes and anti-apoptoic genes, which also aid in escaping the antiviral response. The expression of Matrix Metalloproteinases (MMPs) and proangiogenic molecules allow vessel destabilization and migration of infected ECs. Chronic inflammation may play a role in the pathogenesis of the disease. KSHV excites downregulation of Th1-mediated responses (cellular immunity) and hyperactivation of Th2-mediated responses (immune system) through suppression of IFNs and MHC-1 downregulation and secretion of pro-inflammatory cytokines, activation of signaling molecules. Oncogenesis depends on infiltration and proliferation of inflammatory cells secreting VEGF and IL-6 that favor the growth of spindle cells (SCs) and angiogenesis. SCs are the majority of cells that comprise a KS lesion and express endothelial markers such as CD31 and CD34. The exact origin of SCs remains elusive. Initial studies based on histology and tumor location have suggested a lymphatic endothelial cell (LEC) or mesenchymal stem cells (MSC) origin. At present it appears that KSHV may infect both blood vascular endothelial cells (BECs) and LECs, and that infected BECs are reprogrammed towards a more lymphatic expression profile. Therefore the virus may convert one cell type to another, which makes it more difficult to determine the origin of SCs[3,9,10].

CLINICAL FEATURES

KS occur in indolent or aggressive forms with significant morbidity and mortality. Typically the disease presents with disseminated and pigmented skin lesions of variable size (from few millimeters to several centimeters) and appearance (from

TABLE 1. AIDS CLINICAL TRIALS GROUP (ACTG) FOR AIDS-KS STAGING SYSTEM.

	Good risk (0)	**Poor risk** (1)
Tumor (T)	Skin ± lymph node ± minimal oral disease	Edema or ulcerations or extensive oral KS or GI or other visceral disease
CD4 cell count (I)	≥ 150	< 150
Systemic illness (S)	No OI/B-symptoms* PS > 70 (Karnofsky)	OI and/or B symptoms other HIV-related illness PS < 70

*Unexplained night fever or sweats; > 10% unexplained weight loss; persistent diarrhea.

pink to brown), often associated with edema and in over 50% of cases with visceral involvement. At the time of initial diagnosis, approximately 35% and 40% of patients show involvement of the oral cavity and gastrointestinal involvement respectively. Gastrointestinal tract manifestations can occur also in the absence of cutaneous disease, and they may be sometimes symptomatic (malabsorption, diarrhea, obstruction, bleeding). Pulmonary KS is the second most common site of extra cutaneous involvement, and it is the most life-threatening form of the disease. In 15% of cases pulmonary KS occurs without evidence of muco-cutaneous disease; sometimes may be symptomatic (shortness of breath; cough; haemoptysis) or present with asymptomatic findings on chest X-ray (nodular or interstitial or alveolar infiltrates, pleural effusion or isolated pulmonary nodules), which may be indistinguishable from those of more common opportunistic infections. Gallium and thallium scans may differentiate KS from other infections; infact, KS lesions take up thallium but not gallium, whereas infections are gallium-positive and thallium-negative. Planar ^{99m}Tc-MIBI imaging has moderate sensitivity, specificity and accuracy for detecting pulmonary KS. Single photon emission computed tomography (SPECT) is more effective in detecting visceral involvement. ^{99m}Tc-MIBI SPECT can be useful in the evaluation of pulmonary KS[2,11-14].

PROGNOSIS

In the pre-HAART era the AIDS Clinical Trials group (ACTG) devised a staging system based upon the extent of tumor (T), the status of the immune system in terms of CD4 cell count (I), and the presence of systemic illness (S). This classification identified two different risk categories: patients with skin ± lung ± minimal oral disease, CD4 > 150, no OI/b-symptoms and PS > 70 were scored as a good risk (T0I0S0), and those with edema or ulcerations or extensive oral KS and visceral involvement, CD4 < 150, OI and/or B-symptoms and PS < 70 as poor risk (T1I1S1) (Table 1). In 2003 Nasti et al[15] assessed new potential prognostic factors and validated the ACTG staging system in the HAART era. They showed that while tumor extension and systemic disease maintained their correlation with survival, CD4 cell count above or below 100 as predictive of survival was excluded. The analysis of interaction between tumor stage and systemic disease and its correlation with survival identified two major risk categories: a good-risk group (T0S0-T1S0-T0S1) and a poor-risk group (T1S1). Survival analysis of patients with pulmonary involvement indicated that within the T1 risk category pulmonary disease was associated with a significantly poorer survival rate than other T1 features. These data differ substantially from the results of the pre-HAART Krown study in which CD4 count gave independent predictive information, and tumor stage provided additional predictive information in patients with good immune system status. c-ART may be responsible for altering the ACTG classification prognostic value (Table 2). In 2006 Stebbing et al[16] identified four prognostic factors: AIDS-defining illness, age > 50 years, CD4 count, and S stage, which can be used to obtain an accurate prognostic index at diagnosis of AIDS-related KS and to guide therapeutic options. Upon increasing the prognostic score (extended from 0 to 15 starting at 10) by 1 the 1-year death HR increased by 40%. Having KS as an AIDS-defining illness (-3 points), age > 50 years (2 points), increasing CD4 count (-1 point for every complete 100 cells per mmc) and another concomitant AIDS-associated illness (3

TABLE 2. REFINEMENT OF THE ACTG STAGING SYSTEM IN THE HAART ERA.

Good risk	**Poor risk**
T0S0, T1S0, T0S1	T1S1

points) conveyed a poorer prognosis. According to this prognostic index patients with a score >12 should be treated with c-ART plus systemic chemotherapy, or alternatively be considered for clinical studies with novel agents. Patients with a low risk score < 5 should receive c-ART alone as first-line therapy even if they have T1 disease, while chemotherapy should be reserved for progressive disease.

TREATMENT

Treatment decisions must take into consideration the extent and the rate of tumor growth, patient's symptom, immune system conditions and concurrent HIV-related complications.

Local therapy is reserved only for patients with minimal cutaneous disease for cosmesis, and for non-responders to systemic therapy who have rapidly progressive disease as palliative therapy. Radiotherapy is effective and often represents the best local treatment for palliation of pain, bleeding or edema, with response and complete remission rates of over 90% and 70%, respectively. Intralesional vinblastine, oral etoposide, 9-cis-retinoic acid gel, cryotherapy and excisional surgery may be feasible options. The overall response rates range between 35 and 50% with topic skin reactions[17-19]. Electrochemotherapy (ECT) is an emerging local treatment proposed for cutaneous metastatic nodules and different primary skin tumors. This technique is a non-thermal tumor ablation combining the use of electroporation with the administration of bleomycin and cisplatin. Electroporation uses pulsed, high-intensity electric fields to temporarily increase cell membrane permeability by creation of pores, which facilitate drug delivery into the cell. The resulting high drug concentration obtained within tumor cells enhances the chemotherapeutic cytotoxic activity and allows the administration of a lower dose, thus limiting not only drug-related toxicity but also immunodepression. ECT with bleomycin could represent an effective therapy for skin-limited KS, including stage I and stage II disease.

The widespread introduction of HAART has been associated with a marked reduction of KS incidence in resource-rich countries, which is estimated to range between 33% and 95%. Although there are no clinical data comparing the efficacy of different HAART regimens for the treatment of KS, the use of protease inhibitor (PI)-containing regimens seems to be indispensable in the treatment of AIDS epidemic KS in all patients, alone or in combination with systemic and local therapy. The effects of HAART on KS are multifactorial and include inhibition of HIV replication, amelioration of the immune response against HHV-8 and diminished production of HIV-1 transactivating protein Tat[3]. In patients with limited cutaneous lesions (T0 early-stage disease and/or slowly-proliferating disease) a HAART regimen including PI may represent the first step of therapy for KS, with an overall response rate of 66-86% and a complete remission rate of 35%. As virus replication is progressively suppressed and immune restoration begins, KS lesions typically start to decrease in size and many disappear completely within a few weeks or months[20]. Frequently KS may flare dramatically following the initiation of HAART and may be a manifestation of the immune reconstitution inflammatory syndrome (IRIS). This is a heterogeneous and sometimes fatal disorder of immune perturbation after initiation of c-ART that occurs in HIV-positive patients with initial low CD4 count and an incontrollable viral load. KS flare is observed as early as 3 weeks, with most cases diagnosed within 2 months after immunological and virological response to HAART[21]. At present HAART alone may represent the first-line therapy for T0 and T1 slowly progressive disease. HAART with concomitant chemotherapy is indicated for visceral disease and/or rapidly progressive disease, and maintenance (M)-HAART after systemic chemotherapy may be effective as anti-KS therapy after debulking CT (overall response rate of 91%)[2,22]. The resolution of KS with HAART may take several months and generally follows the recovery of host cell-mediated immunity. After starting HAART, CD4+T-cells counts recover in two phases. The first phase is associated with an increase in circulating memory T cells that originate from lymphoid tissue chiefly from the gut. The second phase occurs some months later and is characterized by the production of naïve T cells resulting in an improvement of immune repertoire. It is during this second phase that regression of KS is observed[23]. It has been shown that the association of HAART and anthracyclines may induce and/or select a multidrug resistant (MDR) phenotype for overexpression in tumor cells of members of a highly conserved family of transmembrane proteins characterized by an ATP-binding cassette (ABC). Anthracyclines are substrates of many ABC transporters (such as ABCB1, ABCG2, ABCC1 and ABCC2) and treatment with anthacyclines alone can induce ABCB1 expression resulting in a MDR phenotype. Long-term exposure of KS cells to doxorubicin has been found to induce dose-dependent resistance together with a significant cross-resistance to the taxane compound paclitaxel, suggesting ABCB1- related resistance. Five different PIs (i.e. indinavir, nelfinavir, atazanavir, ritonavir and and lopinavir) were chosen based on their ability to act as substrates for

ABC transporters and their antitumor properties. These compounds were tested either alone or together with doxorubicin at concentrations in line with those achieved in HIV-infected patients undergoing antiretroviral treatment. Physiological concentrations of PIs were able to select a MDR phenotype, because of increased ABCB1 expression and function in KS-derived SCs. Interestingly, the mechanisms resulting in ABCB1 expression of doxorubicin and PIs seem to be different. Whereas doxorubicin induced ABCB1 expression and functionality in SLK cells after acute treatment (72 h), ABCB1 was only expressed in SLK cells after chronic treatment (6 months) with PIs[24].

Systemic CT is reserved for patients who do not respond to HAART and/or have widespread, symptomatic, rapidly progressive, life-threatening disease with visceral involvement and an IRIS-associated flare. Liposomal anthracyclines (pegylated liposomal doxorubicin PLD, daunorubicin citrate liposome DNX) are now considered as first-line therapy for patients with advanced AIDS-KS. In randomized clinical trials the activity of DNX (40 mg/m^2 i.v. every 2 weeks) and PLD (20 mg/m^2 i.v. every 2 weeks) was shown to be equivalent or superior to the ABV and BV combinations, respectively, with an overall response rate of 76-82% and a complete remission rate of 26-40%. Liposomal daunorubicin and doxorubicin are associated with milder alopecia, and reduced gastrointestinal and neurological side effects compared to BV or ABV regimens. Grade 3-4 myelosuppression is common with both drugs; stomatitis and infusion reactions occur with DNX, but hand-foot syndrome is relatively infrequent in the dose schedules used for KS[2,25]. Treatment with paclitaxel is restricted to patients with recurrent or refractory AIDS-related KS after first-line chemotherapy. Paclitaxel is a cytotoxic agent which exerts its antitumor activity by polymerizing microtubules and inhibiting cell division. Two small phase II trials have demonstrated that intravenous paclitaxel (100 mg/m^2 given every 2 weeks as a 3-hour infusion) is 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. Possible side effects are represented by significant myelosuppression, peripheral neuropathy, renal dysfunction and the inconvenience of a 3-hour infusion. Despite the effectiveness of these agents, most patients affected by KS progress within six to seven months of treatment and require additional therapy. Durable remission periods tend to be gradually shorter after each treatment course. Dose reductions may be required when these drugs are coadministered with PIs or NNRTI, as they are all metabolized by cytochrome P450. Paclitaxel and PLD appear to be active first-line agents for advanced, symptomatic KS. However, paclitaxel has been associated with a higher incidence of grade 3-4 hematologic toxicity, alopecia and sensory neuropathy. Although clinical experience with docetaxel is more limited than that with paclitaxel, phase II trials suggest that intravenous docetaxel (25 mg/m^2 over 15-30 minutes weekly for 8 weeks) is safe and effective in the treatment of advanced-stage epidemic KS with 42% partial remission rate and 33% grade 3 leukopenia. Immunosuppression and infections are the major problem in patients treated with cytotoxic chemotherapy. The use of granulocyte colony-stimulating factor (G-CSF) subcutaneously at the dose of 5 mcg/kg daily is standard practice[2,3,26-28] (Table 3).

Current understanding of KS as a convergence of immune evasion, oncogenesis, inflammation and angiogenesis has prompted ivestigators to develop a target therapy based on anti-angiogenic agents, metalloproteinase and inhibitors of cytokine signaling. This therapy may be an effective strategy for patients with AIDS epidemic KS which progressed despite chemotherapy and/or HAART[2]. Irinotecan (CPT-11), a semisynthetic camptothecin derivative converted by decarboxylation into a biologically active form SN-38 (7-ethyl-10-hydroxycamptothecin), belongs to a recently established class of anticancer agents with a cytotoxic mechanism targeting the cellular enzyme DNA topoisomerase I. The model of bFGF-induced angiogenesis in mouse cornea suggests that Irinotecan may be active also in KS. Data from a GICAT phase II study show that intravenous CPT-11 (150 mg/m^2 day 1; 10 every 21 days) plus HAART including PI is active and well tolerated in

TABLE 3. GUIDELINES OF AIDS-KS THERAPY

Extent of tumor cell invasion	Optimal therapy
Local disease	Surgery Intralesional chemotherapy cryotherapy Radiotherapy* HAART**
T1 slowly progressive disease	HAART**
Visceral disease and/or rapidly progressive disease	Chemotherapy + HAART** ± G-CSF ± OI prophylaxis M-HAART** (after debulking chemotherapy)

*For palliation of pain, bleeding or edema in patients with extensive disease who do not respond to CT + HAART.
**Including PI.

HIV-infected patients with KS relapse or progression during HAART. The most important dose-limiting side effects are grade 3-4 myelotoxicity and diarrhea. The co-administration of lopinavir/ritonavir and CPT-11 reduces CPT-11 clearance and AUC of the APC oxidized metabolite by 47% and 81%, respectively, and inhibits development of SN38 glucuronide. This effect results in increased availability of CPT-11 for SN38 conversion and reduced inactivation on SN38 in SN38 AUC[29,30]. The PDGF and c-Kit receptors play critical roles in KS development. KSHV infection of endothelial cells results in a five-fold upregulation of the c-kit receptor and KSHV infected endothelial cell cultures proliferate in response to the c-kit ligand, stem-cell factor. PDGF induces expression of VEGF by cultured KS spindle cells. The βPDGF-receptor (PDGF-R) is expressed in KS tumor specimens and adding PDGF to cultured KS spindle cells induces expression of VEGF. Imatinib is a tyrosine Kinase inhibitor initially approved by the US FDA for treatment of chronic myeloid leukemia. In preclinical studies imatinib was found to be a potent inhibitor of BCR-ABL, PDGF-R and the c-kit receptor. Imatinib mesylate orally (300 mg twice daily) inhibited the activation of 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 leucopenia[2,31]. One phase II study has evaluated the efficacy of bevacizumab, an humanized anti-VEGF-A monoclonal antibody, for the treatment of patients with HIV-associated KS. VEGF-A is an important paracrine and autocrine growth factor in KS and KSHV has developed redundant mechanisms for its upregulation. A possible explanation is that SCs express VEGF-A receptor 3 and the receptor for platelet-derived growth factor (PDGF) in response to VEGF-A receptors 1 and 2 and proliferate in response to ligands for these receptors (VEGF-C and PDGF). In this study, patients with HIV-KS on a stable HAART regimen received bevacizumab 15 mg/kg every 3 weeks after an initial loading dose. Furthermore, a number of KSHV genes, such as latency-associated nuclear antigen (LANA), v-FLIP, v-cyclin, and kaposin-A, can inhibit apoptosis or directly contribute to SCs proliferation. Thus, optimal targeted therapy for KS may require targeting two or more pathways simultaneously. Overall, this study suggests that bevacizumab has utility in combination with other drugs or after initial reduction of the tumor burden with cytotoxic chemotherapy or in patients who are approaching the maximal safe cumulative dose of anthracyclines. In contrast to most cytotoxic agents active in KS, bevacizumab does not seem to impair immune reconstitution, an important feature for therapeutic interventions for HIV-associated KS[3,32].

Interferon-alfa (IFN-α) has been shown to have immunomodulatory, antiviral and antiangiogenic effects, with a 10-40% overall response rate when administered as high-dose single agent, and equal or superior efficacy at lower doses when combined with antiretroviral therapy. Appropriate response to IFN-α requires continuous treatment for at least 6 months. Significant toxicity includes flu-like symptoms and bone marrow suppression[17].

CONCLUSIONS

Although the incidence has dramatically decreased in the HAART-era, KS remains the second most frequent tumor in the HIV-infected patients. There are still many questions to be answered in the management of patients with AIDS epidemic KS such as the short duration of response despite a remarkable percentage of complete remissions obtained with standard chemotherapy, the high incidence of opportunistic infections during and after chemotherapy, the reduced hematological tolerance to conventional doses of chemotherapy, and the potential drug-drug interactions induced by co-administration of chemotherapy and HAART.

Treatment decision making depends on the extend and rate of tumour growth, disease stage, HIV RNA viral load, CD4 T-cell count and patient's overall conditions. Unfortunately, no standard therapy protocols have been defined and there is no eradicating treatment for KS. HAART with PI, either alone or in combination with systemic and local therapy has a crucial role in controlling KS and long-term prognosis; new therapeutic options, including anti-angiogenic agents are available, but large prospective studies are necessary to better establish their impact on KS control and long-term prognosis. With regard to this, large studies on pharmacokinetics and pharmacogenomics are warranted.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

REFERENCES

1. Dal Maso L, Polesel J, Serraino D, Lise M, Piselli P, Falcini F, Russo A, Intrieri T, Vercelli M, Zambon P, Tagliabue G, Zanetti R, Federico M, Limina RM, Mangone L, De Lisi V, Stracci F, Ferretti S, Piffer S, Budroni M, Donato A, Giacomin A, Bellù F, Fusco M, Madeddu A, Vitarelli S, Tessandori R, Tumino R, Suligoi B, Franceschi S; Cancer and AIDS Registries Linkage (CARL) Study. Pattern of cancer risk in person with AIDS in Italy in the HAART era. Br J Cancer 2009; 100: 840-847.

2. Martellotta F, Berretta M, Vaccher E, Schioppa O, Zanet E, Tirelli U. AIDS-related Kaposi's sarcoma: state of the art and therapeutic strategies. Curr HIV Res 2009; 7: 634-638.
3. Ferla LA, Pinzone MR, Nunnari G, Martellotta F, Lleshi A, Tirelli U, De Paoli P, Berretta M, Cacopardo B. Kaposi's sarcoma in HIV-positive patients: the state of art in the HAART-era. Eur Rev Med Pharmacol Sci 2013; 17: 2354-2365.
4. Nasti G, Martellotta F, Berretta M, Mena M, Fasan M, Di Perri g, Talamini R, Pagano G, Montroni M, Cinelli R, Vaccher E, D'Arminio Monforte A, Tirelli U. Impact of HAART on the presenting features and outcome of patients with AIDS-related kaposi sarcoma. Cancer 2003; 98: 2440-2446.
5. Maurer T, Ponte M, Leslie K. HIV-associated Kaposi's sarcoma with a high CD4 count and a low viral load. N Engl J Med 2007; 357: 1352-1353.
6. Cai Q, Verma SC, Lu J, Robertson ES. Molecular biology of Kaposi's sarcoma associated herpesvirus and related oncogenesis. Adv Virus Res 2010; 78: 87-142.
7. De Sanjose S, Mbisa G, Perez-Alvarez S, Benavente Y, Sukvirach S, Hieu NT, Shin HR, Anh PT, Thomas J Lazcano E, Matos E, Herrero R, Muñoz N, Molano M, Franceschi S, Whitby D. Geographic variation in the prevalence of Kaposi sarcoma-associated herpesvirus and risk factors for transmission. J Infect Dis 2009; 199: 1449-1456.
8. Mesri EA, Cesarman E, Boshoff C. Kaposi's sarcoma and its associated herpesvirus. Nat Rev Cancer 2010; 10: 707-719.
9. Douglas JL, Gustin JK, Dezube BJ, Pantanowitz L, Moses AV. Kaposi's sarcoma: a model of both malignancy and chronic inflammation. Panminerva Med 2007; 49: 119-138.
10. Cavallin LE, Goldschmidt Clermont P, Mesri EA. Molecular and cellular mechanisms of KSHV oncogenesis of Kaposi's sarcoma associated with HIV/AIDS. PloS Pathog 2014; 10: E1004154.
11. Ficarra G, Berson Am, Silverman SJ, Quivey JM, Lozadanur F, Sooy DD, Migliorati CA. Kaposi's sarcoma of the oral cavity: a study of 134 patients with a review of the pathogenesis, epidemiology, clinical aspects and treatment. Oral Surg Oral Med Oral Pathol 1998; 66: 554-560.
12. Mitsuyasu RT. Clinical aspects of AIDS-related Kaposi's sarcoma. Curr Opin Oncol 1993; 5: 835-844.
13. Turoglu HT, Akisik MF, Naddaf SY, Omar WS, Kemf JS, Abdel-Dayem HM. Tumor and infection localization in AIDS patients. Ga-67 and Tl-201 findings. Clin Nucl Med 1998; 23: 446-459.
14. Peer FI, Pui MH, Rae WI, Mosam A. 99mTc-MIBI imaging of AIDS-related Kaposi's sarcoma in the lungs. Nucl Med Commun 2008; 29: 86-90.
15. Nasti G, Talamini R, Antinori A, Martellotta F, Jacchetti G, Chiodo F, Ballardini G, Stoppini L, Di Perri G, Mena M, Tavio M, Vaccher E, D'Arminio Monforte A, Tirelli U; AIDS Clinical Trial Group Staging System in the HAART Era--the Italian Cooperative Group on AIDS and Tumors and the Italian Cohort of Patients Naive from Antiretrovirals. AIDS-related Kaposi's Sarcoma: evaluation of potential new prognostic factors and assessment of the AIDS Clinical Trial Group Staging System in the HAART Era--the Italian Cooperative Group on AIDS and Tumors and the Italian Cohort of Patients Naive From Antiretrovirals. J Clin Oncol 2003; 21: 2876-2882.
16. Stebbing J, Sanitt A, Nelson M, Powles T, Gazzard B, Bower M. A prognostic index for AIDS-associated Kaposi's sarcoma in the era of highly active antiretroviral therapy. Lancet 2006; 367: 1495-1502.
17. Aversa SM, Cattelan AM, Salvagno L, Crivellari G, Banna G, Trevenzoli M, Chiarion-Sileni V, Monfardini S. Treatments of AIDS-related Kaposi's sarcoma. Crit Rev Oncol Hematol 2005; 53: 253-265.
18. Aldenhoven M, Bario NP, Sanders CJ. Therapeutic strategies for Kaposi's sarcoma. Int J STD AIDS 2006; 17: 571-578.
19. Becker G, Botte D. Radiotherapy in the management of Kaposi'sarcoma. Onkologie 2006; 29: 329-333.
20. Spano JP, Costagliola D, Katlama C, Mounier N, Oksenhendler E, Khayat D. AIDS-related malignancies: state of the art and therapeutic challenges. J Clin Oncol 2008; 26: 4834-4842.
21. Leidner RS, Aboulafia DM. Recrudescent Kaposi's sarcoma after initiation of HAART: a manifestation of immune reconstitution syndrome. AIDS Patient Care STDS 2005; 19: 635-644.
22. Tirelli U, Bernardi D. Impact of HAART on the clinical management of AIDS-related cancers. Eur J Cancer 2001; 37: 1320-4132.
23. Brower M, Dalla Pria A, Coyle C, Andrews E, Tittle V, Dhoot S, Nelson M. Prospective stage-stratified approach to AIDS-related Kaposi's sarcoma. J Clin Oncol 2013; 32: 409-414.
24. Lucia MB, Anu R, Handley M, Gillet JP, Wu CP, De Donatis GM, Cauda R, Gottesman MM. Exposure to HIV-protease inhibitors selects for increased expression of P-glycoprotein (ABCB1) in Kaposi's sarcoma cells. Br J Cancer 2011; 105: 513-522.
25. Krown SE, Northfelt DW, Osoba D, Stewart JS. Use of liposomal anthracyclines in Kaposi's sarcoma. Semin Oncol 2004; 31: 36-52.
26. Semeere AS, Busakhala N, Martin JN. Impact of antiretroviral therapy on the incidence of Kaposi's sarcoma in resource-rich and resource-limited settings. Curr Opin Oncol 2012; 24: 522-530.
27. Duggan ST, Keating GM. Pegylated liposomal doxorubicin: a review of its use in metastatic breast cancer, ovarian cancer, multiple myeloma and AIDS-related Kaposi's sarcoma. Drugs 2011; 71: 2531-2558.
28. Lim ST, Tupule A, Espina BM, Levine AM. Weekly docetaxel is safe and effective in the treatment of advanced-stage acquired immunodeficiency syndrome-related Kaposi sarcoma. Cancer 2005; 103: 417-421.
29. Vaccher E, Di Gennaro G, Simonelli C, Schioppa C, Tirelli U; Italian Cooperative Group on AIDS, Tumors (GICAT). Evidence of activity of Irinotecan in patients with advanced AIDS-related Kaposi's sarcoma. AIDS 2005; 19: 1915-1916
30. Corona G, Vaccher E, Sandron S, Sartor I, Tirelli U, Innocenti F, Toffoli G. Lopinavir-ritonavir dramatically affects the pharmacokinetics of irinotecan in HIV patients with Kaposi's sarcoma. Clin Pharmacol Ther 2008; 83: 601-606.
31. Koon HB, Krown SE, Lee JY, Honda K, Rapisuwon S, Wang Z, Aboulafia D, Reid EG, Rudek MA, Dezube BJ, Noy A. Phase II trial of imatinib in AIDS-associated Kaposi's sarcoma: AIDS Malignancy Consortium Protocol 042. J Clin Oncol 2013; 32: 402-408.
32. Uldrick TS, Wyvill KM, Kumar P, O'Mahony D, Bernstein W, Aleman K, Polizzotto MN, Steinberg SM, Pittaluga S, Marshall V, Whitby D, Little RF, Yarchoan R. Phase II study of bevacizumab in patients with HIV-associated Kaposi's sarcoma receiving antiretroviral therapy. J Clin Oncol 2012; 30: 1476-1483.