

Kaposi Sarcoma in HIV-infected patients: an infectious-dermatological outpatient service experience

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ABSTRACT:

- **Objective:** Kaposi Sarcoma (KS) remains an important dermatological and/or systemic neoplasia in HIV-infected patients. The aim of this study was to describe the KS incidence and characteristics in our patient population and to evaluate the recurrences in the whole database and in specific subsets of patients.
- **Materials and Methods:** We created a database where we collected retrospectively clinical and laboratory data regarding HIV-infected patients with KS and actively followed in our service. The use, type and duration of cART regimens, chemotherapy, electrochemotherapy or α -interferon (α -IFN) were recorded. Baseline was set at the diagnosis of KS and follow-up was censored at 2017/06/03. Descriptive statistical analysis was performed. The incidence of recurrences was calculated as the number of events during follow-up time. The survival free from recurrences was evaluated by Kaplan-Meier estimate.
- **Results:** Thirty-five patients were included in the database for a 204.95 patient-year follow-up (PYFU). Median calendar year when KS was diagnosed was 2011. Ten (27%) patients had visceral localizations at baseline. Twelve (33.3%) patients were treated with a median of 11 cycles of chemotherapy for a median time of 4 months, 5 (13.9%) with electrochemotherapy and 9 (24.3%) with α -IFN for a median time of 11 months. Recurrences were observed in seven patients, the incidence was 3.4% PYFU with a median (IQR, range) time free from new episodes of 4.9 (1.4-8.85, 0.39-18.23) years. All the patients with visceral lesions with a sufficient follow-up had documented remission.
- **Conclusions:** KS remains a relevant AIDS-related event and new diagnoses are still frequent even in recent years. In our experience recurrences are infrequent. Even if no unique treatment and no possibly preferred antiretroviral regimens or drug classes are recommended by the International Guidelines for epidemic KS, our experience showed that different strategies proposed for its management are effective and safe.
- **Keywords:** HIV, Kaposi Sarcoma, Chemotherapy, Electrochemotherapy.

INTRODUCTION

Despite the constant improvement in the survival and quality of life in HIV infected patients, and a reduction in the cases of Kaposi Sarcoma (KS) has repeatedly been reported¹⁻³, the incidence of this AIDS-related cancer remains relevant⁴⁻⁶. In fact, KS still represents an important derma-

tological and/or systemic HIV-related neoplasia in patients with late presentation or immune reconstitution syndrome occurring soon after starting combination AntiRetroviral Therapy (cART)⁵. Our Outpatient Service of Dermatology, Sexually Transmitted Disease (STD) and HIV-infection, part of a dermatology hospital, has developed a significant experience in the management of KS.

The Italian and International guidelines for the Management of HIV-infected patients strongly recommend the early treatment of HIV-infected patients with KS at any CD4 cell count and together with the antineoplastic therapy^{7,8}, but no specific recommendations regarding preferred regimens or drug classes are given. Although conclusive treatment evidence is lacking, data suggesting that Protease Inhibitors (PIs) with or without ritonavir-boosting may be a better choice in patients with KS are available in the literature. In particular, PIs have been reported to have a direct effect against KS and an antiangiogenic effect since the earliest cART era⁹⁻¹¹ and to reduce the shedding of the KS-associated HHV8 virus¹². In a large cohort, a longer time on a boosted PI-based cART, but not on other classes-based regimens, has also been shown to be associated to a lower KS incidence¹³ but other cohort studies did not confirmed it¹⁴.

The Italian and English guidelines recommend the use of chemotherapy in addition to the implementation of combination cART in patients with T1 stage KS according to the ACTG classification^{15,16} and in those with Immune-Reconstitution Syndrome (IRIS)-associated lesions or visceral involvement while the patients who develop KS despite virological suppression and high CD4 cell count should be included in clinical trials^{7,17}. Although the English guidelines discuss many different approaches to chemotherapy for KS, no suggestions are offered about the number of cycles and the duration of chemotherapy¹⁷ and electrochemotherapy, a combination between local treatment and systemic chemotherapy, which has been used with good results on patients with classic and epidemic KS¹⁸⁻²¹, is never considered.

Nevertheless, the recent changes in HIV treatment in many international guidelines, which elect the integrase inhibitors as the mainly preferred third drug, and the current availability of new cobicistat-boosted PI regimens may have a new impact on KS. In fact, a first case of a patient presenting a relapse of his KS with a concomitant rebound of HHV8 viral load while on an integrase inhibitors-based cART has been recently described in Milan²². Furthermore, it has to be evaluated the impact of the increasing use of Less Drug regimens (dual or monotherapies) on K, especially in some countries, particularly in Europe and in Italy.

Therefore, we built a database collecting clinical and laboratory data of our HIV-infected patients with KS, who are still actively followed in our service that will be constantly updated in order to check for stable clinical remission or recurrences of KS.

The aim of this paper is to describe our patient population and the history of KS and, in particular, to evaluate the incidence of recurrences in general and in specific subsets of patients.

MATERIALS AND METHODS

This is a retrospective observational analysis. We collected clinical and laboratory data regarding HIV-infected patients who are currently still actively followed in our Out-patient service. The clinical data included time between

the diagnosis of KS and HIV infection, treatment with chemotherapy or electrochemotherapy or alpha-interferon with number of applications and treatment duration and the outcome of KS (remission of cutaneous and/or visceral lesions or recurrences). Baseline was set at the diagnosis of KS and follow-up was censored at 2017/06/03. Recurrence of KS was defined as the appearance of new KS lesions after a documented remission. Whenever possible the ACTG response criteria were used to identify the clinical response^{15,16}. In case of multiple recurrences, the follow-up was censored at the first episode.

Liposomal doxorubicin was used for chemotherapy at the recommended dose of 20 mg/m² every three weeks¹⁷ and the number and duration of cycles were recorded for each patient. Intravenous Bleomycin was administered intravenously eight minutes before electrochemotherapy as previously described¹⁸. Alpha-interferon was administered at the dose of 6000000 units with a subcutaneous injection every other day and the treatment duration was recorded.

Descriptive statistical analysis was performed as appropriate for continuous and categorical variables. The incidence of recurrences was calculated as the number of events during the follow-up time. The survival free from recurrences was evaluated by Kaplan-Meier estimate.

RESULTS

Currently, 35 patients with an established diagnosis of KS are still actively followed in our Service and were included in the database for a 204.95 patient-year follow-up (PYFU). Twenty patients were diagnosed with KS in this decade, 13 in the last 3 years: 2 in 2014, 4 in 2015, 6 in 2016 and by now 1 in 2017). All of them were male, none had HCV or HBV co-infection, all but one were Italian and all but one weren't exposed to suboptimal antiretroviral regimens before KS was diagnosed.

The patients' characteristics at the first diagnosis of KS of the entire population and in the specific subgroups of patients who are currently receiving a boosted atazanavir- or boosted darunavir- based cART and in those who were switched to a cobicistat-boosted cART are summarized in Table 1.

The presentation of KS and the treatment choices are summarized in Table 2. The patients who underwent surgery were particularly those with lesions in the oral cavity. Among the patients who underwent electrochemotherapy, one patient required two sessions for two different episodes and a single non-responder patient received up to 20 sessions complicated by left leg ulcer requiring specific advanced medications and subsequent plastic surgery. He had an aggressive KS, which was diagnosed ten months before acquiring HIV-infection.

After KS was diagnosed in treatment naive patients, a standard three-drug cART was prescribed to 83.8% of patients; only one patient was prescribed a mega-cART with more than 3 antiretrovirals. The prescribed antiretroviral regimen was boosted PI-based in 83.8% of patients. Only 4 (11.4%) patients were on cART before KS was diagnosed, two of them were exposed to a ritonavir-boosted lopina-

Table 1. Patients' characteristics at the first diagnosis of KS in the whole database and in the specific subgroups of patients who are currently receiving a boosted atazanavir-(ATV) or boosted darunavir(DRV)- based cART and in those who were switched to a cobicistat-boosted (Cobi) cART.

	All pts (n= 35)	Current ATV (n= 16)	Current DRV (n= 15)	Cobi booster (n= 19)
Age at diagnosis of KS, median (IQR, range), years	41 (35-47, 26-70)	40 (34-45, 26-67)	42 (38-55, 31-70)	39 (35-47, 26-60)
Calendar year KS was diagnosed, median (IQR, range)	2011 (2008-2015, 1999-2017)	2013 (2006-2015, 1999-2016)	2011 (2008-2014, 2001-2017)	2011 (2008-2015, 2002-2017)
Median (IQR, range) time between the KS and HIV diagnosis, months	0 (0-0.6, -3-22.7)	0 (0-0.6, -0.12-22.7)	0 (0-2.6, -3-13.6)	0 (0-0.5, -3-13.6)
Time between the KS and HIV diagnosis, n (%)				
– KS three years before HIV	1 (2.9)	0	1 (6.7)	1 (5.3)
– KS -0.12 to 0.92 years after HIV	26 (74.3)	13 (81.2)	10 (66.7)	14 (73.7)
– KS 1 to 3 years after HIV	5 (14.3)	2 (12.5)	3 (20)	3 (15.7)
– KS more than 10 years after HIV	2 (5.7)	1 (6.3)	1 (6.7)	1 (5.3)
Nadir CD4 cell count, median (IQR) cells/mm ³	190 (97-298)	231 (140-311)	164 (66-273)	210 (97-338)
Zenith VL, median (IQR) log ₁₀ copies/mL	5.12 (4.84-5.55)	5.12 (4.77-5.55)	5.3 (4.87-5.51)	5.23 (4.86-5.51)
BLCD4 cell count, median (IQR) cells/mm ³	200 (113-318)	231 (140-311)	199 (103-359)	210 (97-338)
BLCD4 percent value, median (IQR)	15 (11-20)	15 (12-22)	13 (12-20)	14 (12-25)
BL CD4/CD8 ratio, median (IQR)	0.21 (0.16-0.4)	0.28 (0.15-0.41)	0.2 (0.17-0.45)	0.21 (0.17-0.45)
BLVL, median (IQR) log ₁₀ copies/ml	5.07 (4.56-5.46)	4.98 (4.21-5.52)	5.17 (4.7-5.4)	5.23 (4.77-5.51)

vir-based regimen, another one to an efavirenz-based regimen and the last one to seven regimens before. The patient who was exposed to seven regimens before his first KS diagnosis had switched to a ritonavir-boosted atazanavir-based dual regimen just one month earlier after eight years on a nevirapine-based regimen when KS emerged; his dual regimen was then reinforced by switching from lamivudine to dolutegravir, with no recurrences.

The remission of visceral lesions was documented in eight patients (two patients are still on chemotherapy and restaging was not performed yet); the only patient in whom the remission could not be documented has no clinical signs of active disease since eight years.

Recurrences were observed in seven patients with an incidence of 3.4% PYFU with a median (IQR, range) time free from new episodes of 4.9 (1.4-8.85, 0.39-18.23)

Table 2. KS presentation and treatment choices in the whole database and in the specific subgroups of patients who are currently receiving a boosted atazanavir- or boosted darunavir- based cART and in those who were switched to a cobicistat-boosted cART.

	All pts (n= 35)	Current ATV (n= 16)	Current DRV (n= 15)	Cobi booster (n= 19)
Biopsy available, n (%)	21 (56.8)	3 (18.8)	8 (53.3)	12 (63.2)
Visceral localization, n (%)	10 (27)	2 (12.5)	8 (53.3)	7 (36.8)
Mucosal, n (%)	5 (13.5)	1 (6.3)	4 (26.7)	4 (21.1)
Gastric, n (%)	3 (8.1)	1 (6.3)	2 (13.3)	2 (10.5)
Colon, n (%)	3 (8.1)	1 (6.3)	2 (13.3)	2 (10.5)
Pulmonary, n (%)	1 (2.7)	1 (6.3)	1 (6.7)	None
Surgery, n (%)	3 (8.1)	1 (6.3)	2 (13.3)	2 (10.5)
Chemotherapy (liposomal Doxorubicin), n (%)	12 (33.3)	11 (4-13, 4-42)	4 (2-9, 2-29)	5 (31.3)
N Chemotherapy cycles, median (IQR, range)	10 (4-14, 4-15)	2 (2-5, 2-6)	5 (33.3)	12 (4-27, 4-42)
Months chemotherapy, median (IQR, range)	6 (3-21, 2-29)	5 (26.3)	12 (8-29, 4-42)	7 (2-25, 2-29)
ECT, n (%)	5 (13.9)	1 (6.3)	3 (20)	4 (22.2)
α-IFN	9 (24.3)	4 (25)	4 (26.7)	4 (21.1)
Time on α-IFN, median (IQR, range) months	11 (5-19, 2-50)	12 (3-19, 2-20)	11 (5-41, 4-50)	10 (5-16, 4-16)
BLCD4 percent value, median (IQR)	15 (11-20)	15 (12-22)	13 (12-20)	14 (12-25)
BL CD4/CD8 ratio, median (IQR)	0.21 (0.16-0.4)	0.28 (0.15-0.41)	0.2 (0.17-0.45)	0.21 (0.17-0.45)
BLVL, median (IQR) log ₁₀ copies/ml	5.07 (4.56-5.46)	4.98 (4.21-5.52)	5.17 (4.7-5.4)	5.23 (4.77-5.51)

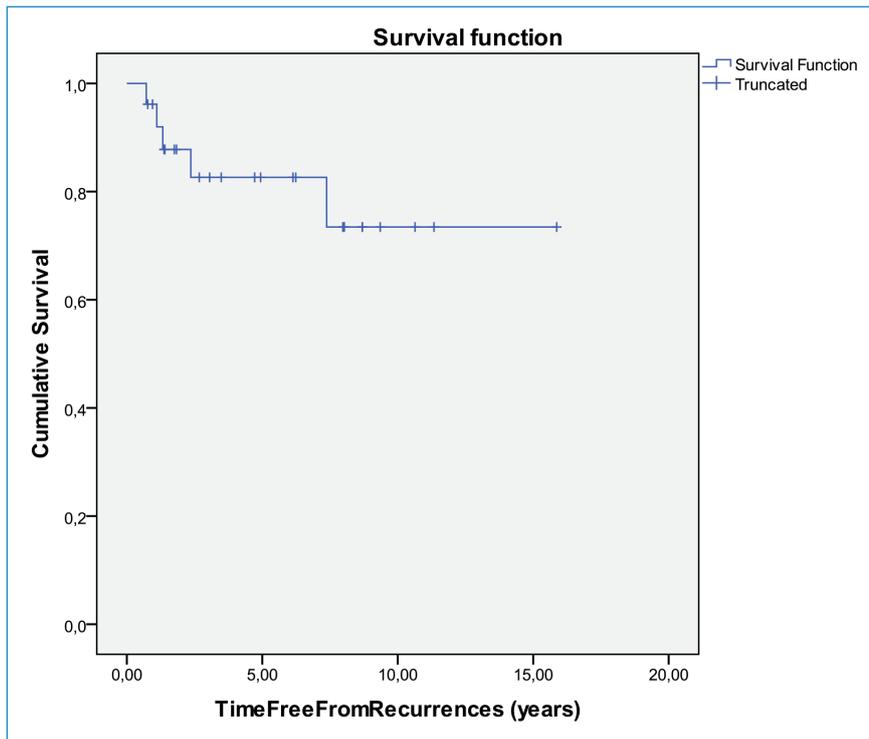


Figure 1. Kaplan-Meier estimated time free from recurrence events, years.

years; the Kaplan-Meier estimated survival free from recurrences is shown in Figure 1. Three patients had multiple episodes. The first of them had one new lesion at the end of 2013, two years after the first diagnosis and it didn't require specific treatment; he had no further episodes. The second one had two recurrences: in 2014 he experienced a worsening of cutaneous KS of the legs after two years on cART, he did not respond to three cycles of liposomal-doxorubicin chemotherapy and he was successfully treated with electrochemotherapy in June 2015; one year later a new lesion appeared and it was successfully treated with a new session of electrochemotherapy. Both patients were receiving tenofovir disoproxil fumarate plus emtricitabine and efavirenz at the recurrence; they didn't change their therapy after the episodes. The last one (the same patient who was diagnosed with a very aggressive KS before acquiring HIV infection and who is on mega-cART and non responder to electrochemotherapy and to chemotherapy) had two episodes in the subsequent two years, the last one in 2015. This last patient was also the only one among these five who had visceral lesions at diagnosis and their remission was documented in 2011.

Currently, sixteen of our patients are receiving boosted atazanavir and fifteen are receiving boosted darunavir. In the subgroup of patients receiving atazanavir, the three patients with visceral localization had one mucosal lesion in the oral cavity, one gastric and colon localization, and one pulmonary localization. Seven patients in this subset have currently been receiving a dual cART for a median (IQR, range) of 3.2 (0.95-5.6, 0.6-8.4) years with no recurrences; only one patient underwent re-intensification with tenofovir/raltegravir plus emtricitabine due to unconfirmed virological blips. Four out of these seven were switched to cobi-

cistat-boosted atazanavir since February 2017 with no virological rebounds and no KS recurrences observed.

Among the 15 patients receiving darunavir, four patients with visceral localizations had mucosal lesions in the oral cavity, two had gastric and two colon localizations; all of them had documented visceral remission except the previously described non-responder. Two of the 4 patients with oral cavity lesions were treated with surgery without recurrences. Among the patients treated with electrochemotherapy, the one who received multiple sessions was the previously described non-responder patient. Only two patients are receiving a darunavir-based LDR regimens (a dual regimen with maraviroc since September 2013 as 5th cART regimen and a monotherapy since March 2013 as second cART regimen, switched to Cobicistat in April 2017) with no new episodes observed. Six out of these eight patients switched to Cobicistat since February 2017 and no recurrences were observed after the switch, including the non-responder patient whose last episode occurred in October 2015.

DISCUSSION

This is a retrospective observational descriptive analysis of the patient population with KS in HIV in a Service who uniquely joins the skills of Dermatology and Venerology as well as of the Infectious Disease specialists in Rome, Italy.

Despite the efforts and advances in HIV care, KS remains a relevant AIDS-related event, mainly in advanced naïve patients. In our study population the majority of diagnosis occurred in advanced treatment naïve patients with 74% being diagnosed with KS within one year from the diagnosis of HIV infection and median

baseline CD4 cell count of 200 cells/mm³ and median baseline viral load of 5 log₁₀ copies/ml.

In our database above one third of the patients was diagnosed with KS recently, with 2011 as the median year of diagnosis. The choice to include only patients who are still currently followed in our Service has probably biased the data, nevertheless this choice was functional to our aim to look at the impact of the current antiretroviral regimens and the other therapies for KS.

All treatment regimens for KS were effective; chemotherapy required a median of 11 cycles in a median of 4 months while a single session of electrochemotherapy was sufficient for almost all patients. One of the two patients who underwent multiple electrochemotherapy sessions had two distinct episodes, one year apart from each other, and the non-responder patient had a very aggressive KS disease, which was acquired three years before HIV infection. Such peculiar KS diseases in young HIV-negative homosexual men were described in literature before²³. In this case the subsequent acquisition of HIV infection worsened the aggressive KS disease; the patient completed 42 chemotherapy cycles by the end of March 2017 and at the last observation (June 30th 2017) no active KS lesions were observed. All the patients with visceral lesions with a sufficient follow-up had documented remission.

Recurrences were infrequent; the limited size of our patient population prevented us from looking for possible associated factors at this stage; in particular, no conclusions can be drawn on the role of the different antiretroviral classes in our small dataset. The item could deserve a more extensive evaluation in a larger and less homogeneous cohort. Boosted protease inhibitors-based less drug regimen are used in well selected patients since at least 5 years in our Service while co-bicistat-boosted atazanavir or ritonavir fixed dose were not introduced before February 2017; the patients who were switched did not show recurrences at the moment, but this observation will require confirmation in a longer follow-up time. In the patient who presented his first KS episode soon after switching to a ritonavir-boosted protease inhibitor-based dual regimen after years on a nevirapine-based regimen we can't exclude that immune-reconstitution could have played a role.

CONCLUSIONS

KS remains a relevant AIDS-related event and new diagnoses are still frequent even in recent years. In our experience recurrences are infrequent and all the treatment proposed for its management are effective and safe, including electrochemotherapy, which has showed to be effective in our experience. The impact of new antiretroviral regimens remains to be evaluated in an extended follow-up and possibly in a larger dataset.

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CONFLICT OF INTEREST:

The Authors declare that they have no conflict of interests

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