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Lucia BRAMBILLA, Giovanni GENOVESE, Emilio BERTI, Ketty PERIS, Franco RONGIOLETTI, Giuseppe MICALI, Fabio AYALA, Silvia DELLA BELLA , Roberta MANCUSO , Piergiacomo CALZAVARA-PINTON, Athanasia TOURLAKI

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Lucia Brambilla [1], Giovanni Genovese [1,2], Emilio Berti [1,2], Ketty Peris [3,4], Franco Rongioletti [5], Giuseppe Micali [6], Fabio Ayala [7], Silvia Della Bella [8,9], Roberta Mancuso [10], Piergiacomo Calzavara Pinton [11], Athanasia Tourlaki [1]*

[1] U.O. Dermatologia, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milano, Italy.

[2] Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano

[3] Fondazione Policlinico Universitario A. Gemelli IRCCS, Dermatologia, Roma, Italy

[4] Università Cattolica del Sacro Cuore, Dermatologia, Roma, Italy

[5] Unit of Dermatology, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

[6] Dermatology Clinic, University of Catania, Catania, Italy

[7] Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

[8] Unit of Clinical and Experimental Immunology, Humanitas Clinical and Research Center-IRCCS, Rozzano, Milano, Italy.

[9] Department of Medical Biotechnologies and Translational Medicine, University of Milan, Milan, Italy

[10] IRCCS Fondazione Don Carlo Gnocchi, Milano, Italy

[11] Department of Dermatology, University of Brescia, Brescia, Italy

Corresponding author:

Dr. Athanasia Tourlaki, U.O. Dermatologia, Ospedale Maggiore Policlinico, Via Pace 9, 20122 Milano, Italy. E-mail: atourlaki@gmail.com

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ABSTRACT

Kaposi's sarcoma (KS) is a lymphangioproliferative disorder associated with human herpesvirus 8 (HHV8) infection. Four clinical subtypes are recognized: classic, endemic, epidemic (HIV-related) and iatrogenic. KS diagnosis is based on clinical features, histopathological assessment, and HHV8 serology. Classic KS is usually skin-limited and has a chronic course, while the iatrogenic variant may show mucosal, nodal or visceral involvement. Clinical staging is fundamental to guide the management. Localized disease may be treated with different local therapies, even if there are no randomized trials comparing these different modalities. Aggressive, disseminated KS and cases with visceral involvement usually require systemic chemotherapy, most commonly vinblastine, bleomycin or paclitaxel. Iatrogenic KS needs immunosuppression tapering/withdrawal and, if possible, switch to m-TOR inhibitors in post-transplant KS. The present work by a panel of Italian experts provides guidelines on KS diagnosis and management based on a critical review of the literature and a long and extensive personal experience.

INTRODUCTION

Kaposi's sarcoma (KS) is a multifocal neoplasm of lymphatic endothelium-derived cells primarily involving the skin. Four variants of KS have been distinguished based on clinical and epidemiological criteria: classic, endemic, epidemic (HIV-related) and iatrogenic.[1,2]

Classic KS usually occurs among elderly men of the Mediterranean area or of Jewish descent and is mainly associated with a long indolent course. Iatrogenic KS is linked to immunodeficiency due to immunosuppressive therapies and is often observed in organ transplant recipients or in patients with autoimmune disorders.[1,3] Since 1994, when the human herpes virus 8 (HHV8) was identified,[4] it became clear that the virus is necessary but not sufficient for development of KS. Although HHV8 has been reported worldwide, it has a high prevalence in some regions, such as the Mediterranean basin. Two Italian hot spots for KS are Sicily and, particularly Sardinia, where a general HHV8 seroprevalence of 35%, with a range of 15.3% to 46.3%, has been detected.[5,6] HHV8 infection is usually latent in endemic areas, and the virus may be transmitted via saliva, grafted organ, sexual contact, perinatal infection or blood transfusion.[2]

Primary infection in most individuals does not progress to a neoplastic disease; a CD8-cell response, in fact, controls HHV8 replication.[5,6] Nevertheless, in elderly people or individuals with impaired immune response, like organ transplant recipients, the prevalence of KS is higher than in the general population.[3] Staging procedures and therapeutic approaches for classic KS and iatrogenic KS are not standardized; therefore, instrumental examinations and treatments proposed to patients can vary amongst institutions.

The present guidelines have been developed by an Italian group of experts and are based on personal experience and literature search on MEDLINE from 1952 up to November 2019 for publication in all languages on classic KS and iatrogenic KS. Keywords used included: "Kaposi's sarcoma", "classic", "Mediterranean", "iatrogenic", "staging", "therapy", "treatment", "follow-up". Furthermore, we considered the European Dermatology Forum (EDF), European Association of Dermato-Oncology (EADO) and European Organization for Research and Treatment of Cancer (EORTC) international consensus-based guidelines for the treatment and management of KS[7], to provide the Italian dermatological community easily applicable recommendations adapted to the Italian healthcare system for the diagnosis and management of classic and iatrogenic KS.

EPIDEMIOLOGY

Classic KS

Incidence of classic KS is higher in the Mediterranean countries compared with Northern European countries. In Italy, the overall incidence rate of classic KS was estimated to be 1/100000 in men and 0.4/100000 in women, with substantial variations across the country.[8] The highest incidence was found in Sardinia, where a standardised incidence of classic KS ranged from 1.58/100000 to 2.49/100000.[9,10] Interestingly, high standardised rates (2.5/100000 in men and 0.7/100000 women) were also observed in the province of Mantua (Northern Italy).[11] Classic KS predominates in men with a sex ratio of 2.5:1.[8,9] Age is also an important risk factor,[12] with a peak incidence in the sixth decade.[13] Due to its indolent clinical course, classic KS does not significantly influence mortality rate of the affected population. A study on 204 classic KS from Italian population-based cancer registries showed a median survival of 9.4 years, similar to the Italian general population of the same sex and age.[14]

Iatrogenic KS

The incidence of KS in organ transplant recipients (OTR) is between 100- and 500- fold higher than in the general population, with variability in different geographical areas,[15,16] whereas it is two- to four-fold lower compared with OTR in patients immunosuppressed for other medical conditions.[17,18] A recent Italian single-center retrospective study identified 143 iatrogenic KS (prevalence: 10.3%) in a cohort of 1389 patients.[3] The mean latency period to develop KS was longer in OTR than in non-OTR: 41 versus 28 months, respectively. In a previous study, the peak of occurrence of KS was found during the first 2 years after transplantation, ranging from a few weeks to 18 years.[19] In a recent French case-series, renal graft survival in post kidney transplant KS patients was 85% and 75% at 5 and 10 years, similar to overall survival in kidney transplant recipients.[20]

CLINICAL PRESENTATION

Both classic and iatrogenic KS typically present with violaceous, reddish or brownish macules, patches, plaques and/or nodules on the skin. Nodules may ulcerate and bleed or become hyperkeratotic. Some dermoscopic findings, such as polychromatic colour change, collarette sign, white lines, white clods, and serpentine vessels may suggest the diagnosis of KS, especially in case of nodular lesions.[21]

Lymphedema is the most common local cutaneous complication, occurring in 20% of classic KS patients, and may seriously impair patients' quality of life, sometimes in the earliest stages of the disease.[22,23] Cutaneous localization and severity, mucosal, nodal and visceral involvement depend on the type of KS. Lower limbs are the most commonly involved cutaneous site in classic KS,

followed by upper limbs, head and trunk.[24] Oral,[25] genital[26,27] and, less commonly, conjunctival[28] mucosal involvements are possible. Gastrointestinal[29] and lymph node localizations are the most common visceral involvements in classic and iatrogenic KS, while bladder,[30] bone,[31] lung[32] and kidney[33] localizations are exceptional.

The skin lesions can remain stable for months or even years without progression, or grow rapidly over a few weeks and disseminate. Classic KS has generally an indolent course, whereas post-transplant KS may be disseminated and life-threatening if immunosuppressive therapy is not adjusted. Anaplastic transformation of classic KS, first described in 1959 by Cox and Helwig,[34] is a rare event clinically characterized by increase in local aggressiveness, propensity for deep invasion and increased metastatic capacity.

DIAGNOSTIC WORK-UP AND STAGING

Patients with suspect KS should be evaluated in a tertiary care Dermatological referral center by well-trained dermatologists.

Diagnosis

After diagnosis confirmation upon histology and HHV8 DNA detection and/or HHV8 serology, patients should be clinically and instrumentally staged (Figure 1).

Histopathology

Histopathology is the gold standard for diagnosis of KS and the different clinical stages share similar histologic findings. KS patches are characterized by increased number of dilated, convoluted, thin-walled vascular spaces covered by thin endothelium cells in the dermis. They are normally associated with a sparse to moderate inflammatory lymphocyte- and plasma cell-rich infiltrate in the dermis. The above findings are more prominent in plaques of KS, which show markedly dilated, jagged vascular spaces lined by normal or slightly atypical endothelial cells. In addition, there may be oval and spindle cells between collagen bundles in the entire dermis. Nodular lesions of KS are characterized by numerous atypical spindle cells, forming large aggregations and interweaving fascicles throughout the dermis. Erythrocytes and siderophages are usually present between the spindle cells, and there is often a mixed inflammatory-cell infiltrate consisting of plasma cells, lymphocytes, and dendritic cells. Regressed KS lesions show only fibrous tissue with hemosiderin pigment deposits and no spindle cells.

While the clinical-pathological classification described above has no prognostic value,[35] anaplastic KS which is an extremely rare variant resembling angiosarcoma, has a poor prognosis. More similar

to angiosarcomas than classic KS, anaplastic KS shows a significant degree of cellular pleomorphism and a high mitotic index.[36,37]

KS spindle cells stain positive for vascular markers such as ERG, CD34 and CD31, and they are frequently positive for lymphatic endothelial markers such as D2-40 and LYVE1.[38]

HHV8 in lesional tissue

Immunohistochemistry for antigens of HHV8 plays a key role in differentiating KS from other types of vascular tumours.[38,39] In fact, immunohistochemistry using a monoclonal antibody against HHV8 latent nuclear antigen (LANA) is routinely used in most pathology laboratories.

On the other hand, PCR-based methods detecting HHV8 viral sequences in KS lesions, are generally available in a few highly specialized pathology laboratories.[40,41]

HHV8 serology and viral load

Serological tests commercially available have been developed based on immunofluorescence, Western blot and enzyme-linked immunosorbent assays to detect antibodies against latent and lytic genes of HHV8.[42] Although HHV8 viral load in peripheral blood mononuclear cells of KS individuals correlates with tumour burden, this test is useful only for the diagnosis and should not be used during the follow-up or to predict the occurrence of KS in transplant recipients due to low interval variations.[43]

Clinical and instrumental staging

Classic KS is an endothelial sarcoma primarily affecting the skin with a possible visceral involvement, mainly lymph nodes and gastrointestinal tract. Each localization should be considered primary and not metastatic; therefore, the TNM classification is not useful.

There is no universally accepted staging classification for classic KS and iatrogenic KS. Brambilla *et al*.[44] proposed a 4-stage scoring system, with each stage further subdivided into two categories (A and B) according to the speed of disease evolution (Table 1), evaluated on the basis of nodule and/or plaque enlargement, or appearance of new lesions after three months of observation. Complications may be subjective, such as functional impairment and pain, and objective, such as lymphedema, bleeding and ulceration, and may be present in all stages, even if they are more common in stages III and IV. The visceral involvement also, if present, occurs generally in stage III or IV.

After clinical staging, the patient should undergo specialist consultations and instrumental investigations to exclude evidence of internal organ involvement (Table 2).

THERAPY

Classic KS is a chronic disease which is rarely life-threatening. However, since it negatively affects the quality of life of elderly patients, any therapeutic choice should consider not only the clinical and instrumental staging but also the patient's comorbidities and psycho-physical conditions. Symptomatic skin or mucosal KS lesions are generally treated, while for asymptomatic, slow evolving lesions, a wait-and-see attitude may be chosen, as a spontaneous improvement may occur. Local treatments can be used alone in localized KS, or in combination with systemic treatments in advanced disseminated KS (Table 3).

Local therapy

Topical therapy alone, mainly intralesional vincristine,[24] curettage of nodular lesions[45] and silver nitrate cauterization[46] may be used in patients with macular-nodular (stage 1) or infiltrative (stage 2) KS with a slow disease progression. Elastic stockings have been demonstrated to be important tools for the management of lymphedema of the lower extremities associated to classic KS,[47] and they are also important for the treatment of KS plaques, according to the clinical experience of some of the experts of our guidelines.

Surgical excision and curettage

Classic surgical excision of KS lesions has the disadvantages of post-treatment scarring, functional impairment, and high recurrence rates.[45,48] A recent Italian prospective study showed that curettage followed by the application of 130 volume hydrogen peroxide for haemostasis, is a safer, effective and simple alternative to classic surgical excision for the treatment of KS nodules.[45]

Local or intralesional chemical or immune modifying agents

Intralesional chemotherapies are local approaches characterized by good response rates for KS nodules. Intralesional vincristine, a vinca alkaloid antiblastic drug that acts disrupting microtubular function, is an inexpensive option and gives excellent therapeutic response with full healing in most of the cases, low cutaneous reactions and negligible systemic absorption.[24,49] A prospective trial on 151 patients demonstrated the effectiveness of intralesional vincristine in classic KS, with a response rate of 98.7% at week 12.[24] In addition, intralesional vincristine injection treatment is less painful than intralesional vinblastine, which has been reported to have a response rate of about 70%.[50]

Other physical and chemical treatments

CO_2 laser therapy and cryosurgery can be used in superficial lesions, with reported 80 to 90% overall response rate. As KS lesions are vascular tumours located in the dermis, the necrosis caused by CO2 laser vaporization and cryosurgery often lead to hypopigmented sequelae and scarring.[51-54] On the other hand, recent published data report very encouraging results in patients with nodular KS treated with neodymium-doped yttrium aluminum garnet (Nd:YAG) laser delivered through a tilted angle.[55] Silver nitrate cauterization may represent a safe, effective, cheap and easy-to-use treatment for fungating, oozing KS tumours.[46] Other topical treatments used for KS include: intralesional bleomycin,[56] which is more painful and less effective than intralesional vincristine; intralesional α-interferon, often associated with pain, inflammatory reaction and elevated costs;[57,58] topical application of imiquimod [59-61] or alitretinoin [62,63] both more expensive and less effective than other local treatments.

Electrochemotherapy

Electrochemotherapy is a procedure consisting of the injection of chemotherapeutic agents followed up by the application of electric pulses directly into the cutaneous tumour lesions, leading to enhanced membrane permeability and increase drug cytotoxicity. In a two-center prospective phase II trial involving 23 patients with unresectable KS, complete response was observed in approximately 60% of patients.[64] Similarly, high response rates were described by Latini *et al*.[65] and Di Monta *et al*.[66] in two independent cohorts of KS patients treated with electrochemotherapy with intravenous bleomycin. The need of general or spinal anaesthesia is the main drawback of this treatment. Furthermore, pain and erythema in the treated and surrounding area are common side effects.

Radiotherapy

Radiotherapy is an efficient local treatment for KS, but it is not a first-line therapy because of its possible acute and chronic side effects, especially in the pretibial and malleolar region. Moreover, radiotherapy cannot be repeated in the same area for the increasing risk of radiodermatitis and chronic ulcerations. It can be applied to nodular lesions and plaques, and fractionated doses (2-6 Gy/fraction) of 20 to 30 Gy is the preferred schedule.[67] Complete response rates have been achieved in 98.7% of patients belonging to an Italian series of classic KS.[67,68] However, response rates in the literature vary widely, depending on the study, device and radiation dose.[67-69]

Systemic treatment

Aggressive, diffuse and/or visceral cases of KS are usually managed with systemic therapy. Prospective trials for systemic treatment of classic KS are few, and clinical practice is based on retrospective studies with limited data on the effectiveness and safety of systemic agents. Systemic chemotherapy is generally proposed to patients with rapidly evolving stage II disease and to patients with stage III and IV disease. Taking into consideration that patients with classic KS or iatrogenic KS are usually elderly with comorbidities, the recommended first-line agents are vinblastine alone, vinblastine associated with bleomycin, or paclitaxel.

First line treatment

Vinblastine as monotherapy or combined with bleomycin

Vinblastine as monotherapy (up to 10 mg intravenous every 3 weeks) is associated with an overall response rate of 58%.[70] Combination therapy with intramuscular bleomycin 15 IU every 3 weeks resulted in an overall response rate of 97% (partial response rate 76%; complete response rate 21%), with a limited toxicity.[71] The most common side effect of vinblastine is myelosuppression, while bleomycin may frequently cause fever, rash and Raynaud's phenomenon. The most severe bleomycin-related adverse event, occurring upon increasing dosage, is impaired lung function and pulmonary fibrosis.

Paclitaxel

Paclitaxel (PCT) has been found effective in the treatment of refractory or life-threatening HIV-negative KS, with an overall response rate higher than 95%.[72,73] A recent Italian study found that intravenous paclitaxel administered at a fixed dose of 100 mg weekly is effective for the treatment of HIV-negative KS, both as first or second-line treatment, and can be repeated without loss of efficacy.[74] Paclitaxel is generally well tolerated with low toxicity, even in elderly patients. Neutropenia, leukopenia, anaemia, nausea/vomiting, and peripheral neuropathy (mostly reversible) are possible side effects.[72,73] Immediate hypersensitivity reactions, which occur in 5 to 10% of patients treated with taxanes, may be prevented by premedication with oral dexamethasone 4 mg the day before, and dexamethasone 4-8 mg i.v. plus clorpheniramine maleate 10 mg i.m. just before starting paclitaxel infusion.[72,75]

Second line treatment

Pegylated liposomal doxorubicin (PLD)

PLD can be considered as a second-line treatment for aggressive/disseminated HIV-negative KS. In a cohort of 20 patients with advanced classic KS, PLD 20mg/m2 administered intravenously every

3 weeks was associated with complete and partial response rates of 10% and 70%, respectively.[76] Potouridou *et al*.[77] found a similar response rate in a cohort of 10 elderly patients with classic KS. The safety profile of PLD was good, with approximately 5% grade 4 neutropenia and 5% hand-foot syndrome.[76,78,79] Cardiotoxicity is a possible side effect, more common with the non-encapsulated precursor of doxorubicin.

Third line treatment

Gemcitabine

Gemcitabine is a third-line chemotherapy in classic KS showing good response rates with long progression-free survival periods in a small case series.[80] Indeed, 10 patients with recurrent aggressive classic KS were treated with gemcitabine (administered intravenously at the dose of 1.2 g/week for 2 weeks, followed by a 1-week interval, until maximal response was reached) achieving a complete response in 1/10 patients and a partial response in 9/10 patients.[81] Gemcitabine toxicity includes bone marrow suppression, vomiting/nausea, raised liver transaminases, and rash.

Vinorelbine

Intravenous vinorelbine administered at the dosage of 20 mg/m^2 once every two weeks for 5 cycles and subsequently at a dose of 30 mg/m^2 once every three weeks, is regarded as a third-line chemotherapy scheme, with an overall response rate of 74% in a cohort of 19 patients. In this study, grade 3 or 4 toxicities were neutropenia, deep vein thrombosis and constipation.[82]

Etoposide

Oral etoposide has been suggested as an effective and safe treatment option in advanced classic KS, with a complete response rate of 10% and an overall response rate of 87%, in a cohort study of 30 patients with classic KS.[83] Brambilla *et al*. reported a response rate of 73.5%.[70,84] The main advantage of this chemotherapy is the oral administration, while common side effects include arterial hypotension, myelosuppression and gastrointestinal toxicity.

Pomalidomide

Pomalidomide is an oral thalidomide analogue with immune modulatory, antiangiogenic, and antiproliferative activities.[85] The US Food and Drug Administration (FDA) has recently approved pomalidomide for the treatment of KS, in both the HIV-negative and HIV-positive setting. Its main adverse effects include neutropenia, thrombocytopenia and teratogenicity, and its use is not yet mainstream in Italy due to limited availability.

Special indications for iatrogenic KS

The first step to be followed in the management of iatrogenic KS is the cautious reduction of immunosuppressive agents, most commonly systemic corticosteroids.[3] Moreover, the change of immunosuppressive drugs from calcineurin inhibitors to mammalian targets of rapamycin inhibitors, such as sirolimus and everolimus, provides a significant regression of KS in post-transplant KS.[86] Patients with extensive or life-threatening post-transplant KS can require the use of systemic chemotherapy although this is poorly evaluated in this KS subtype.

Special indications for classic KS in anaplastic evolution

Given the rarity of anaplastic classic KS, a gold standard therapy is not defined yet. However, systemic chemotherapy followed by surgery in case of lack of response, is the most commonly adopted option.[87-89] The most effective chemotherapeutic agent has not yet been established.[37] In a case series published by some of the authors of the present article, 5 of 8 patients with anaplastic KS required amputation.[37]

FOLLOW-UP

Follow-up procedures depend on the KS variant, the stage and the type of treatment chosen (Figure 1). Clinical examination, standard blood tests including complete blood count and protein electrophoresis, and radiological examinations should be proposed at variable intervals. In slowly progressive classic KS, follow-up visits can be scheduled every 6 to 12 months, essentially based on clinical examination. In life-threatening conditions, clinical evaluation and follow-up will be done on a patient-by patient basis but at least monthly, and other examinations at least every 6 months until disease stabilisation (Table 4). Notably, repeated biopsies followed by histological examination are not required but may be useful in case of atypical presentation and/or suspected angiosarcomatous (anaplastic) evolution. Biopsies are also needed in order to confirm nodal/visceral involvement.

CONCLUSIONS

Different KS patients may require different treatment strategies such as clinical observation only, surgery, local or systemic chemotherapy. As there is a lack of high-quality evidence for many therapies described in the literature, it is recommended that the dermatologist carefully evaluates efficacy and safety of each treatment plan. Disease type and severity, patient's age and

comorbidities need also to be considered to optimize outcomes. Patients with aggressive, disseminated and/or visceral KS generally need multimodality therapies for optimal disease control.

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TABLE 1. Staging of cutaneous Kaposi's sarcoma

Stage	Prevalent cutaneous lesions	Progression	Visceral involvement (V)
I Macular-nodular	Macules and/or nodules predominantly on the lower limbs	A, slow	± V
		B, rapid	
II Infiltrative	Plaques predominantly on the lower limbs	A, slow	± V
		B, rapid	
III Florid	Exuberant angiomatous nodules predominantly on the lower limbs	A, slow	± V
		B, rapid	
IV Disseminate	Angiomatous lesions on the head, trunk and mucosae	A, slow	± V
		B, rapid	

TABLE 2. Diagnostic tests at first presentation of Kaposi's sarcoma

Standard	Personalized
Blood tests: full blood count, kidney and liver function, iron, protein electrophoresis, lymphocyte subpopulation analysis, HIV test, anti-HHV8 antibodies and HHV8 DNA	
Fecal occult blood test on three samples, if positive →	Colonoscopy
Oesophagogastroduodenoscopy (OGDS)	
Abdomen and lymph nodes ultrasound	Total body computerized tomography
Ears, nose and throat (ENT) visit	

TABLE 3. Treatment of cutaneous Kaposi's sarcoma

Staging	Standard	Personalized
I	· Clinical observation · Intralesional vincristine · Curettage	· Elastocompression for edema or bullous Kaposi's sarcoma · Silver nitrate for soft, fungating and/or oozing lesions
II	Elastocompression	Radiotherapy for florid and localized lesions
III	Systemic chemotherapy*	Elastocompression for edema or bullous Kaposi's sarcoma
IV	Systemic chemotherapy*	Elastocompression for edema or bullous Kaposi's sarcoma

* Possible schemes:

First-line treatment
- Vinblastine: induction 4, 6, 8 mg i.v./week, then 10 mg i.v. every 3 weeks
- Vinblastine (as above) + Bleomycin 15 mg i.m. every 3 weeks starting from the end of vinblastine induction.
- Paclitaxel 75-100 mg /m^2 i.v./week

Second-line treatment
- Pegylated liposomal doxorubicin 20 mg/m^2 every 3 weeks

Third-line treatment
- Gemcitabine 1200 mg/ m^2 i.v./week for 2 weeks, with an interval of three weeks
- Bleomycin 15 mg i.m. every 2 weeks
- Vinorelbine: induction: 20 mg/m2 every 2 weeks for 5 cycles; consolidation with 30 mg/m^2 every 3 weeks (off label).
- Etoposide oral 150 mg/m^2 for 3 consecutive days every three weeks.

Every chemotherapy scheme should be maintained until the best therapeutic outcome, followed by three consolidation cycles with 3-, 6-, and 12-month follow up visits.

TABLE 4. Follow-up of patients with Kaposi's sarcoma

Standard	Frequency
Clinical examination	Every 1-12 months (depending on disease progression)
Blood tests: full blood count, kidney and liver function, iron, protein electrophoresis	Every 6-12 months
Fecal occult blood test	Every 1-2 years
Lymph node ultrasound	In the case of rapid progression of skin lesions on the thigh or if lymph nodes are palpable
Oesophagogastroduodenoscopy (OGDS)	In the case of rapid progression of skin lesions or if GI bleeding is suspected
Abdomen ultrasound	Every 1-3 years (depending on the progression of skin lesions)
Ears, nose and throat (ENT) visit	In the case of appearance of visible lesions adjacent to external ears, nostrils or oral cavity

FIGURE 1. Diagnostic-therapeutic guide for Kaposi's sarcoma.

Authors' contribution

Lucia Brambilla: conception and design of the presented work, acquisition and interpretation of data and critical revision of the manuscript

Giovanni Genovese: acquisition of the data, writing of the manuscript

Emilio Berti: interpretation of data and design of the presented work, critical revision of the manuscript

Ketty Peris: acquisition and interpretation of data of the presented work, critical revision of the manuscript

Franco Rongioletti: acquisition of data of the presented work, critical revision of the manuscript

Giuseppe Micali: acquisition of data of the presented work, critical revision of the manuscript

Fabio Ayala: acquisition of data of the presented work, critical revision of the manuscript

Silvia Della Bella: acquisition of data of the presented work, critical revision of the manuscript

Roberta Mancuso: acquisition of data of the presented work, critical revision of the manuscript

Piergiacomo Calzavara Pinton: acquisition of data of the presented work, critical revision of the manuscript

Athanasia Tourlaki: conception and design of the presented work, acquisition and interpretation of data, drafting supervision and critical revision of the manuscript

All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.