Treatments for classic Kaposi sarcoma: A systematic review of the literature

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Background: Treatment guidelines are lacking for classic Kaposi sarcoma.

Objective: We sought to review the evidence on efficacy of treatments for classic Kaposi sarcoma.

Methods: Articles published in English or French in MEDLINE, Trip, Cochrane Library, and Pascal databases from 1980 to December 2010 were screened. Studies reporting at least 5 patients treated for histologically confirmed classic Kaposi sarcoma were selected. Primary outcome was a decrease in the number or size of lesions or of lymphedema. We reviewed 26 articles matching the inclusion criteria for methodologic quality, classifying them according to World Health Organization criteria.

Results: The percentage of patients with a 50% or greater decrease in lesions was 71% to 100% for pegylated liposomal doxorubicin, 58% to 90% for vinca-alkaloids, 74% to 76% for etoposide, 93% to 100% for taxanes, 100% for gemcitabine, 97% for the combination of vinblastine and bleomycin, 71% to 100% for interferon alfa-2, 43% for thalidomide, and 12% for indinavir. For local treatments, a decrease of 50% or greater was achieved in 62% of lesions for intralesional vincristine, 50% to 90% for intralesional interferon alfa-2, 56% for imiquimod, and 25% for nicotine patches. A complete response was attained in 60% to 93% of lesions with radiotherapy.

Limitations: Eligible trials were of poor quality. The lack of standardized classification of disease activity and clinical outcomes precluded the comparison of studies.

Conclusion: The evidence for efficacy of any particular intervention is of low quality and does not support recommending any particular therapeutic strategy. Further studies are required and it will be important to standardize the assessment of disease activity and clinical response. (J Am Acad Dermatol 2013;68:313-31.)

Key words: classic Kaposi sarcoma; Mediterranean Kaposi sarcoma; systematic review of literature; therapeutics.

Kaposi sarcoma (KS) is a lymphoangioproliferative disease often caused by KS-associated herpesvirus, also known as human herpesvirus 8.[1] There are 4 known variants of KS: epidemic or AIDS-associated KS, endemic or African KS, iatrogenic posttransplantation KS, and Mediterranean or classic KS (CKS). CKS mostly affects elderly Eastern European Jewish or Mediterranean men (male/female ratio: 10-15/1). Lesions occur mostly on the skin of the lower limbs and, more rarely, in internal organs.[2]

Abbreviations used:

CKS:	classic Kaposi sarcoma
KS:	Kaposi sarcoma
RCT:	randomized controlled trial
WHO:	World Health Organization

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KS is an opportunistic tumor and the restoration of immunity is the best way to treat sarcoma in organ transplant recipients (reduction or switch to a mammalian target of rapamycin inhibitor, eg, rapamycin)[3] and in AIDS-associated KS (antiretroviral therapy).[4] In CKS, immunosenescence is not controllable and cannot therefore be targeted by treatment.

CKS is usually chronic, persisting over many years, but is not life threatening. For localized forms, the available options are radiotherapy, surgery, intralesional injections, and observation.

However, the clinical course of CKS may be characterized by lymph node and visceral involvement and by local complications that may seriously impair quality of life. These more aggressive forms require systemic therapy with antiproliferative drugs.

The precise indications for each type of treatment have yet to be defined.

We therefore carried out a systematic review of the literature concerning the treatment of CKS and aimed to identify the areas on which future studies should focus.

CAPSULE SUMMARY

- Classic Kaposi sarcoma occurs in elderly patients, and may cause pain and difficulty walking.
- We reviewed the evidence on efficacy of treatments for classic Kaposi sarcoma. A total of 26 trials were selected.
- Evidence does not support recommending any particular therapeutic strategy. Further studies are required and it will be important to standardize the assessment of disease activity and clinical response.

METHODS

Search strategy

We carried out a computerized search of the MEDLINE, Trip, Cochrane Library, and Pascal databases for relevant articles on human subjects, published in English or French, from 1980 to December 2010. We also searched Google Scholar; National Guideline Clearing House; Guidelines Finder; Agency for Healthcare Research and Quality; Health Canada; Catalogue and Index of French-speaking Medical Sites; *Kenniscentrum—Centre d'Expertise* (the Belgian Federal Center for Health Care Assessment); Lemanissier Library; Vidalrecos; e-dermato; databases of the French Societies of Dermatology, Oncology, and Infectious Disease; and *Bibliothèque InterUniversitaire de Médecine*, in which all French medical theses are listed.

The search terms were either from a thesaurus (medical subject headings [MeSH] descriptors for MEDLINE) or from the title or the abstract (free words), combined with "AND" or "OR." The successive stages of the MEDLINE search are presented in the supplementary online material available at http://www.jaad.org.

The lists of references generated were searched by hand, to identify additional studies. If trial results were updated, we used the data from the most recent publication.

Study selection

One reviewer screened all titles and abstracts for eligibility.

The inclusion criteria were: (1) study reporting at least 5 patients treated for CKS; (2) study population consisted of cases of histologically proven CKS excluding posttransplantation, endemic KS, and epidemic KS (after 1985, a negative HIV test was required and, between 1980 and 1985, the epidemiologic features of patients were analyzed); (3) the aim of the study was to decrease the number and/or size of cutaneous, mucous, nodal, and/or visceral lesions or to decrease lymphedema; and (4) intervention consisting of any type of treatment or no treatment, with no comparison required.

All potentially relevant studies and studies for which the abstract provided insufficient information for inclusion or exclusion were retrieved as full articles.

Quality assessment

We assessed the overall quality of the study. We determined whether inclusion and exclusion criteria were clearly defined, whether treatment was standardized, the time points used for assessment, and whether the primary outcome was clearly defined and objectively measured; we also assessed the use of statistical tests and of comparable groups at baseline, the description of missing data and data for patients lost to follow-up, and the statistical differences observed and their clinical significance. For randomized controlled trials (RCTs), we determined whether the study was blinded and the method of randomization, and assessed the a priori calculation of the number of subjects required and analysis by intention to treat. For other studies, we looked at the methods used to select cases and controls, consecutive cases, and the duration of follow-up.

Based on this analysis, we were able to classify each item in terms of the level of evidence, according to World Health Organization (WHO) criteria

Table I. Level of evidence and grading of recommendations: general guidelines for methodologies on research and evaluation of traditional medicine, World Health Organization 2000

Level of evidence	Grading of recommendations
Level 1a Evidence obtained from meta-analysis of randomized controlled trials	**A** Requires at least 1 randomized controlled trial as part of body of literature of overall good and consistency addressing specific recommendation
Level 1b Evidence obtained from at least 1 randomized controlled trial	**B** Requires availability of well-conducted clinical studies but no randomized clinical trials on topic of recommendation
Level 2a Evidence obtained from at least 1 well-designed controlled study without randomization	**C** Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities; indicates absence of directly applicable studies of good quality
Level 2b Evidence obtained from at least 1 other type of well-designed quasiexperimental study	
Level 3 Evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies	
Level 4 Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities	

(Table I). As usually done in the literature, we downgraded trials with several methodologic flaws.[5] Provided there was at least 1 study of higher quality on the same subject, we excluded case series from the final list of studies.

Data extraction

Structured data were extracted from full texts with a standardized list. The data derived from the articles included items such as the author and the year of enrollment, study setting, methods, type of participants, Kaposi activity, type of intervention, follow-up, outcome measures, and results.

RESULTS

Publications included

We retrieved 407 abstracts/titles and examined 57 publications in full. Attempts were made to contact the authors of 7 trials to resolve uncertainties, and clarification was successfully obtained in all these cases. In all, 25 articles did not meet the inclusion criteria for the following reasons: series less than 5 cases (N = 13), no histologic analysis (N = 6), HIV status not documented (N = 1), data subsequently updated (N = 4), and duplicate data (N = 1). In all, 32 articles were selected, but 6 of these articles corresponded to case series that were excluded because other higher-quality studies on the same topic were identified.[6-10] Fig 1 shows a flow chart of the study selection process.

The remaining 26 publications consisted of: 16 publications about systemic treatments (1 RCT,[11] 7 prospective uncontrolled studies,[12-18] 1 case-control study,[19] 7 retrospective studies or case series[20-26]); 6 publications about local treatments (1 RCT,[27] 3 prospective controlled studies,[28-30] 2 prospective uncontrolled studies[31,32]); and 4 publications about radiotherapy (1 prospective controlled study,[33] 3 retrospective studies or case series[34-36]).

Systemic treatments

Eligible studies of systemic treatment are summarized in Table II.

Local treatments

Eligible studies of local treatment are summarized in Table III.

DISCUSSION

KS is an opportunistic polyclonal tumor associated with viral infection. Studies in HIV-infected patients and transplantation recipients have shown that immune restoration is the best treatment for KS in these patients.

The risk factors for CKS include advanced age, diabetes, and the use of corticosteroid medication[37,38]; age and corticosteroid medication are also associated with CKS progression.[39] If immunosenescence cannot be modified, then an immunodeficiency (exogenous

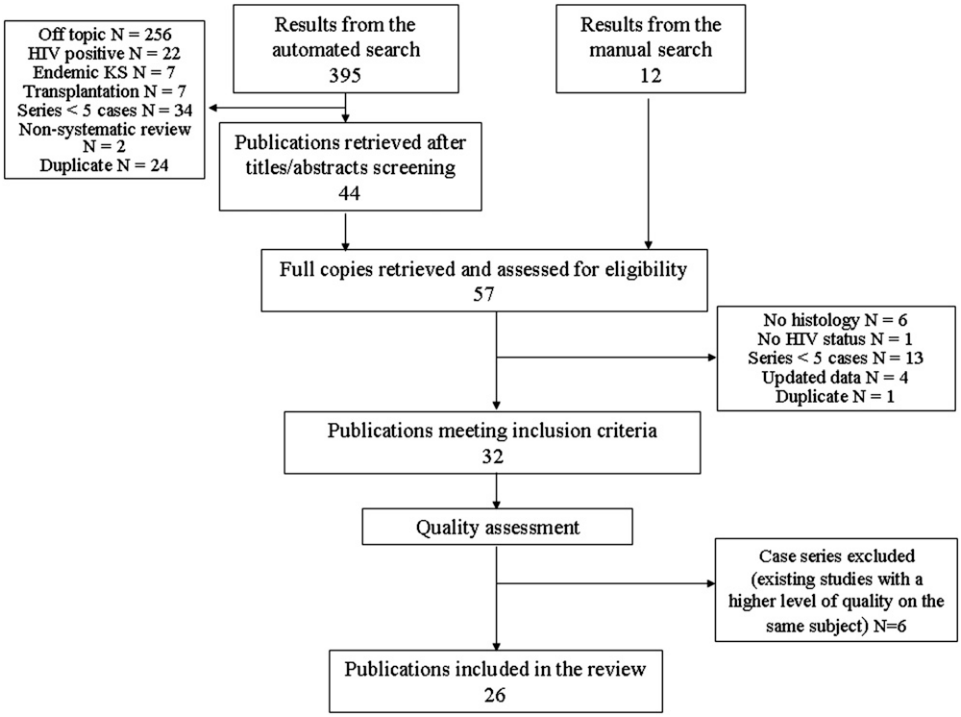

Fig 1. Flow chart of study selection process. *KS*, Kaposi sarcoma.

or endogenous) that could potentially be corrected should always be sought.

Cases of KS remission have been reported after a decrease in the use of corticosteroid medication.[40-42] No study has evaluated the effects on CKS of discontinuing or decreasing immunosuppressive therapy.

Efficacy

Our systematic review found that the evidence for any intervention decreasing the number or size of lesions or edema in patients with CKS was very poor.

The eligible trials were of poor quality: the 2 RCTs included biases and were classified as level 2a in the WHO staging system, the 4 prospective controlled studies and the case-control study were classified as level 3, and all the others were classified as level 4.

Moreover, sample sizes were mostly small (16/27 [59%] ≤ 20 patients, 21/27 [78%] ≤ 50 patients), probably because of the low incidence of CKS and the high frequency of decisions not to treat.

The only placebo-controlled RCT was of no real clinical relevance as it demonstrated the inefficacy of nicotine patches. Three prospective controlled trials compared local interventions with clinical observation. Injections of vincristine or interferon alfa-2 decreased the size of the lesions into which the treatment was injected and elastic stockings decreased leg volume to a greater extent than observed in control patients, but these studies were subject to many biases. As there is no gold standard treatment for CKS, the other 3 controlled studies did not aim to prove treatment efficacy.

Only global trends can be extracted from the results of the other studies and results are sometimes inconsistent across trials, particularly for subcutaneous interferon alfa-2.

Thus response rates ($\geq 50\%$ decrease in lesions) for chemotherapies ranged between 71% and 100% of patients for pegylated liposomal doxorubicin, 58% and 90% for vinca-alkaloids, 74% and 76% for etoposide, and 93% and 100% for taxanes. Only 1 study was performed on gemcitabine and on a combination of vinblastine and bleomycin. These 2 studies reported response rates of 100% (decrease $\geq 50\%$) and 97% (decrease not clearly quantified), respectively. For the other systemic treatments, a decrease in lesions of at least 50% was achieved in 71% to 100% of patients treated with interferon alfa-2 whereas the studies evaluating thalidomide and indinavir (1 study for each of these drugs) reported response rates of 43% (decrease $\geq 50\%$) and 12% (decrease not clearly quantified), respectively.

For local therapies, a decrease of 50% or greater was achieved in 62% of lesions treated with intralesional vincristine, 50% to 90% of lesions treated with intralesional interferon alfa-2, 56% of lesions treated with imiquimod, and 25% of lesions treated with nicotine patches. Studies of radiotherapy frequently reported only the complete response rate, which reached 60% to 93% with local field

radiotherapy, 70% with extended field radiotherapy, and 89% with megavoltage radiotherapy with a water bolus.

Indication and ranking of treatments

Few controlled studies have been carried out in this area and it is not possible to compare studies, because of the lack of standardized classification systems for disease activity and clinical outcomes.

One major problem is the absence of a consensual classification of disease activity. Brambilla et al[43] have published a number of studies relating to the treatment of CKS and based on their own classification. The Mitsuyasu[44] and AIDS Clinical Trials Group[45] (designed for HIV-positive patients) or Krigel et al[46] classifications are also used in some studies of CKS. Moreover, in 15 of the 27 (56%) eligible studies, no classification was documented. The absence of uniform staging prevents meaningful comparison between studies and the description of treatment indications.

Another problem affecting meaningful comparisons between studies was the variability of the criteria used for clinical outcome assessment. Objective clinical response was the primary outcome in most studies but the definition of response differed between studies. For instance, some studies assessed the number of lesions, whereas others assessed the size of lesions (defined in different studies on the basis of, eg, diameter, area, volume, infiltration). The progression of complications (especially edema) was included in the definition of clinical response in a few studies. Moreover, the response rate, expressed as a percentage, was determined on a per patient basis in some studies and per lesion in others.

As pointed out above, there were only 7 controlled studies, 3 of which were designed to compare the activity of 2 treatments.

One RCT compared intravenous vinblastine (31 patients) and oral etoposide (34 patients) as first-line chemotherapy and failed to demonstrate the superiority of etoposide. A multicenter case-control study showed pegylated liposomal doxorubicin to be superior to subcutaneous interferon alfa-2, but only 12 patients were treated with pegylated liposomal doxorubicin and 6 with interferon. A prospective study compared local field radiotherapy administered as single fractions of 8 or 6 Gy and found no significant difference, other than for complete response.

Other therapeutic approaches

Surgery is one of the types of treatment not documented in publications about CKS that is useful for the treatment of localized disease. Brenner et al[47] retrospectively reported results for the surgical treatment of 52 localized symptomatic cases of CKS: the median time to progression was 60 months and 67% of patients remained progression-free after 2 years. However, cases of Koebner phenomenon on surgery scars have been reported[48,49] and this should be taken into account when deciding to excise lesions surgically.

Not treating CKS should also be considered as an alternative position. Indeed, CKS frequently occurs in elderly patients and is usually indolent and slowly progressive (mean survival, 10-15 years).[2]

Only 1 study tried to assess the effects of not treating the patient. Brenner et al[47] retrospectively reported the follow-up of 123 consecutive CKS cases receiving various treatments, depending on disease activity. Clinical observation was the option selected for 39 asymptomatic CKS cases: the median time to progression was 14 months and 34% of the patients remained progression-free after 2 years. A clear trend was established in this study, despite poor documentation of the characteristics of the patients at baseline and of outcome criteria.

CONCLUSION

This systematic review of the literature on CKS addresses a little-discussed issue. However, we found that all evidence of efficacy was of very low quality, for all the interventions considered, and there was therefore insufficient evidence to recommend any particular intervention. CKS is generally chemosensitive, but the lack of consistency in the methods used to assess the clinical response is a major obstacle to the development of recommendations. However, although these studies provide some overview of the response of the tumor, we still know nothing about the duration of this response and its impact on survival and quality of life. It is also not possible to determine who needs treatment and when treatment should be started from the information available.

Only 2 randomized trials on CKS have been carried out in the last 3 decades. CKS is relatively rare and only small numbers of patients are treated at each center. The best way to improve CKS treatment would be to establish collaborative networks for the planning and running of international clinical trials in the near future, making it possible to identify and to implement the most effective strategies and treatments. It will also be essential to standardize the assessments of disease activity and clinical response, which currently

Table II. Systemic treatments

	Reference	Intervention, follow-up	Method	Activity of CKS, treatment line	No. of patients	Outcome criteria	Results	Side effects, lost to follow-up	WHO LOE, comments
Chemotherapy	20	PLD intravenously 20 mg/m^2/3 wk Median 9 cycles Median follow-up 50 mo	Retrospective Multicenter International	Brambilla[43] IIa complicated-IV (IIb, III ++) Not visceral First line	55	CR: absence of detectable lesions $\geq$8 wk MR: $\geq$50% decrease in No. of lesions without new lesions mR: 25%-50% decrease PD: appearance of new lesions, >25% increase in lesions, or worsening of complications Stable disease: any other response	CR 29% MR 42% mR 11% PD 7% Stable disease 11%	Grade IV neutropenia 5.5%; anemia 4% Grade III neutropenia 16%; thrombopenia 4%; vomiting 5.5% Hand-feet syndrome 5.5%	LOE 4 Inclusion, exclusion, and outcome criteria well documented Consecutive cases not specified
	21	PLD intravenously 20 mg/m^2/3 wk Median 9 cycles	Retrospective Multicenter	Brambilla[43] IIa complicated-IV (IIb, III ++) Not visceral Second line	20	Objective response as defined in Di Lorenzo et al[20] Assessment after 6 cycles	CR 10% MR 70% mR 0% PD 10% Stable disease 10%	Grade IV neutropenia 5% Grade III neutropenia 20%; thrombopenia 5%; vomiting 10%; mucositis 5%	LOE 4 Inclusion, exclusion, and outcome criteria well documented Not consecutive cases but documented

19	I1 PLD intravenously 20 mg/m^2/mo Mean 14 cycles I2 interferon alfa-2 sc 3 million U × 3/wk Mean follow-up 13 mo	Case-control Multicenter	ACTG T0/1I0S0 Not visceral First-line or sc interferon-pretreated	I1 12 I2 6	CR: absence of lesions (or inactive pigmented macules) and tumor-associated edema ≥8 wk MR: ≥50% decrease in lesions without new lesions, or reduction of edema mR: <50% decrease in lesions without appearance of new lesions or edema PD: appearance of new lesions or worsening of edema Stable disease: any other response	I1 CR 67% MR 25% mR 8% I2 MR 17% ($P < .05$) mR 67% ($P < .05$) Stable disease 17% ($P < .05$)	I1 grade III neutropenia 33%; moderate vomiting 25% I2 fever 67% Flu-like symptoms 50%	LOE 3 Not consecutive cases

Continued

Table II. Cont'd

Reference	Intervention, follow-up	Method	Activity of CKS, treatment line	No. of patients	Outcome criteria	Results	Side effects, lost to follow-up	WHO LOE, comments
22	PLD intravenously 20 mg/m^2/mo Mean follow-up 19 mo	Retrospective Monocenter	Mitsuyasu[44] IIa Not visceral First-line or sc interferon-pretreated	10	CR: complete regression of lesions (or biopsy-proven inactive pigmented macules) MR: $\geq$ 50% decrease in No. of lesions, complete flattening of $\geq$ 50% raised lesions or $\geq$ 50% decrease in sum of products with largest perpendicular diameters of indicator lesions mR: decrease <50% without appearance of new lesions or edema PD: increase in either size or No. of lesions Stable disease: any other response	CR 20% MR 80%	1 Widespread bullous eruption after first infusion (treatment stopped)	LOE 4 Consecutive cases not specified

11	I1 vinblastine intravenously 3 mg/m^2 weekly for 3 wk, then 6 mg/m^2/3 wk I2 etoposide po 60 mg/m^2 d 1-3 then d 1-4 then d 1-5 every 3 wk Stop 3 mo after CR or maximal PR Mean cycles: I1 13/I2 12	Randomized controlled trial Not blind Multicenter	Brambilla[43] IIa complicated-IV (IIb, IVb ++) Visceral 19% First-line chemotherapy (interferon?)	65 I1 31 I2 34	WHO criteria CR: complete disappearance of all known disease for at least 4 wk PR: $\geq$50% decrease in tumor size NC: any response not meeting criteria for PR, but not progressing PD: appearance of new lesions or $\geq$25% increase	I1 CR 26% PR 32% CR + PR 58% NC 35% PD 3% I2 CR 24% PR 50% CR + PR 74% (P = .3) NC 18% PD 3%	I1 grade III leukopenia 6% 1 Lost to follow-up (reason?) I2 nausea vomiting grade I-II 44% Alopecia grade III 18%; grade I-II 20% 2 Lost to follow-up (reason?)	LOE 2a Not blind More severe CKS in group I1 (more stage IVb cases, more visceral cases) Duration of follow-up not documented (long time to response)
24	Vinblastine intravenously 6 mg/m^2/ fortnight Stop 2 mo after CR or maximal PR Mean duration 8 mo Mean follow-up 31 mo	Retrospective? Monocenter	Disseminated >30% body area Limited to legs 80% Not visceral First-line chemotherapy (interferon?)	10	CR: complete disappearance of lesions PR: $\geq$50% decrease in No. and/or size of lesions Stable disease: <50% reduction, but no progression	CR 50% PR 40% Stable disease 10%	Grade IV leukopenia 10% Nausea 10%	LOE 4 Unclear methodology: prospective or retrospective Imprecision of inclusion and exclusion criteria Consecutive cases not specified

Continued

Table II. Cont'd

Reference	Intervention, follow-up	Method	Activity of CKS, treatment line	No. of patients	Outcome criteria	Results	Side effects, lost to follow-up	WHO LOE, comments
16	Vinorelbine intravenously 17.5 mg/m^2/ fortnight for 10 wk then every 3 wk until maximal response Mean duration 11 mo	Prospective open phase II Monocenter	Brambilla[43] IIa complicated-IV Visceral not specified First or second line	15	CR: resolution of 100% of lesions PR: resolution of >50% of lesions Improvement: resolution of >25% of lesions	CR 0% PR 60% Improvement 40%	Grade II leukopenia 27%; nausea vomiting 7%; alopecia 7% Grade I-II neurotoxicity (constipation) 7% Grade I thrombopenia 7%	LOE 4 Consecutive cases not specified No description of population
14	Etoposide po 100 mg d 1-3 then d 1-4 then d 1-5/3 wk Then 100-150 mg d 1-5/4 wk, 9-12 times	Prospective open Monocenter	Locally aggressive 82% Disseminated and visceral 18% First or second line	17	WHO criteria, as described in Brambilla et al[11]	CR 35% PR 41% PD 6% NC 18%	Grade I leukopenia 35%; nausea 65%	LOE 4 Consecutive cases but 5/22 not evaluable and analysis not carried out on intention-to-treat basis
15	Paclitaxel intravenously 100 mg/wk, 12 cycles, then 100 mg/fortnight until CR or stable 4 wk Mean 17 cycles (final response)	Prospective open Monocenter	Brambilla[43] IIIb complicated, IVb complicated Visceral 12% Second line	15	CR: total regression of complications and lesions (or flat pigmented inactive patches) PR: size reduction of all lesions with stable improvement of complications PD: increase in lesions and/or symptoms	After 12 cycles CR 20% PR 73% PD 7% Final response CR 67% PR 27% PD 6%	Serious systemic allergy during second infusion 12% Grade I neutropenia 13%; asthenia 27%; diarrhea 7%; neurotoxicity 7% 17 inclusions; 2 discontinuations (allergy)	LOE 4 Imprecision of inclusion and exclusion criteria Consecutive cases not specified Analysis not carried out on intention-to-treat basis

25	Docetaxel intravenously 60 mg/m^2/3 wk **OR** Paclitaxel intravenously 175 mg/m^2/3 wk Mean 7 cycles	Retrospective Multicenter	+-Visceral First or second line	7	ACTG criteria CR: absence of residual disease including edema $\geq$4 wk PR: $\geq$50% decrease in No. of lesions, complete flattening of $\geq$50% raised lesions or $\geq$50% decrease in sum of products with largest perpendicular diameters without new lesion or worsening of edema PD: $\geq$25% increase in size of lesions, formation of new lesions or change in $\geq$25% of lesions from flat to nodular or increase in edema Stable disease: any other response	PR 100% Disinfiltration: complete 57%, partial 43%	Neutropenia grade III 14%; grade IV 14% Alopecia grade I 50%	LOE 4 Consecutive cases 6 Patients treated with docetaxel and 1 with paclitaxel

Continued

Table II. Cont'd

	Reference	Intervention, follow-up	Method	Activity of CKS, treatment line	No. of patients	Outcome criteria	Results	Side effects, lost to follow-up	WHO LOE, comments
	17	Gemcitabine intravenously 1.2 g/wk for 2 wk, repeated after 1-wk interval (stop 2 cycles after maximal response) Mean 7 cycles	Prospective open phase II	Brambilla[43] IIa complicated-IV (IVb, IIIb ++) Visceral 25% Second line	11	CR: resolution of 100% of lesions PR: resolution of ≥50% of lesions	CR 9% PR 91%	Grade II hepatic cytolysis 18%; leukopenia 18% 1 Patient stopped treatment (12 patients at baseline) because of drug-induced fixed erythema	LOE 4 Consecutive cases not specified Analysis not carried out on intention-to-treat basis
	13	Vinblastine intravenously up to 10 mg/3 wk + intramuscular bleomycin 15 U d 1, 8, 15, then/ 3 wk Median 8 cycles	Prospective open Multicenter	Brambilla[43] IIb-IV (IIIb, IVb ++) Visceral 7% First or second line	29	CR: disappearance of lesions (or plain purple inactive lesions) and of complications IR: lasting reduction of No., width, and thickness of all lesions and improvement of complications	CR 21% IR 76%	Neutropenia 38% (grade IV 10%) Neurotoxicity grade I 7%	LOE 4 Consecutive cases not specified
Immunotherapy	12	Interferon alfa-2 sc 5 million U × 3/wk for ≥6 mo Mean 21 mo Mean follow-up 45 mo	Prospective open phase II Monocenter	Krigel[46] I-IV (IIa, IV++) Visceral 25% First or second line	16	Objective response, as defined by Potouridou et al[22]	CR 6% MR 56% mR 31% Stable disease 6%	Weight loss 19%; neutropenia 6% (1 case); depressive syndrome 6%; grand mal seizure 6%	LOE 4 13 CKS + 3 endemic KS; consecutive cases not specified Inclusion, exclusion, and outcome criteria well documented

	23	Interferon alfa-2 sc 5 million U × 3/wk for 6 mo (adaptation: 1-6 million U × 3-6/wk)	Retrospective Monocenter	Extensive lesions Limited to legs 73% Visceral not specified First line	11	CR: complete flattening of ≥90% lesions PR: ≥50% decrease in size or complete flattening of ≥50% of raised lesions PD: ≥2 new lesions or progression of ≥2 lesions from flat to nodular Stable disease: any other response	CR 64% PR 18% Stable disease 18%	Fever and asthenia	LOE 4 Imprecision of inclusion and exclusion criteria Consecutive cases not specified Variables doses of interferon (dose reduction 6/11 = 55%, 1 increase)
	19	See above				See above			
	26	Thalidomide po mean dose 100 mg daily (50-100 mg daily for 4 wk then up to 200 mg daily) Median 112 d	Retrospective Monocenter	Median No. of lesions 24 Not visceral Second line	7	ACTG criteria	CR 0% PR 43% PD 14% Stable disease 43%	Grade I sensory neuropathy (paresthesia) and vertigo 27% (thalidomide stopped)	LOE 4 Consecutive cases
Antiviral	18	Indinavir po 800 mg × 2 daily For 12 mo	Prospective open	Brambilla[43] 50% stage I-II, 50% stage III-IV Visceral not specified First or second line	26	ACTG criteria	Complete remission 4% Partial regression 8% Improved disease 19% PD 27% Stabilization of PD 31% Stable disease 11%	Mild asthenia, joint pain Nonspecific skin manifestations	LOE 4 No definition of outcome criteria Imprecision of inclusion and exclusion criteria Consecutive cases not specified

ACTG, AIDS Clinical Trials Group; *CKS*, classic Kaposi sarcoma; *CR*, complete response; *I1*, intervention 1; *I2*, intervention 2; *IR*, intermediate response; *KS*, Kaposi sarcoma; *LOE*, level of evidence; *mR*, minor response; *MR*, major response; *NC*, no change; *PD*, progressive disease; *PLD*, pegylated liposomal doxorubicin; *po*, by mouth; *PR*, partial response; *sc*, subcutaneous; *WHO*, World Health Organization; *?*, unclear in the original article.

Table III. Local treatments and radiotherapy

	Reference	Intervention, follow-up	Method	Activity of CKS, treatment line	No. of patients	Outcome criteria	Results	Side effects, lost to follow-up	WHO LOE, comments
Local chemo-therapy or immuno-therapy	28	I1 vincristine sulfate, intralesional, 1 injection 0.03-0.08 μg for nodule 0.3-0.8 cm in diameter I2 no treatment (1 control nodule/ patient) Follow-up 12 wk	Prospective open controlled	Brambilla Ib not complicated except for stage I lymphedema Not visceral First line not specified	151 (302 lesions) I1 151 I2 151	CR: disappearance of nodule PR: $\geq$50% decrease in diameter Improvement: reduction $<$50% PD: $\geq$25% increase Stable disease: any other response Assessment after 12 wk	I1 CR 76% PR 18.5% Improvement 4% PD 0.7% Stable disease 0.7% I2 CR 4·6%	I1 erythema or itching 14% (grade I 10%, grade II 2%, grade III 2%)	LOE 3 No results for control nodules except CR and no statistical analysis Consecutive cases not specified
	29	I1 interferon alfa intralesional and perilesional 50,000 U $\times$ 2/ wk I2 interferon alfa + IL-2 intralesional and perilesional: interferon alfa 50,000 U $\times$ 2/ wk ; IL-2 32-64 U $\times$ 2/wk I3 no treatment (1 control nodule in each patient) For 4-6 wk	Prospective open controlled	1 Injected and 1 control uninjected nodule in each patient Visceral not specified +- Pretreated	20 (40 lesions) I1 12 (12) I2 8 (8) I3 20 (20)	Color change Decrease in consistency Decrease in volume	Color change I1 100% I3 25% ($P < .001$) I2 100% I3 12.5% ($P < .01$) Decrease in consistency I1 100% I3 17% ($P < .001$) I2 100% I3 0% ($P < .001$) Decrease in volume I1 50% I3 0% ($P < .05$) I2 62.5% I3 0% ($P < .05$)	No clinical or biological side effects	LOE 3 Method of statistical analysis not specified No comparison of I1 and I2 Method of allocation of patients to groups not specified Consecutive cases not specified No definition of outcome criteria

31	Interferon alfa-2 intralesional 3 million U 5 d/wk for 4 wk and variable dose for additional 4 wk Mean dose 104 million U	Prospective open Monocenter	Injection 1 lesion 3-6 cm Not visceral +-Previous radiotherapy	10 (10 lesions)	CR: disappearance of lesion $\geq$1 mo (biopsy proven) PR: $\geq$50% decrease in area mR: decrease <50% PD: extension Assessment after 8 wk	CR 20% PR 70% NR 10%	Flu-like symptoms 80% Mild lymphopenia or increase in alkaline phosphatase levels (20% each)	LOE 4 Consecutive cases not specified Imprecision of inclusion and exclusion criteria Accurate assessment of end point (same investigator + photographs)
32	Imiquimod 5% cream under occlusion, 3 times/wk for 24 wk Follow-up 36 wk	Prospective open phase II Monocenter	$\leq$10 Lesions ($\leq$100 cm^2) treated/patient (median 5) Limited to lower limb 60% Not life threatening +-Pretreated	17 (90 lesions)	ACTG criteria Response per patient or per lesion Assessment after 36 wk	Per patient CR 12% PR 35% CR + PR 47% Per lesion CR + PR 56%	Local itching and erythema (grade < III) 53% of patients (treatment stopped in 3 patients 18%) Study withdrawal: 2 progression, 2 personal reasons	LOE 4 17 Patients including CKS and endemic KS (proportions missing) 7/17 Discontinued treatment, but intention-to-treat analysis Consecutive cases not specified Inclusion, exclusion, and outcome criteria well documented; assessment of compliance

Continued

Table III. Cont'd

	Reference	Intervention, follow-up	Method	Activity of CKS, treatment line	No. of patients	Outcome criteria	Results	Side effects, lost to follow-up	WHO LOE, comments
Radiotherapy	33	I1 LFR (megavoltage): 1 fraction 8 Gy I2 LFR (megavoltage): 1 fraction 6 Gy Mean follow-up: I1 101 mo/I2 47 mo	Prospective open controlled Monocenter	Limited to lower limb 89% Visceral not specified +-Previous chemotherapy	47 (203 fields) I1 (51) I2 (152)	CR: complete disappearance of lesion PR: ≥50% regression NR: <50% regression PD: growth of lesions or increase in symptoms Percentage response/field Assessment after 12 mo	I1 CR 93% PR 0% CR + PR 93% NR 7% I2 CR 60% ($P < .0001$) PR 26% CR + PR 86% (P = not significant) NR 14%	Fibrosis and edema grade I 91%, grade II-III 6%	LOE 3 Consecutive cases (I1 1994-1997; I2 1998-2004) 17% Posttransplantation KS and 83% CKS No description of groups at baseline Imprecision of outcome criteria
	34	LFR (orthovoltage): mean dose 29 Gy (98% contact x-ray therapy 5 Gy × 1-2/wk) Mean follow-up 93 mo	Retrospective Monocenter	Symptomatic lesions: located on lower (61%) or upper (35%) limbs +-Previous local treatment	70 (711 lesions)	CR/PR not defined Percentage response/lesion	CR 98.5% PR 1% Not evaluable 0.5%	Acute radiodermatitis in 3 lesions (1 patient)	LOE 4 Case-control study: comparison with LFR for HIV KS Imprecision of inclusion, exclusion, and outcome criteria
	35	I1 LFR (orthovoltage) from 3-8 Gy single fraction to 35 Gy in 5 fractions I2 EFR (megavoltage) from 8 Gy single fraction to 10-35 Gy	Retrospective Monocenter	Limited to lower limbs 77% Visceral 3% Previous treatment not specified	I1 25 I2 50	CR: disappearance of nodule PR: ≥50% decrease in diameter Improvement: reduction <50% PD: ≥25% increase Stable disease: any other response Assessment after 12 wk	I1 CR 76% PR 18.5% Improvement 4% PD 0.7% Stable disease 0.7% I2 CR 4.6%	I1 erythema or itching 14% (grade I 10%, grade II 2%, grade III 2%)	LOE 3 No results for control nodules except CR and no statistical analysis Consecutive cases not specified

	36	Megavoltage radiotherapy with water bolus 30 Gy (1.5 Gy × 20 fractions) Mean treatment duration 48 d Mean follow-up 32 mo	Retrospective Monocenter	Multifocal lesions; limited to lower limbs 57%, 4 limbs 39% Lymph nodes 11% +-Previous treatment	28	Total disappearance of skin lesions Complete regression of lower limb oedema	Total disappearance of the skin lesions 89% Complete regression of lower limb oedema 55% (10/18)			Skin blisters 7% Slight erythema 100%	LOE 4 Consecutive cases? No definition of outcome criteria. Imprecision of inclusion and exclusion criteria.
Others	27	I1 local nicotine patch: 1 patch every 2 d I2 placebo patch: 1 patch every 2 d I3 mo treatment For 15 wk	Randomized controlled trial Blind (I1, I2)	Mean 11 lesions/patient 3 Lesions (0.5-3 cm), separated >6 cm Visceral not specified +-Pretreated Nonsmoking	24 (72 lesions) I1 24 (24) I2 24 (24) I3 24 (24)	CR: complete disappearance PR: ≥ 50% decrease in area mR: 30%-50% decrease NR: −30% to +30% change PD: >30% increase Assessment after 15 wk	I1 CR 8% PR 17% mR 0% NR 33% PD 42%	I2 CR 4% PR 21% mR 4% NR 38% PD 33%	I3 CR 4% PR 8% mR 0% NR 38% PD 54%	I1-I2 severe local erythema 29% of patients (temporary suspension of patch use 19%; definitive suspension 10%) Study withdrawal: 2 patients (1 progression, 1 mitral surgery) and 1 lesion patch I1 (excision of hemorrhagic lesion)	LOE 2a No a priori sample size calculation; no statistical analysis but intention-to-treat analysis Accurate assessment of end point (score + numeric tool) and of compliance

Continued

Table III. Cont'd

Reference	Intervention, follow-up	Method	Activity of CKS, treatment line	No. of patients	Outcome criteria	Results	Side effects, lost to follow-up	WHO LOE, comments
30	I1 elastic stockings (40 mm Hg at ankle) I2 no stockings Mean follow-up 65 wk	Prospective open controlled	Unilateral grade II lymphedema (below knees) Visceral not specified	65 I1 50 I2 15	Total limb volume (calculated from circumferences taken every 1.5 cm)	I1 Reduction 60% (mean: 6.9% decrease in volume) Increase 40% (mean 6.7%) I2 Increase 100% (mean 5.8%) ($P < .0001$)	Well tolerated	LOE 3 Method for selecting control patients Mean limb volume in each group at baseline not documented Concomitant treatments of CKS (chemotherapy I1 36%/I2 53%) No assessment of compliance

ACTG, AIDS Clinical Trials Group; *CKS*, classic Kaposi sarcoma; *CR*, complete response; *EFR*, extended field radiotherapy; *I1*, intervention 1; *I2*, intervention 2; *I3*, intervention 3; *IL*, interleukin; *KS*, Kaposi sarcoma; *LFR*, local field radiotherapy; *LOE*, level of evidence; *mR*, minor response; *NR*, no response; *PD*, progressive disease; *PR*, partial response; *WHO*, World Health Organization.

differ considerably between studies, precluding comparisons.

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