Management of Kaposi's Sarcoma in Resource-limited Settings in the Era of HAART

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Abstract

The introduction of highly active antiretroviral therapy (HAART) has changed the natural history of AIDS-associated Kaposi's sarcoma (KS). Although the use of HAART remains limited in low-resource settings, there are global initiatives to make these drugs available to several millions of HIV-infected persons. While there are multiple reports of KS regression during HAART with or without chemotherapy, there is little documentation on KS management in resource-limited settings. In this paper we review current KS treatments available worldwide and discuss the implications of the increased access to antiretrovirals for KS treatment strategies in resource-limited settings. **(AIDS Reviews 2005;7:13-21)**

Key words

Kaposi's sarcoma. AIDS. HAART. Resource-limited settings. Developing countries.

Introduction

In countries with limited resources, in the absence of highly active antiretroviral treatment or HAART, Kaposi's sarcoma (KS) was treated for palliative reasons with chemotherapy, and often not treated at all. Chemotherapy was often considered too expensive and not effective enough. Moreover, the conditions to deliver such treatment in a safe way were generally not fulfilled.

Today, HAART is becoming increasingly available in developing countries thanks to global initiatives like the World Health Organization's "3x5" strategy and global efforts from the Global Fund against AIDS, Tuberculosis and Malaria[1,2]. In the developed world, the availability of HAART has already dramatically changed the way we treat KS[3,4].

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In this paper we review current KS treatments available worldwide, and discuss the implications of the increased access to antiretrovirals for KS treatment strategies in developing countries.

Epidemiology and pathogenesis

Kaposi's sarcoma is a multifocal neoplasm involving skin and mucous membranes. Lungs, gastrointestinal tract, and lymph nodes can be affected as well. KS is a stage IV-defining event, and is associated with human herpesvirus 8 (HHV-8), or Kaposi's sarcoma-associated herpesvirus (KSHV).

It is the most frequently seen malignancy in AIDS patients. Before the era of HAART, 15% of HIV patients in the USA presented with KS as the primary AIDS-defining event[5]. Over the past two decades, some African countries with a high HIV prevalence have seen a 20-fold increase in the incidence of KS, and it has become the most common cancer in men[6,7]. Nevertheless, the incidence of KS varies from country to country and among different risk groups[5,8]. In Southeast Asia, for example, AIDS KS is a very rare event[9].

HAART has caused a sharp decline in the incidence of KS[10-12.] This decline in incidence is due to the immune restoration following HAART, and there are indications that this coincides with immunological control

Table 1. Staging of AIDS KS

T_0 = lesions confined to the skin and/or lymph nodes and/or minimal oral disease*	T_1 = tumor-associated edema or ulceration; extensive oral KS; gastrointestinal KS; KS in other non-nodal viscera
S_0 = No history of OI or oral thrush; no "B" symptoms†; performance status ≥ 70 (Karnofsky)	S_1 = history of OI and/or oral thrush; "B" symptoms† present; performance status < 70; other HIV-related illness (e.g. neurological disease, lymphoma)

*Minimal oral disease = non-nodular single KS confined to the palate.
†B-symptoms = unexplained fever, night sweats, >10% involuntary weight loss or diarrhea > 2 weeks.
Partially modified of reference 51.

of KSHV[13]. AIDS KS can as such be considered as an opportunistic infection (OI).

Clinical presentation and diagnosis

Clinical manifestations of AIDS KS vary from macular skin lesions to papules and nodular tumors, to life-threatening visceral involvement of the lungs, leading to lymphatic obstruction and respiratory failure, and the gastrointestinal tract. KS is often accompanied or preceded by local lymphedema[5]. AIDS KS lesions can wax and wane related to the occurrence of other opportunistic infections. Corticosteroid therapy has been associated with the induction of KS and with the exacerbation of pre-existing KS in HIV-infected persons[14].

Steroids are frequently used in HIV-infected patients with a variety of disorders including immune thrombocytopenic purpura and *Pneumocystis carinii* pneumonia. In such patients, KS lesions may regress upon reduction or withdrawal of steroids.

Gastrointestinal lesions are often asymptomatic, but can cause ulceration and bleeding. Pulmonary KS is rapidly fatal when left untreated. Patients may present with dyspnea, without fever, accompanied frequently by hemoptysis. Most of the times, there are skin lesions present as well. A chest X-ray may show reticulonodular infiltrates, enlargement of the mediastinal shadow, and sometimes a pleural effusion.

The diagnosis of KS can be confirmed by biopsy, but generally lesions can be recognized clinically. In the early stages it may be difficult to differentiate KS from bacillary angiomatosis. The latter is caused by *Bartonella henselae* and responds to doxycycline. Other conditions that might simulate KS include: mycosis fungoides, cutaneous leishmaniasis, and pruritic papular eruption of HIV.

Staging/prognosis

Staging of KS is modified since HAART. Staging is based on whether lesions are confined to the skin, or if there is mucosal and visceral involvement (T), and whether patients have constitutional symptoms or not (S) (Table 1).

In patients on HAART with AIDS KS, two different risk categories can be identified: a "good prognosis" category T_0S_0, T_1S_0, and T_0S_1 with a respective three-year survival of 88, 80 and 81%; a "poor prognosis" category T_1S_1 with a three-year survival of 53% (46% if pulmonary involvement and 77% if no pulmonary involvement)[15]. This is much better than the three-year survival of any stage IV disease before HAART.

Failure of KS treatment was related to failure to control HIV. Survival was not influenced by the CD4 count at the start, nor by the type of HAART used – either protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based[15-18].

When is treatment for KS indicated?

In the absence of HAART

In the absence of HAART, there is no cure for AIDS KS. No local or systemic therapy has proven to increase survival[5]. Therefore, chemotherapy is only initiated when patients have disfiguring lesions in visible areas of the body, extensive painful skin lesions and edema, oral lesions that cause obstruction or dysphagia, evidence of rapid tumor progression, or visceral involvement.

Influence of HAART

The natural history of KS has changed with HAART. Several studies have shown a response rate up to 90% after two years of HAART treatment[3]. Complete responses were more frequently observed in patients with better immunological response. Predictors of a complete response were an increase of CD4 count > 150/µl after 12 months of HAART and T_0S_0 or T_0S_1 stage of KS at inclusion[19]. The initial CD4 count does not seem to predict response to HAART.

Another small study in patients with progressive KS showed a response rate of 85% with HAART alone or

combined with chemotherapy. In this study, the baseline CD4 count also was not predictive of outcome[20].

Disease-free survival after treatment for KS has increased from six months before HAART to 1.7 years since the introduction of HAART[21]. High remission rates of KS under HAART, up to 86%, have been reported after a median follow up of 22 months[22].

Once patients are responding to therapy (partial or complete response) the chemotherapy can be interrupted while immune restoration does the work, even in pulmonary KS, where the median survival before HAART was less than four months after diagnosis[3,5]. At two to three years follow up, only 15% of the patients are still in need of chemotherapy.

Given the increased availability of HAART in developing countries, the increased disease-free survival after treatment for KS in the presence of HAART, and the fact that chemotherapy can be interrupted after treatment response, enthusiasm for treating KS in developing countries is growing.

Note that, occasionally, HAART has led to serious clinical presentations in the framework of an immune reconstitution inflammatory syndrome that might be due to an increased response to HHV-8[23].

Direct control of KSHV is a new approach to the treatment of KSHV. Antivirals like ganciclovir, valganciclovir, and foscarnet all seem to slow down the progression of KS[24]. However, because of the limited clinical efficacy of these antivirals, we do not recommend their use in the treatment of KS.

What treatment options do we have? What can be safely applied in a resource-limited setting?

Treatment of localized disease

The most easy and acceptable treatment is a local treatment where available. This is only indicated in patients with limited lesions (T_0) and no systemic signs (S_0).

Possibilities are:

Vinblastine (0.1 to 0.2 mg/ml), by injecting 0.1 ml per 0.5 cm^2 of lesion, has resulted in response rates of 70 to 90%[25,26]. A second series of injections is usually needed after three to four weeks. Injections are painful and one has to be careful not to inject in healthy tissue because of severe necrosis. Treated lesions will fade and regress but will not disappear. Without HAART, the median duration of effect is about four months.

Cryotherapy with liquid nitrogen can be quite useful in localized lesions, and response rates up to 80% have been described[27].

Alitretinoin (0.1%) topical gel (9-cis retinoic acid) is the only topical, patient-administered therapy approved for the treatment of cutaneous KS lesions. It has been shown to give a response in 30 to 35% of patients (> 50% reduction in size). The gel is applied twice daily and the dose may be gradually increased up to five times daily as tolerated. Side effects consist of irritation of the skin. It may take several weeks before a response is seen (up to 14 weeks)[28]. The cost of a four to six month treatment ranges from USD 3900 to USD 5800.

Radiation therapy, if available, has good results, especially in single big lesions (> 3 cm) on the extremities[29]. Indications for irradiation would include: painful, bleeding ulcers, lymph edema due to obstruction, and medically uncontrolled pain. Single 8 Gray fractions result in clinically good responses in a palliative setting[30].

Although these local treatments seem attractive, they are usually not available in resource-poor settings because they are too expensive. They also do not prevent the appearance of new lesions.

In the group T_0S_0 and T_0S_1 it is likely that HAART alone is sufficient in the majority of patients.

Therefore, the indications for local treatment for palliative or cosmetic reasons has little place in AIDS care in resource-limited settings once HAART is available.

Treatment of extensive disease

Cytotoxic chemotherapy is indicated in patients who have rapidly progressive cutaneous disease causing pain, edema, and ulceration, but also in patients with visceral involvement.

In the beginning of the epidemic of AIDS KS, the most frequently used chemotherapeutic combinations were ABV (Adriamycin™, bleomycin and vincristine) or BV (bleomycin, vincristine). These regimens caused significant toxicity and response rates varied from 70 to 90%[31]. However the duration of treatment effect was limited to a median of four months (before HAART).

Bleomycin alone at the dose of 15 mg IM (or 5 mg/d IM for three days) every two weeks has a response rate of 10 to 75% and has the advantage that it is less myelosuppressive[31,32]. Problems of pulmonary fibrosis only occur at cumulative doses > 400 mg or single doses of > 30 mg, in elderly patients, in smokers, and patients with prior radiation therapy or receiving concurrent oxygen[33]. However, relapses are very likely to occur once the drug is stopped.

Vincristine alone in a dose of max 2 mg per week IV is rarely used[31]. In combination with bleomycin it is still used for patients who have pancytopenia and who need a rapid tumor response. However, very careful monitoring of the IV line needs to be done to avoid extravasation of vincristine, which can lead to severe cellulitis and extensive tissue necrosis. The dose-limiting

toxicity of vincristine is neurological symptoms that include constipation, ileus, peripheral neuropathy, both sensory and motor symptoms, and loss or decrease of peripheral reflexes. Peripheral reflexes need to be tested before the administration of the next dose of vincristine.

Interferon alpha (IFN-α) has immunomodulatory and antiviral effects. It has good response rates (up to 40%) at a dose of 8 million units SC daily, when given with antiretroviral therapy (ART)[34]. It is especially effective in patients with CD4 counts > 150 to 200/µl and with only skin lesions[33]. Toxicity includes asthenia, loss of appetite, rigors, and an increase in liver function tests. IFN is also associated with neutropenia that could require dose delay, a decrease in CD4 count, and an increase in opportunistic infections; response is slow (two to three months).

The "gold standard" in the Western world for the treatment of systemic KS is now liposomal anthracyclines.

Two new formulations, liposomal daunorubicin (40 mg/m^2 IV every two weeks) and liposomal doxorubicin (20 mg/m^2 IV every three weeks) have been used as monotherapy in the treatment for AIDS KS, and studies have shown for the latter a superior efficacy compared to BV or ABV (response rate 58 *vs.* 23%), with a better side-effect profile for both[35,36]. Response to treatment is often slow (three to six months). Even if less toxic than bleomycin/vinca alkaloids, they are myelosuppressive and potentially increase the risk of opportunistic infections by aggravating HIV-related immune deficiency. However, there is evidence that when given together with HAART, there is no decrease in CD4 count with the liposomal anthracyclines, and therefore no need to change the guidelines for prevention of opportunistic infections under chemotherapy[37].

Neutropenia and anemia occur usually after eight to 10 cycles and require dose reduction or delay in treatment. Being the first choice in the developed world, their cost price is far beyond reach of developing countries (USD 11,000 per responding patient) and is unacceptably high even in the HAART era.

Paclitaxel, a drug with cellular targets similar to the vinca alkaloids, is a second-line treatment for patients who failed or do not tolerate liposomal anthracyclines. Response rates up to 71% have been noted, and this drug is also effective in pulmonary KS[28].

Oral etoposide is another second-line treatment for patients who have progressive disease while on liposomal anthracyclines. Because of its oral administration, it is an ideal self-administrable drug in an outpatient setting in low-resource settings.

Different dosing schedules have been used (either fractionated doses of 20 mg/m^2 every eight hours for 7 out of 21 days or as a once daily dose of 50 mg for 7 out of 21 days, 100 mg/day during five days, once a month). Response rates varied from 36 to 83%, and the median duration of response from 12 to 25 weeks[38,39].

However 30 to 60% of patients developed grade 3 and 4 neutropenia; thrombocytopenia and anemia are other reported side effects. This makes it a difficult drug to use in first-line therapy in developing countries because of the need for frequent monitoring and the risk of other bacterial and fungal infections. The cost price might be a barrier for its use in resource-poor settings. Oral etoposide exists in a generic version (Cipla, Etoposide 50 mg, 28 tablets, USD 300).

What about HAART alone?

Especially early stage AIDS KS (T_0S_0) seems to respond very well (complete remission of 80%) to HAART alone[19,40].

Little data are available from studies looking into the effect of HAART alone in advanced KS. A recent Spanish study compared the use of pegylated liposomal doxorubicin and HAART versus HAART alone in moderate-to-advanced KS[16]. They found a significantly better response rate in the combined therapy group (76 *vs.* 20%). In the HAART-only group two thirds had progressive disease and needed chemotherapy, and in half of them the progression occurred in the first three months of HAART. This phenomenon is mainly due to the inability of HAART to control the natural progression, rather than an immune reconstitution inflammatory syndrome. Others have shown better results with HAART alone, with complete remissions of KS in 50% of patients without systemic tumor therapy, but these were not randomized clinical trials, and may be biased[3,17].

Where does that leave us for resource-limited settings?

A recent Cochrane review on this question did not really provide an answer[41]. The treatments discussed in this review are unlikely to be available or affordable in developing countries, where the bulk of HIV infection and KS occur, apart from radiotherapy that may be available in a few tertiary centers.

With the more widespread availability of HAART, trials with the cheaper and more widely available chemotherapeutic agents in combination with HAART should be conducted in a resource-limited setting. A summary of chemotherapeutic regimens that could be available and feasible in developing countries is given in table 2, with corresponding doses and response rates.

Vincristine alone (2 mg IV once a week) in combination with HAART is probably the least expensive, on the condition that it can be administered in a safe way. Careful monitoring of the IV line needs to be done to avoid extravasation of vincristine, which can lead to

Table 2. Suggested chemotherapy for KS in low-resource settings

Therapy	Dose	Overall response rate*
Vincristine	1.4 mg/m^2 (max 2 mg) 1x/week IV	10-85%
Vincristine/vinblastine	Vincristine 2 mg IV, and vinblastine 0.1 mg/kg IV alternating weekly	Up to 43%
Vincristine/bleomycin	Vincristine 2 mg and bleomycin 10 mg/m^2 every 2 weeks IV	60-75%
Bleomycin	15 mg single doses every 2-3 weeks IM or 6 mg/m^2/day over 4 days IV every 4 weeks	10-75%
Etoposide	50 mg for 7 of every 21 days PO or 100 mg for 5 days every month	36-85%

*Overall response rate is partial and complete response combined.
Adapted from Schöfer[31].

severe cellulites and extensive necrosis. The limiting factor will be the development of neurotoxicity, which needs to be monitored at every visit. As vincristine has little hematologic toxicity, it is the preferred regimen in patients with anemia and neutropenia. It should be avoided in patients with pre-existing neuropathy, concomitant use of didanosine (ddI) or stavudine (d4T). Drugs to prevent constipation are needed.

Some specialists use vincristine 2 mg (maximum dose) every other week, alternating with vinblastine 0.1 mg/kg every other week IV. This regimen is less neurotoxic, but more myelosuppressive. The vinblastine dose is reduced for WBC counts of < 3000/mm^3 or platelet counts < 50,000/mm^3. Vincristine has to be discontinued for detectable-to-moderate muscle weakness or severe paresthesias. The dose can be reduced for moderate paresthesias[42].

Vincristine 1.4 mg/m^2 (maximum dose 2 mg) + bleomycin 10 mg/m^2, although more expensive, is probably the best available combination in resource-limited settings. Both drugs are administered IV on alternate weeks.

Bleomycin IM alone at the dose of 15 mg IM every two weeks is more expensive, but easier to administer. It is the preferred regimen in patients who have developed neuropathy (ddI, d4T, HIV-related or secondary to vincristine). The cost price of one vial is around USD 30. For IM administration, the drug is reconstituted by adding 1 to 5 ml of sterile water for injection, 0.9% sodium chloride injection, or bacteriostatic water for injection to the vial labeled as containing 15 units of bleomycin to provide solutions containing 3 to15 units/ml (1 unit = 1 mg).

Its efficacy in combination with HAART needs to be determined, and the feasibility of its use in an African setting evaluated. Bleomycin can cause allergic reactions, ranging from anaphylaxis, hypotension, wheezing, fever, chills, and confusion, and may have a delay in onset of symptoms. Skin reactions have also been noticed with the use of bleomycin.

The toxicity of bleomycin, especially pulmonary fibrosis, increases with cumulative doses, and therefore a total dose > 400 units should be avoided[33].

In case this therapy does not yield good results, oral etoposide, wherever available as a second-line chemotherapy, is an option. Etoposide is given PO in a dose of 50 mg per day during one week, every other week. The major dose-limiting toxicity of etoposide is myelosuppression. In 30 to 60% of the patients the dose has to be interrupted or decreased because of grade 3 or 4 neutropenia; thrombocytopenia is another frequent complication (the WBC nadir occurs around 7 to 14 days after therapy, while platelets reach nadir between 9 to 16 days after therapy and usually recover by day 20). Before starting another cycle of etoposide, one should check the laboratory findings. In case the absolute neutrophil count (ANC) is < 500 cells/mm^3, the Hb < 8 g/dL or the platelets < 50,000/mm^3, the dose of etoposide should be postponed until lab values have normalized. When the WBC count is between 2000 and 3000 cells/mm^3, and the platelets between 50,000 to 75,000/mm^3, the dose of etoposide should be reduced to 50%[43].

Timing of HAART in patients with AIDS KS

In patients with T_0S_0 or T_0S_1 the first-line treatment is HAART alone. Chemotherapy should be reserved for patients who do not respond to HAART alone, or who have extensive cutaneous or visceral and pulmonary disease. When to initiate HAART in a patient with large KS lesions/disseminated KS needs further study.

In general we prefer not to start HAART when there is an active opportunistic infection, because the risk of mortality is primarily due to opportunistic infections, because of reasons of complexity of treatment, adherence issues and possibility of cumulative drug toxicity and worsening symptoms due to immune reconstitution

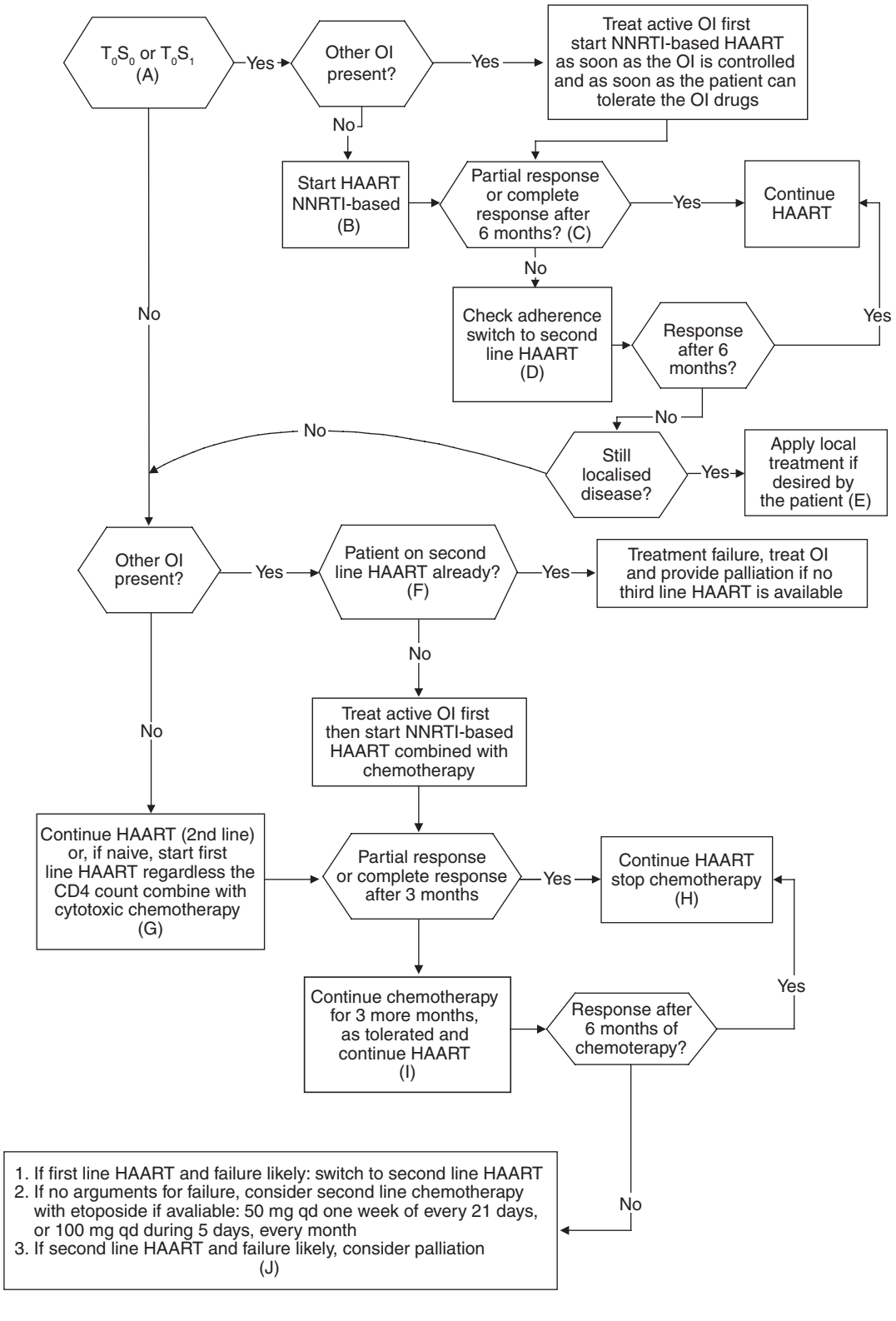

Figure 1. *Recommendations for management of AIDS KS in limited-resource settings (see annotations).*

Annotations to algorithm AIDS KS

(A) In patients who present with limited disease, there is no indication to start chemotherapy. These patients are likely to benefit from HAART alone. To be sure, a chest X-ray needs to be taken to exclude pulmonary KS lesions, as these may present with little symptoms. KS is a WHO stage 4 disease, and following the WHO guidelines all stage 4 patients should receive HAART, regardless the CD4 count. Whenever the patient has another opportunistic infection, make sure to treat this first, and only start HAART when the patient is stabilized and can tolerate the drugs.

(B) There is no evidence that PI-based regimens are better than NNRTI-based regimens for treatment of AIDS KS. As PI-based regimens are usually reserved as second-line HAART regimens in resource-poor settings, it is better to start patients with KS on the same regimen as all other patients.

(C) A partial response is defined as no new lesions and one of the following: a > 50% decrease in the total number of lesions; or a > 50% reduction in the size of the index lesions; or marked flattening of KS lesions; or clinical complete response but with residual edema. A clinical complete response is the absence of any residual symptom or lesion after treatment. The median time to response is six months[22].

(D) If, after six months of HAART, lesions still progress or remain stable, adherence to HAART should be checked. Failure of KS to regress under HAART is linked with virological failure to HAART. This case should be managed as a suspected treatment failure and adherence to HAART should be reinforced. If, despite good adherence, there is still treatment failure, change the complete HAART regimen to a second-line, PI-containing regimen.

(E) Local therapy for KS lesions in the mouth consists of intralesional injections with vinblastine 0.1 mg/ml (see treatment of localized disease). Single big lesions on the extremities respond well to radiotherapy if available. Smaller lesions could be treated with cryotherapy if available.

(F) A patient who is developing an active opportunistic infection after 12 months of HAART is probably failing his second-line HAART. If possible, confirm this with a viral load. In most situations there will be no third line available. Stop HAART, treat the opportunistic infection and provide palliation.

(G) Cytotoxic chemotherapy should be started in combination with HAART when patients have symptoms of pain, edema, obstruction, and difficulty to swallow or speak because of KS. In a resource-limited setting, bleomycin 15 mg IM every fortnight seems to be a feasible option, as is vincristine-vinblastine.

(H) In most of the cases when a partial or complete response is obtained under HAART and chemotherapy, it is possible to interrupt the chemotherapy. The patients who have a complete response are more likely to have a good increase in CD4 count. If lesions should increase in size again later, or recur, we can still restart some cycles of chemotherapy, while continuing to improve immunity by HAART.

(I) The time to response has medians ranging from three to nine months[40]. In case the response after three months is not good, the patient may benefit from three cycles chemotherapy more.

(J) 1. Patients who fail on chemotherapy and HAART, or who need again treatment for KS while on HAART, have a high likelihood to have a treatment failure for HIV as well. Carefully check adherence. Is there drug resistance or failure due to bad adherence? In case of failure on a first-line HAART regimen, despite good adherence, it makes sense to switch to a second-line treatment with PI. 2. In case there are no arguments for treatment failure on HAART, consider second-line chemotherapy. When etoposide is used, there is a high risk for pancytopenia. AZT should not be combined with etoposide, and the full blood count should be checked before etoposide is given for another week. 3. In case the patient was already on second-line HAART, and treatment failure is likely, stop chemotherapy and HAART and provide palliation. Lesions of KS are painful when extensive, and tumors can cause edema. Palliation is important. If chemotherapy is not helping, adequate pain control has to be installed. The size of tumors can be reduced by radiotherapy if available. The ulcerated KS lesions may present with an offensive smell; metronidazole powder can be used to diminish this.

inflammatory syndrome. The latter has also been described in KS[44-47].

However, because the response to chemotherapy is slow in KS, and because it is now generally accepted that HAART is an essential part of first-line KS treatment, it is good practice to start HAART soon after or concurrent with the chemotherapy, especially in patients with advanced immune deficiency. In case chemotherapy is given concomitantly with HAART, Zidovudine (AZT) should not be combined with doxorubicin because of an increased risk of anemia, and ddI and d4T should not be used together with vincristine because of an increased risk for neuropathy. Raynaud's syndrome occurs with concurrent use of bleomycin, and vincristine/vinblastine[48].

Choice of HAART regimen

There has been considerable debate about the appropriateness of NNRTI-based regimens in the treatment of KS. There is some *in vitro* evidence that PI may have an antitumor effect on KS[49,50]. The response of KS to HAART is related to immune restoration and an undetectable KSHV load. This response is better in patients who have a higher increase in the CD4 count. Failure of HAART to control KS is correlated with failure

of HIV therapy[18]. So far there is no convincing evidence that a PI regimen is better than a NNRTI regimen in patients with AIDS KS[15-18]. Figure 1 summarizes the recommendations for managing AIDS KS in resource-limited settings.

Conclusion

With the increasing availability of HAART in developing countries, we need to develop new treatment strategies for KS in resource-limited settings. Early diagnosis of HIV allows for timely treatment with HAART and will decrease the incidence of AIDS-related KS. In case of early stage KS, the use of HAART alone is likely to be successful. For advanced-stage KS, combined treatment of HAART with systemic chemotherapy is needed. IM bleomycin or oral etoposide may represent feasible options, at least if price reductions can be obtained for the latter. Clinical trials are needed to determine how to combine these agents with HAART for an optimal treatment of KS in a resource-limited setting.

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