In his article, Dr. Mitsuyasu concisely reviews a large body of data concerning the etiology, pathogenesis, epidemiology, and treatment of Kaposi’s sarcoma (KS) in the setting of the human immunodeficiency virus (HIV) infection. As he correctly points out, effective highly active antiretroviral therapy (HAART), with its consequent improvements in immune function and decrease in production of viral and cytokine cofactors that promote KS growth, has been partly responsible for the decline of KS incidence in areas with ready access to HIV therapy.

However, as Dr. Mitsuyasu correctly observes, this trend may not continue as resistant HIV becomes more prevalent and treatment failures occur. Furthermore, there remain a substantial number of patients with established KS in whom the disease persists and progresses despite effective HIV suppression, or in whom HIV suppression cannot be achieved. In addition, KS incidence remains high in places such as Africa, where access to effective antiretroviral therapy is limited and infection with both HIV and human herpesvirus type 8 (HHV-8) is common.

**Limitations of Local Treatment**

Although there are many items on which Dr. Mitsuyasu and I agree, I have some philosophical differences with his approach to treatment of early-stage cutaneous disease. In my view, just as cytomegalovirus (CMV) retinitis is generally the first local clinical manifestation of systemic CMV infection, limited cutaneous KS can be considered the first local clinical manifestation of systemic HHV-8 infection.

As with CMV retinitis, which can be controlled for a time with vitreal ganciclovir (Vitrasert) implants, KS lesions can often be controlled by various local means. However, local approaches do not address the underlying cause of the disease, and there is no reason to believe that they will prevent future disease progression. In the case of CMV retinitis, systemic ganciclovir (Cytovene), administered alone or as an adjunct to local therapy, has been shown to significantly reduce rates of new CMV disease compared to local treatment only.[1,2] For KS, there is evidence that HHV-8-infected endothelial-cell precursors circulate in the blood[3] which probably accounts for the frequent appearance of lesions at multiple sites as the first manifestation of the disease.

I interpret this to mean that a logical long-term therapeutic strategy for KS should include systemic therapies that influence factors involved in disease pathogenesis. This interpretation does not entirely exclude a role for local approaches to KS management, but I believe that role to be far more limited than Dr. Mitsuyasu’s article suggests.

When long-term survival with acquired immunodeficiency syndrome (AIDS) was uncommon, there may have been a stronger rationale for the use of local approaches that were primarily intended for symptomatic palliation of KS. Now that survival with HIV infection is often measured in decades, even when viral suppression is incomplete, we should focus on the development of potentially curative antineoplastic strategies for patients who continue to develop KS.

It seems likely that the success of pathogenesis-based strategies for KS treatment will be greatest at the earliest, relatively asymptomatic phase of KS, when the disease may be thought of as an angiogenic, proliferative process rather than a true malignancy. Furthermore, the severity of KS...
appears to be an independent factor associated with survival.[4] Therefore, targeted intervention early in the course of the disease—before the development of widespread symptomatic lesions and true malignant potential—is a logical strategy.

**Current and Projected Trials for KS**

It is ironic that the explosive growth in our understanding of the processes of KS pathogenesis and the introduction of numerous novel investigational agents with the potential to inhibit these processes should occur at a time when the incidence of KS is decreasing in this country. Current and projected trials for patients with AIDS-associated KS will assess inhibitors of vascular endothelial growth factor (VEGF) signaling, vascular integrin receptors, matrix metalloproteinases, cytokine production, and endothelial cell proliferation and migration; and antibodies and antisense molecules directed at angiogenic growth factors and cytokines.

Trials of these agents not only hold the promise of improving therapies for KS and other malignancies that depend on neoangiogenesis for their growth and dissemination, but will also provide correlative laboratory studies that may help to uncover or clarify pathophysiologic mechanisms. Agents of this type are currently under active phase I and phase II investigations for KS through the AIDS Malignancy Consortium, a National Cancer Institute–sponsored clinical trial network established in 1995 for the specific purpose of conducting innovative, multicenter trials in AIDS-associated malignancies.

**Conclusion**

Thus, rather than advocating local, lesion-directed therapy as the initial approach for patients with limited cutaneous KS, I would advocate referral of such patients for participation in well-designed, pathogenesis-directed clinical trials long before KS becomes aggressive and symptomatic.

**References:**


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