Tumor markers and treatments for Kaposi sarcoma.


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Kaposi sarcoma (KS), in addition to being the most common malignancy among people with AIDS in the USA [1], has become the most common malignancy overall in entire countries of sub-Saharan Africa [2,3]. AIDS KS prognosis has greatly improved with highly active antiretroviral therapy (HAART) [4], but this tumor is still a major cause of disfigurement, other morbidities, and mortality [4,5].

Shortly after the discovery of human herpesvirus 8 (HHV-8, also known as Kaposi sarcoma-associated herpes virus) [6], which is the primary cause of KS, Whitby et al. reported that 52% of AIDS KS patients had HHV-8 DNA detectable in their peripheral blood mononuclear cells (cellular viremia) [7]. Moreover, they showed that HHV-8 cellular viremia was highly predictive of incident KS in patients with untreated HIV infection [7]. During the ensuing 12 years, HHV-8 cellular viremia was shown to be relatively common in non-AIDS KS patients, including those with classical (Mediterranean), endemic (African), and transplant (iatrogenic) KS [8–11]. However, the level of HHV-8 viremia (viral load) is very low and frequently undetectable even in AIDS KS patients [7,12–16]. Thus, cellular viremia is not effective for prediction of KS incidence in a clinical setting [8,17]. In contrast, HHV-8 cellular viremia or viral load may be useful for prediction of KS progression.

In the current issue, Laney et al. report the results of a prospective, observational study of 47 AIDS KS patients in Atlanta [18]. Corroborating a study of patients with transplant KS [11], three rather small studies [10,12,19], and their previous report [20], Laney et al. found that HHV-8 cellular viremia and higher viral load were associated with KS disease progression [18]. They propose that monitoring HHV-8 cellular viremia and viral load may help to predict disease progression and potentially prompt treatment with antiviral medications [18].

Ganciclovir, foscarnet, and cidofovir inhibit in-vitro HHV-8 lytic replication [21–23], and the use of ganciclovir was associated with a reduced incidence of AIDS KS in a randomized clinical trial [24]. Nonetheless, as the vast majority of infected cells are not undergoing lytic replication, antiviral medications have had little or no effect on established KS or HHV-8 cellular viremia [21,23]. Efforts to induce lytic replication or to attack the episomal (latent) HHV-8 genome are in progress [22].

In contrast to antiviral medications, HAART is paramount and relatively effective for treatment of AIDS KS. With limited KS (i.e., without visceral involvement, extensive oral involvement, tumor ulceration, or symptomatic lymphedema), complete or partial tumor response may occur in 80% of patients in whom HAART is initiated without specific cancer chemotherapy [25], typically with a drop in HIV load and increase in CD4 cell count [26]. Continuous HAART for at least 12 months may lead to clearance of HHV-8 cellular and plasma viremia [27], and KS responses may correlate with clearance of HHV-8 cellular viremia [28,29]. Such clearance occurs, however, after the tumor responses in many cases [27], negating the use of cellular viremia as a predictive marker.

KS chemotherapy, added to HAART, is necessary and more effective against advanced AIDS KS than is
HAART alone [25,30]. In many cases, however, KS fails to respond completely or recurs even if HIV itself appears to be well controlled. Thus, there is need to assess combinations of current medications and newer chemotherapies [31,32]. AIDS KS clinical trials in the setting of HAART are, however, hampered on several fronts, including the inherent clinical complexities of AIDS, as well as heterogeneity in the treatment regimens, the staging of KS, and the assessment of outcome [25].

Whether HHV-8 cellular load or viremia is clinically useful could be more clearly determined among patients with classical KS, as they have fewer co-morbidities and require fewer treatments than those with AIDS KS [18]. Results from the classical KS population probably would be replicated in the AIDS KS population. Classical KS is rare, but this need not be an impediment. Sensitive, specific, reproducible, and accurate tumor markers have been defined and have improved treatments for patients with an equally rare malignancy, nonseminomatous germ cell tumors of the testis [33–35]. The current and previous studies provide evidence that HHV-8 cellular viremia and viral load may predict KS progression and potentially provide a systemic measurement of the efficacy of KS treatments [10–12,18–20].

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References


