Stage-Stratified Approach to AIDS-Related Kaposis’s Sarcoma: Implications for Resource-Limited Environments

To the Editor: Bower et al1 recently reported the results of a prospectively applied management strategy for newly diagnosed Kaposis’s sarcoma (KS) in people living with HIV (PLWH) presenting to their center in London. Their approach, which emphasized optimization of combination antiretroviral therapy (cART) in all patients and use of systemic liposomal anthracycline chemotherapy for advanced-stage (T1) tumors, resulted in excellent overall survival, although approximately one quarter of patients with limited-stage (T0) KS treated with cART alone eventually showed KS progression.

In an accompanying editorial, Krell and Stebbing2 recommended that the same stage-stratified approach, yielding good outcomes when applied as a (nonrandomized) strategy at a single site in a high-resource setting, be adopted globally, and that if cost and chemotherapy-related infrastructural barriers could be overcome, pegylated liposomal doxorubicin should be made available for all patients with advanced-stage KS in sub-Saharan Africa (SSA), where the world’s burden of HIV-associated KS is concentrated. As investigators involved in studying HIV-associated KS in SSA, we believe that more complex issues must be rigorously addressed before recommendations for optimal treatment in this setting can be made.

The editorial2 does not consider significant differences between patients in resource-rich and resource-limited settings that may influence KS management. For example, 93% of patients described by Bower et al were men, and nearly two thirds had T0 tumors. In SSA, one third to over one half of adult patients with KS are women,3,4 and female sex has been associated, in some series, with significantly poorer survival.4 Pediatric KS, rare outside of Africa, is common among HIV-infected children in SSA,5 but no information is available on its optimal management. Moreover, the vast majority of PLWH in SSA with KS have T1 disease at diagnosis. Whereas KS rarely causes death in high-resource settings, it is a leading cause of early death after initiation of antiretroviral therapy in SSA.6-8 Most studies of KS in high-resource countries show restricted, primarily latent, HHV-8/KSHV gene expression in tumor biopsies, and scant evidence for benefit from antiretroviral therapy.13 However, recent studies of KS specimens obtained from Ugandan and Malawian PLWHs14,15 indicate that KS lesions from a subset of patients from SSA express high levels of lytic HHV-8/KSHV gene products, including viral kinases, suggesting that some African patients with KS may benefit from treatment with noncytotoxic agents, including drugs targeting herpesviral kinases or viral gene products that influence KS development and progression.

Adding to these clinical differences is evidence for biologic differences between KS arising in different settings, including different subtype distributions that have been associated with differences in tumor behavior.10-12 Most studies of KS in high-resource countries have restricted primarily latent, HHV-8/ KSHV gene expression in tumor biopsies, and scant evidence for benefit from antiretroviral therapy.13 However, recent studies of KS specimens obtained from Ugandan and Malawian PLWHs14,15 indicate that KS lesions from a subset of patients from SSA express high levels of lytic HHV-8/KSHV gene products, including viral kinases, suggesting that some African patients with KS may benefit from treatment with noncytotoxic agents, including drugs targeting herpesviral kinases or viral gene products that influence KS development and progression.

The approach chosen by Bower et al1 worked well for their patients in London. However, for the reasons discussed above, we cannot conclude that it should be considered the global standard. Only now are prospective, randomized studies to assess KS management strategies in resource-constrained settings being conducted that will systematically address critical questions regarding the ability of different regimens to induce KS regression, the appropriate time to initiate therapy, the impact of treatment on survival and quality of life (including effects on KS-associated signs and symptoms, drug-related toxicities, and HIV control), prognostic factors, ease of administration (which may influence adherence), and cost-effectiveness. We agree that more effective approaches to the treatment of HIV-associated KS are urgently required in SSA. However, we believe that the editorial recommendation that WHO recommend pegylated liposomal doxorubicin as the global standard for advanced KS is premature.

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