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Stage-Stratified Approach to AIDS-Related Kaposi Sarcoma: Implications for Resource-Limited Environments

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To the Editor:

Bower and colleagues[1] recently reported results of a prospectively-applied management strategy for newly-diagnosed Kaposi 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 only 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 Stebbing[2] recommended that the same, stage-stratified approach yielding good outcomes when applied as a (non-randomized) 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 (PLD) 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

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investigators involved in studying HIV-associated KS in SSA, we believe that more complex issues must be rigorously addressed before recommendations on optimal treatment in this setting can be made.

The editorial 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 KS patients are women[3,4] and female gender has been associated, in some series, with significantly poorer survival.[4] Pediatric KS, rare outside 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 ART in SSA.[6-8] Among HIV-infected adults newly initiating cART in Uganda, those with KS had substantially higher mortality than those without KS[9] even when adjusted for confounding factors. Other differences, including the frequent presence of comorbidities (e.g., tuberculosis, malaria, anemia) that are uncommon in high-resource settings, and limited resources to manage treatment-related adverse events, may also influence the choice, tolerance and outcome of KS therapy.

We disagree with the conclusion reached by Bower *et al*[1] that the results of a prospectively randomized South African study[4] support their recommendation that *all* patients with T1-stage KS should receive chemotherapy. Although most patients in that trial had T1-stage disease, Mosam *et al*[4] excluded T1 patients with symptomatic visceral KS or fungating lesions and included only those who they did not believe required urgent chemotherapy. Their intuition proved correct: despite better KS control in the chemotherapy arm, no survival difference was observed between patients who were, and were not, randomized to receive chemotherapy. Deaths from KS-related and KS-unrelated causes were similar in both arms. However, interpreting the results of that study is complicated because a significant proportion of patients never received their randomized treatment, and the planned chemotherapy was often substituted by an alternative regimen.

Adding to these clinical differences is evidence for biological differences between KS arising in different settings, including different HHV-8/KSHV subtype distributions that have been associated with differences in tumor behavior.[10-12] 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 antiherpesvirus therapy.[13] Recent studies of KS specimens obtained from Ugandan and Malawian PLWHs,[14,15] however, indicate that KS lesions from a subset of SSA patients express high levels of lytic HHV-8/KSHV gene products, including viral kinases, suggesting that some African KS patients may benefit from treatment with non-cytotoxic agents, including drugs targeting herpesviral kinases or viral gene products that influence KS development and progression.

The approach chosen by Bower *et al*[1] worked out 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 the editorial recommendation that WHO recommend PLD as the global standard for advanced KS is premature.

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