Commentary (Remick): Management of Anal Cancer in the HIV-Positive Population

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The article by Kauh and colleagues provides a timely review of the therapeutic approach to invasive carcinoma of the anus in human immunodeficiency virus (HIV)-infected patients, which is an emerging clinical problem. Important limitations of the published experience, however, need to be pointed out; given the present pursuit of more targeted anticancer therapy, new avenues are being explored, even in the management of HIV-associated anal cancer.

Epidemiology of Anal Cancer in the HAART Era
While anal cancer is clearly seen in increased incidence in HIV-infected patients, the emergence of this disease in men having sex with men occurred nearly a decade prior to the onset of the acquired immune deficiency syndrome (AIDS) epidemic.[1-3] It has long been established that human papillomavirus (HPV) infection is linked to the development of squamous cell carcinoma of the anogenital tract and cervix in particular. Not surprisingly, HIV-infected women have high rates of HPV infection, as patients at risk for HIV and HPV infection share common risk behaviors. It is well recognized that cervical intraepithelial neoplasia (CIN) is a sentinel marker for the development of invasive cervical carcinoma. Similarly, anal intraepithelial neoplasia (AIN) is a well-characterized clinical entity in HIV-infected homosexual men, and HPV infection is implicated in the pathogenesis of AIN.[4,5] The model of concurrent and/or compounding HPV and HIV infection in CIN is likely applicable to the development of AIN, in which long-term dysplasia with prolonged periods of immunosuppression precedes the onset of invasive disease. It is not surprising, therefore, that patients with HIV infection are at increased risk for developing genital and anogenital malignancy. What complicates the picture, however, is that for men or other patients with HIV-associated AIN it is not precisely clear at what point it is best to intervene, and what is the optimal therapy. Furthermore, the development of invasive disease does not appear linked to the degree of immunosuppression, and highly active antiretroviral therapy (HAART) does not diminish the excess risk of anal carcinoma as it does for Kaposi's sarcoma and non-Hodgkin's lymphoma.[6,7] Given this backdrop, it can be anticipated that invasive anal carcinoma will be an increasing problem as patients in the HAART era live longer with HIV infection. Published Data on Therapy
Turning our attention to the treatment of advanced disease, Kauh and colleagues provide an excellent overview of published studies for which several comments are in order. Foremost among them is that the majority of studies they cite were conducted prior to the HAART era. It is recognized that, in general, chemotherapy is better tolerated in the HAART era, and the more active antiretroviral regimens may have salutary or bone marrow-sparing effects.[8] Accordingly, combined-modality strategies commonly employed in the management of anal cancer in the HAART era may not be as myelotoxic. Nonetheless, bone marrow suppression, especially in patients with advanced AIDS, can certainly complicate therapy and present the clinician and treatment team with distinct challenges. The time-honored approach of adding colony-stimulating factor (CSF) support cannot be pursued. The pelvis is the primary source of functional marrow in the adult. Patients with advanced AIDS and already compromised bone marrow reserve are at great risk with the use of concurrent radiation and CSF support. Radiation has the potential to destroy any remaining stem cells that may be stimulated by CSF support. There are no data on the routine use of dose modification, which prior to the HAART era, at least for patients with advanced AIDS-related lymphoma, was equally efficacious as fulldose therapy and less myelotoxic.[8] Certainly, sound clinical judgment is of paramount importance in sorting out how best to proceed with combined-modality therapy in patients with AIDS-associated cytopenias, as Kauh and colleagues
address in their report. On the other hand, it is not at all clear that toxicity of combined-modality therapy is worse in HIV-infected patients, as the authors discuss. The reports on this are mixed, and again clinicians are cautioned as the bulk of these data were derived in the pre-HAART era.[9-16] We have generally encountered acceptable toxicity and safety profiles in our patients treated with combined-modality therapy (with mitomycin and 96-hour infusion of fluorouracil [5-FU]) in a preliminary review of our experience.[ 17] In general, patients with higher CD4 lymphocyte counts tend to do better.

**Future Directions**

Clearly, new strategies and drugs are needed in the management of HIV-associated anal cancer. It is likely that improved conformal techniques, new intensity-modulated therapies, and other computerized methods of radiation delivery will result in better local control. But equally important is the notion of sparing normal tissue toxicity including bone marrow function. The results of the largest phase III study conducted by the Radiation Therapy Oncology Group (R9811, a comparative trial of combined-modality therapy of concomitant radiation with mitomycin and 5-FU vs cisplatin and 5-FU) in immunocompetent patients are eagerly awaited. They may shed light on a less toxic regimen for use in patients with HIV-associated anal cancer as a departure point. With this in mind, the National Cancer Institute-sponsored AIDS Malignancy Consortium is about to launch a pilot phase II study (AMC 026) of combined-modality therapy consisting of cisplatin at 75 mg/m² IV on days 1 and 29; 5-FU at 1,000 mg/m²/d by continuous 96-hour infusion on days 1-4 and days 29-32; and cetuximab (Erbitux) at 400 mg/m² IV on day 1 and then 250 mg/m² IV on days 8, 15, 22, 29, 36, 42, and 49; with concurrent radiation to the tumor site and inguinal nodes (at a daily dose of 1.8 Gy, 5 days per week, to a dose of 45 Gy in 25 fractions over 5 weeks).[18] There are no scheduled breaks. The rationale for this particular combination builds on the notion that there are abundant preclinical and clinical data to support the use of epidermal growth factor receptor as a therapeutic target in many epithelial tumors, especially squamous cell carcinoma of the head and neck, and including anal carcinoma. Some data suggest that cetuximab is active in colorectal carcinoma and may be safely combined with platinum-based regimens in head and neck and colorectal tumors.[19,20] These data indicate that blocking the function of this important cellular survival factor may enhance the effects of chemotherapy and/or radiation-induced tumor regression. It is hoped that newer strategies will be translated shortly into the management of patients with AIDS-associated anal carcinoma.

**Disclosures:**
The author has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

**References:**
18. AIDS Associated Malignancies Clinical Trials Consortium: Phase II trial of combined modality therapy plus cetuximab in HIV-associated anal carcinoma. Sponsored by the National Cancer Institute, Division of Cancer Treatment and Diagnosis (AMC protocol 026, version 1.0, 3/10/05).

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