Commentary (Landry et al): Current Perspectives on Anal Cancer

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The article by Drs. Bendell and Ryan reviews the association between anal cancer and human papillomavirus (HPV) infection and discusses current management strategies for patients with squamous cell carcinoma of the anal canal. The authors should be complimented on a thorough review of the literature, which supports that association and the use of chemoradiation as the gold standard for treatment of this group of patients.

Most data that demonstrate an association between anal cancer and HPV infection emanate from studies of human immunodeficiency virus (HIV)-positive homosexual men. Bendell and Ryan state that HPV can cause both high-and low-grade premalignant anal squamous intraepithelial lesions, and that the progression of these lesions to invasive cancer is affected by HIV seropositivity, low CD4 count, the HPV subtype, and high DNA levels of high-risk HPV subtypes.[1] In fact, HPV type 16 is present in 30% to 75% of all cases of anal cancer, and types 6, 11, and 18 in up to 10% of cases.[2,3-5] High-grade intraepithelial lesions or intraepithelial neoplasia may progress in a similar fashion to invasive cervical cancer in women.[5,6]

Screening Possibilities

Given these associations, screening programs such as those for HPV and cervical cancer should be initiated to identify high-risk individuals. Two trials that assessed screening of both HIV-positive and -negative homosexual men found that it was cost-effective and had life expectancy benefits.[7,8] Additional well-controlled trials of screening are necessary and could possibly demonstrate similar cost-effective and life expectancy benefits in nonhomosexual men. If screening proves to be effective in the general male population, then it may be possible to develop a vaccine such as the one being developed for patients at risk for cervical cancer.

Shifting Treatment Paradigm

Although surgery—abdominal perineal resection with colostomy—was the primary treatment for anal cancer 20 years ago, the use of radiation with 5-FU-based chemotherapy has shifted the paradigm, achieving comparable cures with maintenance of the anal sphincter. The authors highlight data that support the use of 5-FU and mitomycin (Mutamycin) with radiation; omission of mitomycin in an intergroup Radiation Therapy Oncology Group (RTOG)/Eastern Cooperative Oncology Group (ECOG) trial (RTOG 87-04) resulted in a decrease in local tumor control, colostomy-free survival, and disease-free survival.[9]

However, concerns about myelodysplastic syndrome and leukemia risk associated with the use of mitomycin, and the encouraging results achieved with 5-FU, cisplatin, and radiation (ie, complete responses in 80% to 94% of cases, colostomy-free survival of 56% to 86%, and overall survival of 78% to 84%), prompted the intergroup to initiate a randomized trial (RTOG 98-11) comparing cisplatin, 5-FU, and radiation with mitomycin, 5-FU, and radiation. The trial will evaluate whether cisplatin-based therapy can replace mitomycin. Eligible patients should be encouraged to enroll in this trial, as a large accrual will provide greater statistical validation, and thus, shape future treatment of this disease. In patients treated off protocol, the following questions often arise: What is the optimal radiation dose? Is a treatment break advisable? How toxic is the treatment regimen?
Boosting Radiation

In critiquing RTOG 87-04, the authors point out that on subset analysis, the addition of mitomycin for patients with T3 and T4 tumors did not affect outcome significantly.[9] This conclusion is supported by the negative posttreatment biopsy rate of 86% in tumors greater than 5 cm. The radiation dose in this trial was 45 Gy, with an optional 5-Gy boost to a total of 50.4 Gy. Data confirm a dose-response relationship for control of gross tumor burden. Data from both Massachusetts General and M. D. Anderson hospitals show that radiation doses above 54 to 55 Gy result in improved responses and local tumor control.[10-12] The RTOG 98-11 trial mandates that patients with T3, T4, or node-negative tumors receive a boost dose to 59.4 Gy. To improve local tumor control in patients with T3 and T4 tumors, RTOG launched a phase II dose-escalation trial (RTOG 92-08), using a radiation dose of 59.4 Gy with 5-FU and mitomycin. A 2-week treatment break was mandatory due to concerns about acute toxicity. Significantly more local failures and a higher rate of colostomy (23%) compared to 6%-were reported in this trial than in RTOG 87-04. A subsequent trial delivered a radiation dose of 59.4 Gy and eliminated the treatment break, with a resultant 11% decrease in the colostomy rate.[13] The incidence of acute toxicity did not increase. The current intergroup trial RTOG 98-11 does not mandate a break, and anal cancer patients treated off protocol should not be given a mandatory break.

Acute Toxicities

The use of chemotherapy and radiation in the treatment of anal cancer is associated with acute toxicities. The most common acute side effects are generally grade 2 and 3 skin reactions such as erythema, pigmentation change, and desquamation that sometimes lead to treatment interruptions. In large measure, impairment of anal function depends on the extent of prior surgical intervention or on subsequent biopsy-this can become a permanent problem. In RTOG 92-08, 20 patients with anal carcinoma underwent treatment without a mandated break.[13] The predominant grade 3 and 4 toxicities in 18 evaluable patients were dermatitis (78%), hematologic effects (78%), infection (17%), and gastrointestinal reactions (28%). No treatment-related deaths occurred. Although acute toxicity is common, the potential for sphincter preservation overshadows toxicity concerns. Chemoradiation is the new gold standard for the treatment of anal cancer, and future trials will attempt to improve on the already encouraging results.

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