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ORIGINAL CONTRIBUTIONS

Squamous-Cell Carcinoma of the Anus in HIV-Positive Patients

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PURPOSE: Patients diagnosed as having anal cancer and human immunodeficiency virus (HIV)-positive disease were evaluated for response to treatment and its associated toxicity. METHODS: We studied nine HIV-positive patients with squamous-cell carcinoma of the anus. Among them, three patients had acquired immunodeficiency syndrome (AIDS). The stage of disease at presentation included: one Stage 0, two Stage I, two Stage II, and four Stage III patients. Seven patients received combined modality treatment, *i.e.*, radiation therapy and chemotherapy, and two patients received radiation therapy alone. The radiation therapy field included the pelvis and a conedown boost. Chemotherapy consisted of two cycles of 5-fluorouracil and mitomycin C. Patients have been followed from 2 to 42 (median, 8) months. RESULTS: Seven patients achieved a complete response clinically. All Stage I/II patients and one of four Stage III patients remain alive and have no evidence of disease. Radiation Therapy Oncology Group/European Organization for the Research and Treatment of Cancer Grades 3 and 4 skin toxicity were noted in six patients, and Grades 2 and 3 myelosuppression were noted in eight patients. The response rates achieved are comparable to the experience in non-HIV patients reported in the literature, but toxicity seems to be increased. CONCLUSION: It would seem reasonable to offer combined modality treatment to early stage, HIV-positive patients with good performance status and a history of minor opportunistic infections. The value of combined modality in AIDS patients and those who present with advanced stages of the disease is questionable. [Key words: HIV-positive; Combined modality treatment; Squamous-cell cancer; Anus]

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Epidemiologic studies show an increased incidence of squamous-cell carcinoma (SCC) of the anus in the homosexual population.[1,2] There is evidence that the loss of cellular immunity with human immunodeficiency virus (HIV) infection can both increase the infection rate of human papillomavirus and exacerbate the cytologic abnormalities/dysplasia associated with the virus.[3] Since the homosexual population is at risk both for HIV infection and cancer of the anus, the two conditions may coexist. There are very little data in the literature on the response and tolerance of treatment for anal cancer in patients who are HIV positive.

PATIENTS AND METHODS

In a retrospective analysis, 48 patients were seen in the Department of Radiation Oncology between 1987 and 1991 with a diagnosis of anal malignancies. The male to female ratio was 1.5:1. Among this group of patients, six patients were HIV positive and three had acquired immunodeficiency syndrome (AIDS) by virtue of previous infections and/or Kaposi's sarcoma lesions. Patient demographics are listed in Table 1. Over half of the patients had associated anal conditions. In five patients, the tumor was examined by *in situ* hybridization for human papillomavirus subtypes; no viral DNA was identified. Staging work-up included history, physical examination, biopsy of the primary lesion, chest x-ray, and computed tomographic scan of the abdomen and pelvis. In addition, four patients

Table 1.
Patient Characteristics I

SCC histology	9 patients
Sex	Male
Age (yr)	
Median	52
Range	28–69
Risk factors	
Homosexual	6 patients
Intravenous drug abuser	3 patients
Associated anal conditions*	5/9 (55%)
Symptoms	
Pain/itching	7
Mass	3
Bleeding	5
Abscess	2

* Condyloma, fissure, Bowen's disease.

Table 2.
Patient Characteristics II

Stage of Disease* Presentation	No. of Patients
0	1
I	2
II	2
IIIa	2
IIIb	2
Treatment type	
External radiation therapy (ERT) alone	2
ERT + chemotherapy (CMT)	7

* TNM staging.

underwent sigmoidoscopy and one had a barium enema. The stage at presentation included one stage 0, two Stage I, two Stage II, two Stage IIIa, and two Stage IIIb diseases (Table 2). The patient with Stage 0 received radiation therapy alone. One Stage I patient did not receive chemotherapy due to the physician's preference. Seven patients received combined modality treatment (CMT). The chemotherapy regimen was two cycles of 5-fluorouracil and mitomycin C; 5-fluorouracil was to be administered at a dose of 1,000 mg/m^2 on days one to four by continuous intravenous infusion and 10 mg/m^2 of mitomycin C on day one. Chemotherapy cycles were planned for the beginning and completion of radiation therapy. Six patients also received zidovudine during treatment.

All patients received a course of external radiation therapy. The radiotherapy field included the primary tumor and the pelvic nodes. In addition, five patients received a conedown boost to the primary. Table 3 lists the radiation treatment parameters for this study group. The average field size used was 17 cm × 24 cm. The median pelvic dose was 4,000 cGy, and the median boost dose was 1,000 cGy. The radiation therapy course spanned 32 to 112 (median, 49) days. All patients had weekly evaluations during treatment, including physical examinations and complete blood counts.

RESULTS

Patients had a median follow-up of 8 (range, 2–12) months. Patients' follow-up status is shown in Table 4. One patient was lost to follow-up. Response to therapy, evaluated four to six weeks after completion of radiation therapy, showed seven patients achieved a complete response clinically. One of the two patients with persistent disease was a Stage 0, who received a protracted course of radiation therapy (4,500 cGy in 112 days), due to noncompliance, and the second was a Stage IIIb at diagnosis. Two patients have died; one patient died of AIDS-related infection and one patient had recurrent sepsis. Only one patient who had been treated with radiation therapy alone progressed from HIV-positive to clinical AIDS.

Acute Toxicity

The acute toxicity was scored using the Radiation Therapy Oncology Group/European Organization for the Research and Treatment of Cancer scores (Table 5). In six patients, Grade 3/4 skin toxicity was noted. Gastrointestinal toxicity was noted in two patients. Grades 2 and 3 myelosuppression were noted in eight patients. The leukocyte nadir occurred at a median of day 17.

The radiation therapy course was protracted in that five patients needed a treatment delay >14 days because of acute skin morbidity. Also, in seven of the eight patients on the combined modality treatment, the observed hematologic toxicity necessitated modifications in chemotherapy which included dose reductions, interruption, and/or elimination of the second cycle.

Chronic Toxicity

One patient remains symptomatic with chronic diarrhea requiring medical therapy. Two patients had protracted skin morbidity with fistula and local infections; one patient experienced this in the face of uncontrolled cancer. The other patient is a complete responder who required a colostomy to facil-

Table 3.
Radiation Treatment Parameters

Patient	Field Size (cm)	Beam Energy	Radiation Therapy Dose (cGy)	Boost Dose (cGy)	Elapsed Days
1	17 × 23	10MV	4,000	1,000	40
2	10 × 23.5	10	4,500	—	112
3	21 × 30	10	4,000	—	32
4	16 × 21	10	4,000	1,000	49
5	17 × 27	1.25	3,000	—	22
6	16.5 × 20	1.25	4,000	—	53
7	13 × 16.5	1.25	3,060	1,980	51
8	24 × 31	10	4,500	900	51
9	17 × 23	1.25	3,960	540	50
All patients	17 × 24 (average)		4,000 (median)	1,000 (median)	49 (median)

Table 4.
Follow-up Status

Patient	Stage	Treatment	Follow-up (mo)	Disease Status	Survival Status
1	I	CMT	42	NED	Alive
2	0	RT	18	PD*	Alive
3	IIIb	CMT	8	PD*	Alive
4	II	CMT	8	NED	Alive
5	IIIa	CMT	12	NED	Alive
6	I	RT	2	NED	LFU**
7	IIIa	CMT	3	NED	Dead
8	IIIb	CMT	9	LF@	Dead
9	II	CMT	11	NED	Alive

RT = radiation therapy; PD = persistent disease; LFU = lost to follow-up; LF = local failure.

Table 5.
Toxicity Scores

Site/ Toxicity*	Gastrointestinal	Skin	White Blood Cells
I	1	1	
II	1	2	6
III		5	2
IV		2	

* Radiation Therapy Oncology Group/European Organization for the Research and the Treatment of Cancer grade.

itate healing. However, this patient subsequently developed a local relapse/recurrence.

DISCUSSION

In HIV-infected individuals, anal cancer can be viewed as an opportunistic malignancy. It is, however, difficult to establish a causal relationship since epidemiologic data indicated an increase in this type of cancer among homosexual men prior to the AIDS epidemic.[4–8] Daling *et al.*[2] have reported a strong association of the occurrence of anal cancer with the history of receptive anal intercourse related to homosexual behavior. In our experience, more male patients present with this disease than females; this is consistent with the epidemiologic observations by others. There is an association of this disease with anal condylomata. Over half of the study patients had an associated history of anal conditions prior to the diagnosis of SCC. An association of human papillomavirus with anal cancer is reported.[6] However, in our population, no viral DNA was noted.

Various studies have established the feasibility and efficacy of CMT for anal SCC.[8–13] Ongoing randomized trials are being conducted by the Radiation Therapy Oncology Group, European Organization for the Research and Treatment of Cancer, and in the United Kingdom to further evaluate the optimal treatment sequencing and chemotherapy drug combinations. Complete clinical regression of the primary tumor can be expected in approximately 85 percent and biopsy-proven complete tumor disappearance has been documented in 80 percent of patients treated with CMT.[14–16]

In the non-HIV setting, the toxicity of this approach has been evaluated. The reported acute toxicity ranges from 30 percent to 50 percent. Cummings *et al.*[17,18] noted acute toxicity in 56 percent of the patients receiving chemotherapy with continuous radiotherapy schedule as compared with 36 percent in patients receiving chemotherapy and split radiotherapy. In one report, 40 percent of the patients did not complete chemotherapy because of acute toxicity. The use of

smaller fraction sizes or smaller irradiation volume has been suggested to improve the patients' tolerance to the CMT without necessitating a delay/interruption in their radiation course.[18–20]

The tolerance of HIV-positive patients to chemotherapy and radiation therapy treatment modalities is inferior compared with HIV-negative patients.[21] Several studies on AIDS-related Kaposi's sarcoma[22] report that the mucosal surfaces of these patients tolerate radiation therapy poorly, possibly because lesions become colonized with *Candida albicans* or other opportunistic organisms. Also, because of immunocompromise and inadequate bone marrow reserve, these patients tolerate cytotoxic chemotherapy poorly and are prone to myelosuppression.[23] Our experience using CMT in HIV-positive patients with SCC of the anus, although limited by the small number of patients, indicates that high-response rates (7/9) can be achieved. In almost all cases, the treatment course could be completed after allowing for interruption and dose modification. All six patients with Stages I/II/IIIa have no evidence of disease. Both Stage IIIb patients failed treatment. Treatment-related morbidity is enhanced in this treatment group; six of seven (86 percent) patients did not complete the planned chemotherapy because of hematologic toxicity and six of nine (66.6 percent) patients had Grade 3/4 skin toxicity. Only one patient received the full-dose second cycle of the chemotherapy program as originally intended; therefore, the absolute contribution of the second cycle of chemotherapy to the combined program is unclear.

Lorenz *et al.*[24] reported their experience with six HIV-infected patients. They suggested that these patients be offered conservative treatment using external radiation therapy alone or local excision and external radiation therapy.

CONCLUSION

The optimal treatment recommendations for these patients, in the face of sensitivity to cytotoxic therapy and the compromised life expectancy related to the HIV infection, remain unclear. It appears unlikely that CMT accelerates the HIV disease. For early stage anal cancer, it seems reasonable to recommend CMT if the patient has an otherwise good performance status, a history of minor or no prior opportunistic infections, and adequate physiologic parameters. The role of CMT in AIDS patients and those who present with an advanced stage of disease is questionable. With the AIDS epidemic unchecked, we will be confronted with a significant number of such patients in our clinical practice. There remains, therefore, the need to better understand the natural history of anal carcinoma in HIV-infected patients and to develop optimal drug combinations, dose schedules, and optimal radiation volume and fraction schedules.

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