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Treatment of HIV-associated invasive anal cancer with combined chemoradiation

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Abstract

There is an increased frequency of invasive anal cancer in HIV-seropositive men. Early treatment strategies in this patient group employed reduced dosages of chemotherapy or radiotherapy alone to reduce toxicity. Since 1989 we have used combined modality treatment consisting of chemotherapy 5-fluorouracil (5-FU) and mitomycin C, and concomitant radical radiotherapy to the pelvis (38–51 Gy in 20–30 fractions), with most patients receiving a perineal boost (10–18 Gy). 12 homosexual HIV-positive men have been treated. The median CD4 count at diagnosis of anal cancer was 209 cells/μl (range: 29–380 cells/μl), 5 had prior AIDS defining diagnoses. No patients had metastatic disease. Complete remissions were obtained in 9/11 evaluable patients and in 1 further patient following surgery. 2 patients relapsed both within 6 months of diagnosis. At a median follow-up of 4.8 years (range: 0.4–10 years), 4 patients have died (2 from anal cancer, 1 from treatment-related consequences and 1 from opportunistic infection in remission). Actuarial 2-year survival is 60% (95% confidence interval (CI): 29–91%). Grade 3 haematological toxicity was recorded in 3 patients, grade 4 and 5 gastrointestinal toxicity in 1 patient each and grade 3 skin toxicity in 1 patient. Radical chemoradiation may be given safely at conventional doses in HIV-positive patients, with a high complete response rate.

Keywords: AIDS; Anal cancer; Chemoradiation; HIV

1. Introduction

There is a strikingly increased incidence of anal carcinoma amongst HIV-positive patients [1] but it has been shown that homosexual men were at increased risk of this malignancy before the onset of the AIDS epidemic [2]. Indeed the incidence of anal cancer amongst homosexual men in the pre-AIDS era was estimated to be 35/100 000 which resembles the incidence of cervical cancer before the introduction of routine Pap smear screening. None the less, anal cancer is twice as common in HIV-positive homosexual men as it is in HIV-negative homosexual men [3] although unlike invasive cervical cancer, invasive anal cancer is not an AIDS defining diagnosis. Human papilloma virus (HPV) is suspected to play an important role in the disease pathogenesis [4]. High grade squamous intraepithelial lesion (SIL) or anal intra-epithelial neoplasia (AIN) of the anus is believed to progress to invasive anal cancer in a fashion analogous to the progression to invasive cervical cancer, and cohort studies of men with SIL have demonstrated that these lesions do not regress with highly active antiretroviral therapy (HAART) despite the established benefit of HAART on other viral infections and associated diseases in HIV-infected patients [5]. The prolonged survival of HIV-infected people in the era of HAART and the lack of regression of anal SIL suggests that the incidence of invasive anal cancer will increase in this population.

Historically, most anal carcinoma was managed surgically, with 5-year survival rates in the region of 55%. In 1974, Nigro and colleagues reported that combined modality therapy (CMT) of chemotherapy 5-fluorouracil ((5-FU) and mitomycin C) with radiation treatment could result in microscopic and histological tumour ablation with sphincter preservation [6]. Subsequently it

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was demonstrated that the resulting survival rates were at least as good as those achieved with surgery alone although a randomised trial has never been performed to confirm this. Most centres report that approximately 85% of tumours can be controlled locally with 5-year survival rates in the range of 65–85% [7]. The superiority of CMT over radiation alone was later confirmed by two large multicentre, randomised trials. Both the UKCCCR and EORTC trial reported superior local control rates with CMT, without an overall survival advantage [8,9].

HIV-infected people tolerate both chemotherapy and radiotherapy poorly. For this reason coupled with the limited prognosis of patients with HIV prior to the introduction of more active antiretroviral regimens, there was some reluctance to treat anal carcinoma in the setting of HIV with standard dose CMT [10–12]. However, over the last 10 years we have adopted a policy of treating HIV-positive patients with invasive anal cancer according to a standard CMT regimen, and we report the results here.

2. Patients and methods

A review of the Chelsea and Westminster Hospital database of 2500 HIV-seropositive patients identified 12 patients who were treated at our centre for invasive (epidermoid) anal carcinoma with CMT between 1989 and 1999. A retrospective case record review was performed. Complete clinical staging was performed at diagnosis for all patients.

2.1. Radiotherapy

All patients were treated with a phase I anterior and posterior opposed field delivering a central axis dose of 38–51 Gy in 1.8 Gy fractions to a volume including the anal canal and inguinal lymph nodes. The superior border or the clinical target volume was set at the mid-pelvic line and the inferior border was positioned to include the whole perineum. After a rest period of 4–6 weeks those patients who were responding went on to receive a perineal boost of 10–18 Gy as electrons or photons.

2.2. Chemotherapy

Infusional 5-FU was commenced on day 1 of radiotherapy, prior to the delivery of the first fraction. The dose was 1000 mg/m^2 over 24 h days 1–4 or 750 mg/m^2 over 24 h days 1–5. Mitomycin C 10 mg/m^2 was given as an intravenous bolus injection on day 1 only. A second course of 5-FU was given with the fifth week of radiotherapy, no mitomycin C was given with this second course.

2.3. Toxicity

Toxicities were recorded according to the criteria of the Radiation Therapy Oncology Group (RTOG) [13]. Morbidity was classified as skin, gastrointestinal or haematological. Morbidity during treatment or up to 2 months later was defined as early. Late morbidity refers to reports more than 2 months after the end of treatment.

2.4. Statistical methods

Survival was calculated from the day of diagnosis until death or the date of last follow-up. Overall survival duration curves were plotted according to the method of Kaplan and Meier [14]. The log rank method was used to test for the significance of differences in survival distributions [15].

3. Results

3.1. Patients

Between 1989 and 1999, 12 patients were diagnosed with HIV-related invasive anal cancer and all were treated with CMT. All were homosexual men and the mean age at diagnosis of anal cancer was 43 years (range: 30–53). The median CD4 count at diagnosis of anal cancer was 209 cells/μl (range: 29–380 cells/μl). 5 patients had previous AIDS defining diagnoses. Staging was as follows: T1 in 5, T2 in 4, T3 in 3, N0 in 11, N1 in 0 and N2 in 1. No patients had metastatic disease and there was no correlation between T stage and CD4 cell count ($P=0.08$). 9 patients were taking antiretroviral treatment including 4 patients receiving HAART, 4 patients on nucleoside reverse transcriptase inhibitor monotherapy and 1 on zidovudine and loviride. Details of individual patients are shown in Table 1. Eight tumours were described as squamous cell carcinomas and 4 basaloid/cloacogenic cancers. Half the tumours (6/12) were poorly differentiated grade 3 tumours.

3.2. Responses

The median follow-up was 4.8 years (range: 0.4–10 years). In most cases response was assessed clinically and radiologically, that is, without the aid of a biopsy. 11 patients were assessable for response. 1 patient with a CD4 count at start of treatment of only 29/μl died 4 months after diagnosis (at which stage treatment response had not been formally assessed), as a result of opportunistic infection. Complete remissions were obtained in 9 patients, 1 patient achieved a partial response and subsequently has had a abdomino-perineal (AP) resection and is disease-free, 1 patient had progressive disease on CMT and died of anal cancer.

Table 1
Clinico-pathological details of patients[a]

Patient	Age (years)	Tumour stage	CD4 count cells/μl	Prior AIDS defining illness	Antiretroviral treatment
1	53	T1N0M0	136	None	Triple HAART
2	49	T1N0M0	318	Kaposi's sarcoma	AZT, Loviride
3	47	T1N0M0	209	Lymphoma	None
4	34	T2N0M0	115	None	Triple HAART
5	30	T2N0M0	141	PCP	AZT
6	48	T2N0M0	29	Oesophageal candida	AZT
7	43	T1N0M0	234	None	AZT
8	50	T1N0M0	266	None	DDI
9	41	T3N2M0	336	None	None
10	42	T2N0M0	121	None	None
11	39	T3N0M0	380	Kaposi's sarcoma	Triple HAART
12	48	T3N0M0	377	None	Triple HAART

[a] PCP, pneumocystis carinii pneumonia; HAART, highly active antiretroviral therapy; AZT, zidovudine; DDI, didanosine.

3.3. Relapses and deaths

7 of the 9 patients who achieved a complete remission remain alive and disease-free including 1 at 26 months, 1 at 32 months, 1 at over 7 years and 1 at 10 years. 2 patients who achieved complete remission have died. One patient with T1N0M0 disease who was biopsy negative 2 months after following completion of treatment, relapsed with a positive biopsy approximately 2 months after this. He subsequently required a defunctioning colostomy for recurrent faecal peritonitis, thought to be disease related rather than treatment related, and died from his anal carcinoma 7 months following diagnosis. The other patient with T2N0M0 disease and previous pneumocystis carinii pneumonia (PCP) infection died of recurrent bowel obstruction attributed to radiation enteritis 7 months after diagnosis.

The only other relapse was recorded in a patient with T2N0M0 disease deemed to be in partial remission clinically and radiologically initially but who was required to undergo an AP resection for rapidly progressing local disease 3 months following completion of treatment and remains alive in remission 3 months later.

One patient with T3N2M0 disease but no previous AIDS-defining illness responded poorly to chemoradiation and required a defunctioning colostomy and died of local disease 9 months after diagnosis.

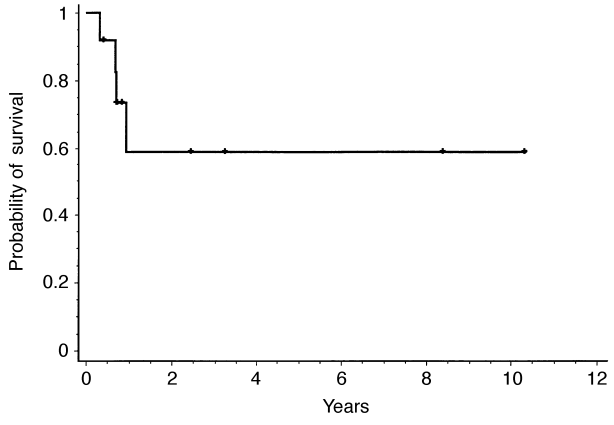

Fig. 1. Actuarial survival duration curve for 12 patients treated with chemoradiotherapy for HIV-associated invasive anal cancer.

3.4. Overall survival

The actuarial 5-year survival was 60% (95% CI: 29–91%), as displayed in Fig. 1. In this small cohort there was no significant correlation between overall survival and tumour stage (log rank $P=0.41$), antiretroviral usage (log rank $P=0.40$), age (proportional hazards $P=0.27$) or CD4 count at anal cancer diagnosis (proportional hazards $P=0.11$).

3.5. Toxicity

One patient developed fatal recurrent bowel obstruction and at laparotomy biopsies revealed radiation enteritis. The frequency of acute toxicities is listed in Table 2. There was no difference in the toxicity scores between patients with a CD4 count of $<200/\mu l$ or $>200/\mu l$ for haematological (χ^2 $P=0.30$), dermatological (χ^2 $P=0.11$) or gastrointestinal (χ^2 $P=0.17$) toxicity.

Table 2
Recorded toxicities according to the criteria of the Radiation Therapy Oncology Group (RTOG) [13]

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5 (fatal)	Overall
Haematological	2	1	3	0	0	6 (50)
Dermatological	3	7	1	0	0	11 (92)
Diarrhoea	5	3	0	1	1 (radiation enteritis)	10 (83)

4. Discussion

Anal carcinoma remains an uncommon malignancy with approximately 300 new cases reported in the UK each year. However, we can anticipate an increase in the incidence amongst the HIV population as the survival is improved by more active antiretrovirals, and a palliative approach to anal carcinoma in this setting is unacceptable. Treatment of the disease in the non-HIV population with combined chemoradiation is now well established as standard practice. It is still not clear whether the effect of the two treatment modalities are additive or synergistic. Mitomycin C may be important because of its relatively greater toxicity against hypoxic cells [16]. Historically, there has been some reluctance to treat HIV patients according to these standardised regimens because of concerns regarding the possibility of unacceptable toxicity. Toxicity in non-HIV patients can be considerable, though rarely life-threatening. Furthermore, late complications are relatively uncommon [17]. It has been observed that the radiation tolerance of mucosal surfaces is poor in patients treated for AIDS-related Kaposi's sarcoma, possibly because of colonisation with *Candida albicans* [18]. It is accepted that HIV patients tolerate chemotherapy less well due to decreased bone marrow reserves. Furthermore, antiretroviral drugs are associated with considerable side-effect profiles which have the potential to reduce treatment tolerability, as well as a tendency to interact unfavourably with chemotherapy.

There are three similar small studies of chemoradiation for HIV-associated anal cancer in the literature although none present mature data. Chadha and colleagues report on the treatment of 7 HIV-positive patients treated similarly to ours [19]. 5 (71%) patients achieved complete remission, and no recurrences were recorded with a median follow-up of 8 months. Holland and associates also report on 7 HIV-positive patients treated with combined chemoradiation, although only 2 patients received mitomycin C in addition to 5-FU. Again 5 (71%) patients achieved complete remission but toxicity was considerable with all requiring a break from treatment [20]. The median follow-up was 16.3 months and 3 patients had local failure and died with disease. The largest series has been reported from San Francisco by Hoffman and coworkers who treated 16 patients with chemoradiation and 15 (94%) achieved remission. At a median follow-up of 17 months, all 8 patients who had a CD4 count at anal cancer presentation of $>200/\mu l$ are alive in remission. In contrast, 3 of the 7 patients with a CD4 count of $<200/\mu l$ required colostomies although 6 eventually achieved remission and only 1 patient has died of anal cancer [21]. These results compare with our series of 12 patients which is more mature with a median follow-up of 4.8 years (0.4–10). 9 of 11 evaluable patients achieved complete remission and a further patient achieved complete remission after AP resection following the chemoradiotherapy. There were two relapses including the latter patient and both occurred within a matter of months and it may be that neither achieved a full remission despite the biopsy in 1 patient suggesting otherwise. Indeed, it has been argued that response should not be assessed earlier than 3 months after completing chemoradiation since this represents the median time to complete remission [22]. 2 patients died of anal cancer, 1 died of treatment-related toxicity and 1 died of opportunistic infection.

The treatment-related toxicity in all series has been considerable. We report in this series a patient with fatal radiation enteritis following chemoradiation for HIV-associated anal cancer. The majority of our patients experienced diarrhoea (83%) and skin reactions (92%) and half had haematological toxicity. The toxicities were grade 3 or above in 25% (haematological), 17% (diarrhoea) and 8% (skin reaction). It should be noted that in our series only a single dose of mitomycin C was administered and the rest period before the perineal boost was 4–6 weeks. Both these modifications may have favourably influenced the toxicity but adversely affected the treatment outcome. Similar high toxicity profiles have been described in other series [19,21]. The incidence of treatment-related toxicity in the San Francisco series was higher amongst patients with lower CD4 counts ($<200/\mu l$) at diagnosis [21], however, this difference was not observed in our series. The toxicity of this chemoradiation regimen has been assessed in immunocompetent patients. Sischy and colleagues [17] describe in detail the toxicity they observed in 79 patients treated with chemoradiation as part of an RTOG pilot study. Eighteen per cent experienced moist desquamation (equivalent to grade 2/3), and 85% of patients developed low white cell counts. In the UKCCR trial [8], 292 patients received chemoradiation of whom 50 (17%) experienced 'severe' skin toxicity and 46 (16%) 'severe' gastrointestinal toxicity. In Flam and colleagues' study [23] in which patients received two doses of mitomycin C, 23% of patients experienced grade 4 toxicity and 2.7% experienced fatal toxicity. Compared with these statistics the acute toxicity recorded for our patients, though considerable, can be viewed as acceptable.

Approaches to reduce the toxicity of chemoradiation might be considered in view of the reported higher incidence of side-effects in patients with low CD4 counts, although this was not seen in our series. The possible modifications aimed at reducing toxicity include radiation dose reduction, radiation field limitation and chemotherapy schedule alterations. Peddada and colleagues treated 8 HIV-positive patients with anal carcinoma with standard chemotherapy but reduced dose radiotherapy, (30 Gy in 15 fractions over 3 weeks, with 1 patient requiring a boost for residual disease) [12].

Encouragingly, all 8 achieved complete remissions, but toxicity was still considerable with 50% patients experiencing moist desquamation. However, it is probable that local control is compromised by radiation dose reduction. Nigro and Vaitkevicius reported disappointing local control rates in 104 HIV-negative patients treated with 30 Gy and concomitant 5-FU/mitomycin C, 35% of whom required AP resection [24]. Similarly, reduction in radiation field size could reduce toxicity. However, although most patients relapse with local disease, surgical series suggest that the pararectal, superior haemorrhoidal or internal iliac lymph nodes are positive in 30% and the inguinal nodes in 20% [25]. Nonetheless, radiation field reduction has been successfully used for node-negative non-HIV patients where the radiation field was reduced to exclude the inguinal nodes. 59 patients were treated with reduced field irradiation without chemotherapy and in only 5 patients was inguinal disease the first site of recurrence and all 5 were successfully salvaged with surgery and/or further radiotherapy [26]. Toxicity may also be reduced by the omission of mitomycin C, but a randomised study conducted by the Radiation Therapy Oncology Group (RTOG) and Eastern Cooperative Oncology Group (ECOG) demonstrated that this compromised disease-free and colostomy-free but not overall survival [23].

The use of radioprotectants such as amifostine might be one way of reducing radiation-induced reactions, thereby allowing more effective treatment delivery and subsequent better outcomes.

The results presented here with medium-term follow-up, combined with the three previously published series support the use of combined modality therapy in HIV-associated anal cancer. We recommend that anal carcinoma in HIV-positive patients should be treated according to standard combined modality therapy regimens. Toxicity is such that reduction in the intensity of radiation or chemotherapy is not merited and indeed would be expected to compromise local control rates.

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