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HIV STATUS AND ACUTE HAEMATOLOGICAL TOXICITY AMONG CERVIX CANCER PATIENTS UNDERGOING RADICAL CHEMORADIATION

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Abstract

INTRODUCTION—Women infected with the human immunodeficiency virus (HIV) have a higher risk of developing cervix carcinoma than other women and are thought to be more vulnerable to acute toxicities during chemoradiation. We compared HIV-positive and -negative cervix carcinoma patients at a single institution with respect to cancer treatment toxicities.

METHODS AND MATERIALS—Among patients with Stage Ib1-IIIb invasive cervical carcinoma who received radiation or chemoradiation with curative intent, we evaluated demographic and clinical characteristics of HIV-positive and –negative patients. Treatment regimens were documented and toxicities scored as per Radiation Therapy Oncology Group (RTOG) guidelines. We developed logistic regression models for the associations of grade 3/4 toxicities with HIV status.

RESULTS—Complete data were available on 213 patients, including 36 (16.8%) who were HIV-positive. More than 85% of both HIV-positive and HIV-negative patients received a minimum of 68Gy equivalent dose in 2Gy fractions (EQD_2) external beam and high dose rate brachytherapy. More HIV-positive than –negative patients were prescribed radiation alone (38.9% vs 24.29%, p=0.01), experienced at least one grade 3/4 toxicity (38.9% vs 26.6%) or developed grade 3/4 leucopaenia (30.6% vs. 10.2%) (p=0.003).

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In a multivariable model, patients who developed a grade 3/4 toxicity were 4 times as likely to have received chemotherapy [OR 4.41 (95%CI 1.76–11.1) p=0.002] and twice as likely to be HIV-positive [OR 2.16 (95% CI 0.98–4.8) p=0.057] as women who did not experience such toxicities.

CONCLUSION—HIV-positive patients with cervical carcinoma received adequate radiotherapy but were less likely than HIV-negative patients to complete chemotherapy. Few HIV-positive or –negative patients who received radiotherapy *without chemotherapy* experienced grade 3/4 toxicity. However, among patients who received chemotherapy, those who were HIV-positive were more likely than others to experience haematological toxicity.

Keywords

cervical cancer; human immunodeficiency virus; AIDS-defining malignancy; radiation; chemoradiation; toxicity

INTRODUCTION

Cervical carcinoma remains one of the leading causes of cancer and cancer mortality among women in the developing world, including women infected concurrently with human papilloma virus (HPV) and human immunodeficiency virus (HIV)[1]. Most research on the co-occurrence of the two conditions has focused on incidence. Recent studies suggest that, by prolonging the life expectancy of HIV-positive women, antiretroviral therapy (ART) may have actually contributed to rising incidence rates of cervix carcinoma[2].

Treating patients with the two conditions challenges the oncology and infectious disease teams. Treatment involves balancing oncological therapy, concomitant anti-retroviral treatment (ART), and antimicrobials; and trying to cure the underlying malignancy, to control HIV-related opportunistic infections, and to minimize treatment toxicities. Yet very little research has dealt with the effects of HIV status on cervix carcinoma treatment and its outcomes. In a previous study of cervix cancer patients treated between 2007 and 2010, we found that 79.7% of HIV-positive patients and 89.8% of HIV-negative patients received adequate radiation and that 44.9% of HIV-positive patients vs. 70.9% of HIV-negative patients completed both radiation and 4 or more cycles of platinum-based chemotherapy[3]. Poor response at 6 weeks was found to be related to Stage IIIb disease and inadequate radiation. The aim of the current study was to compare treatment toxicities in another cohort (overlapping the first) of HIV-positive and HIV-negative patients whose treatment toxicity data were collected prospectively.

METHODS AND MATERIALS

Patient Records

For this prospective cohort study, we reviewed the charts of all patients diagnosed with Stage Ib1 to IIIb invasive cervical carcinoma who were categorized as HIV-positive or HIV-negative, received radiation or chemoradiation with curative intent, and had complete toxicity data between November 2009 and December 2011 at the Division of Radiation

Oncology, Tygerberg Hospital.. Patients who underwent primary surgery were excluded. Ethical approval was obtained from the University of Stellenbosch human ethics committee.

In late 2009, our oncology clinic consultant introduced clinic residents to the use of a modified RTOG toxicity score sheet that included haematological, renal, gastrointestinal, urinary, skin and weight parameters.[4] the team then began reviewing charts, recording demographic and clinical characteristics of the patients, and collecting toxicity data at the time of treatment. The consultant reviewed the completed sheets weekly. We determined whether or not the HIV-positive patients had commenced ART prior to treatment for cervix cancer and recorded their initial CD4 cell count. Treatment regimens, including external beam radiation therapy (EBRT) dose, high dose rate (HDR) brachytherapy dose, and chemotherapy cycles, were documented. The total doses of EBRT and HDR were calculated using equivalent dose in 2 Gy (EQD_2) fraction formulas[5].

Treatment

The radiotherapy protocols used for the study participants have been previously reported[3]. Patients without contraindications received 46 - 50Gy external beam radiation in 23- 25 fractions, using conformal 3-D planning and 18MV energy, 4 field arrangement. This was followed by 20–25 Gy high dose rate intracavitary brachytherapy in 4–5 fractions. A straight intrauterine source and standard plans for the appropriate intracavitary length were used. At the time of the study, no image-guided brachytherapy was available. For patients who had a history of extensive abdominal surgery or were HIV-positive, the daily dose per fraction was dropped to 1.8Gy. The absolute minimum total dose considered adequate was 68Gy EQD_2 (45Gy external beam radiotherapy and 18Gy in 3 fractions HDR brachytherapy).

If renal function allowed, 40mg/m2 Cisplatin was given weekly; if calculated glomerular filtration rate (GFR) or ethylenediaminetetraacetic acid (EDTA) GFR was <50ml/min, Carboplatin area under the curve $(AUC)^2$ weekly was given. No dose modifications were made for CD4 cell count unless it fell below 200, in which case chemotherapy was omitted. Due to pressure on the radiotherapy waiting list, in some cases of Stage IIIB disease chemotherapy was omitted and a hypofractionated regimen of 40.05Gy in 15 fractions, or 42.72Gy in 16 fractions, was used with standard HDR brachytherapy. The same fractionation was also employed for patients with poor renal function or poor performance status.

At our institution, patients with locally advanced cervix carcinoma are routinely tested for HIV at first presentation. All HIV-positive patients are scheduled for HPV screening annually, thus very few develop locally advanced disease. Almost all of the patients in this cohort were diagnosed with HIV at the time of the cervix cancer diagnosis. Cervix carcinoma patients who test positive patients start receiving ART either just before or as soon as possible after commencing radiation treatment. ART at the time of the study included triple therapy with lamivudine, efavirenz and tenofivir unless the creatinine clearance was low, in which case the patient received stavudine instead of tenofivir. Every HIV positive patient commencing radiation or chemoradiation receives concurrent co-trimoxazole. Because HIV infection is a large burden for tertiary centres many of our

patients receive their HIV care at community health centres, and we were unable to obtain data on viral load, compliance, medication changes and ART toxicities for this study.

Statistics

The statistical significance of differences in demographic factors, clinical parameters and toxicity between HIV-positive and HIV-negative patients was evaluated by means of t-tests for continuous variables and chi-square tests for categorical variables. Multivariable logistic regression models were developed to analyse the risk of developing a grade 3/4 toxicity controlling for HIV status, total dose of radiation and prescription of chemotherapy. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI). All tests were 2-sided, and p values ≤0.05 were considered significant. Data were analysed using the SPSS Statistics software program (version 21.0; SPSS, Inc., Chicago, Ill)

RESULTS

Patient Characteristics

259 patients with cervical carcinoma stages IB-IIIB commenced radical radiotherapy during the study period, 46 patients had no toxicity data. Of the patients with no toxicity scores; 36 were HIV-negative and all completed their prescribed radiotherapy; of the 10 patients who were HIV-positive, 6 completed radiotherapy. Complete toxicity data was available on 213 patients, 36 (16.8%) who were HIV-positive. The HIV-positive patients were younger than the HIV-negative patients but did not differ from them with respect to the prevalence of either squamous cell carcinoma or Stage IIIB disease (see Table 1). The median CD4 cell count of the HIV-positive patients was 341 (range 33–790); 30 patients had a CD4 >200. Sixteen patients began ART prior to the commencement of radiotherapy. All others commenced ART either during or after radiotherapy.

Chemoradiation

More than 85% of both HIV-positive and HIV-negative patients received external beam and HDR brachytherapy totalling more than 68Gy EQD2. Significantly more HIV-positive than -negative patients were prescribed radiation alone (38.9% v.s.24.3%, p=0.01) (see Table 2). The reasons for not commencing chemotherapy in the HIV-positive group included active pulmonary tuberculosis (N=2), a CD4 cell count below 200 (N=6), and prescription of a hypofractionated radiation regimen (N=5). A similar proportion of the HIV-negative patients (N=33) also received the hypofractionated RT regimen without chemotherapy.

Of the 22 (61.1%) HIV-positive patients who were prescribed chemoradiation, 15 (68.9%) completed 4 or more cycles of chemotherapy and received adequate RT (see Table 2). Of the 177 HIV-negative patients, 137 (75.7%) commenced chemoradiation and 129 (94.2%) completed it (p=0.05).

Amongst *both* HIV-negative and HIV-positive patients, 62% who received 4 or more cycles of chemotherapy had a reduction in dose to either 30mg/m2 or 20mg/m2 Cisplatin because their creatinine clearance had fallen by 10% or below 50ml/min. These criteria are strictly adhered to in the clinic to minimize risk of renal toxicity.

Toxicity

Fourteen HIV-positive patients (38.9%) and 47 HIV-negative patients (26.6%) had at least one grade 3–4 toxicity (p=0.16) (Table 3). Eleven HIV-positive patients (30.6%) but only 18 HIV-negative patients (10.2%) developed grade 3–4 leucopaenia (p=0.003). All patients whose white cell count dropped substantially had received chemotherapy.

Looking only at haematological toxicity the HIV-positive patients were also more likely to develop grade 2 anaemia and neutropaenia (Table 4). HIV status was not associated with increased gastrointestinal, renal, skin or weight toxicities.

Fifty-seven patients were prescribed radiation alone; they were prescribed either 1.8Gy or 2Gy fractionated EBRT, or hypofractionated EBRT, and brachytherapy. Overall only eight of these patients (14.0%) had a recorded grade 3–4 toxicity compared to 54 patients of the 159 (34.0%) who received any chemotherapy (p=0.03). Four HIV- negative patients had grade 3–4 anaemia and two had grade 3–4 creatinine toxicity. Two HIV-positive patients had grade 3 anaemia.

In a multivariable model that included HIV status, total dose of radiotherapy received and prescription of chemotherapy, patients who developed a grade 3–4 toxicity were nearly 4 times as likely to have received chemotherapy as patients without such a toxicity [OR 4.41 (95%CI 1.76–11.1) p=0.002]. In the same model, patients who developed a grade 3–4 toxicity were twice as likely to be HIV-positive as patients who did not [OR 2.16 (95% CI 0.98–4.8) p=0.057]. As expected, those who received less than 68Gy EQD_2 showed a lower risk of toxicity though this was not significant. (Table 5)

DISCUSSION

Among 213 patients with cervical carcinoma in this study, HIV-positive patients generally received adequate radiotherapy but were less likely than HIV-negative patients to complete chemotherapy. These results are similar to those of our previously reported study[2]. Nearly 40% of HIV-positive patients in the current study either were not prescribed concurrent chemotherapy at the outset of treatment due to low CD4 counts or were prescribed a hypofractionated regimen. Very few HIV-positive or –negative patients who received EBRT (whether hypofractionated or prescribed in conventional 1.8 or 2 Gy fractions) and HDR brachytherapy *without chemotherapy* experienced a grade 3–4 toxicity.

Unfortunately, in the developing countries where cervical cancer and HIV are common, many patients have no access to radiation therapy or have access only to low energy machines, such as Co^{60}, which lack the skin-sparing benefits of the 18MV treatment prescribed in this study. They also lack access to 3-D conformal planning with CT-based techniques, which allow beam shaping with multi-leaf collimators, thereby decreasing dose to normal tissues.

The literature regarding radiotherapy toxicity in HIV-positive patients with cervical carcinoma is very limited. Gichangi et al found that more than 50% of both HIV-positive and -negative patients in Kenya who received radiation therapy experienced Grade 3–4

toxicity[6]. However, those patients were treated with large parallel-opposed fields with low energy Co^{60}. In a survey in Uganda, 12% of patients experienced skin, 7% gastrointestinal and 3% genitourinary toxicity[7]. A study at Tata Memorial Medical Centre in India retrospectively examined radiotherapy toxicity among HIV-positive patients[8]. Of 32 patients who commenced radical EBRT, 22 completed treatment; Grade 3–4 gastrointestinal toxicity occurred in 14% of patients and 27% had a grade 3–4 toxicity leading to treatment delays. These reports did not include enough details about the patient population and the treatment to permit direct or full comparisons with our own cohort. Although those of our patients who received radiation alone had very few toxicities, the overall grade 3–4 toxicity rate approached 30%, and nearly 40% of HIV-positive patients who received chemoradiation experienced such toxicities, most of them haematological. It should probably not be surprising that HIV-positive patients who receive chemotherapy on top of pelvic radiation develop leucopaenia. An ongoing prospective randomised study sponsored by the IAEA is currently comparing outcomes among HIV-positive cervical cancer patients receiving either chemoradiation or radiation alone. If completed, this study would be the first randomised trial of the two treatment modalities in HIV-positive patients, however it is uncertain if data collection will be completed[9].

The literature on chemoradiation toxicity among HIV-positive patients with pelvic malignancies is sparse. Most reports focus on anal carcinoma. Although anal carcinoma patients are not comparable to cervix carcinoma patients and have different chemotherapy regimens, HIV-positive patients are less likely to complete chemoradiation for either cancer than HIV-negative patients.[10,11,12]

We were unable to evaluate the effects of ART on patients receiving chemoradiation because most of our patients commenced ART either just prior to or during their cancer treatment. Some studies have shown an association of ART with adverse changes in haematological parameters. However, we are unable to draw conclusions regarding the role of ART in leucopaenia in the few HIV-positive patients in our cohort.

Of the HIV-negative patients in our cohort, nearly 95% completed chemoradiation, and just over 25% had a recorded grade 3–4 toxicity. These proportions are comparable to those in international studies of chemoradiation vs. radiation alone. In a study by Keys et al, 90% of patients receiving weekly cisplatin completed their prescribed treatment, and 35% developed grade 3–4 toxicity[13]. In the study published by Rose et al, 93% of patients completed 4 or more cycles of weekly cisplatin and received adequate radiation[14]. The patients in our study cohort achieved comparably high rates of completion of radiation, due to part to the use of high energy megavoltage radiation, multi-leaf collimation, and conformal volumes. However, many of our patients required a chemotherapy dose reduction, probably because they were in poorer overall health than patients in developed countries. In a phase 1 study by Nyogensa et al in a patient population similar to ours, the maximum tolerated dose of Cisplatin was found to be 25mg/m2[15]. Further in- depth study of toxicities and dose reductions in limited resource settings is urgently needed.

A limitation of this study is the relatively small number of HIV-positive patients in our sample; however, we included consecutive patients who met the eligibility criteria on our

analysis, and ours is one of the largest HIV-positive cohorts in the published literature. 10 patients who were HIV positive did not have toxicity data recorded which may introduce bias into the statistical results. Another limitation is that several different clinicians assessed and recorded the toxicities; they may not have used consistent criteria, but their use of a detailed standard toxicity sheet may have helped to minimise inconsistencies. A strength of the study is that both HIV-positive and -negative patients adhered to our radiation treatment protocols.

The challenge is to find ways to help cervical cancer patients, with and without HIV, in the many parts of the developing world where aging equipment or no equipment for radiation therapy is available. Unless screening becomes sufficiently widespread to downstage detected disease, or until HPV vaccination eliminates the carcinogenic strains of HPV, how to provide better treatment for the patients who need it most will remain a conundrum for health policy.

CONCLUSION

This study found that HIV-positive patients undergoing curative chemoradiation for cervical cancer had a higher risk of developing acute haematological toxicity than patients treated with radiation alone. Oncologists should exercise caution in the use of chemotherapy for such patients, in particular in the developing world setting where patients overall have poorer health and limited access to healthcare services. The data do not definitively support omitting chemotherapy from the treatment protocol for HIV-positive patients because only 36 of our 213 patients were HIV-positive. Overall, this cohort of HIV-positive and –negative patients tolerated radiation alone very well, most likely because they were treated with state-of-the-art equipment and radiation planning techniques. In the developed world setting use of advanced techniques such as intensity-modulated radiation therapy (IMRT) may be beneficial in further reducing dose to normal tissue. However, we have as yet no information about long-term treatment effects, recurrence, or survival in our patients, and studies of those endpoints among cervical cancer patients with and without HIV in the developing world are much needed. Recurrence and survival data will be reported on a larger cohort from this institution. Randomised trials will hopefully provide data on how to maximise efficacy whilst minimising side effects.

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Table 1

Demographic and clinical characteristics of patients with cervix carcinoma, by HIV status

	HIV STATUS						
CHARACTERISTIC	**POSITIVE**		**NEGATIVE**		**TOTAL**		**P**
	n	**%**	**n**	**%**	**n**	**%**	
	36	16.9	177	83.1	213	100	
MEDIAN AGE in years	41		50		49		<0.001*
Range	26–62		23–79		23–79		
HISTOLOGY							0.27
Squamous	34	94.4	163	91.6	197	92.1	
Adenocarcinoma	1	2.8	5	2.8	6	2.8	
Other	1	2.8	9	5.6	10	5.1	
FIGO STAGE							0.55
Ibi-IIIa	9	25%	56	31.6%	65	30.5%	
IIIb	27	75%	121	68.4%	148	69.5%	

* p≤0.05 considered significant

Table 2

Completion of treatment by HIV status

	HIV STATUS						
TREATMENT	**POSITIVE**		**NEGATIVE**		**TOTAL**		**P**
	n	**%**	**n**	**%**	**n**	**%**	
	36	16.9	177	83.1	213	100	
Completed >EQD2[c] 68Gy (ALL PATIENTS)	31	86.1	160	89.8	191	89.2	0.55
PRESCRIBED EBRT ALONE	14	**38.89**	43	**24.29**	57	26.76	**0.01***
Completed >EQD2 68Gy	10	71.4	32	74.42	42	73.68	1.0
PRESCRIBED CHEMORADIATION	22	61.1	134	75.7	157		0.10
>EQD2 68Gy+ 4 cycles of weekly platinum	15	**68.18**	117	**87.31**	132		**0.05***

[a] EBRT= External beam radiotherapy;

[b] HDR= High dose rate brachytherapy;

[c] EQD_2 = Equivalent dose in 2 Gy fractions;

[d] SD= Standard deviation;

* P≤0.05

Table 3

Grade 3–4 toxicities by HIV status

	HIV STATUS						
TOXICITIES	**POSITIVE**		**NEGATIVE**		**TOTAL**		
	N	**%**	**N**	**%**	**N**	**%**	**P**
	36	16.9%	177	83.1	213	100	
OVERALL	14	38.9	47	26.6	61	28.6	0.157
LEUCOPENIA	11	**30.6**	18	10.2	29	14.0	**0.003***
THROMBOCYTOPENIA	1	2.8	0	0	1	0.5	0.169
ANAEMIA	3	8.3	12	6.8	15	7.0	0.723
NEUTROPANEIA	3	8.3	7	4.0	10	4.7	0.378
CREATININE	0	0	4	2.3	4	1.9	1.0
NAUSEA	1	2.8	14	8.0	15	7.0	0.476
VOMITING	1	2.8	4	2.3	5	2.3	1.0
DIARRHOEA	1	2.8	5	2.8	6	2.8	1.0
CYSTITIS	0	0.0	1	0.6	1	0.5	1.0
SKIN	1	2.8	2	1.1	3	1.4	1.0
WEIGHT	0	0.0	0	0.0	0	0.0	1.0

* p≤0.05 considered significant

* P≤0.05

Table 4

Grade 2 Haematological Toxicities by HIV status

	HIV STATUS						
TOXICITY	**POSITIVE**		**NEGATIVE**		**TOTAL**		
	n	**%**	**n**	**%**	**n**	**%**	**P-value**
LEUCOPAENIA	10	27.7	47	26.6	57	26.8	0.839
THROMBOCYTOPAENIA	2	5.5	3	1.7	5	2.35	0.199
ANAEMIA	23	63.8	71	40.1	94	44.1	**0.01***
NEUTROPAENIA	7	19.4	15	8.5	22	10.3	**0.02***

* P≤0.05 considered significant

Table 5

Factors associated with grade ¾ toxicity

	P value	OR	95% CI Lower	95% CI Upper
HIV Status				
Negative		1.0	Referent	
Positive	0.05*	**2.16**	.98	4.8
TotalEQd2[a]				
≥68Gy		1.0	Referent	
<68Gy	0.15	0.44	0.15	1.33
Concurrent chemotherapy				
No		1.00	Referent	
Yes	0.023*	**4.41**	1.76	11.1

*P≤0.05 considered significant;

[a]EQd2 Equivalent dose in 2Gy fractions

OR= odds ratio

CI= confidence interval