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RESEARCH

Acute toxicity in cervical cancer HIV-positive vs. HIV-negative patients treated by radical chemo-radiation in Zambia

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Background: The current standard of radical treatment for patients with cancer of the cervix is combination therapy in the form of radiotherapy with chemotherapy. Generally the same treatment protocol is applied to HIV-positive and HIV-negative patients. However, HIV-positive patients with invasive cervical cancer have not been evaluated in detail regarding treatment response, its toxicities and compliance.
Methods: This prospective, quantitative comparative study was conducted to evaluate acute toxicity in radical combination therapy, in HIV-positive (on HAART) and HIV-negative patients for cervical cancer at the Cancer Diseases Hospital, Lusaka, Zambia. In total, 120 stage IB_2–IIIB cervical cancer patients were serially recruited to have an equal number of participants in each arm. Participants received cisplatin-based radical chemo-radiation for five to six weeks and were assessed for acute reactions in four systems: genitourinary, haematopoietic, skin, and gastrointestinal. Toxicity was scored using the NCI CTC v2.0.
Results: The results revealed that there was no significant difference with regard to major acute reactions between the two groups. Radical chemo-radiation is therefore well tolerated by HIV-positive patients.
Conclusion: Radical chemo-radiation in conventional doses was safely tolerated by a well-selected cervical cancer HIV-positive group on HAART and could be considered suitable for similar patients.

Keywords: chemotherapy, cervical carcinoma, HAART, HIV, radiotherapy

Introduction

The Cancer Diseases Hospital (CDH) in Lusaka, Zambia, relies on internationally standardised treatment protocols, as it has not developed a locally based protocol. Currently, cervical cancer stage IB_2–IIIB HIV-positive patients are treated with radical chemo-radiation in the form of external beam radiotherapy (EBR), brachytherapy and cisplatin. However, this is in contrast to some available literature or protocols practised by certain oncology departments that omit the cisplatin from the protocol for this group of patients.[1–3]

Acute side effects have not been studied on a large scale in cervical carcinoma patients who are infected with human immunodeficiency virus (HIV-positive) and are on radical chemo-radiation.[3,4] Standards of treatment for HIV reactive cervical cancer patients have equally not been well defined.[4] This situation prompted the research question addressed here: Does HIV infection and highly active anti-retroviral therapy (HAART) enhance acute toxicity in invasive cervical cancer, in HIV-positive patients when compared with the HIV-negative patients during radical chemo-radiation? It is for this reason that this study was conducted at CDH in order to determine the acute side effects in this cluster of patients. The study also attempted to establish the most common acute side effects in HIV-positive patients being treated with radical chemo-radiation.

The main purpose of this study was to evaluate acute toxicity in radical combination therapy, in the form of radiotherapy and chemotherapy, in HIV-positive (on HAART) and HIV-negative patients being treated for cervical cancer at the CDH, Lusaka, Zambia. The study would therefore assist in ascertaining and assessing the relationship between acute toxicity and HIV infection in cervical cancer patients on radical chemo-radiation. This is critical for the protocol development for the management of patients since the CDH treats a significant number of patients with cervical cancer who are co-infected with HIV.

Methods

A quantitative, two-arm comparative descriptive approach was used to evaluate acute toxicity of radical combination therapy, in the form of radiotherapy and chemotherapy, in HIV-positive (on HAART) and HIV-negative patients for cervical cancer. The study was conducted at the CDH in Lusaka, Zambia where the data were collected over a period of 12 months. The CDH is the only hospital in the country that offers cancer treatment in the form of radiotherapy.

Data were collected using the modified National Cancer Institute (NCI) (Bethesda, United States of America) CTC, v2.0, which has been proven to be a well-defined instrument for reproducible grading and more accurate recording of toxicity. It also allows comparison with other studies. The four systems, namely skin, gastrointestinal (GIT), genito-urinary (GU) and haematopoietic, were evaluated. The NCI CTC manual was part of the day-to-day reference material during weekly participant reviews conducted by the oncologist.

The study population comprised stage IB_2–IIIB cervical cancer (squamous cell carcinoma [SCC] or adenocarcinoma) patients who met the inclusion criteria (see below). A modified systematic random sampling method was used to recruit every second patient meeting the inclusion criteria. Recruitment was made after the initial radiotherapy treatment simulation since it was only at this stage that the treatment prescription was completed.

The inclusion criteria for the HIV-positive study participants were:

- HIV-positive on HAART and performance status ECOG I & II;
- histologically confirmed cervical cancer FIGO stages IB2 to IIIB without hydronephrosis; haemoglobin > 10 g/dl without or with transfusion;
- adequate renal function with creatinine clearance of > 60 ml/min;
- CD4 count equal or greater than 200/mm^3;
- histology: either squamous cell carcinoma or adenocarcinoma.

The inclusion criteria for the HIV-negative study participants were:

- HIV-negative patients with performance status ECOG I & II;
- histologically confirmed cervical cancer FIGO stages IB2 to IIIB without hydronephrosis; haemoglobin > 10 g/dl without or with transfusion;
- adequate renal function with creatinine clearance of > 60 ml/min;
- histology: either squamous cell carcinoma or adenocarcinoma.

Exclusion criteria for both arms were:

- previous radiotherapy to the pelvic region;
- any other active AIDS-defining illness;
- hydronephrosis;
- uncontrolled previous malignancy;
- any severe medical ailment that may interfere with the proposed treatment;
- previous chemotherapy in the last one year;
- severe psychiatric disorder, pregnancy or breast feeding.

Treatment

The patients were treated using a combination of radiotherapy and chemotherapy given concurrently. EBR was administered to a clinical target volume that included the primary cancer, uterus, internal iliac, presacral, upper external iliac and lower common iliac lymph nodes. Patients with stages IB$_2$–IIB lesions received a dose of 46 Gy in 23 fractions of EBR delivered homogeneously to the pelvis five days/week, supplemented with high dose rate (HDR) brachytherapy. Patients with stage IIIA–IIIB received 50 Gy in 25 fractions five days per week plus HDR brachytherapy. A pair of parallel opposed anterior–posterior (AP) fields or 'four-field box technique' was used depending on the AP separation and weight of the patient. The AP–PA fields were open fields with no shielding while the four-field box technique used alloy shielding for the lateral fields. These field arrangements and energy were chosen as follows:

- AP separation less than 18 cm: AP–PA parallel opposed fields on Cobalt-60, which has an average energy of 1.25 MeV.
- AP separation more than 18 cm but below 24 cm, and lateral separation below 36 cm: a four-field box technique on Cobalt-60.
- AP separation between 18 cm and 24 cm, and lateral separation > 36 cm: AP–PA on Linac with a photon energy of 6MV.
- AP separation greater than 24 cm: four-fields on Linac.

HDR brachytherapy was given concurrently during the final weeks (not started earlier than the third week) of EBR, and not on the same day as chemotherapy. Brachytherapy was given in the form of three or four intracavitary applications to treat the uterus, upper vagina, cervix and part of the parametria on both sides using either 8 Gy x 3 fractions or 6.5 Gy x 4 fractions to point A. Bladder and rectal doses were optimised to less or equal to 80% of the prescribed point A dose.

The chemotherapy was administered in the form of cisplatin over three to four hours, at 80 mg/m^2 intravenously (IV) at days 1, 22 and 43 of EBR. The creatinine clearance was calculated and only patients with values of 60 ml/min and above, white cell count > 3 000, platelets > 100 000 and HB > 10 g/dl received the chemotherapy with one litre of normal saline for prehydration, supplemented by one vial of calcium gluconate, one vial of magnesium sulphate and one vial of potassium chloride. Then 16 mg of dexamethasone IV and 100 mg dalasentrone IV bolus injections were administered to prevent emesis. Another litre of normal saline was given with oral antiemetic for the patient to take home for post hydration.

Evaluation of toxicity

Acute treatment-related toxicity was graded prospectively by the oncologist at weekly intervals during the course of treatment and one month after the completion of treatment, using the modified NCI CTC. The toxicities were scored using a scale of 0 to 4, with 0 being no reaction and 4 being life-threatening. The assessment of GU, skin and GIT was clinical, while the haematopoietic system and renal function were laboratory based.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS®) version 16 (and later version 18) (SPSS Inc, Chicago, IL, USA) was used to analyse data collected during the study. Descriptive data analyses were used as the primary statistical analysis tool, to report demographics and adverse events or acute reactions. Chi-square tests were used to indicate the strength and direction of the relationship between variables and the level of significance. A *p*-value of 0.05 was used to define the chosen level of statistical significance. Repeated measures of ANOVA were also used since the data were collected repeatedly at different intervals.

Ethical considerations

The Faculty Academics Ethics Committee of the University of Johannesburg as well as the Biomedical Research Ethics Committee of the University of Zambia, School of Medicine granted ethical approval for the study. Research ethics that were observed and adapted to this study are in accordance with those stated by Brink,[5] namely, the principles of respect for persons, of beneficence and of justice. Potential participants were given full details of the study, and their rights to anonymity, confidentiality and withdrawal without prejudice were explained. Informed written consent was obtained from each participant. The study posed no potential risks or harm to the participants and it did not alter the treatment regimen for each patient.

Results

A total of 120 patients met the inclusion criteria with 60 patients allocated to the HIV-positive arm and 60 to the HIV-negative arm according to the predetermined criteria. However, 10 participants (five for each arm) were not eligible for inclusion in the analysis as they did not satisfy entry criteria at the time of commencement of chemo-radiation, i.e. their creatinine clearances were low. Therefore, only 110 patients, 55 from each arm, were eligible for data analysis. The HIV-positive arm had a median CD4 count of 360 cells/mm^3 with a range of 200–720 cells/mm^3 and the viral load data were not recorded for these participants. All the participants had a functional status equivalent to ECOG I at the

Table 1: FIGO cervical cancer stage of study participants (n = 110)

Stage	HIV-negative arm		HIV-positive arm		Total	
	n	%	*n*	%	*n*	%
IB2–SCC	5	9.1	7	12.7	12	10.9
IIA–SCC	4	7.3	4	7.3	8	7.3
IIB–Adeno-carcinoma	2	3.6	0	0.0	2	1.8
IIB–SCC	34	61.8	33	60.0	67	60.9
IIIA–SCC	2	3.6	1	1.8	3	2.7
IIIB–SCC	8	14.6	10	18.2	18	16.4
Total	55	100	55	100	110	100

Table 2: Acute toxicity for the skin vs. HIV status (n = 110)

HIV status	Grades of acute dermatitis toxicity				Total	*p*-value
	Grade 1	Grade 2	Grade 3	Grade 4		
HIV-negative	28	27	0	0	55	0.190
HIV-positive	24	28	3	0	55	
Total	52	55	3	0	110	

beginning of the study. This is a performance status, which meant that the participants had symptoms of cervical cancer, but were still ambulatory.

The median age for patients in the HIV-negative group was 55 years and that in the HIV-positive group was 40 years. The chi-square test indicated that the differences in age between the two groups were significant (p = 0.0009). There was not much difference in the disease stage in either arm, as illustrated in Table 1. The analysis further showed that the majority of the participants in both arms had locally advanced disease (IIB) followed by stage IIIB.

All study participants received and completed the EBR and HDR as prescribed and this was considered to be a significant finding because it is common that not all participants complete the treatment regime. All the participants were treated with AP–PA fields except 10 who were treated with four fields, three in the HIV-positive arm and seven in the HIV-negative arm. The median number of days it took to complete treatment was 38 days and 37 days in the HIV-negative group and HIV-positive group, respectively. The average EBR dose delivered was 48 Gy since 52 (20 HIV-negative and 32 HIV-positive) participants received 46 Gy while 58 (35 HIV-negative and 23 HIV-positive) received 50 Gy. The difference in the dose received was shown to be statistically significant with regard to HIV status (p = 0.022).

The distribution of participants regarding brachytherapy fractionation showed that the HIV-positive arm had more participants (58%) treated with 6.5 Gy x 4 fractions. The results also showed that there were more HIV-negative participants (58%) treated with 8 Gy x 3 fractions. The analysis of acute toxicities did not factor in the impact of the differences in the brachytherapy dose; future studies may look at this effect separately. The number of chemotherapy cycles received by study participants in both arms ranged between one and two, with a median of two cycles per patient. Eighty (73%) participants received at least two cycles of chemotherapy. The full two intended courses of cisplatin per patient (day 1 and day 22), were not administered in 30 (27%) participants. Day 43 chemotherapy was not included in the analysis since it fell outside the radiotherapy delivery period.

Acute toxicity

Acute toxicity in all the four systems was evaluated prospectively and no statistically significant differences in toxicity were observed between the two groups with regard to severe toxicity (grades 3 and 4).

Skin

The results of this study showed there was no statistically significant difference between the two study arms. The study participants mainly experienced grades 1–2 acute skin toxicity with only three study participants (all in the HIV-positive arm) experiencing grade 3 acute skin toxicity (p = 0.190) (Table 2).

GIT system

With regard to diarrhoea versus HIV status, the results of the CDH study established no statistically significant difference between the two arms (p = 0.946). Regarding nausea, the analysis of data and results of the CDH study showed that there was no statistically significant difference between the two arms (p = 0.063). However, the results showed that there was a statistically significant difference in acute vomiting toxicity between the two arms (p = 0.000). Cross-tabulation of proctitis and HIV status did not establish any statistically significant difference between the two arms (p = 0.450) (Table 3).

GU system

There were no grade 3 or 4 toxicities experienced within this system. No significant statistical difference in the grade 1 and 2 toxicity levels was noted for cystitis for the two arms. Therefore, the HIV-positive status did not contribute to increased levels of acute toxicity. These results showed that chemo-radiation does

Table 3: Acute toxicity for GIT vs. HIV status (n = 110)

HIV status	Grades of toxicity					Total	*p*-value
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4		
Diarrhoea							
HIV-negative	1	17	36	1		55	0.946
HIV-positive	1	20	33	1		55	
Total	2	37	69	2		110	
Acute nausea							
HIV-negative	2	52		1		55	0.063
HIV-positive	5	44		6		55	
Total	7	96		7		110	
Acute vomiting							
HIV-negative	0	2	52	1		55	0.000
HIV-positive	11	10	31	3		55	
Total	11	12	83	4		110	
Acute proctitis							
HIV-negative	1	41	13			55	0.45
HIV-positive	1	35	19			55	
Total	2	76	32			110	

Table 4: Acute toxicity for GUT vs HIV status (n = 110)

HIV status	Grades of acute cystitis toxicity					Total	p-value
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4		
HIV-negative	1	29	25	0	0	55	0.513
HIV-positive	1	23	31	0	0	55	
Total	2	52	56	0	0	110	

Table 5: Acute toxicity for haemopoietic system vs. HIV status (n = 110)

HIV status	Grades of toxicity					Total	p-value
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4		
Acute haemoglobin toxicity							
HIV-negative	34	13	7	1	0	55	0.122
HIV-positive	25	13	15	0	2	55	
Total	59	26	22	1	2	110	
Acute WBC toxicity							
HIV-negative	16	16	19	4	0	55	0.26
HIV-positive	10	17	18	10	0	55	
Total	26	33	37	14	0	110	
Acute platelet toxicity							
HIV-negative	46	9	0	0	0	55	0.003
HIV-positive	32	23	0	0	0	55	
Total	78	32	0	0	0	110	

not confer additive toxicity upon the HIV-positive population who have an intact immune status (on HAART) (Table 4).

Haemopoietic system

The analysis of data and the results of the CDH study (see Table 1) did not establish statistically significant differences in acute toxicity level regarding haemoglobin and white cell count (p = 0.122 and 0.260, respectively). Conversely, there was a statistically significant difference in acute toxicity of platelet count with respect to HIV status (p = 0.003) (Table 5).

Discussion

In spite of the small number of participants in the CDH study, the results showed that toxicity scores were lower than those reported in other published studies. Skin reactions in the CDH study participants were usually confined to areas with skin folds and the perineum. Treatment to the pelvis may result in mild hyperpigmentation within the treatment fields, and moist desquamation in folds of abdominal skin, in the groin and between the buttocks (natal cleft). Treatment to the perineum usually results in brisk erythema 10–14 days after treatment has been initiated, with moist desquamation shortly thereafter. Acute skin toxicity in the CDH study participants was statistically comparable to other studies.[6–8] Even with the high number of study participants with advanced disease requiring larger treatment fields and the use of AP–PA fields, acute skin toxicity was not exaggerated in the CDH study participants. The theory that HIV-positive patients have increased sensitivity of the normal tissues to radiotherapy resulting in excessive acute normal tissue reactions[9,10] was not borne out in the case of the HIV-positive study participants at CDH.

The gastro-intestinal toxicities in CDH study participants were mainly grades 1 and 2 for both arms. There were no treatment-related deaths as in the study by Rose *et al*. and Keys *et al*.[6,7] Radiotherapy treatment delay because of toxicity, as noted in Singh *et al*. and Bhavaraju *et al*.,[10,11] was not apparent in the CDH study. Nonetheless, there could have been radiotherapy treatment interruption for one HIV-positive study participant owing to severe toxicity (grade 4 anaemia) but this was corrected through blood transfusion. A treatment gap of six or more days was to be recorded as treatment interruption.

Treatment-induced anaemia in the CDH study participants was less frequent compared with what has been reported in the published literature.[12] Results of the trials by GOG 120, GOG 123 and NCI of Canada, for example, show that study participants at CDH did not experience greater haematological toxicities. The haematological toxicities observed in the CDH study participants were mainly grades1 and 2, similar to that noted by Singh *et al*.[10] There were no exaggerated severe haematological toxicities of grade 3 and 4 as reported in the study by Shibata *et al*.[12] and the meta-analysis of concomitant chemotherapy and radiotherapy for cervical carcinoma.[13]

Cystitis in the CDH study participants became symptomatic after 10–14 days of treatment. Symptoms included dysuria, urinary frequency and urgency. The results were presented as from week 2 up to week 5. Cross-tabulation results of acute cystitis versus HIV status did not show statistically significant differences between the two arms. Therefore, it could be postulated that the HIV-positive status did not contribute to increased levels of acute toxicity in the HIV-positive study participants for as long as they were on HAART when compared with their HIV-negative counterparts.

Comparison with published data was limited as most previous studies did not have patients who were on HAART. In a study by Tan *et al*.,[14] on 74 patients who received radical radiotherapy given concurrently with chemotherapy, the toxicity was recorded using the NCI CTC. The most common side effects were diarrhoea (80.6%), malaise (66.7%) and nausea (62.5%). Only three patients had grade 3 to 4 toxicity (one patient had grade 3 thrombocytopenia, one patient had grade 4 neutropenia and the third patient had grade 3 diarrhoea). Haematological toxicity was mainly anaemia, with 41.7% of the patients developing grades 1–2 toxicity. Only 70.2% of the patients completed the planned number of chemotherapy cycles, with a further 20.3% receiving at least three cycles. Most patients failed to complete the planned chemotherapy due to gastrointestinal toxicity despite all the participants being HIV-negative.

A study by Serkies and Jassem[15] recruited 112 HIV-negative patients with a median age of 48 years. These were treated with radiotherapy plus weekly cisplatin at 40 mg/m^2. Overall, 74% of the patients received at least four cisplatin cycles. The planned five cisplatin cycles were given to only 45% of the patients. A full and timely cisplatin dose was administered to 26% of the patients. The most common toxicities reported were gastrointestinal and renal in nature.

The results of the CDH study showed that the overall treatment duration was shorter than those in most trials since most participants completed their prescribed radiotherapy in less

than eight weeks. The number of chemotherapy cycles received by participants in both arms ranged between one and two. The planned two courses of cisplatin were administered in 80 study participants. The remaining 30 study participants received one cycle of chemotherapy each, and this was either due to the time factor between cycles as a result of participants waiting to recover, or due to treatment toxicity. The results also showed that there were three participants with grade 3 acute skin toxicity and two with grade 4 anaemia. Grade 1 and 2 toxicity levels were mild and transient and resolved with appropriate medical treatment. These results showed that the study participants in both arms tolerated the radical chemo-radiation well and their performance compares fairly well with the published data.

The perceived increased sensitivity of normal tissues to radiotherapy resulting in increased acute adverse effects was not observed in the CDH study. This absence of increased morbidity could be due to the relative immune competence of the HIV-positive study participants.

The CDH study concurs with a systematic review study on the optimal management of cervical cancer in HIV-positive patients, which concluded with a suggestion that HAART should be commenced early to ensure less toxicity and better treatment compliance.[16] The results of this study revealed higher rates of treatment completion for patients who commenced HAART early. In addition, this study reported the average initial CD4 count as 321.06 cells/mm^3, which compares well with the CDH study which had an average CD4 count of 360 cells/mm^3. However, in a study by Mangena *et al*. (p. 44) to investigate the impact of HIV infection on women receiving radiation for cervical cancer where the study population was reported to be much younger, it was concluded that HIV-infected cervical cancer patients experienced poorer survival.[17] This was due to treatment interruptions, which led to prolonged treatment periods or incomplete treatment. This study also reported that the HIV-positive participants often had anaemia and often needed pre-treatment blood transfusion. However, this study did not report on the median CD4 count, which plays a significant role for intact immunity and resistance to disease or other pathological challenges.[17]

Study limitations

The sample size of 120 was small. These findings need to be replicated in far-reaching studies. The non-availability of serial CD4 counts and the viral load data affected the interpretation of some of the results of this study and future studies should include this aspect. The study also recorded a small number of stage III/IIIB Cacx study participants.

Conclusions

This study has demonstrated that, in a well-selected group of Cacx patients (on HAART) at the CDH, Lusaka, Zambia, chemo-radiation was well tolerated and could be considered suitable for similar patients.

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