Original Article

Acute toxicity to radical combination treatment in human immunodeficiency virus-positive cervical cancer patients: Experience from a resource-constrained center

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Abstract

Background and Purpose: To determine acute toxicity to radical combination treatment in invasive cervical cancer patients seropositive to human immunodeficiency virus (HIV).

Subjects and Methods: This is a retrospective review of HIV-seropositive patients managed for invasive cervical cancer between January 2012 and December 2017 at the radiotherapy and oncology center of our institution. Patients' sociodemographics, disease characteristics, and acute treatment-induced toxicity were extracted from their clinical case notes and were studied.

Results: A total of 83 confirmed HIV patients with histologically diagnosed invasive cervical cancer were studied. Their median age at presentation was 37.8 years. The most common presenting symptom of cervical cancer was copious foul-smelling vaginal discharge accounting for 39.8%. Sixty-three (85.6%) patients presented with Eastern Cooperative Oncology Group performance status of 0 and 2 and 74 (89.2%) patients presented with International Federation of Gynecologists and Obstetricians Stage 2B and above. Seventy-four (89.2%) patients had access to highly active antiretroviral therapy. Fifty-five (66.3%) patients were started on radical chemoradiation of which 28 (50.1%) completed prescribed external beam radiotherapy. Thirteen (15.7%) patients were treated symptomatically to control symptoms of cervical cancer. Concurrent chemoradiation appears to be poorly tolerated with 25 (71.4%) of the patients in this arm of treatment developing either Grade 3 or 4 toxicities. Grade 3 hematologic and gastrointestinal tract (GIT) toxicity was seen in 17.9% and 25% of the patients, respectively, while 21.4% of the patients presented with Grade 4 skin toxicity, leading to treatment delays and interruptions. There was excellent symptomatic relief in patients treated with palliative intent.

Conclusions: Radiotherapy and chemotherapy are effective modalities of treatment in a selected group of these set of patients with good control of symptoms related to cervical cancer. Palliative radiotherapy is also effective in patients with poor performance status in relieving symptoms of cervical cancer. Further research needed to be done to identify the optimum management of these patients with radiotherapy and/or chemotherapy to reduce treatment-induced toxicity, thereby minimizing treatment interruptions and delays which ultimately will improve their overall outcome.

Keywords: Cervical cancer, chemoradiation, human immunodeficiency virus, treatment toxicity

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INTRODUCTION

Cervical cancer is the most common gynecologic malignancy managed in our environment[1] and is considered to be one of the acquired immune deficiency syndrome (AIDS) defining illnesses.[2] Several studies have pointed to an association between human immunodeficiency virus (HIV) infection and carcinoma of the uterine cervix.[3-5] Cervical cancer has a combined worldwide incidence of about 570,000 new cases with a mortality of about 312,000 deaths annually.[6] In Nigeria, it accounts for about 30.8% of all female malignancies.[7] The reported seroprevalence of HIV among women aged 15–49 years in Nigeria was 3.1 (95% confidence interval, 2.3%–3.8%) with significant regional variation.[8] In Ibadan (Southwestern Nigeria) and Zaria (Northwestern Nigeria), about 2.7% and 4%, respectively, of patients with cervical cancer were found to be HIV seropositive.[9,10] The standard treatment for cervical cancer includes external beam radiotherapy (EBRT) with concurrent cisplatin chemotherapy, brachytherapy, and surgery for early-stage disease in HIV-seronegative patients.[11] However, the clinical management of cancers in HIV/AIDS patients is very challenging because of concerns on their immune status. Various studies have shown that HIV-infected patients have impaired bone marrow function as well as impaired cellular immunity, thus making them more vulnerable to the effects of anticancer treatments.[12] This makes it difficult to effectively utilize all available cancer treatment modalities, such as EBRT,[13] brachytherapy, and chemotherapy.[14] Similarly, a rapid progression to more advanced stages of cervical carcinoma,[15] higher recurrences and metastases to unexpected sites,[16,17] poor treatment compliance, increased treatment toxicity,[18] and poor general condition of the patients had been associated with HIV infection in patients with cervical cancer.[19]

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 patients on highly active antiretroviral therapy (HAART) in our institution. This assists in assessing the relationship between acute toxicity and HIV infection among cervical cancer patients and could culminate into a protocol development for the management of these patients in our institution.

SUBJECTS AND METHODS

Between January 1, 2012, and December 31, 2017, 98 women with histologically diagnosed invasive cervical cancer with confirmed seropositivity to HIV were managed at the Radiotherapy and Oncology Centre, Ahmadu Bello University Teaching Hospital, Zaria, Nigeria. Eighty-three of these patients' case files contained adequate information and were included in this retrospective descriptive study. Patients' sociodemographics and disease characteristics such as type and duration of symptoms, clinical stage of disease at presentation, and histological type were extracted for analysis. Also extracted for evaluation were education, marital status, parity, type of treatment received, and type of acute toxicity to treatment. Others are serial results of urea, electrolytes, creatinine, and liver function tests; complete blood counts, chest radiographs, and ultrasound of abdomen and pelvis reports. Results of the findings are presented in figures and charts.

Treatment

The radiotherapy and oncology department of the hospital where this study was conducted, typical of a resource-constrained setting, is equipped with only a cobalt-60 teletherapy machine and a low-dose-rate (LDR) cesium-137 (Cs-137) brachytherapy machine. Our institution relies on internationally standardized treatment protocols as it has not developed a locally based protocol for the treatment of cervical cancer. Currently, operable patients with International Federation of Gynecologists and Obstetricians (FIGO) Stages 1 and 2A were treated with primary surgery. The postoperative adjuvant therapy was discussed and decided at a combined multidisciplinary meeting. Patients with inoperable disease were treated with primary radiotherapy or concomitant chemoradiation. The addition of chemotherapy to EBRT and the dosage depend on general health, performance status, and kidney function. Cisplatin was the drug of choice, administered weekly at a dosage of 35–40 mg/m^2, provided that the CD4 count was at least 200 cells/mm^3. Primary radiation treatment intent was either radical or palliative, depending on the FIGO stage and medical condition. The total dose of radical radiation without any planned breaks was usually 45–50 Gy in 25–27 fractions, followed by a single LDR brachytherapy insertion and radiation dose of 20–30 Gy prescribed to Manchester Point A in patients with FIGO Stages 1B–3B disease. However, patients with FIGO Stage 3B with extensive pelvic disease, bilateral hydronephroses, and FIGO Stages 4A were given palliative radiotherapy using standard radiation portals with radiation dosage of 45 Gy in 25 fractions. There is no brachytherapy boost in these sets of patients. Palliative radiotherapy is also given in patients with FIGO Stage 4B (depending on metastatic sites) with palliative doses varying from 8 to 30 Gy administered between 1 and 10 fractions. Adjuvant postoperative radiation consisted of 45 Gy in 25 fractions, supplemented with LDR brachytherapy treatment of 20 Gy at 0.5 cm from the surface of vaginal cylinder and

chemotherapy, depending on the pathological risk factors. Very ill patients are given single fraction of 8–10 Gy which might be repeated every 3–4 weeks for up to three fractions.

EBRT is given using standard anteroposterior/posteroanterior portals with photons from the telecobalt machine and is followed usually within 2 weeks, by an intracavitary brachytherapy insertion from the LDR Cs-137 machine. Resource limitations do not allow for conformal treatment planning in our patients.

All patients, with consent, were routinely screened for HIV antibodies using an enzyme-linked immunosorbent assay, and positive cases were confirmed by the western blot method. HAART was available during the study period for all HIV-positive women with invasive cervical cancer. Some patients were first diagnosed with HIV infection at the time of cervical cancer diagnosis, and therapy for both diseases was initiated at the same time. During the study period, hemoglobin (Hb) target was 10–12 g/dl before radiation, and the transfusion trigger during radiation was 9 g/dl, tested weekly. Treatment deficit was calculated as the difference between prescribed and actual received dosage. If this was 20% or more, it was considered a major deviation and unacceptable and therefore defined as incomplete treatment. Patients who received <4 courses of the prescribed six courses of chemotherapy are also categorized as incomplete treatment.

Chemotherapy was administered concurrently with EBRT and within 16 h of EBRT in the form of cisplatin over 4–6 h at 35–40 mg/m^2 intravenously on days 2, 9, 16, 23, and 30. The creatinine clearance was calculated, and only patients with values of 60 ml/min and above, white cell count >2500, platelets >100,000, and Hb ≥10 g/dl received the chemotherapy. Adequate prechemotherapy hydration supplemented with a vial each of calcium gluconate, magnesium sulfate, and potassium chloride is given. Bolus intravenous hydrocortisone 100 mg, dexamethasone 8 mg, and ondansetron 8 mg are given as antiemetics. A liter of mannitol (for diuresis) is given last and patients discharged home on oral antiemetics. Majority of the patients received 3 weekly cisplatin-based chemotherapy at 50 mg/m^2 sequentially (neoadjuvant or adjuvant) to EBRT. To be eligible for radical radiotherapy and/or chemotherapy, patients' biochemical and hematological parameters must be within reference range; CD4 + count must be at least 200 counts/ml and Eastern Cooperative Oncology Group performance must be at least 1 (patient has cervical disease but is ambulatory).

RESULTS

Between January 1, 2012, and December 31, 2017, 98 cases of histologically confirmed cervical cancer patients with confirmed seropositivity to HIV were managed at the Radiotherapy and Oncology Centre of Ahmadu Bello University Teaching Hospital, Zaria, Nigeria. Eighty-three of them were evaluable for this study. The mean age of the patients was 37.8 years (range 27–51) and the median parity was 6 (range 4–12). Seventy-four patients (89.0%) were diagnosed with advanced-stage disease (FIGO 2B and above) with only two patients presenting with FIGO Stage 1B disease. The single most common symptom at presentation was copious foul-smelling vaginal discharge followed by per vaginal bleeding in 33 (39.8%) and 13 (15.7%) of the patients, respectively, with a median duration of symptoms of 4 months. The predominant histologic type seen was squamous cell carcinoma in 74 (89.0%) followed by adenocarcinoma in 5 (6.0%) of the patients. Other histologic types reported included adenosquamous carcinoma and a case of cervical lymphoma. Seventy-six (91.6%) patients were graded as poorly differentiated. Seventy-four (89.2%) of the patients had been on HAART for varying length of time, with a mean duration of use of 4 years (range 2 months to 8 years). Fifty-six percent of the patients were educated to secondary school level with only 16.8% never married. Detailed characteristics of the patients are shown in Table 1, and the proportions of the patients' disease stages at presentation are summarized graphically in Figure 1.

Of the 83 patients, 55 (66.3%) were started on radical chemoradiation, 15 on palliative radiotherapy, and 13 on symptomatic treatment of cervical cancer-related complications such as pain, bleeding, and urinary tract obstruction. EBRT with radical intent was planned with radiation dose of 45–50 Gy in 25–27 fractions over 5–5½ weeks and supplemented with brachytherapy at 20–30 Gy

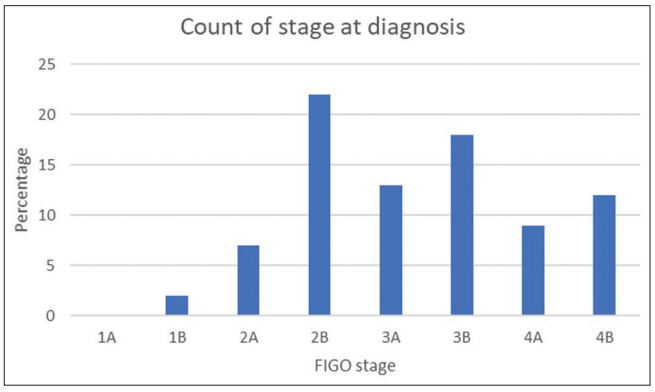

Figure 1: Stage at presentation among 83 human immunodeficiency virus-positive patients with invasive cervical cancer

Table 1: Characteristics of 83 human immunodeficiency virus-positive patients with cervical cancer

Characteristics	Frequency (%)
Age (years)	
<30	11 (13.3)
30–40	52 (62.7)
>40	20 (24.0)
Marital status	
Married	41 (49.4)
Divorced	11 (13.3)
widowed	17 (20.5)
Never married	14 (16.8)
Parity	
Nulliparous	9 (10.8)
Para 1–4	27 (32.5)
Para>5	32 (38.6)
Parity not recorded	15 (18.1)
Educational status	
Nonformal/illiterate	23 (27.6)
Primary	13 (15.7)
Secondary	11 (13.5)
Tertiary	29 (34.8)
Postgraduate	7 (8.4)
ECOG performance status	
0	19 (22.9)
1	39 (46.9)
2	13 (15.8)
3	9 (10.8)
4	3 (3.6)
Symptoms at presentation	
Foul-smelling vaginal discharge	33 (39.8)
Bleeding per vaginum	13 (15.7)
Foul-smelling vaginal discharge with per vaginal bleeding	17 (20.5)
Backache	3 (3.6)
Vaginal discharge with backache	5 (6.0)
Symptoms referable to metastatic sites	12 (14.5)
Duration of symptoms (months)	
<6	20 (24.1)
>6	63 (75.9)

ECOG – Eastern Cooperative Oncology Group

to Manchester point A. Fifteen patients were planned with palliative intent with total radiation dose of 45 Gy in 25 fractions over 5 weeks with no brachytherapy boost. Symptomatic treatment in the form of analgesics and antibiotics was offered to 12 patients in addition to palliative radiotherapy to metastatic sites at doses of between 8 and 30 Gy in 1–10 fractions in patients with FIGO Stage 4B disease. One patient with poor performance status and FIGO Stage 4A disease was treated for severe pelvic pains and tumor-related vaginal bleeding with 8 Gy single fraction every 3 weeks for three fractions. In the 55 patients planned for radical chemoradiation therapy, sequential chemotherapy and concurrent chemoradiation were administered in 47 (85.5%) and 8 (14.5%) patients, respectively. Twenty-six (47.3%) of the 47 patients on sequential chemoradiation, and two in the concurrent chemoradiation arm successfully completed their planned EBRT treatment without breaks. All the 28 patients who completed radical EBRT received intracavitary brachytherapy successfully. Similarly, patients on both arms completed at least four courses of prescribed chemotherapy. Of the 27 patients who could not complete planned radical radiation dose, 19 discontinued after 5–13 fractions of EBRT on the account of Grade 4 acute toxicities (8 in the skin, 5 from acute Hb toxicity, three from acute proctitis, and three from acute white blood cell [WBC] toxicity with associated febrile neutropenia). Of the remaining eight patients who could not complete the planned treatment, four were lost for unknown reasons, two switched to traditional medicine practitioners, and two could not continue on account of paucity of funds. Similarly, 13 (86.7%) of the 15 patients planned for palliative radiotherapy completed the planned dose of EBRT with significant resolution of symptoms related to their cervical disease. The remaining two were lost for unknown reasons.

Intracavitary brachytherapy boost was given to 24 (92.3%) of the 26 patients who completed the sequential chemoradiation and both patients from the concurrent arm. Two of the 28 patients planned for intracavitary applications had bulky residual disease making intracavitary insertion of ovoids difficult and were therefore given boost of 25 Gy with intravaginal cylinder and dose calculated at 0.5 cm from the surface of the cylinder [Table 2].

Toxicity was scored using the Radiation Therapy Oncology Group criteria of acute radiation morbidity. Twenty-eight patients completed radical dose of radiotherapy with some developing one form of acute toxicity or the other and accounted for treatment interruptions and delays in some of them. Six (21.4%) of the patients developed Grade 4 skin toxicity, leading to a 3-week treatment break, which was resumed after adequate perineal and natal cleft wounds (from extensive moist desquamation and ulcerations) healing was achieved. Three (10.7%) of the patients developed Grade 3 genitourinary system (GUS) toxicity necessitating treatment suspension and resuscitation with blood transfusion and analgesics. Three patients developed Grade 3 GIT toxicity (diarrhea) and 2 (severe vomiting) with treatment interruption and admission to the ward for parenteral support and correction of electrolyte imbalance in addition to parasympatholytic medication. Twenty-one patients with Grade 2 GIT (diarrhea) and 13 (vomiting) toxicity were managed conservatively. Similarly, Grade 3 proctitis was documented in two patients requiring blood transfusion, portent analgesics, and resuscitation on the ward. Grade 4 hematologic toxicity was seen in two patients whose Hb dropped below 5 g/dl during treatment and was given packed cell transfusion, while broad-spectrum antibiotics

were commenced in five patients with acute Grade 3 WBC toxicity [Table 3].

DISCUSSION

From the results of our study, we observed that majority 74 (89.2%) of the patients presented with an advanced stage disease, FIGO Stage 2B and above, thus reflecting the enormous burden of late presentation of cervical cancer patients in our environment, and may also highlight an overall lack of cervical cancer screening and early diagnosis. Similar findings of late presentation were reported in studies from other parts of Nigeria. A study in Lagos found that <10% of cervical cancer patients presented at operable stages with the majority presenting with advanced disease.[20] Similarly, a clinicopathological analysis of cervical cancer seen in a tertiary health facility in Nnewi, Southeastern Nigeria, found that 89.3% of the patients presented at advanced stages.[21] Similar high incidence findings were reported in Zimbabwe, a country in Southern Africa.[22] These studies highlight the huge challenge posed by late presentation of cervical cancer in countries with very limited treatment facilities and very few trained oncology specialists with attendant limited availability of treatment options.

Majority of patients with HIV-positive invasive cervical cancer present with symptoms of cervical cancer rather than that of immunosuppression.[23,24] In this study, all our patients presented with symptoms due to cervical cancer with copious foul-smelling vaginal discharge being the most common symptom. The mean age at diagnosis of the patients was 37.8 years which is about a decade lower than the HIV-negative patients, whose mean age is 47.6 years from a study conducted in our institution.[25] Several studies reported that patients with HIV-positive status are 5–10 years younger in age than their HIV-negative counterparts with cervical cancer, thus confirming the observation in other parts of the world and pointing toward the hypothesis that HIV shortens the latent period observed in progression of premalignant cervical lesion to invasive disease. The implication of this is that mortality and morbidity in this younger group of patients

Table 2: Stage distribution and treatment offered to 70 human immunodeficiency virus-positive patients on highly active antiretroviral therapy

FIGO stage (*n*=83), *n* (%)		HAART (*n*=74), *n* (%)	Treatment administered			Total
			Radiotherapy			
			Radical		Palliative (*n*=15), *n* %	
			EBRT+brachytherapy+sequential chemotherapy (*n*=47), *n* (%)	EBRT+concurrent chemoradiation+brachytherapy (*n*=8), *n* (%)		
1B	2 (2.4)	2 (2.4)	2 (4.3)	-	-	
IIA	7 (8.3)	7 (8.3)	6 (12.8)	1 (1.8)	-	
IIB	22 (26.5)	20 (24.1)	20 (42.6)	2 (3.6)	-	
IIIA	13 (15.7)	9 (10.8)	8 (17.0)	3 (5.5)	2 (2.9)	
IIIB	18 (21.7)	16 (19.3)	9 (19.0)	2 (3.6)	7 (10)	
IVA	9 (10.8)	8 (9.6)	2 (4.3)	-	6 (8.5)	
IVB	12 (14.5)	12 (14.5)	-	-	-	
		74 (89.1)	47	8 (14.5)	15 (21.4)	
Total	83		55		15	70

HIV – Human immunodeficiency virus; HAART – Highly active antiretroviral therapy; FIGO – International Federation of Gynecologists and Obstetricians

Table 3: Acute toxicity during chemo-radiotherapy in 28 human immunodeficiency virus-positive patients with cervical cancer

System	Grades of toxicity					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Hematopoeitic system						
Acute platelets toxicity	19	7	2	0	0	28
Acute WBC toxicity	4	9	10	5	0	28
Acute hemoglobin toxicity	14	5	7	0	2	28
GIT toxicity						
Acute nausea	5	22	3	0	0	28
Acute vomiting	9	6	13	2	0	28
Acute diarrhea	2	4	21	3	0	28
Acute proctitis	14	5	7	2	0	28
Skin toxicity	0	7	13	2	6	28
Genitourinary system toxicity	0	8	17	3	0	28

WBC – White blood cells; GIT – Gastrointestinal tract

may be more challenging to cope with, and HIV-infected women should undergo cervical cancer screening at an earlier age.[4,26]

The clinical management of invasive cervical cancer in HIV/AIDS patients has huge challenges, which are mainly due to the concerns of immune status. Various studies have shown that HIV-infected patients have impaired marrow function as well as impaired cellular immunity, thus making them more vulnerable to the effects of anticancer treatments.[27,28]

At present, optimal uniform treatment modalities for cervical cancer in HIV/AIDS patients are yet to be established; the consensus is that they are treated like their non-HIV infected counterpart: surgery for early disease, EBRT, brachytherapy, and concurrent or sequential cisplatin-based chemotherapy.[29,30] Most of our patients were thus offered full treatment with EBRT, brachytherapy, and chemotherapy, with the aim of achieving maximal disease control. Use of HAART concurrently with other modalities of cancer treatment, though at the risk of higher toxicity, had been found to be beneficial, with a study suggesting that HIV-infected women on HAART can expect to live longer if management for chronic conditions such as human papillomavirus and cervical cancer is controlled to optimize overall survival.[31] Similarly, some studies confirm that patients on HAART are more likely to tolerate chemoradiotherapy than those without,[32] and HAART is associated with profound and sustained suppression of HIV viral replication, a dramatic reduction in opportunistic infections, AIDS-defining illnesses, and mortality among HIV-infected persons as well as a reduction in AIDS-associated malignancies.[33-35] The inclusion of HAART in the management of all patients enrolled in this study is therefore appropriate.

Treatment toxicity is an acknowledged outcome of oncological intervention in cancer patients and may be more accentuated in patients with HIV infection. A probable explanation might be due to inherent cellular radiosensitivity and enhanced mucosal toxicity as a result of glutathione deficiency.[36] In our study, 25 (71.4%) evaluated for toxicity developed either Grade 3 or Grade 4 toxicities in the GIT, GUS, hematopoietic, and dermatologic systems, leading to significant treatment interruptions or delays. This could be explained by the findings from a study, suggesting that acute toxicity due to concomitant chemoradiation is higher than toxicity of radiation alone.[37] The facility where this study was done had no equipment for conformal treatment planning which could conveniently shield away critical structures; GIT, bladder, and bone marrow in the pelvic bone to minimize treatment-induced side effects. This could explain the high-grade 3 toxicity rates of 17.9% and 25% in the hematologic and GIT systems, respectively, and Grade 4 toxicity of 21.4% in the skin observed in our patients [Table 3].

Barring the small sample size and retrospective nature of this study as a limitation, this study revealed that properly selected HIV-positive invasive cervical cancer patients may be considered for radical combination treatment with tolerable and manageable toxicity. Enhanced treatment toxicity, limited response to treatment, treatment interruptions, and comparatively poor outcomes are some of the hallmarks of the outcome of treatment in this patient population. Large multicenter prospective treatment trials have been lacking in the HIV-positive group of patients, and this needs to be explored so that the optimum management for cervical cancer among these patient populations can be identified and appropriate modifications may be recommended to improve the overall treatment outcome.

CONCLUSIONS

This study had shown that HIV-positive patients with invasive cervical cancer may be treated with radical combination treatment like their non-HIV-positive counterparts. Treatment-related toxicity is significant and sometimes manageable and occasionally reversible. Given the prolonged life expectancy with the advent of HAART, opportunities to enhance cervical cancer control in partnership with a comprehensive care approach to HIV disease management ought to be thoroughly explored. Screening for cervical cancer in HIV-positive women should be commenced at an earlier age. These results need to be replicated in more rigorous extensive studies so that local treatment protocols could evolve from the results of findings.

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Conflicts of interest

There are no conflicts of interest.

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