Concurrent chemo-radiation induced renal and haematological toxicities in patients with invasive cervical cancer undergoing treatment

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Background. Cervical cancer constitutes a major problem in women's health in South Africa (SA). Concurrent chemo-radiation is the standardised treatment for patients with invasive cervical cancer. There is limited evidence on the differences in the concurrent chemo-radiation treatment toxicity between HIV-positive and HIV-negative patients.
Objective. To determine the renal and haematological toxicities associated with concurrent chemo-radiation in women undergoing treatment for invasive cervical cancer, using renal and haematological biomarkers.
Methods. A prospective study was conducted among 82 women that presented for concurrent chemo-radiation treatment at the Inkosi Albert Luthuli Central Hospital in SA. Thirty two (39%) of participants were HIV-positive. Data collected using questionnaires and the hospital's databases were analysed with SPSS data analysis software. Toxicity was scored using the Cooperative Group Common Toxicity Criteria.
Results. More than 90% of both HIV-positive and HIV-negative participants completed all 5 cycles of chemotherapy. The main finding in both cohorts was Grade 1 and 2 haematological toxicity. Haemoglobin was significantly decreased in 74% of participants. No renal toxicity was identified in this study. The reasons for not completing treatment were abscondment during treatment (3%) and discontinuation of treatment by the physician (1%).
Conclusion. Concurrent chemo-radiation was well tolerated in both HIV-positive and HIV-negative participants. The same concurrent chemo-radiation protocol can be applied to both HIV-positive and HIV-negative patients. However, the study population was small and findings need to be replicated in more extensive studies.

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Concurrent chemo-radiation therapy (CCRT) using cisplatin as the chemotherapeutic agent is the standard of care for the treatment of invasive cervical cancer.[1] In the African setting, HIV infection is a common comorbidity in patients with invasive cervical cancer.[2] There is a paucity of data on the best concurrent CCRT treatment regimen for HIV-positive women with invasive cervical cancer as the 5 randomised phase III clinical trials (GOG 85, GOG 120, GOG 123. SWOG 8797 and RTOG 9001) did not take HIV status of women into account.[1] In sub-Saharan Africa, AMC-081 was the first phase II clinical trial to investigate the outcome of CCRT in HIV-positive women with invasive cervical cancer.[1] Cisplatin is a nephrotoxic drug and acute kidney injury (AKI) is a well-known complication of cisplatin administration.[3] There is a higher risk of AKI in the HIV-positive population, resulting in poorer outcomes and higher mortality.[4] The mechanisms of cisplatin-induced AKI are proximal tubular injury, oxidative stress, inflammation and vascular injury in the kidney.[3]

Haematological toxicities have been reported in patients that undergo CCRT for cervical cancer.[5] These patients have an increased risk of developing neutropenia, thrombocytopenia and anaemia.[6] Reduction in haemoglobin (Hb) below normal for the age and sex of the patient results in anaemia.[7] Anaemia is a common condition in patients with malignancy.[8] The anaemia associated with malignancy may be due to both myelosuppression of stem cells by tumour cell products and chemotherapy (CT).[8] Anaemia is a strong risk factor for disease progression to acquired immune deficiency syndrome (AIDS) in HIV-positive patients, independent of the CD4 count and viral load.[9] Neutropaenia is a decrease in the absolute neutrophil count (ANC) below the normal limit.[7] Among HIV-positive women, there is an increased risk of neutropenia during CCRT, and they are less likely to complete CT with cisplatin.[10] Cancer treatment is a competing cause of neutropaenia in HIV-positive patients and may increase the risk of CCRT-induced neutropaenia, which may influence the course of the patient's treatment and risk of infection.[10] Myelosuppression and neutropenia occurs in up to 30 - 83% of HIV-positive patients.[10] Patients receiving fewer than 5 cycles of cisplatin have a decreased overall survival compared with those who completed the treatment.[10]

This study was conducted to address the paucity of data on the renal and haematological toxicities of CCRT in invasive cervical cancer patients undergoing treatment in the Durban population in KwaZulu-Natal Province, South Africa (SA). Findings from this

study can contribute to the body of knowledge used to generate CCRT trials specific for SA patients and to better educate healthcare workers and the community about the toxicities associated with CCRT.

Methods

This was a prospective study conducted between November 2018 and July 2019 at the Inkosi Albert Luthuli Central Hospital (IALCH), Durban, KwaZulu-Natal, SA. This hospital is 1 of 3 hospitals in Kwazulu-Natal that offers CCRT treatment for invasive cervical cancer.

The sample size for this study was calculated using unpublished data from the Oncology Unit of the IALCH. Power analysis for a chi square-test was conducted in G*Power to determine a sufficient sample size using an alpha of 0.05, a power of 0.80, and a medium effect size (w=0.3). Based on the above assumptions, the desired sample size was 82.

Eligible participants were women with histologically-confirmed invasive cervical cancer that qualified for CCRT treatment as decided by a multi-disciplinary team (standard of care). Women were excluded if they had renal impairment, haematological disorders, previously failed CT, previous neo-adjuvant CT, previous radiation therapy or hydronephrosis. Women who declined to be a part of the study and those who chose to withdraw from the study were excluded.

Eighty-two patients undergoing CCRT for invasive cervical cancer were eligible to participate in this study, following informed consent. Participants were categorised into HIV-positive and HIV-negative patients from the sample pool of eligible patients. Demographic information accessed from the hospital's databases included date of birth, age, ethnic group, place of residence and the following clinical parameters: histology, FIGO stage, HIV status, CD4 count, antiretroviral treatment, protocol for cervical cancer, other illnesses and treatment. Prior to CT, patients had routine blood specimens drawn to check their renal and haematology biomarkers. The biomarkers investigated in the present study, were routinely assessed as part of the patient's treatment and no additional biomarkers were done for this study. Biomarker testing was conducted by the National Health Laboratory Service based in the hospital complex. The patients' renal and haematological biomarker results were monitored prior to commencement of CCRT (baseline), during CCRT and one week post-CCRT. Biomarker results for urea, creatinine and estimated glomerular filtration rate (eGFR) were used to assess renal toxicity. The full blood count biomarker results for white blood cells (WBC), Hb, platelet count (PLT) and ANC were used to assess haematological toxicities.

Participants were prescribed radiation therapy concomitant with up to 5 weekly doses of cisplatin. All participants received 50.4 Gy external beam radiation therapy in 1.8 Gy fractions from Monday - Friday. All participants were required to complete 5 CT cycles with cisplatin. The cisplatin dose was either 30 mg/m^2 or 40 mg/m^2 as prescribed by the oncologist. The preferred day for CT administration was on a Wednesday, but CT could have been administered on any day prior to radiation therapy. Antiretroviral therapy was started for all HIV-positive participants that were not already receiving the treatment prior to commencement of CCRT. The CD4 count was not monitored for the duration of treatment. However, this did not pose a problem as the CD4 count was not expected to fluctuate much for the duration of CT. Also, patients with lower CD4 counts may have a decreased lymphocyte count, but not specifically a neutropaenia, which was monitored in this study.

Each participants' renal function was evaluated by an oncologist prior to CT administration. If eGFR was ≥60 ml/min, weekly cisplatin of either 30 mg/m^2 or 40 mg/m^2 was prescribed by the oncologist. CT was deferred if the eGFR was <60 ml/min and resumed once the eGFR was >60 ml/min. CT was deferred if the ANC dropped below 1 × 10^9/L and resumed once the ANC recovered. CT was deferred if the PLT dropped below 75 × 10^9/L. Patients were transfused if the Hb dropped to <7g/dL and CT was discontinued if the Hb, ANC or PLT did not recover.

Ethical clearance for this study was obtained from the Durban University of Technology Ethics Committee (ref. no. IREC 116/8). Permission to proceed with this study was obtained from the KwaZulu-Natal Department of Health, IALCH Management and the Provincial Health Research Committee. Written informed consent was obtained from participants prior to inclusion in the study. Participation in this study was voluntary and participants were not coerced into participating. Participants were informed that they would be free to withdraw from the study at any time. All participant information was strictly confidential. Patients were identified using a study record number.

The Cooperative Group Common Toxicity Criteria[11] was used to assess renal and haematological toxicity. The Wilcoxon test was used for comparisons between 2 groups. The Kruskal-Wallis test was used for comparison between more than 2 groups. Multivariate tests were used where applicable. The significance of the toxicities was determined using p-values. A p-value <0.05 was considered significant.

Results

Ninety women with invasive cervical cancer undergoing CCRT treatment at the IALCH were recruited to participate in this study. Based on the exclusion criteria, 8 women were excluded. The reasons for the exclusions were renal impairment, haematological disorders, hydronephrosis and previously failed CT. The total number of participants included was 82. Fifty participants were HIV-negative and 32 were HIV-positive. The profiles of participants qualifying for CCRT for invasive cervical cancer are shown in Table 1.

A significant finding was that the median age of HIV-positive participants was 9 years younger than HIV-negative participants. There was no significant difference in the histopathological diagnoses of squamous cell carcinoma and adenocarcinoma as well as the disease stage variation between HIV-negative and HIV-positive participants. Four (5%) of participants with stage I disease were treated with CCRT due to their ineligibility for surgery. Eight (10%) of participants with stage III disease had CCRT as they did not show evidence of pelvic wall involvement.

Table 1. Patient profile of participants in the study (N=82)

Variable	HIV-negative, n (%)*	HIV-positive, n (%)*	p-value
Age, years (median (IQR))	52	43	<0.01
(25 - 71)	(32 – 71)	(25 – 68)	
Histological type			
Squamous cell carcinoma	45 (90)	31 (97)	0.108
Adenocarcinoma	5 (10)	1 (3)	0.102
FIGO (2009) stage			
Stage I	3 (6)	1 (3)	0.317
Stage II	43 (86)	27 (84)	0.056
Stage III	4 (8)	4 (13)	1.000

Participants were required to complete 5 cycles of CT. The variables related to treatment delivery and compliance based on the HIV status of participants are represented in Table 2.

The average number of cycles completed by participants in this study was 5, regardless of HIV status. Ninety five percent of participants completed 5 cycles of CT with very few treatment gaps. Overall, compliance of participants to CT was excellent. There was one nontreatment-related death. The participant developed meningitis a week after completion of CT.

Toxicities were graded using the Cooperative Group Common Toxicity Criteria. The toxicity grade reflects the most severe degree occurring during treatment. Based on this criteria, no renal toxicities were identified in this study. Table 3 represents a summary of the mean (standard deviation (SD)) renal biomarker results from baseline to post-CCRT.

Figs 1 and 2 represent the trend for urea and creatinine from baseline to post-CCRT. Urea increased from a baseline level of 4.4 mmol/L to 5.6 mmol/L post-CCRT (p-value >0.05). Creatinine increased from a baseline level of 65 umol/L to 72 umol/L post-CCRT (p-value >0.05). The mean eGFR was >60 ml/min and remained unchanged for the duration of treatment and post-CCRT.

The haematological toxicities in participants post-CCRT are represented in Table 4. Grade 1 - 2 toxicity was the predominant finding regardless of HIV status. Hb was more significantly affected than other cellular components in blood in both cohorts.

Discussion

Cervical cancer has been found to occur at a younger age in HIV-positive women. In this study, the median age of HIV-positive participants was 43 years old compared with HIV-negative participants (mean of 52 years old). Findings were similar in the studies by Simonds *et al.*[5] and Einstein *et al.*[1] The risk of developing cancer is up to 7 times higher in HIV-positive women compared to HIV-negative women due to the higher HPV persistent prevalence in HIV-positive women.[12]

In this study, ~90% of HIV-positive and HIV-negative women had a histopathological diagnosis of squamous cell carcinoma and stage II disease. Findings were similar in the studies by Simonds *et al.*[5,15] The advanced disease stage at which women with cervical cancer present is probably due to cases being diagnosed late in SA.[16] The late diagnosis is due to limitations in the SA health care system.[17] Delays of up to 7 months have been reported in SA from the onset of symptoms until treatment of the disease.[17]

Tolerance for CT in this study was high (>90%) regardless of HIV status. The high tolerance for CT was most likely due to the administration of a lower cisplatin dose (30 mg/m^2) upfront for the majority of participants.

Administration of cisplatin can lead to AKI, which is characterised by a rapid decrease in renal function with an increase in waste products like urea and creatinine.[3] Nephrotoxicity is the dose-limiting factor of cisplatin treatment and could warrant dose reduction or withdrawal.[3] In the HIV-positive population, HIV-associated nephropathy (HIVAN) may present as AKI or chronic kidney disease but is not encountered frequently due to antiretroviral treatment.[4] Other HIV-associated kidney disease includes HIV immune complex kidney disease and thrombotic microangiopathy.[4] The renal function of participants in this study showed an upward trend for urea and creatinine from cycle 4, suggestive of deteriorating renal function. However, no cisplatin dose reductions or withdrawal were required and no renal toxicities were identified in this study.

Haematological toxicity was the main finding in this study. Haematological toxicity was most likely due to myelosuppression, which is a side effect of CT and cytotoxic drugs.[7] The changes are usually reversible after withdrawal of the drug.[7] Hb was more significantly decreased than other cellular components in both cohorts, followed by WBC. Anaemia is defined as Hb <10 g/dL.[9] The cause of anaemia is mainly impaired erythropoeisis resulting from the release of inflammatory cytokines as well as decreased production of haematopoietic growth factors, together with malabsorption and impaired recycling of iron.[9] Other causes of anaemia include nutritional deficiencies, haemolysis, malignant bone marrow infiltration and bone marrow infection.[9] Even in HIV-positive patients receiving antiretroviral treatment, anaemia is a strong risk factor for disease progression to AIDS and an increased risk of death.

Table 2. HIV status in relation to therapy (N=82)

Variable	HIV negative, *n (%)*	HIV positive, *n (%)*	*p*-value
Mean number of cycles completed	5 (96)	5 (94)	
Participants who did not complete therapy	2 (4)	2 (6)	0.641
Absconded during treatment	1 (1)	2 (6)	0.557
Treatment discontinued	1 (1)	0	1.000
Number of participants who had treatment delays	3 (6)	3 (9)	0.674
Low Hb	0	1 (3)	0.390
Low ANC	1 (2)	2 (6)	0.557
Low eGFR	2 (4)	0	0.518
Participants requiring hospitalisation	1 (2)	2 (6)	0.557
Transfused	1 (2)	1 (3)	1.000
Grade 4 toxicity	1 (2)	0	1.000
Death	1 (2)	0	1.000

Hb = haemoglobin; ANC = absolute neutrophil count; eGFR = estimated glomerular filtration rate.

Table 3. Mean (SD) results for renal biomarkers

Variable	Urea, mmol/L	Creatinine, umol/L	eGFR, ml/min
Reference range	2.7 - 7.1	49 - 90	>60
Baseline	4.4 (1.5)	65 (13.1)	>60
Cycle 1	4.3 (1.5)	67 (14.8)	>60
Cycle 2	4.5 (1.6)	69 (15.6)	>60
Cycle 3	4.5 (1.5)	69 (16.9)	>60
Cycle 4	4.3 (1.6)	68 (14.4)	>60
Cycle 5	5.3 (1.5)	69 (17.8)	>60
Post-CCRT	5.6 (1.8)	72 (23.3)	>60

SD = standard deviation; CCRT = continuous renal replacement therapy.

Table 4. Haematological toxicities in participants post-treatment

	Grade 1 - 2 toxicity		Grade 3 - 4 toxicity	
Toxicity type	**HIV negative, *n* (%)**	**HIV positive, *n* (%)**	**HIV negative, *n* (%)**	**HIV positive, *n* (%)**
Hb	34 (68)	27 (84)	2 (4)	4 (13)
WBC	13 (26)	12 (38)	2 (4)	2 (6)
PLT	11 (22)	11 (34)	0	0
ANC	8 (16)	7 (22)	0	1 (3)
			***p*-value**	
WBC v. Hb	<0.001	<0.001	1.000	0.492
WBC v. PLT	0.815	1.000	0.495	0.672
WBC v. ANC ancaancANC	0.326	0.274	0.495	1.000
PLT v. Hb	<0.001	<0.001	0.495	0.113
PLT v. ANC	0.611	0.405	-	1.000
ANC v. Hb	<0.001	<0.001	0.495	0.355

Hb = haemoglobin; WBC =white blood cell count; PLT = platelet count test; ANC = absolute neutrophil count.

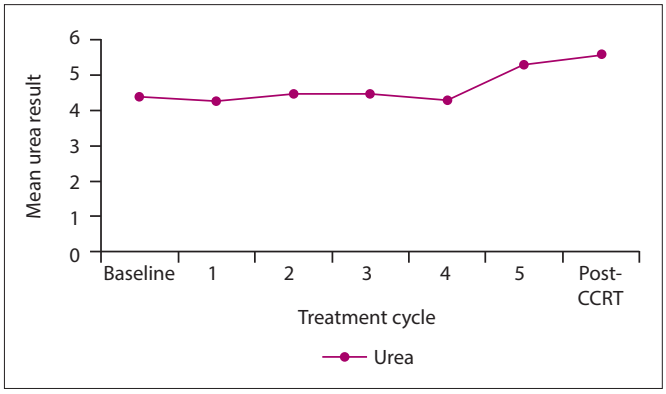

Fig. 1. Trend for urea based on mean result per treatment cycle. (CCRT = concurrent chemo-radiation therapy.)

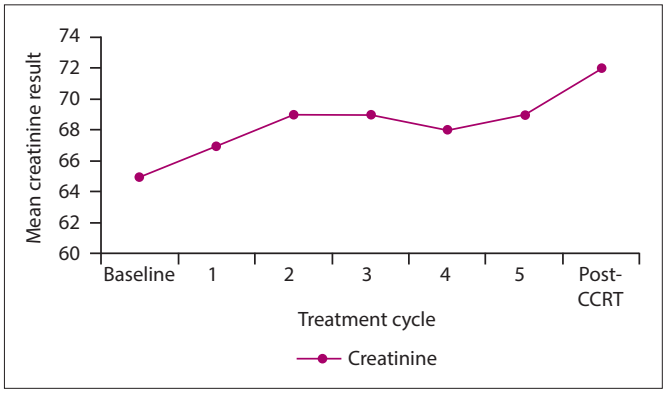

Fig. 2. Trend for creatinine based on mean result per treatment cycle. (CCRT = concurrent chemo-radiation therapy.)

Conclusion

The predominant finding in this study was haematological toxicity in both HIV-positive and HIV-negative participants. The blood component that was most significantly decreased was Hb, followed by WBC. The CT component of CCRT was well tolerated in both HIV-positive and HIV-negative participants. Compliance to planned CT was excellent regardless of HIV status and there were minimal treatment delays. Based on this study, the same CCRT protocol can be applied to both HIV-positive and -negative patients. The study population was small and these findings need to be replicated in more extensive studies. The upward trend for urea and creatinine needs to be investigated in further studies with a longer monitoring period, to determine the effect of cisplatin on renal function post-CCRT.

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1. Einstein MH, Ndlovu N, Lee J, et al. Cisplatin and radiation therapy in HIV-positive women with locally advanced cervical cancer in sub-saharan Africa: A phase II study of the AIDS malignancy consortium. Gynecol Oncol 2019;153(1):20-25. https://doi.org/10.1016/j.ygyno.2019.01.023
2. Gichangi P, Bwayo J, Estambale B, et al. HIV impact on acute morbidity and pelvic tumor control following radiotherapy for cervical cancer. J Gynecol Oncol 2006;100(2):405-411. https://doi.org/10.1016/s0167-8140(04)80601-7
3. Ozkok A, Edelstein CL. Pathophysiology of cisplatin-induced acute kidney injury. Biomed Res Int 2014:1-18. https://doi.org/10.1155/2014/967826
4. Wyatt CM. Kidney disease and HIV infection. Kidney. Top Antivir Med 2017;25(1):13-16.
5. Simonds HM, Neugut AI, Jacobson JS. HIV status and acute haematological toxicity among cervix cancer patients undergoing radical chemoradiation. Int J Gynecol Cancer 2015;25(5): 884-890. https://doi.org/10.1097/igc.0000000000000441
6. Albuqueue K, Giangreco D, Morrison C, et al. Radiation-related predictors of hematologic toxicity after concurrent chemoradiation for cervical cancer and implications for bone marrow–sparing pelvic IMRT. Int J Radiation Oncology Biol Phys 2011;79(4):1043-1047. https://doi.org/10.1016/j.ijrobp.2009.12.025
7. Hoffbrand VA, Moss PAH. Hoffbrand's Essential Haematology. 7th ed. West Sussex: Wiley Blackwell; 2016:1-281.
8. Lind M, Vernon C, Cruickshank D, et al. The level of haemoglobin in anaemic cancer patients correlates positively with quality of life. Br J Cancer 2002;86(8):1243-1249. https://doi.org/10.1038/sj.bjc.6600247
9. Takuva S, Maskew M, Brennan AT, et al. Anemia among HIV-infected patients initiating antiretroviral therapy in South Africa: Improvement in haemoglobin regardless of degree of immunosuppression and the initiating ART regimen. J Trop Med 2013;2013:1-6. https://doi.org/10.1155/2013/162950
10. Vendrell M, Ferreira A, Abrunhosa-Branquinho A, et al. Chemoradiotherapy completion and neutropenia risk in HIV patients with cervical cancer. Medicine 2018;97(30):e11592. https://doi.org/10.1097/md.0000000000011592
11. 11.Radiation Therapy Oncology Group (RTOG). 2019. Cooperative Group Common Toxicity Criteria. https://www.rtog.org/ResearchAssociates/AdverseEventReporting/CooperativeGroupCommonToxicityCriteria.aspx (accessed 15 September 2019).
12. Basu P, Taghavi K, Hu S, et al. Management of cervical premalignant lesions. Curr Probl Cancer 2018;42(2):129-136. https://doi.org/10.1016/j.currproblcancer.2018.01.010
13. Ghebre RG, Groverd S, Xue MJ, et al. Cervical cancer control in HIV-infected women: Past, present and future. Gynecol Oncol Rep 2017;21:101-108. https://doi.org/10.1016/j.gore.2017.07.009
14. Firnhaber C, Westreich D, Schulze D, et al. Highly active antiretroviral therapy and cervical dysplasia in HIV-positive women in South Africa. J Int AIDS Society 2012;15(2):17382. https://doi.org/10.7448/ias.15.2.17382
15. Simonds HM, Wright JD, du Toit N, et al. Completion of and early response to chemoradiation among HIV-positive and HIV-negative patients with locally advanced cervical carcinoma in South Africa. Cancer 2012;118(11):2971-2979. https://doi.org/10.1002/cncr.26639
16. Botha MH, Richter KL. Cervical cancer prevention in South Africa: HPV vaccination and screening both essential to achieve and maintain a reduction in incidence. S Afr Med J 2015;105(1):33-34. https://doi.org/10.7196/samj.9233
17. Wu ES, Jeronimo J, Feldman S. Barriers and challenges to treatment alternatives for early-stage cervical cancer in lower-resource settings. J Glob Oncol 2017;3(5):572-582. https://doi.org/10.1200/jgo.2016.007369

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