Effects Of Fractionated External Beam Radiotherapy On The CD4 And Full Blood Counts Of HIV+ Patients Undergoing Radiotherapy To The Head And Neck Region

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Citation

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Abstract

The purpose of this study was to assess the effects of fractionated external beam radiotherapy on the cd4 counts and full blood counts of HIV+ and HIV- patients undergoing radiotherapy to the head and neck region. Twenty seven patients participated in the prospective study. The weight, CD4 count, FBC, and mucositis grade were recorded before commencement of treatment and fortnightly thereafter, and also at six weeks, 12 weeks and 18 weeks after completion of treatment. The patient's HIV status was determined before commencement of treatment and the HIV+ patients were put on HAART. On all variables measured the HIV+ patients performed worse than the HIV- patients. The HIV+ patients recorded sharper decrease in CD4 count, more weight loss, sharper decreases in full blood counts and experienced severe oral mucositis at a much smaller radiation dose. The CD4 count of the HIV+ patients remained depressed even after completion of treatment but that of the HIV-patients recovered. There were more treatment days lost due to unscheduled breaks in the HIV+ group. The HIV+ patients did not tolerate the treatment well and weekly immunological monitoring is recommended for this group of patients.

BACKGROUND

The prevalence of HIV in Southern Africa is one of the highest in the world. This high prevalence has also been associated with an increased incidence of cancer among the HIV positive populations. These cancers can be broadly categorized as AIDS defining cancers such as Kaposi Sarcoma, cervical cancer and Non Hodgkin's Lymphoma; and non-AIDS defining malignancies which include breast cancer and most head and neck cancers. It has been reported that between 30% and 40 % of people infected with HIV will develop one malignancy or another during their life time1. The availability of Highly Active Anti Retroviral Therapy (HAART) brings with it the welcome mitigation against the disease. However, as the people infected with HIV live longer the incidence of non-AIDS defining cancers also increases in this group.

Treatment options for patients suffering from these malignancies include surgery, chemotherapy and radiotherapy. All these treatment options have well documented side effects in cancer patients that are not HIV infected. Radiotherapy causes hematological toxicity and depletes the circulating lymphocytes. The effect of radiotherapy on the immunological status of HIV positive patients with cancer has also been reported. More specifically, a decrease in CD4 count has been noted in both HIV positive and negative patients undergoing radiation treatment for cervical and anal cancer2, 3. This was attributed to the deleterious effect of radiation on the bone marrow and the volume of pelvis irradiated.

The present study reports on the effect of irradiation on CD4 count and the severity of oral mucositis on patients undergoing radiotherapy to the head and neck region where, unlike the pelvic region, there is little bone marrow. The study was designed as an exploratory prospective observational study at a private Oncology center in Gaborone, Botswana.

METHODS

After obtaining ethical approval from the local Research Ethics Committee, all patients presenting for treatment for head and neck cancer and consenting to participate in the study were included over a period of 12 months. A total of 27 patients were included of which 9 patients were HIV positive and 18 were HIV negative; 24 were male while 3 were female. The following data was captured before commencement of radiotherapy and thereafter after every 14

days from the day of commencement: weight, dose of radiation, mucositis grade using the WHO grading system, FBC and CD4 count. After completion of radiotherapy patients were followed up every six weeks and data was recorded up to eighteen weeks post treatment.
All radiation doses were delivered using 6Mv photons using standard departmental protocol. The protocol used for treatment was: 300Gy times 7 fractions, then off chords at 300Gy times 3 fractions followed by a two weeks break for the palliative regime. The treatment was given on alternate days. Thus for this phase of the treatment the patients received 30 Gys (i.e. 300x7 plus (300x3)) over a period of three weeks. After the two weeks break the patient continued with the off chords treatment at 300Gy x 7 fractions and then a boost field was given for 3 fractions of 300Gy each. The total dose given was therefore 60 Gys. Including the rest period the treatment was given over a period of eight weeks. For radical treatment the treatment regimen was 2Gy per fraction up to 60-74 Gys depending on the diagnosis in 30-37 fractions. Five fractions were given a week. The treatment was generally delivered over 6-8 weeks. Eleven patients received the palliative regime while sixteen were treated radically. For all patients the target volume included the tumor site, all areas of gross disease to encompass microscopic spread as well as lymphatic drainage with a margin. No patient received concurrent chemotherapy and there was no IMRT treatment because the department did not have the technology. Dental assessment was done on all patients prior to commencement of radiotherapy. All the patients were reviewed weekly during the course of the treatment, at which time they were assessed for toxicity and had Full Blood Counts (FBCs) done.

RESULTS

The patient characteristics and summary of results are presented in Tables 1 and 2 above respectively. The most common site was the oropharynx with 8 cases followed by the larynx and Squamous cell carcinoma of the conjunctiva with 5 cases each.

Table 1

Primary Cancer Sites.

Primary Cancer	Cases
Oropharynx	8
Hypopharnyx	3
Nasopharynx	3
Larnyx	5
SCC Tongue	3
SCC Conjuctiva	5

Table 2

Summary of the results

	HIV+	HIV-
Number of participants	9	18
Mean Age	42 (27-58)yrs	46 (31-74)yrs
Mean Cd4 Count before Rx	361	694
Mean CD4 Count After Rx	122.7	402.5
Mean % Decrease in CD4 count at the end of Rx	66%*	42%*
Mean % Decrease in CD4 count after 20 Gys.	47.0%	28.8%
Mean % Weight Loss	23.2%*	12.7%*
Mean WBC before Rx	6.7	8.4
Mean WBC after Rx	3.3	5.5
Mean Decrease in WBC	3.4*	2.9*
Incidence of Grade 4 Mucositis	44.4%	22.2%
Unscheduled Rx breaks	44.4%	22.2%

 # Decreases in CD4 count,Weight and WBC for both sets of participants were statistically significant p<0.04.

Of the HIV negative patients 17 had a baseline CD4 count at commencement of treatment of over 650 cells per microliter, while one had a baseline CD4 count of 424 cells per microliter. In the HIV positive group all the baseline CD4 counts were below 500. HAART was commenced on all the HIV positive patients before the commencement of the radiotherapy treatment.
The CD4 count for both groups of patients decreased as the

dose given increased; however, the drop was sharper and more pronounced for the HIV positive group. Thirteen (72%) patients from the HIV negative group had a drop of more than 30% in their CD4 counts by the time they had received 20Gys of radiation. In the HIV positive group all the patients had recorded drops in CD4 counts of more than 40% by the time they received 21Gys of radiotherapy. By the time the patients completed their respective treatments all the HIV positive patients had CD4 counts below 100 with two patients having CD4 counts less than 30. The mean CD4 count for the HIV+ and HIV- group were 122.7 and 402.5 respectively. There was a statistically significant correlation ($p=0.001$; $R=0.537$) between HIV status and decrease in CD4 count.

After completion of treatment the patients were followed up after every six weeks. The CD4 counts of the HIV negative group actually recovered very quickly and seventeen (94.4%) of them had CD4 counts above 500 at the time of the first six week follow up appointment.

The CD4 counts of the HIV positive group recovered very slowly after completion of treatment. All of the HIV positive patients had CD4 counts less than 350 cells per micro liter eighteen weeks after completion of treatment. Out of the nine positive patients five (55.6%) had CD4 counts below 200 cells per microliter eighteen weeks after completion of radiotherapy.

Mucositis and Treatment Breaks

Four (44.4%) of the nine HIV positive patients developed grade four oral mucositis by the time they had received 21Gys of radiation (Two of these patients required hospitalization.). These patients were rested from the treatment. On average eight treatment days were lost in this group due to the unscheduled treatment breaks resulting from severe oral mucositis. During the rest period the CD4 counts of the HIV positive patients continued to decrease but at a much slower rate.

Two (22.2%) patients from the HIV negative group developed grade four mucositis and had to be rested from the treatment. The one patient who was HIV negative but had a baseline CD4 count of 424 cells per microliter developed Grade 4 mucositis after 24 Gys and was rested for two weeks. During the rest period the CD4 counts of this patient and also of the other HIV negative patient increased. After 54 Gys the CD4 count for the HIV negative patient who had a low baseline CD4 count was 63 cells per micro liter and at completion of treatment the CD4 count was 27 cells per micro liter. The CD4 count remained depressed as it was still below 200 cells per micro liter even 18 weeks after completion of treatment. All patients completed their prescribed courses of radiotherapy. The other patient developed grade four mucositis after 36Gys of irradiation. No cumulative radiation effect (CRE) calculations and corrections were performed to compensate for the treatment breaks.

Full Blood Counts Analysis

The base line hemoglobin counts for all patients before treatment was above 11 cells per micro liter. However, during the course of treatment two (22.2%) of the nine HIV positive patients recorded hemoglobin counts below 9 cells per microliter by the time they had received 21Gys.They both received blood transfusion. Both were male and had stage four diseases. In the HIV negative group no patient needed transfusion.

The mean baseline white blood cell (WBC) counts were 8.4 and 6.7 cells/microliter for the HIV negative and HIV positive groups respectively. At completion of treatment the mean WBC count, had decreased to 3.3 cells/micro liter in the HIV positive group and 5.7 cells per micro liter in the HIV negative group. The mean WBC count for the HIV+ (3.3) was below the normal threshold (4.0). However, only two patients in this group had WBC counts below the clinically critical 2.5 cells per microliter by the time they had received 21Gys of radiation. This coincided with the third week of radiotherapy. There was a statistically significant correlation ($p=0.031$; $R=0.354$) between HIV status and decrease in WBC count.

Weight Loss

The average weight loss in the HIV positive and negative groups were 23.2% and 12.7% respectively. The patient who was HIV negative but had a low CD4 count baseline experienced a 15.4% weight loss from baseline. The weight loss can be attributed to two factors namely the oral mucositis grade and the patient's immunological status. Patients suffering from severe oral mucositis find it increasingly difficult to consume food, especially solids. Consequently their nutrition status deteriorates, and this exacerbates weight loss. In the current study the HIV+ patients developed more severe oral mucositis, and as expected also recorded higher weight losses.

DISCUSSION

The baseline CD4 counts of HIV positive patients were decreased in comparison to HIV negative patients as expected. All (100%) of the HIV positive patients in the current study experienced CD4 count decreases of more than 40% before receiving 21Gys of irradiation and had CD4

counts below 100 cells per micro liter by the time they completed treatment. When a patient's CD4 count falls below 200 per micro liter many kinds of HIV-related diseases such as opportunistic infections, can occur9. In this study all the patients were on HAART. In a study that enrolled HIV positive patients that commenced HAART at the same time with radiotherapy Kaminuma5 et al (2010) reported an increase of CD4 lymphocyte count with radi¬ation therapy. This was attributed to the fact that the patients started treatment with HAART therapy at the same time as radiation therapy.

The combined effect of HAART and radiotherapy has not been extensively studied. However, some of the drugs such as zidovudine have been reported to be myelosuppressive, hence it has been suggested that this drug be avoided if patients are to receive radiotherapy to large fields encompassing the bone marrow6. In the current study the HAART drugs that the patients were on were not recorded and there was little bone marrow in the treatment fields. It is therefore not possible to pin point the exact cause of the decrease in CD4 counts in these patients. However, it must be noted that even HIV- patients experienced decreases in CD4 counts. The decrease in the CD4 counts of HIV negative patients undergoing radiotherapy to the head and neck region in the current study is consistent with previous reports7. This decrease in CD4 count can be attributed to the combined effects of the disease and the radiotherapy on the patient's immune system. The current study did not observe the occurrence of opportunistic infections. Whereas previous studies have reported on the CD4 counts before and after treatment only, the current study also reported on the decline of the CD4 counts during the course of treatment. As observed earlier all HIV positive patients in this sample had their CD4 counts decreasing below 200. If CD4 count is used as a surrogate for immunological status, then it can be concluded that the immunological status of HIV positive patients declines with the dose of radiotherapy to the head and neck region.

The safety of continuing to give radiation to immuno-compromised patients with CD4 counts less than 200 cells per micro liter has not been investigated. In a report on eight ART naive patients who had initial CD4 counts between 250 and 320 cells/ul, all of them had values below 200 after one month of treatment and two out of these patients died without completing their treatment while the remaining six developed recurrent or persistent disease8. The same study reported two other ART naïve patients with Kaposis' sarcoma who had initial CD4 cells counts of 46 and 80cells/ul respectively. They were given palliative radiotherapy and commenced on HAART. They died within three months of presentation. The smallness of the sample sizes makes definite conclusions impossible, but underscores the need for more studies with larger sample sizes. Furthermore, close collaboration between the radiotherapists and the physicians is recommended.

It has been reported that in the general HIV negative population the first mucosal reaction can be observed after a total dose of 10 Gys has been admin¬istered, a deepening erythema is visible after 20 Gys irradia¬tion, and severe mucositis will develop after 30 Gys4. In the current study 44.4% of the HIV positive patients developed grade four mucositis after 21Gys of irradiation, which is much lower than the threshold noted in the normal population. These findings are in keeping with other studies that have reported that radiation induced mucositis tends to occur earlier in the HIV positive patients compared to the general HIV negative population5 after irradiation of the head and neck region. The severe mucositis reported in this study resulted in unscheduled treatment breaks which can have negative implications on tumor control. However, all patients completed the prescribed treatments. The onset of severe mucositis in the HIV positive patients and the potential loss of tumor control due to unscheduled treatment breaks need to be studied with larger sample sizes.

A decrease in WBC counts was noted in both groups of patients with a sharper decrease being recorded in the HIV positive group. However, the decreases in the WBC counts were not clinically significant save for the two patients whose WBC counts fell below 2.5 cells per micro liter. Both these patients were HIV positive, and the nadir occurred in the third week of radiotherapy. Furthermore, two patients required transfusion because of low hemoglobin levels. The cost of weekly FBCs can be very prohibitive in resource constrained settings. It has been suggested that weekly immunological monitoring of patients is not necessary for a majority of patients10. Although the sample size of the current study is small the current findings suggest that weekly FBCs may be necessary for the HIV+ patients.

In resource constrained environments, it is not uncommon to have one radiotherapist or radiation oncologist per center. This places added responsibility on the therapy radiographer (radiation therapist). In the interests of better patient care the therapy radiographer working in areas with high incidence of

HIV should liaise more closely with the oncologist and other clinicians to make sure those patients are tested for HIV, and where necessary commenced timely on HAART. Furthermore, the radiographers can take a more active role in ensuring that weekly full blood counts are done and the patients are reviewed regularly to assess the development of mucositis. The relatively high incidence of radiation toxicity induced treatment breaks among the HIV positive demands that radiotherapy departments should have CRE protocols in place. The shortage of radiotherapists, medical physicists and radiobiologists in most countries means that the responsibility to calculate CREs lies with radiographers. Hence the training of therapy radiographers should take into consideration this ever expanding role of the radiographer.

CONCLUSION

The HIV positive patients in this sample did not tolerate the radiotherapy treatment well. There is need for further investigations with larger samples to establish the effect of radiotherapy on viral load and the interaction of radiotherapy and HAART. There is also need to review the training of therapy radiographers in resource constrained environments so as to facilitate an expansion of their roles beyond the prosaic role of the therapy radiographer.

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