A pilot study of two radiation fractionation regimens in patients with cancer of the cervix, who were HIV positive and not on antiretroviral therapy

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Abstract
The Department of Radiation Oncology at the previously named Pretoria Academic Hospital (now the Steve Biko Hospital) undertook a pilot study between 2000 and 2001 of 20 patients who were human immunodeficiency virus-positive with locally advanced cancer of the cervix. At the time of the study, these patients were not on antiretroviral therapy, as per government policy. The patients were randomised into two arms. Six patients underwent a short palliative course of radiotherapy and 13 received a protracted and radical course of radiotherapy. One patient was lost to follow-up. Although the results were not statistically significant, the short course of palliative radiotherapy was adequate in terms of toxicity. As expected, the radical course was associated with a greater and more significant toxicity, because of the suppressed immune status of the participants.

Introduction
Between 2000 and 2001, at the previously named Pretoria Academic Hospital (now the Steve Biko Hospital), insufficient data were available on the tolerability of radiation in patients who were human immunodeficiency virus-positive who were not receiving antiretroviral therapy (ART), but who required radiotherapy treatment for advanced cervical cancer. For this reason, the hospital’s department of radiation oncology undertook a pilot study to determine the effect of pelvic irradiation on CD4/CD8 counts and survival in HIV-positive patients with cancer of the cervix.

Reduced CD4/CD8 counts are found in patients with cervical cancer. Whole-pelvic irradiation, which is the standard treatment for cervical cancer, has its own immune-suppressing effect. It has been shown that lymphocyte counts fall following radiotherapy treatment. An analysis of subgroups of lymphocytes has shown T- and B-cell lymphopenia after radiotherapy. The primary aim of this study was to gauge the tolerability between a regimen of high and low doses of radiotherapy, and what the effect of the higher dose would be on CD4 counts. A secondary aim was to determine if there was a difference in the survival rates of patients exposed to low doses of radiotherapy compared to those who had high doses.

Method
Twenty patients who were HIV positive and diagnosed with cervical cancer, with a performance status of 0-2 and without active co-morbid diseases, were staged and referred to the hospital’s Department of Radiation Oncology by the Department of Gynaecology. The participants were all older than 18 years of age, received counselling and consented to participate in the study. A simple randomisation technique of coin tossing was used to allocate each participant to one of two treatment arms.

Ethics approval was obtained from the ethics committee of the Faculty of Health Sciences of the University of Pretoria. At the time of the study, no ART was available. For this reason, staging of the cervical cancer was considered to be of secondary importance to treatment.

CD4/CD8 levels were determined in all patients prior to
treatment. Only 19 of a possible 20 participants were eligible for analysis, as one was lost to follow-up.

**Treatment**

The patients in the first treatment arm received a short course of radiotherapy of 20 Gy in five fractions, given over five days using a rotational field and covering the whole pelvis. After a two-week break, this treatment was followed-up by a boost to the cervix of 20 Gy, in five fractions using external beam radiotherapy.

The second treatment arm received a radical and protracted course of 36 Gy in 12 fractions covering the whole pelvis, given four times a week. This course was followed by a parametrial (true pelvis) boost of 12 Gy in four fractions, four times per week. The course was completed with an external boost to the cervix of 20 Gy in five fractions four times a week using a rotational field. At the time, both of these regimens were departmental policy because of restricted access to use of the machinery due to time constraints, as well as lack of equipment.

Patients were clinically assessed on a weekly basis for acute toxicity related to the skin, genitourinary tract and small and large bowel. Weekly CD4 counts were determined. After treatment, patients were followed up on a monthly basis, and thereafter, at three-monthly intervals.

**Statistical analysis**

The Student t-test was used to compare the two arms of treatment and to determine the statistical significance between both arms. The logrank test was used to compare the survival rates of the patients in the two groups. The unpaired t-test was used to analyse the CD4/CD8 counts. An analysis of covariance was performed to adjust the baseline count.

**Results**

Table I details the patient characteristics. Of the 19 patients who were eligible for the study, 13 received a radical course of radiotherapy, and six a palliative course. Patients were not evenly distributed between the two groups with respect to numbers, age and stage. Most of the patients had Stage III disease.

The patients who received the more aggressive therapy showed an increase in toxicity. Thirty per cent of patients in the radical arm had Grade III toxicity, compared with 15% of patients in the palliative group who had significant toxicity. Unfortunately, this was not statistically significant. Patients were followed up monthly to assess acute toxicity, and thereafter, every three months.

The median survival of the patients who were exposed to the radical course of radiotherapy was 39 weeks (range: 9-97) vs. 29 weeks (range: 10-150) for those in the palliative arm, although this result was not statistically significant (Figure 1 and Table II).

The CD4 values dropped to a lower level in the patients who underwent the protracted course of treatment, compared with the patients who had palliative treatment, but this result was not statistically significant either (Figure 2). After 14 weeks of follow-up, the CD4 count in the high-dose group had not recovered, but was recouping. Although the CD4 count was low, there were no intercurrent infections. The toxicity was more marked in the intensive arm. Two patients had severe radiation proctitis and required admission to hospital (Table III).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Radical</th>
<th>Palliative</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Median age</td>
<td>34 (30-62)</td>
<td>46.5 (33-56)</td>
</tr>
<tr>
<td>Stage I</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Stage II</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Stage III</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>PS 1</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>PS 2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

PS 1: performance status 1, PS 2: performance status 2

* One patient alive after 70 weeks
** One patient alive after 150 weeks

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**Figure 1**: Kaplan-Meier survival estimates by treatment group

**Table II**: Median survival of the patients in the two groups
Discussion

During the early years of the acquired immune deficiency syndrome (AIDS) epidemic in the developed world, relatively few women were diagnosed with the disease. In the late 1980s, the link between invasive carcinoma of the cervix and HIV became evident. As a result, the Centers for Disease Control and Prevention designated invasive carcinoma of the cervix as an AIDS-defining condition.

Cervical cancer in women who are HIV positive is sufficient to diagnose AIDS, regardless of the CD4 count. Invasive carcinoma of the cervix, and its intraepithelial precursors, behaves like a sexually transmitted disease. Cervical carcinoma continues to be the leading cause of cancer morbidity and death in women in many developing countries, including South Africa. Some of the risk factors include multiple sexual partners and viral exposure to human papillomavirus (HPV). HPV infection plays an essential causative role in the development of cervical malignancy. Cancer of the cervix is a more aggressive disease in patients who are HIV positive.

Recent data from developed countries have shown that the use of ART has had a beneficial effect in decreasing the relative risk of cervical intraneoplasia (CIN). The ability of highly active antiretroviral therapy is limited in clearing HPV infection and inducing regression of CIN in women who are HIV positive. Judicious use of radiation and ART can improve control of malignancies. Innovative therapeutic modalities need to be investigated, as no clear guidelines are defined for the management of women who are HIV positive with advanced carcinoma of the cervix in developing countries.

Thus, shortened fractionation was considered by our department because of resource constraints. The rationale was that a shortened course of treatment to control symptoms and bleeding would suffice in patients who were affected by AIDS.

The scope of the problem is highly relevant to South Africa where more than 1 500 new cases of HIV infection occur daily. Also, currently, more than 5 million South Africans are infected. Cancer of the cervix is the most prevalent malignancy in South Africa and accounts for nearly 20% of all neoplasia.

These patients often present with more advanced disease, and at the time of the study, those who were HIV positive were not on ART as per the South African government policy. Another concern was that the radiotherapy might have reduced survival rates by increasing the immunosuppressive effects.

Radiotherapy suppresses the absolute lymphocyte count and has a short-term effect on the cell-mediated immune system. It was found that patients with stage II-IIIb had a decreased CD4/CD8 ratio after radiotherapy treatment. This can remain low for up to 12 months.

The progression of CIN has been shown to be accelerated in patients who are immunocompromised. There has been concern that therapy-induced reduction of CD4 counts could promote progression of disease. The suppression of the HIV viral load may modify the interaction between HPV and HIV, or the effect may be related to an improvement in the CD4 count.

Our study was flawed in many respects. There were a small number of patients. The distribution of the

Table III: Early toxicity: radiation therapy oncology group

<table>
<thead>
<tr>
<th>Organ affected</th>
<th>Radical Grade 1</th>
<th>Radical Grade 2</th>
<th>Radical Grade 3</th>
<th>Palliative Grade 1</th>
<th>Palliative Grade 2</th>
<th>Palliative Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>-</td>
<td>2 (10.5%)</td>
<td>1 (5.2%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GUT</td>
<td>-</td>
<td>2 (10.5%)</td>
<td>1 (5.2%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GIT</td>
<td>1 (5.2%)</td>
<td>3 (15.8%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (5.2%)</td>
</tr>
<tr>
<td>Proctitis</td>
<td>-</td>
<td>5 (26.3%)</td>
<td>2 (10.5%)</td>
<td>1 (5.2%)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

GIT: gastrointestinal tract, GUT: genitourinary tract

Figure 2: Mean CD4 counts vs. treatment time
groups was not equal and the fractionation was not standard.

Given these constraints, palliative radiotherapy with 20 Gy in five fractions was not unreasonable in a situation in which ART was not available to patients with advanced disease and where resources were limited.

Furthermore, the radical arm of the study that was carried out at the hospital showed unexpected high-grade (Grade III) toxicity. This high-grade toxicity would not have been identified without this study. In this way, impetus has been given to the modification of the fractionation regimen at our hospital. It now adheres to a more conventional fractionation scheme.

Conclusion

At the previously named Pretoria Academic Hospital, the Department of Radiation Oncology treated 1 837 new patients in 2000, of whom 26.9% were diagnosed with carcinoma of the cervix.

Constraints that existed within government hospitals, and specifically at this hospital, with regard to staffing and equipment meant that there were long waiting lists of patients who required treatment for cancer of the cervix.

The aim of our pilot study was twofold. The first aim was to assess the tolerability of a high dose of radiotherapy vs. that of a lower dose, and the effect that the higher dose would have on CD4 counts. The second aim was to establish whether or not there was a difference in the survival rates between the two groups of patients who were HIV positive with cancer of the cervix. The fractionation used, although unconventional, was established policy in 2000 and 2001 in the Department of Radiation Oncology and was necessitated by the high volume of patients and lack of radiotherapy resources.

Recent upgrades to the hospital’s equipment and expansion of the Department of Radiation Oncology have allowed the use of standard fractionation of 2 Gy per fraction.

Currently, ART is available in all government hospitals. This means that radical radiotherapy and chemotherapy are possible for selected patients with advanced disease who are HIV positive. In addition, as improved resources became available, data emerged that the more aggressive therapy was the optimum treatment. For this reason, the study was terminated before greater numbers of patients were recruited.

This study is still relevant for developing countries and institutions with limited resources, because patients who are HIV positive with locally advanced cancer of the cervix, and those who are selected for palliative radiotherapy alone, will benefit as a result of the minimal toxicity of the treatment. The limited toxicity will have a less negative influence on their quality of life.

References