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Short Communication

Impact of HIV Status and Protease Inhibitor Use on Blood Counts during Chemotherapy and Radiation Treatment for Anal and Lung Cancers

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Abstract

Purpose

Aggressive cancer treatment for patients with HIV on HAART therapy can achieve similar outcomes to cancer patients without HIV. However, HIV protease inhibitors, often used in HIV treatment, are radiation sensitizers and have been tested in clinical trials to improve the efficacy of treatment. Here, we explore whether HIV status and the use of protease inhibitors during chemoradiation has an impact on blood counts during treatment for anal cancer and lung cancer.

Methods

From 2007-2014, 50 patients with anal cancer were treated at our institution with curative radiation therapy. Another 8 patients with HIV and lung cancer treated with curative radiation therapy were identified. Unpaired t-tests were used to compare blood counts between HIV-infected patients and HIV-uninfected patients, as well as among HIV-infected patients taking protease inhibitors compared to HIV-infected patients not taking protease inhibitors.

Results

Median white blood cell count (WBC) and hematocrit (HCT) were both within normal limits at baseline before beginning radiation or chemotherapy (WBC=6.69 x 10^3/μL and HCT =37 units). Baseline HCT and WBC were lower in the HIV-positive versus negative groups (HCT 34 vs. 38 units, p=0.024; WBC 6.08 x10^3/μL vs. 7.13 x10^3/μL p=0.003). Changes in weekly HCT and WBC counts after starting radiation showed no statistically significant differences between the HIV positive versus HIV negative patient groups. Compared to HIV patients not on protease inhibitors during radiation treatment, protease inhibitor use was found to have a consistently suppressive effect on HCT change during radiation treatment, but no detectable effect on WBC changes during treatment ($p<0.05$).

Conclusion

For patients with HIV and adequate hematocrit and WBC counts prior to starting treatment, concurrent chemoradiation can be delivered without an excess decrease in counts compared to patients without HIV. However, protease inhibitors use during

treatment appears to be associated with an increased drop in hematocrit. Further studies are necessary to validate these results and determine if they are associated with worse outcomes.

Keywords: HIV; Protease Inhibitor; Radiation Sensitizer;W-BC; Blood Counts

Introduction

The immune system is believed to play a critical role in cancer suppression, with a recent surge in immunotherapies that help promote the body's immune system to fight cancers [1, 2]. In addition, a number of studies have shown an association between pretreatment lymphopenia and shortened survival in cancer patients [3, 4]. Patients with Human Immunodeficiency Virus (HIV) pose a special challenge in cancer treatment since some patients are already significantly immune compromised and may not be able to tolerate standard chemotherapy and radiation. Anal squamous-cell carcinoma is a relatively uncommon disease in the general population but has a significantly higher incidence in HIV—infected patients [5]. Recent reports have indicated that with highly active antiretroviral therapy (HAART), patients with HIV can achieve similar cancer control rates as patients without HIV [6]. However, there have also been reports of increased radiation sensitivity with concurrent use of HIV protease inhibitors such as nelfinavir in head-and-neck cancer and non-small cell lung cancer via downregulation of Akt [7, 8]. There is potential for increased toxicity with the addition of a radiosensitizer to concurrent chemoradiation, a published phase I trial in pancreatic cancer showed promising activity with a combination of nelfinavir and chemoradiation but also substantial toxicity [9].

Hematopoietic toxicity is one of the most treatment-limiting toxicities in concurrent chemoradiation for anal cancer [6]. Although previous studies have compared the toxicities and clinical outcomes of chemoradiotherapy for anal carcinoma in HIV-negative vs HIV-positive patients, there is less information available on the impact of HIV protease inhibitors on blood counts during treatment. Here, we propose to examine the blood counts of patients with anal cancer undergoing concurrent chemoradiation and ascertain whether the use of HIV protease inhibitors has an impact on changes in blood counts during and after chemoradiation in the modern era. We will also compare the HIV-positive patient population against the HIV-negative population. In addition to anal cancer, we will also examine a population of HIV-positive patients with lung cancer, to ascertain the impact of protease inhibitor therapy on blood counts in that population.

Materials and Methods

Study population

This study was reviewed and approved by the Institutional Review Board of the University of Washington. Patients with anal or lung carcinoma were identified using a database of cancer patients treated at the University of Washington Medical Center between 2007 and 2014. The following eligibility criteria were used to select the study population: (1) ≥ 18 years of age, (2) anal or lung cancer; (3) treatment with radiation therapy at our institution; (4) baseline and follow-up for a minimum of 6 weeks with complete blood counts available for review. Patients receiving chemotherapy concurrent with radiation therapy had to start chemotherapy within one day of starting radiation treatment.

Treatment details

Medical records for included patients were reviewed for dose and duration of radiation therapy, dose, type and duration of chemotherapy, clinical staging, and HIV status and treatment medications. Additional data obtained included age at the time of therapy, site of radiation therapy, complications resulting from treatment, and recurrence of the disease. These patients were then subdivided into groups based on HIV status, and the HIV-positive patients were further subdivided based on HAART with a protease inhibitor versus no protease inhibitors. Protease Inhibitors that were used by patients in this study were ritonavir, darunavir, atazanavir, and saquinavir.

Treatment and lymphocyte count and hematocrit examination

White blood cell counts and hematocrit were collected prior to starting treatment, weekly during chemo/radiation therapy, and thereafter for up to 3 months. CD4 counts prior to therapy were collected, but there was not enough consistency in the availability of these blood counts to be able to reference an accurate analysis.

Statistical analysis

Patient baseline characteristics were summarized using descriptive statistics. Unpaired t-tests were used to compare blood counts between HIV-infected patients and HIV-uninfected patients, as well as among HIV-infected patients taking protease inhibitors compared to HIV-infected patients not taking protease inhibitors. All p values are reported as one-sided. P values less than 0.05 were regarded as significant.

Results

Patient characteristics

From 2007-2014, 50 patients with anal cancer were treated

Table 1. Patient demographics and treatment details.

	All Patients (N=58)	
Demographic Data		
Age: median (range)	53.5	(33-80)
Age <45 years (%)	8	(14%)
Age 45-55 years (%)	23	(40%)
Age 55-65 years (%)	19	33%
Age ≥ 65 years (%)	8	(14%)
Male/Female: no. (%)	25/33	(43%/57%)
HIV- anal cancer: no. (%) HIV+ anal cancer: no. (%) HIV+ lung cancer: no. (%) HIV- lung cancer: no. (%)	39 11 8 0	(67%) (19%) (14%) (0%)
HIV+ patients on protease inhibitor	10	(53%)
HIV+ patients not on protease inhibitor	9	(47%)
Baseline laboratory data		
WBC: median (range)	6.69 x 10^3/µL	(1.85-14.65)
WBC in HIV+ patients (mean)	6.08 x 10^3/µL	
WBC in HIV- patients (mean)	7.13 x 10^3/µL	
Hematocrit: median (range)	37 units	(25-47)
Hematocrit in HIV+ patients (mean)	34 units	
Hematocrit in HIV- patients (mean)	38 units	
CD4 count pre-treatment (range)	282 cells/mm^3	(46-778 cells/mm^3)
Adjuvant treatment data		
Radiation dose (Gy): median (range)	50.4	(45-74)
Concurrent chemotherapy (mitomycin + 5-FU): no. (%)	29	(50%)
Other chemotherapy	21	(36%)
No chemotherapy	8	(14%)

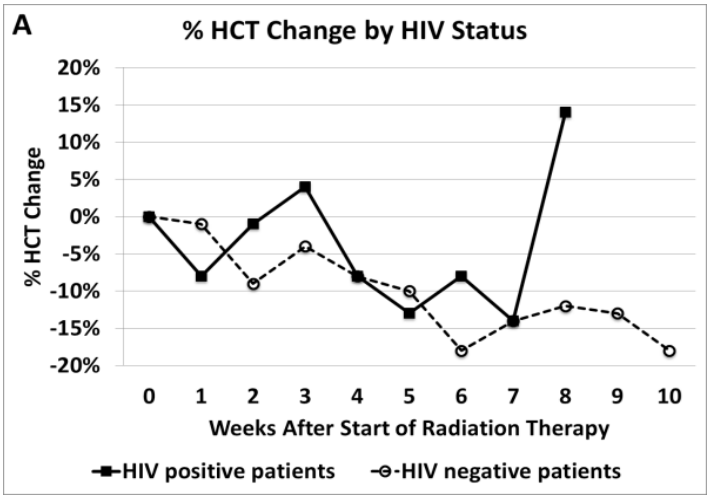
and followed at our institution. An additional 8 HIV-positive patients with lung cancer were also identified for analysis of blood counts in patients who were on protease inhibitors versus not. Table 1 provides a summary of patient characteristics. For the 50 patients with anal cancer identified for this study, 39 were without HIV and 11 with HIV. For patients with anal cancer, mean administered dose of radiation was 50.4 Gy. Concomitant with this radiation, most patients (29/50) were treated with mitomycin plus 5-FU, some patients (17/50) were treated with other chemotherapy regimens (such as capecitabine, cisplatin plus 5-FU, and mitomycin C plus capecitabine), and a few patients (4/50) were not treated with concomitant chemotherapy. For the 8 patients with HIV who received curative radiation for lung cancer, they were treated to 60-74 Gy, with half the patients (4/8) receiving concurrent cisplatin/etoposide.

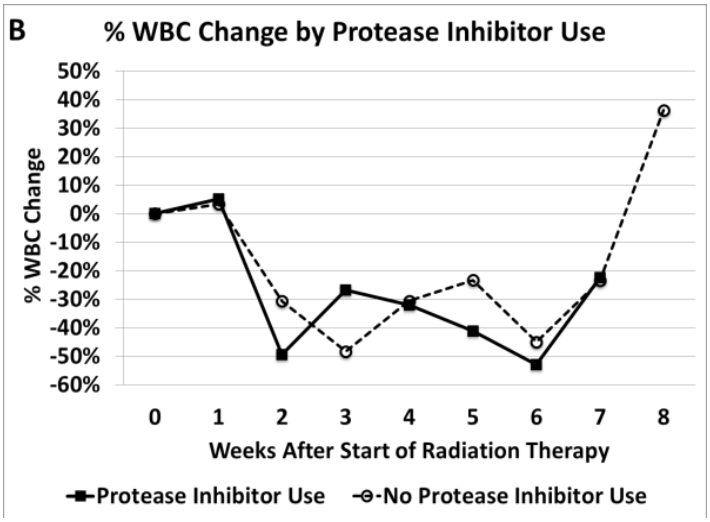
HIV positive versus negative population

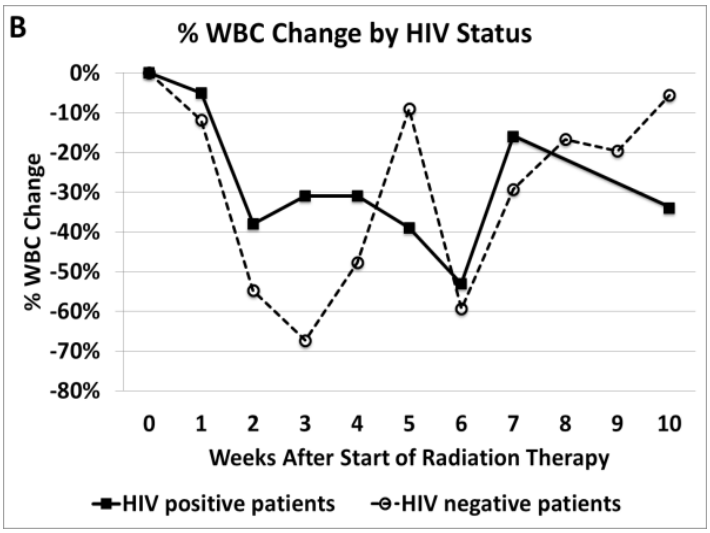
For the 50 patients with anal cancer, median white blood cell count (WBC) and hematocrit

(HCT) were both within normal limits at baseline before beginning radiation or chemotherapy (WBC=6.69 x 10^3/µL and HCT =37 units). Baseline HCT and WBC were lower in the HIV-positive versus negative groups (HCT 34 vs. 38 units, p=0.024; WBC 6.08 x10^3/µL vs. 7.13 x10^3/µL p=0.003). However, both groups were treated with similar chemotherapy regimens and dosing. Average CD4 count pretreatment was 282 cells/mm^3. Changes in weekly HCT and WBC counts after starting radiation showed no statistically significant differences between the HIV positive versus HIV negative patient groups (Figure 1). Radiation and chemotherapy typically lasted 5-6 weeks. Data points with less than 5 patients were not included in the analysis.

Figure 1. Effect of HIV status on percent changes in blood counts from baseline after the start of radiation therapy. (A) Hematocrit (HCT); (B) White blood cell count (WBC).



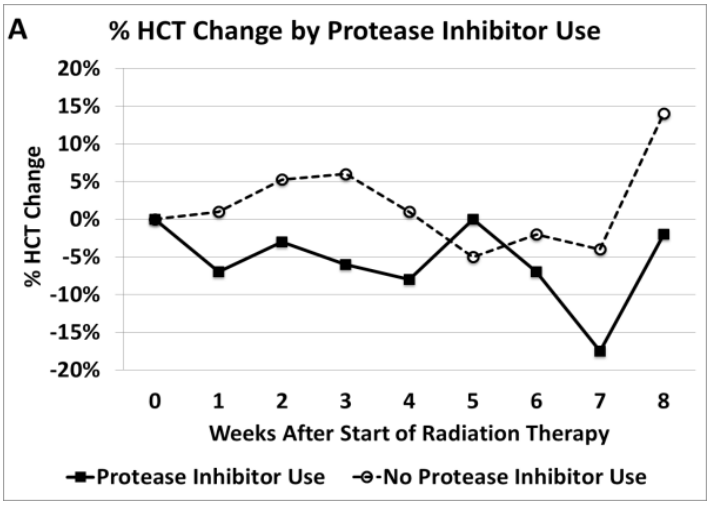




HIV protease inhibitor use

To look at the effect of HIV protease inhibitor use on blood counts during radiation treatment, we looked at 11 patients with HIV and anal cancer, and 8 patients with HIV and lung cancer. Ten patients were taking protease inhibitors during chemoradiation and 9 patients were not. Compared to HIV patients not on protease inhibitors during radiation treatment, protease inhibitor use was found to have a consistently suppressive effect on HCT change during radiation treatment, but no detectable effect on WBC changes during treatment (Figure 2). Change in HCT during treatment was statistically significantly different between patients on protease inhibitors and patients not on protease inhibitors during weeks 1-4 during treatment and at weeks 7 and 8 post-treatment (radiation treatment lasted 5-6 weeks) with $p<0.05$.

Figure 2. Effect of protease inhibitor uses on percent changes in blood counts from baseline after the start of radiation therapy in patients with HIV. (A) Hematocrit (HCT); (B) White blood cell count (WBC).



Discussion

Similar to prior publications, we find that patients with HIV on HAART therapy and adequate marrow function can be treated with curative intent for cancers, including the use of concurrent chemotherapy and radiation (6, 10, 11). HIV status did not seem to impact changes in blood counts during radiation and chemotherapy treatment, supporting the conclusion that patients with HIV that is controlled can be treated with full dose chemotherapy and radiation. However, also similar to prior publications, the use of protease inhibitors during therapy may have a sensitizing effect, and led to lower HCT in patients during treatment, compared with HIV patients not on protease inhibitors. WBC does not appear to be affected by the use of protease inhibitors during treatment. The exact cause for this is unclear. These findings suggest that HIV-infected patients undergoing chemoradiotherapy while on protease inhibitors may be at greater risk for anemia. Further studies are necessary to validate these results and determine if they are associated with worse outcomes.

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