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Clinical Investigation

Effect of CD4 Count on Treatment Toxicity and Tumor Recurrence in Human Immunodeficiency Virus–Positive Patients With Anal Cancer

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Summary

In this retrospective cohort study of 142 human immunodeficiency virus (HIV)-positive US veterans with anal cancer, pretreatment immunosuppression resulted in greater acute hematologic toxicity, and posttreatment immunosuppression resulted in a higher risk of tumor recurrence. This suggests that the immune system may play an important role in posttreatment cancer control.

Purpose: To study the effects of immunosuppression on treatment toxicity, long-term cancer recurrence risk, and survival among human immunodeficiency virus (HIV)-positive anal cancer patients.

Methods and Materials: From a nationwide retrospective cohort of veterans with anal cancer we identified 142 HIV-positive patients with stage I-III disease, diagnosed between 2000 and 2015 and treated with definitive-intent chemotherapy and radiation. We used regression models to study the impact of pretreatment CD4 counts and longitudinal posttreatment CD4 counts on outcomes including acute toxicity, long-term ostomy rates, cancer recurrence, cancer-specific survival, and overall survival. All models were adjusted for potential confounders.

Results: The median pretreatment CD4 count was 375 cells/mm^3, which dropped to 157 cells/mm^3 after treatment. Each 100-cell/mm^3 decrease in pretreatment CD4 count was associated with an increased risk of acute hematologic toxicity (odds ratio 1.19, 95% confidence interval [CI] 1.01-1.42, $P = .04$) and hospitalization for hematologic toxicity (odds ratio 1.24, 95% CI 1.00-1.54, $P = .049$) but not gastrointestinal toxicity, tumor recurrence, or cancer-specific mortality ($P > .05$). Each 100-cells/mm^3 decrease in posttreatment CD4 count increased the risk of recurrence by 54% (hazard

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ratio 1.54, 95% CI 1.09-2.17, $P=.01$) and cancer mortality by 46% at a trend level (hazard ratio 1.46, 95% CI 0.99-2.14, $P=.06$). Neither pre- nor posttreatment CD4 count influenced long-term ostomy rates or overall survival (all $P>.05$).

Conclusions: Lower pretreatment CD4 counts were associated with acute hematologic toxicity, and lower posttreatment CD4 count levels were associated with an increased risk of tumor recurrence. These results suggest that immune surveillance may play an important role in long-term disease control in anal cancer.

Introduction

Human immunodeficiency virus (HIV) infection and other immunosuppressive conditions are well-known risk factors for developing malignancy, particularly with cancers driven by oncogenic infections, such as human papillomavirus (HPV). Human immunodeficiency virus–positive individuals have a 40- to 80-fold increased risk of developing anal squamous cell carcinoma (SCC) compared with the general population (1). Although the link between HIV and anal cancer is partly driven by high rates of HPV co-infection, the immunosuppression associated with HIV infection may play a direct role in reducing tumor surveillance by depleting immune effector cells. In the "immune surveillance" hypothesis, an intact immune system destroys dysplastic cells before they develop into invasive cancer—a process that might be impaired by HIV infection (2, 3). For instance, immune surveillance is particularly important for SCC of the skin, because immunosuppression is associated with a significantly increased risk of nonmelanomatous skin cancers (4).

Although we understand the impact of immunosuppression on developing cancer, we lack a clear understanding of the role of immunosuppression *during* and *after* cancer treatment. A poorly functioning immune system could increase risks of treatment-related toxicity, raising the question of whether we should modify therapy in the immunosuppressed population. Additionally, impaired long-term posttreatment immune surveillance could lead to increased risks of cancer recurrence. Answering these questions will help us better understand the role of the immune system in patient-oriented cancer outcomes.

$CD4^+$ T-cell levels in HIV-positive (HIV+) patients serve as a proxy for immune system function, with a low CD4 count indicating an immunosuppressed state. A few studies have attempted to determine whether pretreatment CD4 counts correlate with toxicity and oncologic outcomes, though the combined rarity of anal cancer and HIV has led to studies with limited sample sizes (5-11). Furthermore, there has been no study evaluating the effects of posttreatment CD4 counts on long-term anal cancer outcomes. This study evaluates the impact of pre- and posttreatment CD4 counts on toxicity and long-term oncologic outcomes among a large nationwide cohort of HIV+ anal cancer patients.

Methods and Materials

Data source

We identified anal cancer patients utilizing the Department of Veterans Affairs (VA) Informatics and Computing Infrastructure (VINCI). VINCI is a comprehensive informatics platform that allows researchers access to patient-level electronic health record information and administrative data for all veterans within the VA healthcare system. VINCI incorporates tumor registry data uploaded from individual VA sites; these data are gathered at individual VA medical centers by trained registrars according to standard protocols issued from the American College of Surgeons (12). These data include veterans who are treated at non-VA facilities if they received any care at a VA facility over the course of their illness. This study was approved by the local institutional review board.

Patient cohort and treatment variables

From a large cohort of anal cancer patients (n=1104), we identified HIV+ patients with nonmetastatic AJCC stage I-III (13) anal SCC diagnosed between 2000 and 2015 (Fig. 1). We included patients who were treated with curative intent concurrent chemotherapy and radiation (14). All patients were treated to a radiation dose of ≥45 Gy and received chemotherapy within 2 weeks of the radiation start date.

HIV status and CD4 count data

Human immunodeficiency–positive patients were identified with International Classification of Diseases (ICD)-9/10 diagnosis codes for acquired immunodeficiency syndrome or HIV infection any time before the date of anal cancer diagnosis through 6 months after diagnosis (to include HIV workup started at the time of cancer diagnosis). The ICD-9 diagnosis codes included 042.X-044.X and V08.X; ICD-10 diagnosis codes included B20.X-B24.X and Z21.X (15, 16). This approach to ascertaining HIV status has been validated elsewhere (15).

Longitudinal CD4 counts were identified from VA laboratory data across all VA facilities. CD4 counts were classified into pretreatment and posttreatment groups. The

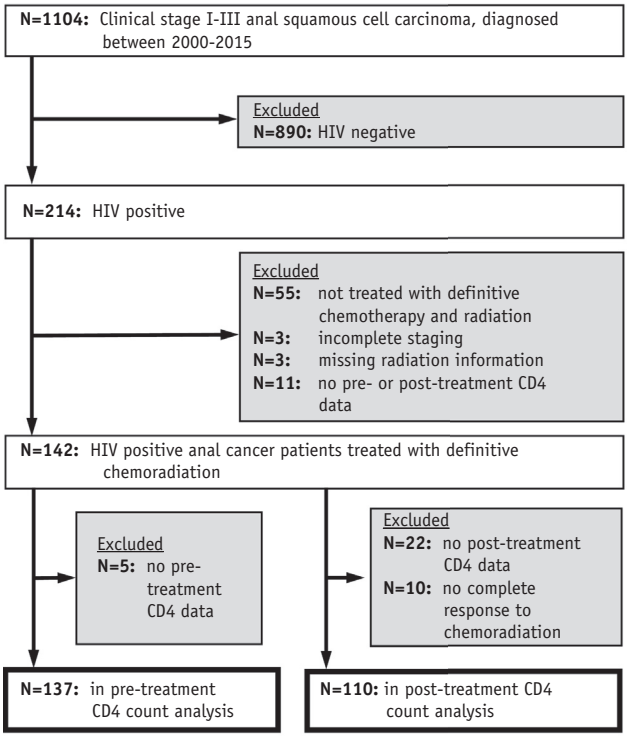

Fig. 1. Cohort selection process. *Abbreviation:* HIV = human immunodeficiency virus.

pretreatment group consisted of the most recent CD4 count from 1 year before treatment through the start of treatment. Posttreatment CD4 counts included all laboratory values extending from 3 months after the start date of treatment through last follow-up.

Outcomes

Tumor recurrence was determined through chart review. We defined recurrence as findings on physical examination, imaging, and/or biopsy that were interpreted by the treating physician as recurrent disease. We included both local and distant recurrence. Cause of death was determined by chart review; anal cancer−specific death was defined as death directly related to progression of locoregional or distant disease. Complete response to chemoradiotherapy was defined as no evidence of disease any time after the end of treatment on imaging, biopsy, or physical examination; 5 patients who were lost to follow-up immediately after treatment were excluded from the analysis of complete response.

Acute treatment-related toxicity within 90 days of chemoradiotherapy was scored using the Common Terminology Criteria for Adverse Event, version 4.0. Acute toxicities were assessed with VA laboratory data for hematologic toxicity (leukopenia, neutropenia, thrombocytopenia, or anemia), hospitalization records, and records for blood product transfusion. Reason for hospitalization was assessed by chart review of admitting diagnoses. Treatment breaks were ascertained by subtracting the number of delivered radiation fractions from the number of non-holiday weekdays in each patient's radiation treatment course. Failure to complete 5-fluorouracil (5-FU)/mitomycin C (MMC) chemotherapy was defined as dropping the second cycle of either chemotherapeutic drug. All-cause ostomy (colostomy and ileostomy) placement was determined through chart review. Follow-up was current through March 2017.

Covariates

Tumor stage, nodal stage, age at diagnosis, race, year of diagnosis, and history of prior malignancy were obtained through VA tumor registry data. Radiation dose, fractionation, and modality (intensity modulated radiation therapy vs conventional 3-dimensional conformal radiation) were obtained via chart review. Pretreatment positron emission tomography scan was determined through inpatient and outpatient CPT codes. Pre-existing comorbidity was assessed with the Charlson comorbidity index, which was determined from comorbid conditions noted in the year before diagnosis (12, 16, 17).

We obtained chemotherapy regimen and highly active antiretroviral therapy (HAART) administration information via VA pharmacy records, bar code administration records, intravenous infusion records, and clinical orders. Intended chemotherapy dosages and dose reductions were obtained through manual chart review. Patients were defined as receiving pretreatment or posttreatment HAART if they had a prescription for any HAART drug within 6 months before or after the start of treatment, respectively.

Statistical analysis

To study the effect of pretreatment CD4 counts on acute and long-term outcomes, CD4 count was included as a continuous variable in all regression models. Initial response to chemoradiation, 90-day hospitalization rate, failure to complete 5-FU/MMC chemotherapy, radiation treatment breaks, and 90-day hematologic toxicity rates were analyzed with multivariable logistic regression models. Ostomy rates were assessed with multivariable Fine-Gray regressions treating all-cause mortality as a competing event. Patients with a pretreatment ostomy were excluded from the ostomy analysis (n = 7). Cause-specific survival outcomes were modeled with multivariable Fine-Gray competing risk regressions to account for the competing risk of other-cause mortality. Effects on overall survival were analyzed with a Cox proportional hazards model. Patients were censored at last follow-up with a VA provider. Covariates in each model included pretreatment CD4 count, tumor stage, nodal stage, Charlson comorbidity index, age at diagnosis, and delivery of at least 1 cycle of 5-FU/MMC chemotherapy (vs other chemotherapy regimens).

To assess the effect of posttreatment CD4 count on risk of recurrence and survival outcomes, we used a joint modeling approach that combines a linear mixed-effects model for subject-specific CD4 trajectories and a multivariable Cox model for the time-to-event outcome. This approach has been shown to be appropriate for analyzing the impact of longitudinal data measured at differing time points (18-20). For the analyses of posttreatment CD4 counts, we included only patients who achieved a complete clinical response to chemoradiation. Patients who had any evidence of residual or progressive disease after treatment and patients who received salvage surgery were excluded. Because of short follow-up, 10 patients only had 1 post-treatment CD4 count measurement before recurrence; for these patients, in the mixed-effects model we imputed 1 CD4 measurement at time zero according to the population mean trajectory. To assess the sensitivity of the model to this imputation procedure we performed sensitivity analyses in which we varied the imputed slope from positive to negative values, which had negligible impact on the results (details included in Table E1 in the Supplemental Data; available online at www.redjournal.org). The linear mixed-effects model included random intercepts and slopes, and the Cox multivariable models included as covariates tumor stage, nodal stage, pretreatment positron emission tomography scan, age at diagnosis, and Charlson comorbidity index. Baseline hazards were approximated with B-splines (21, 22). Two patients who developed T-cell lymphoma with CD4 counts >2000 were excluded from the post-treatment CD4 count analysis. All statistical tests were 2-sided. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC) and R (R Core Team, Vienna) (21).

Results

Patient characteristics

The overall sample included 142 HIV+ veterans who had either pre- or posttreatment CD4 data (Table 1). The sample was exclusively male, and most patients had T1 or T2 tumors (68%) and N0 disease (68%). Eighty-three percent of the cohort received at least 1 cycle of infusional 5-FU/MMC chemotherapy, and 75% of these were originally prescribed 2 cycles. Among the patients prescribed 2 cycles, 27% had a second-cycle dose reduction or did not receive a second cycle of 1 or both chemotherapeutic drugs. Overall, of the 126 patients with available chemotherapy dose information, 48 patients (38%) received 2 complete cycles of 5-FU/MMC without dose reductions. Ninety-two percent of patients received a prescription for HAART in the 6 months before treatment, and this increased to 99% in the 6 months after treatment. The median follow-up for the entire study cohort was 3.8 years. The median pretreatment CD4 count was 375 cells/mm^3. CD4 counts dropped during chemoradiation, with a mean pre-post decrease of 213 cells/mm^3 (standard deviation 197 cells/mm^3, $P<.001$; Fig. 2). After the treatment-induced CD4 count nadir the counts trended upward. There was a moderate degree of

Table 1 Characteristics of the sample

Covariate	Value
Sample size (n)	142
Age at diagnosis (y), mean (SD)	53.5 (8.6)
Pre-treatment CD4 count (cells/mm^3), median, IQR	375 (182-539)
Prescribed HAART within 6 mo before treatment	131 (92)
Race	
White	91 (64)
Black	46 (32)
Other	5 (4)
Male	142 (100)
Charlson comorbidity index	
0	92 (65)
1	23 (16)
2	19 (13)
≥3	8 (6)
Clinical stage	
I	30 (21)
II	63 (44)
III	49 (35)
Tumor stage	
1	34 (24)
2	60 (42)
3	38 (27)
4	10 (7)
Nodal stage	
0	97 (68)
1	14 (10)
2	18 (13)
3	13 (9)
History of prior malignancy	25 (18)
Concurrent chemotherapy	
5-FU/MMC	118 (83)
5-FU/cisplatin	12 (8)
5-FU alone	12 (8)
5-FU administration route	
Infusional	135 (95)
Oral	7 (5)
Year of diagnosis	
2000-2003	19 (13)
2004-2007	41 (29)
2008-2011	45 (32)
2012-2015	37 (26)
IMRT	71 (50)
Cumulative radiation dose (cGy), median (IQR)	5400 (5040-5580)
PET scan	47 (33)
Pretreatment ostomy	7 (5)

Abbreviations: 5-FU = 5-fluorouracil; HAART = highly active antiretroviral therapy; IMRT = intensity modulated radiation therapy; IQR = interquartile range; MMC = mitomycin C; PET = positron emission tomography; SD = standard deviation.

Values are number (percentage) unless otherwise noted.

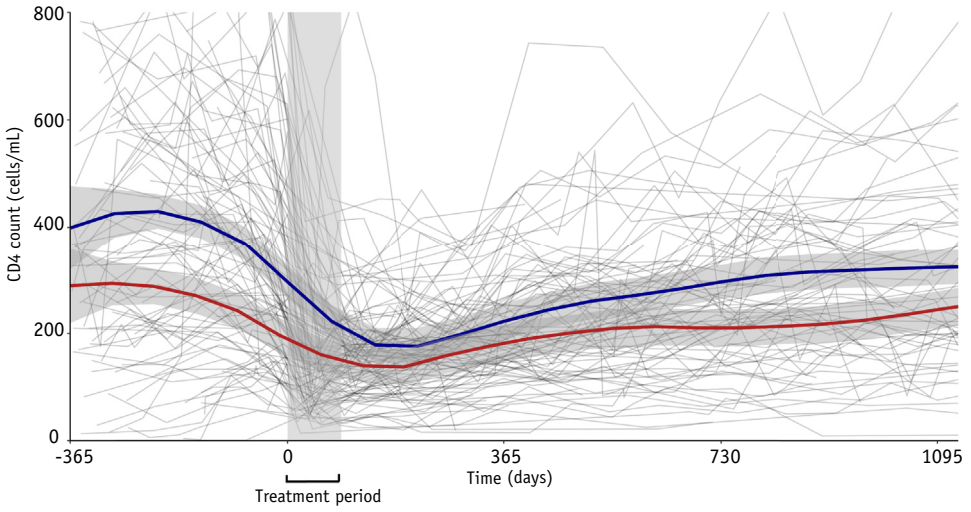

Fig. 2. Longitudinal CD4 count trajectories. This figure shows patient-specific longitudinal CD4 count trajectories with LOESS smoothing and 95% confidence limits (shaded area around lines) for patients without recurrence (blue line) and with recurrence (red line). Time zero is the radiation start date; the vertical shaded region shows the 90-day treatment period. One year of pretreatment time and 3 years of follow-up time are shown. (A color version of this figure is available at www.redjournal.org.)

correlation between pretreatment CD4 counts and the first posttreatment CD4 count (Spearman $\rho = 0.61$, $P<.001$).

Pretreatment CD4 counts

Pretreatment CD4 counts in the year before diagnosis were available in 137 patients. CD4 counts were measured a median of 41 days before treatment (interquartile range, 15-78 days). In the multivariable analyses lower CD4 count was associated with increased acute grade 3 to 4 hematologic toxicity and 90-day admission for hematologic toxicity, though it was not associated with 90-day admission for gastrointestinal toxicity, radiation treatment breaks, failure to complete 2 cycles of 5-FU/MMC, or long-term ostomy placement (Table 2). A total of 115 patients (87%) achieved an initial complete response to chemoradiation. Pretreatment CD4 count was not associated with the achievement of a complete response (Table 3). Among patients with an initial complete response, 35 patients

Table 2 Effect of pretreatment CD4 count on toxicity outcomes

Outcome	Unadjusted rate (%)	Adjusted HR or OR for CD4 (95% CI)*	*P*
Treatment			
Failure to complete 5-FU/MMC chemotherapy†	25	1.28 (0.94-1.75)	.12
Radiation treatment interruption			
≥ 5 d	45	1.08 (0.91-1.28)	.37
≥10 d	21	1.15 (0.92-1.44)	.22
Toxicity			
Grade 3-4 hematologic toxicity	58	1.19 (1.01-1.42)	.04
90-d hospitalization			
Any treatment toxicity	35	1.16 (0.97-1.38)	.10
Hematologic toxicity	24	1.24 (1.00-1.54)	.049
GI toxicity	13	1.00 (0.78-1.27)	.98
Ostomy placement‡	15	0.93 (0.70-1.24)	.63

Abbreviations: CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; OR = odds ratio. Other abbreviations as in Table 1.

Multivariable models included tumor stage, nodal stage, intensity modulated radiation therapy, Charlson comorbidity index, age at diagnosis, and MMC chemotherapy.

* Hazard ratios and ORs are reported per 100-cells/mm^3 decrease in pretreatment CD4 count. Hazard ratios were calculated for ostomy placement; ORs were calculated for the other toxicity outcomes.

† This analysis was restricted to the subset of patients who were prescribed 2 cycles of 5-FU/MMC, and the outcome represents the failure to complete 2 cycles of both chemotherapeutics.

‡ Patients with a pretreatment ostomy were excluded from this analysis (n=7).

Table 3 Effect of pre- and posttreatment CD4 counts on recurrence and survival

Outcome	Pretreatment CD4 count			Posttreatment CD4 count		
	Sample size (n)	Adjusted OR or HR for CD4 (95% CI)	*P*	Sample size (n)	Adjusted OR or HR for CD4 (95% CI)	*P*
Complete response*	132	1.08 (0.84-1.37)	.56	-	-	-
Recurrence†	113	0.89 (0.76-1.04)	.15	110	1.54 (1.09-2.17)	.01
Cancer-specific survival‡	134	1.08 (0.92-1.26)	.34	110	1.46 (0.99-2.14)	.06
Non-cancer survival‡	134	0.90 (0.72-1.13)	.36	110	0.81 (0.51-1.28)	.37
Overall survival‡	134	0.98 (0.86-1.13)	.82	110	1.17 (0.90-1.55)	.24

Abbreviations as in Table 2.

Hazard ratios and ORs are reported per 100-cells/mm^3 decrease in pretreatment CD4 count. Hazard ratios were calculated for recurrence and survival outcomes; ORs were calculated for the analysis of complete response. Multivariable models included tumor stage, nodal stage, Charlson comorbidity index, age at diagnosis, and pretreatment positron emission tomography scan.

* Five patients who were lost to follow-up immediately after treatment were excluded from this analysis.

† The recurrence analysis was performed on the subset of patients with a complete response to chemoradiation.

‡ Three patients with missing cause of death data were excluded from these analyses.

(30%) experienced a subsequent tumor recurrence. Lower pretreatment CD4 counts were not associated with tumor recurrence or cancer-specific survival ($P>.05$; Table 3; full multivariable model results are shown in Table E2 in the Supplemental Data; available online at www.redjournal.org). Pretreatment CD4 counts were not associated with noncancer survival or overall survival ($P>.05$).

Posttreatment CD4 counts

Of the total sample, 110 individuals had both longitudinal posttreatment CD4 data and a complete response to chemoradiation. These patients had a median of 7 posttreatment CD4 measurements (interquartile range, 3-16), for a total of 1386 measurements across all patients. In this cohort there was no association between pretreatment CD4 count and treatment-related variables, including radiation dose and completion of intended chemotherapy ($P>.20$ for all). In the joint model for tumor recurrence, for every 100-cells/mm^3 decrease in posttreatment CD4 count there was a 54% increase in the risk of tumor recurrence (hazard ratio [HR] 1.54, 95% confidence interval [CI] 1.09-2.17, $P=.01$; Table 3; full multivariable model results are shown in Table E2 in the Supplemental Data; available online at www.redjournal.org). To address the possibility of confounding by differences in treatment intensity, we then adjusted for additional treatment-related variables. The relationship between lower posttreatment CD4 counts and higher risk of tumor recurrence persisted when we accounted for chemotherapy regimen and completion of 2 cycles of chemotherapy (HR 2.43, 95% CI 1.32-4.50, $P=.005$), and in a subset analysis including only patients who received at least 1 cycle of 5-FU/MMC chemotherapy (HR 1.95, 95% CI 1.16-3.26, $P=.01$).

There was a trend toward decreased posttreatment CD4 count and diminished cancer-specific survival, with a 46% increase in the risk of death for every 100-cells/mm^3 decrease in CD4 count (HR 1.46, 95% CI 0.99-2.14, $P=.06$) (Table 3). We found no impact of posttreatment CD4 count on noncancer survival or overall survival ($P>.05$).

Discussion

The key finding in this study of 142 HIV+ anal cancer patients is the association between lower posttreatment CD4 counts and an increased risk of tumor recurrence. In HIV+ patients, CD4 counts serve as a proxy for immune system function. We found that lower posttreatment CD4 counts increased the risk of disease recurrence, with a trend toward decreased anal cancer–specific survival. Overall, these results implicate the potential importance of the immune system in improving disease control throughout the course of a patient's disease.

The link between anal cancer and the immune system deserves attention owing to the dramatically increased incidence of anal cancer among HIV patients (1). Substantial research has characterized the link between immunosuppression and tumorigenesis (23, 24), though few studies have addressed the impact of the immune system on anal cancer outcomes. The largest study to date, by Oehler-Janne et al (25), included 40 HIV+ anal cancer patients treated with chemoradiation or radiation alone and found no relationship between lower pretreatment CD4 counts and tumor recurrence. Similarly, we found no link between lower pretreatment CD4 counts and inferior long-term cancer control or mortality.

We found a strong association between long-term depressed CD4 counts and the risk of tumor recurrence after treatment, translating to an increased risk of cancer mortality (although the latter association did not reach statistical significance). To our knowledge this is the first study linking posttreatment immunosuppression with worse oncologic outcomes in anal cancer, and it emphasizes the potential importance of immune surveillance and optimal HIV management after the conclusion of treatment. Our results fit with a large and growing body of literature on the

critical role of the immune system in preventing and controlling cancer, highlighted by the recent successes of immunotherapy in multiple disease sites. A recently reported phase 2 trial with the checkpoint inhibitor nivolumab in metastatic anal cancer showed promising tumor control rates and progression-free survival (26). Further, there is mounting evidence that $CD4^+$ and $CD8^+$ T cells are important for controlling dysplastic and neoplastic cells (27), which provides a plausible biologic explanation for our results. Although the precise mechanisms are debated, $CD4^+$ T cells may stimulate dendritic cells, which in turn induce $CD8^+$ cytotoxic T cells to destroy precancerous cells (28). $CD4^+$ T cells may also support clonal expansion of cytotoxic T cells (29) and increase innate immunity through cytokine secretion (30).

Oncologists have long harbored concerns about increased treatment-related toxicity among HIV+ anal cancer patients, particularly among those with low CD4 counts before treatment. Prior reports have been primarily single-institution case series with varying results; some showed equivalent toxicity (5-8), whereas others suggested worse outcomes (9-11). Our study found a link between lower pretreatment CD4 counts and higher acute hematologic toxicities, including hospitalization for hematologic toxicity. However, severe gastrointestinal toxicity resulting in hospitalization, radiation treatment interruptions, incomplete chemotherapy courses, and long-term ostomy rates did not vary by CD4 count, suggesting that immune function may not substantially influence nonhematologic treatment-related toxicity in anal cancer. Of note, it is possible that pretreatment CD4 counts increase the rate of less-severe toxicities that do not result in hospitalization, because our study was not able to assess these.

Our study has limitations worth noting. Although our sample size is the largest to date, it was nonetheless modest, potentially impacting the precision of estimates and power to detect associations. Although we observed a relationship between decreased posttreatment CD4 counts and tumor recurrence, residual confounding secondary to unmeasured factors is possible. However, we accounted for the major factors associated with anal cancer recurrence reported in the published literature. A possible concern is that patients with lower CD4 counts might have received less-aggressive treatment, which increased the risk for recurrence. We believe this to be unlikely because we found no association between pretreatment CD4 counts and chemotherapy completion rates or treatment breaks, and the association between posttreatment CD4 counts and recurrence persisted in the subset of patients who received 5-FU/MMC chemotherapy, and also after adjustment for chemotherapy regimen and completion of 2 chemotherapy cycles. Although our analysis controlled for the receipt of MMC, other variables relating to chemotherapy delivery, such as variations in prescribed doses, could influence the risk of toxicity and recurrence, and our sample size limited our ability to control for all of these variables in the analysis. Our study is exclusively male, and all patients are US veterans, so further study in a broader population is necessary to confirm our findings. We did not have data on tumor HPV status, which is a known prognostic indicator in anal cancer. Finally, our findings linking CD4 counts and oncologic outcomes in the anal cancer population may not generalize to other cancer types. Further research is needed to understand the generalizability of our findings.

Conclusions

In this study we show that lower pretreatment CD4 counts are associated with acute hematologic toxicity, and posttreatment CD4 counts are a predictor of cancer recurrence. These findings highlight the importance of optimizing HIV control among this vulnerable population of patients and implicate the immune system as an important factor in anal cancer control.

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