Editorial

Cancer related fatigue in prostate cancer

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One of the most commonly experienced toxicities to treatment during cancer management is cancer-related fatigue (CRF) (1). The National Comprehensive Cancer Network defines CRF as "*a distressing*, *persistent*, *subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning*." (2). This symptom represents a massive detriment to quality of life, as 50–90% of cancer patients will experience this phenomenon during their treatment (3). Furthermore, up to 30% of cancer patients will continue to experience fatigue during follow-up visits after treatment completion (4). Severity of fatigue will vary with the site of malignancy, extent of disease, and treatment modality.

CRF is a symptom commonly experienced by patients undergoing external beam radiation therapy (EBRT) for prostate cancer. The typical pattern for CRF during EBRT is a progression in severity throughout the treatment, which peaks just before completion (4). An estimated 71% of men receiving EBRT will experience clinically significant fatigue. Persistent fatigue lasting more than 1 year after completion of EBRT was also reported by 24–33% of men (5).

Fatigue is a nonspecific complaint and can be multifactorial, as anemia, depression, pain, sleep disturbance, and physical deconditioning can partially contribute to the sensation of fatigue (6). Some groups have even proposed that reactivation of latent Cytomegalovirus (CMV) infections could be contributing to observed fatigue in some cancer sites (7). Amongst patients undergoing EBRT for prostate cancer particularly, site specific symptoms such as diarrhea, dysuria, polyuria and nocturia can indirectly cause fatigue (8). Even management of symptoms can exacerbate fatigue, as evidenced by opioid induced fatigue in the management of cancer related pain (2). Another cause of fatigue in patients undergoing treatment for prostate cancer is the addition of androgen deprivation therapy (ADT) to the treatment regimen (9). Resulting hot flashes and night sweats from acute removal of testosterone can inhibit normal sleep patterns, and indirectly contribute to fatigue (10).

Although these contributing factors may sound unique to prostate cancer, the universal nature of CRF across sites and treatment modalities suggests that there may be a single underlying mechanism for future therapeutic targeting. Pinning down this molecular cause of CRF is a multifaceted task and requires controlling the aforementioned confounding factors. The most prominent hypotheses surrounding this issue involve the dysregulation of inflammatory processes induced by cancer treatment modalities (6).

The work of Saligan and colleagues set out to further determine the molecular pathways for CRF for patients undergoing definitive EBRT for prostate cancer (11). Specifically, their objective was to explore the role of T lymphocytes and changes in genetic expression patterns and their relation to CRF during EBRT. Their prospective trial followed men with non-metastatic prostate cancer who were scheduled to receive EBRT. The investigators used the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) subscale to measure fatigue. This is a reliable, often used questionnaire for research involving CRF where higher scores indicate less severe fatigue (12). Genetic expression was observed via peripheral blood samples and

microarray analysis of cDNA derived from free RNA. After identifying expression patterns, the group also looked at plasma arginase I and arginine levels in blood. These were detected by ELISA and liquid chromatography with tandem mass spectrometry, respectively.

The group controlled for confounding factors by excluding patients with progressive disease, known psychiatric disorders in the past 5 years, uncorrected hypothyroidism or anemia, multiple malignancies, or use of non-steroidal anti-inflammatory agents, sedatives, or steroids. Complete blood counts were taken at all time points to help eliminate the confounding variables of anemia, electrolyte abnormalities, and thyroid stimulating hormone levels.

The group found that fatigue levels significantly increased from baseline to midpoint, and from baseline to endpoint. There was no significant change in fatigue levels, however, between midpoint and endpoint. This goes against the typical pattern of fatigue brought on by radiation therapy that progressively worsens during treatment. For this reason, the researchers chose to analyze blood samples from baseline to midpoint, coinciding with the observed increase in fatigue levels.

Changes in gene expression were observed from baseline to midpoint. The results demonstrated a significant increase in expression of the *ARG1* gene that coincided with decreased expression of CD8A, CD27, CD28, and CCR7. These alterations were shown to be correlated via Pearson coefficient analysis. They were also able to prove an inverse correlation between ARG1 expression and absolute lymphocyte count in the high-fatigue group. Finally, levels of serum arginine were shown to have an inverse relationship to levels of serum arginase I.

These findings suggest that EBRT can induce an increase in the expression of arginase I, and therefore lower the levels of available arginine in peripheral blood. Recent data have shown that a suppression of lymphocytic cell lines is correlated with an increased arginase I level in serum (13), a finding that is further corroborated by the reduction in expression of T cell markers in this study. Drawing from this, Saligan *et al.* concluded that tissue damage and cell death from EBRT can upregulate *ARG1* and lead to arginase I production, ultimately depleting available arginine and decreasing the quantity of CD8 positive T Cells. They propose that the resulting immunosuppression could be contributing to CRF.

Based on conclusions drawn from this study, interventions could limit the reduction of cytotoxic T cells. Arginine supplementation could help restore the immune system, and known arginase inhibitors could help limit the removal of available arginine in the blood. These interventions are potential steps to reduce CRF experienced during EBRT that require further exploration.

Therapeutic targets, such as those explored in this article, are of critical importance in this field. Very few options are currently available in the management of CRF. Commonly used non-pharmacologic interventions include cognitive behavioral interventions, exercise, behavioral sleep interventions, and nutritional adjustment (14). Pharmacologic interventions typically focus on alleviating side effects from treatment, such as erythropoietin for anemia or thyroxin in the case of thyroid toxicity (14). Stimulants such as methylphenidate have proven effective in reducing fatigue, as well (15). However, even with current available treatments CRF is often considered by patients to be a symptom that must be endured, and less than 50% brought it up to their physicians during treatment (16).

The symptom of CRF represents a detriment to quality of life in patients of all malignancies. However, more work to identify the mechanism underlying CRF should be elucidated with the goal of eventually identifying therapeutic interventions that can minimize this toxicity. The running theory that has gained the most traction is the idea of inflammatory cytokine and/or cellular dysregulation. It has been demonstrated that radiation alters circulating pro-inflammatory markers which is correlated to severity of fatigue during radiation therapy for prostate cancer (17,18), a finding that is supported by the study conducted by Saligan *et al.*

However, a recent study by Holliday *et al.* found no association to cytokine alterations and fatigue, despite persistently increasing fatigue in prostate cancer patients receiving EBRT. The group also showed that patients actually had improved efficiency of sleep, even though fatigue levels increased throughout therapy (19). Additionally, while the study at hand by Saligan *et al.* proposes that lymphocytic suppression leads to fatigue, other studies have shown that an overall increase in leukocyte count is associated with persistent fatigue (20). These studies provide evidence that the work surrounding CRF is incomplete, and that the modulation of the immune system may not fully explain CRF.

CRF is a universal phenomenon, and the varying patterns of its expression across different disease sites and treatment modalities suggest that several processes could be contributing to a single entity labeled as CRF. Further

work in prostate cancer related CRF requires accounting for the confounding factors. The arginine-based hypothesis proposed in this article is sound, given the supporting translational research behind it. Future work could focus on relating this hypothesis to other cancer sites managed by EBRT. As a control, studies could also be done by looking at arginine and arginase levels in men after castration and/or administration of medical castration.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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