Targeting Inflammation in Prostate Cancer

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Men of African descent are twice as likely to die of prostate cancer than other men. While equal access to care is the key target to improve cancer survival, it is now known that there are differences in disease biology and risk factor exposure across population groups. These differences could be causatively linked to the existing prostate cancer health disparities.

Keywords: prostate cancer ; African American ; inflammation ; health disparity

1. Introduction

Despite substantial improvements in cancer survival overall, men of African descent continue to have about double the rate of fatal prostate cancer compared to other men[1][2]. Prostate cancer disparities are largely explained by health care disparities, lifestyle factors and disparate exposures to carcinogens but even when these are accounted for - some of the cancer disparities persist. Ancestral factors and disparate exposures can lead to altered tumor biology, resulting in a distinct disease etiology by population group.

A growing body of evidence indicates a distinct role for inflammation and the immune response in prostate cancer disparities. Low-grade chronic inflammation is more prevalent in African American patients and has been associated with adverse outcomes[3][4]. An immune-inflammation signature more prevalent in prostate tumors of African American patients is central to the hypothesis that inflammation is a candidate driver of prostate cancer disparities[5]. This signature includes up-regulation of genes in the interferon signaling pathway corresponding to a previously described “interferon-related DNA damage resistance signature”, which has been linked to acquired resistance to radiation and chemotherapy in breast cancer[6][7]. Thus, upregulation of this signature in African American tumors indicates a mechanism by which either inflammatory ancestral factors or a yet unknown infectious agent may contribute adversely to prostate cancer outcomes. Multiple studies reported upregulation of inflammatory mediators in the tumor microenvironment of African American prostate cancer patients, many of which have implications for disease prognosis[8][9][10][11][12]. This review aims to introduce the concept that this inflammation and immune response present immunogenic vulnerabilities that could be exploited to address the adverse outcomes experienced by the African American population with prostate cancer.

2. African American men may have a differential response to certain therapies for metastatic prostate cancer.

There is now some evidence that men of African descent may respond differently to standardized and emerging options of care for prostate cancer including radiation, hormone therapy, chemotherapy, and immunotherapy. Differences in immune response may play a key role in many of these observations. Metastatic castration-resistant prostate cancer (mCRPC) is a main cause of lethal prostate cancer and therefore remains a key focus for research. Despite patients with mCRPC having multiple treatment options targeting a variety of mechanisms, median overall survival is still only around 3 years[13]. This further highlights the need for inclusion of diverse biospecimens in scientific studies and historically understudied populations in clinical trials to determine who is benefitting optimally from these currently approved treatments.

3. Radiation

Radium-223 is an approved therapeutic option for mCRPC patients with symptomatic bone metastases. *Zhao et al* examined response to radium-223 treatment in men from a Veteran Affairs cohort with mCRPC[14]. This group found that African American men may have a better response to this treatment compared to European American men, resulting in a 25% decreased risk of mortality in this equal access to care study. African American men in this study were more likely to have received docetaxel beforehand and the improved response to therapy was despite the African American cases being more likely to not start radium treatment until further along in the disease course. Patients harboring DNA damage repair mutations have prolonged overall survival after radium-223 treatment compared to patients who do not have these alterations[15][16][17]. This is also the subject of another clinical trial currently in the recruitment stage (NCT04489719). With

Awasthi et al reporting decreased DNA damage repair capacity in prostate tumors of African American, it can be speculated that inactivating mutations that decrease the DNA damage repair capacity in tumors from African American may contribute to the positive outcomes post treatment with radium-223[9].

A recent, small, Phase II trial (NCT02463799) found combining radium-223 treatment with Sipuleucel-T increased progression-free survival and overall survival in men with mCRPC[18]. Now that studies have shown better responses from African American men treated with radium-223 and Sipuleucel-T separately[14][19], a planned larger trial may inform on whether African American men may benefit synergistically from this combination approach.

4. Immunotherapy

Immunotherapy has not been as successful in treating prostate cancer as with other hematologic or solid cancers and clinical trials show modest[20] to no effect[13][21][22] on survival. This has been attributed to prostate cancer not being as immunogenic as other cancers. However, recent studies indicate a potential role for immunotherapy in certain patient groups with prostate cancer. Precision medicine strategies targeting immunotherapy to those men with the best response is the preferred goal. Evidence is currently being built to support the hypothesis that African American men may have a differential and perhaps superior response to certain treatments due to changes in immune cell response and a differing tumor biology.

Tumors from men of African descent may have a heightened response to immunotherapies, and specifically to cancer vaccines, as assumed from the presence of an interferon signature in their tumors and increased immune content in the TME[6][9]. Studies have shown that young people who self-report as African American mounted an increased immune response to vaccination[23][24]. *Sartor et al.* recently reported that African American men with mCRPC who were treated with the cancer vaccine, Sipuleucel-T, in the PROCEED trial/registry, had significantly better survival than the European American patients[19]. Increased activation of dendritic cells is a proposed mechanism of action of the vaccine and in agreement with this, activated dendritic cells in localized tumors have subsequently been associated with improved distant metastasis free survival[25]. Mechanistically, evidence points towards a complex interplay of immune cells with tumor biology which may predict prognosis and response to therapy. But the lack of tumor specimens from African American men means that more work must be done to capitalize on the differences in the immune landscape which may improve response to treatment in this population.

Generally, poor immunogenicity has resulted in little success for PD-L1 blockade in treatment of prostate cancer[22][26]. This has been attributed in part to relatively low PD-L1 expression from tumor cells[27][28]. However, this is not consistent across literature with studies also reporting increased PD-L1 expression and association with biochemical recurrence[29] and shorter metastasis free survival[30]. *Petitprez et al* provide preliminary evidence that a composite assessment of both PD-L1 and CD8 expression in localized prostate cancer may be a good strategy for predicting outcomes in mCRPC[30]. A group in Norway reported high PD-L1 expression in post-prostatectomy, hormone naïve tumor epithelial cells with a non-significant trend towards an inverse association between PD-L1 expression and biochemical failure-free survival[31]. However, clinical trials investigating the effect of PD-1 inhibition reported no significant clinical benefit. Yet, they have typically not included men of African descent[22].

Recent work has focused on PD-L1 expression on tumor-infiltrating immune cells. *Bishop et al* reported enzalutamide-resistant prostate cancer patients showing increased PD-L1 expression on dendritic cells and high PD-L1 T cells when compared to enzalutamide-sensitive or treatment naïve patients[32]. African American ethnicity and an aggressive cancer phenotype has been associated with prediction of tumor PD-L1 positivity in hormone naïve tumors[33], suggesting a potential benefit for immunotherapy in African Americans at high risk of aggressive disease but this has not been replicated yet[9]. When tumors are enzalutamide-sensitive, *McNamara et al* preliminarily reported increased overall survival for African American, chemotherapy-naïve men with mCRPC treated with abiraterone or enzalutamide compared to European American men[34]. This study in a Veteran Affairs population was retrospective in design, again pointing to the value of equal access to care across populations. Thus, additional work is warranted including measurement of PD-L1 in tumor samples from African American men post various treatment regimens to account for increased immunogenic response to therapy.

5. Other treatment opportunities

Historically, participation of African American men in clinical trials has been low. Reasons for this are multifactorial but include historical mistrust of the medical profession and a higher prevalence of comorbidities preventing access to trials[35][36][37]. This prevents generalizability across population groups when reporting clinical trial data. A recent example highlights the need to include diverse population groups and possibly stratify clinical trial participants by race to get a fuller

picture of treatment response. *Halabi et al* completed a meta-analysis of survival outcomes for African American versus European American men in phase III clinical trials treating mCRPC with docetaxel[38]. With just 6% of African American participants, they report that while overall median survival was similar, a pooled hazard ratio of 0.81 (95% CI, 0.72 to 0.91) post adjustment for baseline prognostic factors estimated that African American men may have a significantly decreased risk of death compared to European American men. This was despite African American men having baseline characteristics known to be prognostic of overall survival including statistically significant worse performance status, higher testosterone levels, higher PSA levels, and lower hemoglobin levels.

A proposed feature of prostate tumors in African American men that may play a prominent role in differential response to treatment is a deficiency in DNA damage repair capacity. Both germline and somatic alterations to DNA damage repair pathways have now been found in prostate tumors across multiple studies[9][39][40][41]. Tumors from African American men were reported to have a significantly lower level of DNA repair capacity when compared to those from European American men. Notably, these tumors seemed to have an increased radiosensitivity[9].

Altered DNA damage repair pathways may also sensitize tumors to immunotherapeutic approaches. Several clinical trials across many cancer sites including metastatic prostate cancer are currently underway targeting DNA damage repair-deficient tumors with checkpoint inhibitors (extensively reviewed by *Bever et al*)[42]. Mechanistically, in prostate cancer, the stimulator of IFN genes (STING) pathway has been linked to recruitment and activation of interferon-related genes *in vitro*, increasing sensitivity to the immune checkpoint inhibitor PD-L1 in DNA repair deficient tumors[43][44][45][46]. As a low DNA repair capacity may increase tumor genomic instability and tumor mutational burden, this again, might constitute as a vulnerability to immunotherapeutic strategies[47]. It has been suggested that enhancement of this genomic instability through use of radiation, chemotherapy or PARP inhibitors could augment the immunotherapeutic response[42][48][49].

6. Anti-inflammatory drug aspirin for prevention of adverse outcomes in African American men with prostate cancer

The United States Preventative Services Task Force now recommend the anti-inflammatory drug aspirin for prevention of colorectal cancer for an albeit narrow category of adults[50][51][52]. In keeping with the hypothesis that inflammation is one of the drivers of the prostate cancer disparities, our group explored the link between regular use of aspirin and prostate cancer in African American men. We found that regular aspirin use significantly reduces the risk of both advanced prostate cancer and disease recurrence in these men[53]. The finding is consistent with a similar observation in a previous study[54]. Inhibition of the pro-inflammatory cyclooxygenase/thromboxane A2 pathway has been identified as a potential mechanism of action for aspirin in the prevention of metastatic cancer[55]. Using a retrospective cohort, we found a distinct association between high urinary 11-dehydrothromboxane B2 (the stable metabolite of thromboxane A2) and aggressive prostate cancer as well as adverse survival outcomes for African American men. Importantly, high 11-dehydrothromboxane B2 was inversely correlated with aspirin use indicating a potential benefit of aspirin in preventing lethal prostate cancer through inhibition of TXA2 synthesis (article under review).

Lastly, data prospectively obtained in the Southern Community Cohort Study suggested that aspirin use is tentatively associated with a reduced prostate cancer mortality in African American men[56]. *Hurwitz et al* also observed this inverse relationship between aspirin use and prostate cancer mortality in both African American and European American men using the ARIC cohort[57], again pointing to the potential benefit of aspirin use for men at high risk of fatal prostate cancer.

7. Conclusion

Elevated inflammatory processes in African American men with prostate cancer are a candidate biological drivers of disparate disease risks. With evidence now building that suggests increased clinical benefit with certain therapies among African American men when compared to European American men, targeting inflammatory processes and the immune system could be an important strategy to reduce lethal disease in high-risk populations like men of African ancestry.

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