Identifying and Targeting Immunogenic Prostate Cancer at High Risk for Lethal Metastatic Progression

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Background:
Although prior studies have not shown marked T cell infiltrates or high prevalence of programmed death ligand 1 (PD-L1) in prostate cancer, more recent data suggest that there is a subset of prostate cancer that may be immunogenic and responsive to checkpoint inhibition and/or vaccines. Indeed, PD-L1 expression assessed by newer antibodies appears to be increased a substantial subset of advanced and, in particular, high-risk localized prostate cancers. Moreover, its expression correlates with CD8+ T cell infiltrates. In addition, increased tumor mutational burden as a result of mismatch-repair deficiency or other mechanisms may be found in a small subset of prostate cancer and strongly predicts for response to PD-1 inhibition. Prior immune-based therapies have been primarily tested in the advanced castration-resistant setting, but recent evidence suggests that various hormonal manipulations may alter the immune microenvironment. These data provide a rationale for re-evaluating PD-1 inhibition in patients with pre-metastatic biochemical recurrence. Finally, vaccination strategies may also be required to expand tumor-responsive T cells. Personalized vaccines based on tumor-specific neoantigens may increase the effectiveness of this strategy.

Methods:
First, we will identify genomic and immune microenvironmental features that are associated with T cell infiltration and PD-L1 expression in localized high-risk prostate cancers. We will use multiplex immunohistochemistry (IHC) and immunofluorescence (IF) to assess subtypes of tumor-infiltrating immune cells. We will characterize T cell "exhaustion status." We will perform next-generation sequencing (NGS) to assess whether high PD-L1 expression is associated with genomic instability, RNA sequencing to assess the transcriptome profile of tumors, and Luminex assays of changes in pro- and anti-inflammatory cytokines and chemokines.

Second, we are conducting a clinical trial of PD-1 inhibition in patients experiencing biochemical recurrence after primary treatment for prostate cancer, with rapid PSA doubling time indicative of high risk for progression to lethal, metastatic disease. We will investigate PD-L1 expression as a correlate of response to PD-1 inhibition. As above, we will perform IHC to assess subtypes of tumor-infiltrating immune cells and NGS to assess correlations between PD-L1 expression, response to PD-1 inhibition, and genomic instability. Finally, we will phenotype peripheral immune cells and assess plasma cytokines as potential predictors of response to PD-1 inhibition.

Third, we will investigate the presence of tumor-responsive T cells in patients undergoing primary radiation therapy as well as patients in the trial described above. We will perform WES and predict tumor neoantigens, from which we will generate peptides and evaluate for neoantigen-responsive T cells. Identification of T cells capable of recognizing neoantigens would provide a rationale for a trial of personalized vaccines in prostate cancer.

Results:

Preliminary results indicate that there is indeed a population of tumor-infiltrating lymphocytes in primary prostate cancer detectable by multiplex IF that display co-expression of CD8 and T-cell factor 1 (TCF1), in close proximity to MHCII-positive antigen-presenting cells. TCF1 is a transcription factor that marks self-renewing stem-like CD8+ cells (Kratchmarov et al., 2018) that proliferate after PD-1 inhibition (Im et al., 2016) and correlate with response to vaccination and checkpoint inhibition (Siddiqui et al., 2019). We are currently expanding our cohort of cases and quantifying density of lymphocyte subsets.

In material from two patients treated with primary radiation therapy and androgen deprivation therapy, we have performed tumor WES and neoantigen prediction. After ranking candidate neoantigens and eliminating likely germline single nucleotide polymorphisms, we synthesized corresponding peptides. Thawed PBMCs cultured with peptide pools displayed greater proliferation in culture than those cultured without peptides. Flow cytometry revealed a modest increase in CD4+ cells expressing interferon-gamma 9 days after addition of one peptide pool but not the other. We are continuing these experiments in other cases and in patients who respond to PD-1 blockade on the clinical trial.

Conclusions:

In sum, we are conducting several linked investigations of immunologic mechanisms in multiple settings along the clinical spectrum of prostate cancer, with the potential to directly impact treatment options for patients. Preliminary results point to a subset of primary castration-naïve prostate cancer with T cells that are potentially capable of responding to vaccination and/or immune checkpoint inhibition, a hypothesis which we are testing in clinical trials.

Conflict of Interest:

David Einstein reports research funding to institution from Bristol-Myers Squibb for funding the clinical trial.

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