Title: Microsatellite instability may predict response to sipuleucel-T in patients with prostate cancer

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Clinical Practice Points

There is currently no data or findings in the literature in regards to microsatellite instability high (MSI-H) metastatic castrate-resistant prostate cancer (mCRPC) and their response to cell-based immunotherapy such as sipuleucel-T. Our case describes a man with MSI-H mCRPC with a complete response to sipuleucel-T. This raises a clinically significant question of whether MSI status can predict patient's response to sipuleucel-T and what role whole genome sequencing plays in the management of prostate cancer.

Introduction

Microsatellite instability (MSI) is a mutational error in repetitive DNA sequences that is typically corrected by a DNA mismatch repair system. A failure in this system leads to defective mismatch repair (dMMR). The presence of MSI varies amongst different cancers, being present in up to 15-20% of colorectal cancers.[i] Recent data shows that 2.4% of prostate cancers are MSI-H[ii] and up to 8.1% show evidence of dMMR.[iii] Currently, pembrolizumab, an immunotherapy-based PDI-1 inhibitor, is approved for any MSI-H/dMMR cancer. MSI-H tumors may have higher tumor mutational burden and produce a number of neoantigens that trigger the recruitment of tumor-infiltrating lymphocytes. As a result of this, these MSI-H tumors strongly express immune checkpoints ligands, such as PD-1, to promote immune evasion.[iv]

Sipuleucel-T is an autologous immunotherapeutic vaccine approved in 2010 for the treatment of mCRPC that involves activating the patient's own dendritic cells, which are isolated via leukapheresis. These are exposed to a fusion protein, PA2024, consisting of antigen prostatic acid phosphatase (PAP) and GM-CSF. After allowing the incubation to mature, the blood product is reintroduced to the patient over the course of three treatments, stimulating an immune response against the prostate cancer.

Case description

A 71 year-old man with mCRPC presented with Gleason 7 (3+4) prostate adenocarcinoma. He underwent radical prostatectomy. He then developed biochemical recurrence and underwent salvage radiation therapy to the pelvis and prostate bed. He then developed metastatic disease to the lungs with a PSA of 50.36 ng/dL. A chest CT scan demonstrated a right lower lobe pulmonary nodule and fine needle aspiration was compatible with prostate adenocarcinoma. He was started on androgen deprivation therapy with leuprolide for approximately one year before having a rising PSA level. Patient was started on bicalutamide but followed with a subsequent demonstration of disease progression with enlarged mediastinal and supraclavicular lymph nodes and elevation of his PSA to 4.371 ng/dL. The patient received sipuleucel-T. He responded remarkably well with normalization of PSA to 0.418 ng/dL (Figure 1) and scans demonstrated complete response of his disease by RECIST criteria with a stable

superior mediastinal lymph node, reduction in left supraclavicular lymph node, and no other evidence of metastatic disease on CT-imaging and nuclear bone scan. Whole genome sequencing was done on the patient's disease to explore potential future treatment options. Whole genome sequencing demonstrated that the tumor was MSI-H in addition to having a high mutational burden. Patient has been followed since 2014 and continues to be followed, currently on leuprolide and enzalutamide.

Discussion

There is limited information on dMMR prostate cancer and its response to sipuleucel-T immunotherapy. Patients with dMMR/MSI-H showed significant response to immune checkpoint inhibitors and the FDA granted approval of pembrolizumab in all cancer that are MSI-H. However, there is no data about the response to cell-based immunotherapy such as sipuleucel-T in patients with dMMR/MSI-H.

An interesting observation in this patient is his complete response to sipuleucel-T and whether this related to MSI-H status. To the best of our knowledge, this is the first case of a complete response to sipuleucel-T in a known dMMR metastatic castrate-resistant prostate cancer. Whole genome sequencing may play a role in selecting appropriate prostate cancer patients for sipuleucel-T. Ultimately, more research needs to be conducted in order to better understand the response of sipuleucel-T in MSI-H/dMMR prostate cancers.

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