Immunotherapy for Prostate Cancer: Treatments for the "Lethal" Phenotype

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KEYWORDS

• Immunotherapy • Prostate cancer • CDK12 • Sipuleucel T • Vaccines • Tumor microenvironment • Checkpoint inhibitors

KEY POINTS

- Immunotherapy for prostate cancer has been limited by a "bland" or "cold" tumor microenvironment.
- Multiple mechanisms exist within the tumor microenvironment that inhibit infiltration of immune cells.
- Small cell/neuroendocrine prostate cancer represents a unique histologic phenotype that may occur de novo or may emerge following failure of androgen receptor signaling inhibitors.
- CDK12 mutated prostate cancer represents a unique group of tumors with limited sensitivity to checkpoint inhibitors.

INTRODUCTION

Prostate cancer remains the first solid tumor to demonstrate the overall survival (OS) of an autologous cellular therapy, Sipuleucel-T,[1] but despite its success, understanding why prostate cancer has been refractory to a wide range of subsequent immune platforms remains unclear. Modulations in prostate-specific antigen (PSA) have been demonstrated in several approaches,[2] but despite the success demonstrating survival benefit in a phase II trial of PROSTVAC (rilimogene galvacirepvec/rilimogene glafolivec) or F-PSA-TRICOM; PROSTVAC-V,[3] a viral-based immunotherapy consisting of a vaccinia virus and recombinant fowlpox virus given as a prime boost, no change in the biologic behavior of the cancer was seen. Both viruses encode modified forms of PSA, along with 3 costimulatory molecules, B7.1 (CD80), with intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-3 (LFA-3). The phase II study cited a prolonged median OS of 8.5 months versus placebo in men with castration-resistant prostate cancer (CRPC)[3]; the randomized phase III[4] trial did need not meet its primary endpoint of OS in men with castrated metastatic prostate cancer. In fact, at the third interim analysis, criteria for futility were made and the trial was stopped early. The study was designed to compare the superiority of PROSTVAC or PROSTVAC plus granulocyte/macrophage stimulating factor (GM-CSF), versus placebo. Although PROSTVAC induced T-cell–specific responses against PSA, as well as "cascade" antigens,[4,5] the immune response did not translate into clinical benefit.

TARGETING THE TUMOR MICROENVIRONMENT: A CHALLENGE?

It remains unclear whether the lack of response to multiple immunologic approaches is due to one cellular population or a combination of cytokines, cells, and inhibitory factors within this setting. Failures of immune-based therapies have been

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attributed to the "bland" or "cold" tumor microenvironment of prostate cancer due to lack of CD8 infiltration; inhibitory pathways such as adenosine,[6,7] or cellular populations such as myeloid-derived suppressor cells (MDSCs), colony stromal factor-1, or inhibitory macrophages have been closely studied. Multiple agents are currently in clinical trials targeting each of these pathways and cellular populations, but to date, no agent alone has met with success. More recently,[8] the inhibition of BRD4, member of the Bromodomain and ExtraTerminal (BET) family of bromodomain-containing proteins, has been shown to reduce levels of several target genes under androgen receptor (AR) control and can reduce tumor size in preclinical models. It has been postulated that in its role as a transcriptional regulator, BRD4 recruitment may participate in mediating AR and other oncogenic drivers such as MYC, but may have a potential role in immune regulations. As such, targeting BET bromodomains using a small molecule inhibitor has been shown to decrease PD-L1 expression and reduce tumor progression in prostate cancer models. It is likely that BET bromodomain inhibition works via increasing major histocompatibility complex class I expression, thereby increasing the immunogenicity of tumor cells. Furthermore, transcriptional profiling showed that BET bromodomain inhibition can modulate several networks that are involved in antigen processing and immune checkpoint molecules. Murine models treated with an inhibitor have demonstrated increased CD8/Treg populations, suggesting that there may be a role for using a bromodomain inhibitor along with a checkpoint inhibitor[8] in patients.

The greatest conundrum is why prostate cancers have been relatively resistant to checkpoint inhibitors. Although a phase I/II trial[9] using different doses of ipilimumab given alone or after radiation showed long-term benefit and even remission in a minority of patients, nevertheless 2 phase III trials,[10,11] both in early and late disease, respectively, did not meet their endpoints of survival, albeit, the "tail end" of the survival curve had patients with durable responses. Efforts to explain the lack of responsiveness of prostate cancer to this family of immune therapies remains an active area of study. Anecdotal case reports have suggested that some form of "immune modulation" can be seen if patients received enzalutamide first before receiving Sipuleucel-T, leading to a dramatic decline in PSA. In one case report,[12] a patient who had been in a clinical atrial and had received GM-CSF therapy resulting in "a saw-tooth like pattern of PSA declines during treatment," developed continued rises in PSA with development of castration-resistant disease to bone. He went on to treatment with enzalutamide with improvement in disease with declines in PSA but then developed rising PSAs. He then received Sipuleucel-T while continuing the enzalutamide and androgen-deprivation therapy, and after 6 months developed a marked decline in PSA to less than 0.05 that lasted for more than 1 year with regression of metastatic disease. This is clearly an unusual scenario, but raises the question of whether or not enzalutamide can enhance the effects not only of Sipuleucel-T but other immune-based therapies as well. That there was a delay in response may be attributed to an "immune-based mechanism" given prior results from Sipuleucel-T trials that suggested a robust increase in antigen-presenting cell (APC) upregulation. This patient had similar findings. Others[13,14] have demonstrated in small studies that patients with visceral metastases in the presence of genomic alterations such as BRCA 1,2 or MSI^{hi} can respond robustly to pembrolizumab with long-term responses. This has led to a further inquiry as to how these agents may be used in patients with these genomic alterations and whether or not combinations with these agents may provide significant long-term benefits to patients who are otherwise refractory to standard androgen signaling inhibitors or chemotherapies. Antonarakis and colleagues,[15] in a multicohort Keynote 199 study, demonstrated that there may be benefit in a small but unique cohort of patients who received single-agent pembrolizumab, reinforcing our continued efforts to further define patients who may derive benefits from this therapeutic class of drugs.[16]

LETHAL PROSTATE CANCER: DOES IT EXIST AND CAN WE TREAT IT?

The term "lethal" has taken on many connotations, but in particular if usually viewed as a type of tumor that is aggressive at diagnosis or becomes aggressive following therapies, both with rapid progression to end-stage disease. More recently, it has come to be understood as a unique phenotype that has evolved following treatment with AR signaling inhibitors, such as enzalutamide and abiraterone, to unusual histologic subtypes as neuroendocrine prostate cancer.[17] Although adenocarcinoma remains the predominant histologic phenotype of prostate cancer and displays features suggestive of luminal prostate cells that are under androgen regulation, de novo small cell carcinoma of the prostate can appear that

often bears similar histology to small cell carcinoma of the lung. This prostate variant can also appear later in the disease in the more treatment-refractory setting, often posing a challenge for the treating physician, as standard small cell chemotherapies do not provide durable responses. There has been a clinical lack of clarity with response to terminology, as small cell does not always mean neuroendocrine cancer, given that there are features that are either mixed to suggest that small cell and neuroendocrine or poorly differentiated prostate cancer can all align together. As such, the mixed histologic features within a continuum of histologic and behavioral evolution are encompassed under the umbrella of "neuroendocrine prostate cancer" with clear delineations regarding survival[17] (**Fig. 1**).

TREATING THE "LETHAL" PHENOTYPE BASED ON GENOMICS

Carreira and colleagues[18] suggest that there are unique tumor adaptations that may underlie resistance to repeated AR targeting in CRPC. As such, using targeted sequencing and computational approaches, they have systematically profiled genomic changes in a patient's tumor to demonstrate unique mutations in sites of metastatic disease that correspond to behavioral changes within the tumor and demonstrate clonal architectural heterogeneity at different stages of disease progression. This management paradigm may offer a means by which "lethality" can be identified early and treatments can be redirected to the more aggressive clones. Aggarwal and colleagues[19] systematically analyzed 202 patients of whom 148 had prior disease progression on abiraterone and/or enzalutamide and who underwent routine biopsies. The overall incidence of small cell neuroendocrine prostate cancer was 17% with AR amplification and protein expression noted in 67% and 75%, respectively. Detection of neuroendocrine cancer was associated with shortened OS among patients with prior AR-targeting therapy (hazard ratio 2.02; 95% confidence interval 1.07–3.82). A "transcriptional signature" was also developed and validated with greater than 90% accuracy and seems to indicate that this phenotype arises in the context of TP53 and RB1 aberration from adenocarcinoma under a selective process if not pressure of inhibition of the AR pathway.[20] They reported frequent loss of TP53 and/or RB1 at the genome level along with upregulation of E2F. Interestingly, DEK[21] was the highest overexpressed E2F1 target gene in the small cell/neuroendocrine cluster with prior implication into the progression to this phenotype. Other transcriptional factors that have been documented into the progression into small cell/neuroendocrine prostate cancer include POU class 3 homeobox, FOX A2, ASCL1, and BRN2.

It is clear that from a behavioral and histologic standpoint, these "lethal" cancers may also have a unique response to immune agents. Wu and colleagues[22,23] have subsequently identified a unique subtype of prostate cancer that is associated with bi-allelic loss of CDK12 and is mutually exclusive with tumors driven by DNA repair deficiency in addition to ETS fusions and a variety of mutations in SPOP.[23] CDK12 is a cyclin-dependent kinase that forms a heterodimeric complex with cyclin K, its activating partner. Together, they regulate a variety of processes that regulate gene expression.[20] Using an integrative genomic analysis of 360 samples from patients with metastatic CRPC (mCRPC), samples that had CDK12 mutants were associated with increasing burden of neoantigens and increased infiltration and/or clonal expansion of tumor T cells. Interestingly, although most CDK12 mutants retained active AR, suggesting sensitivity to AR blocking or signaling inhibitors, they had a distinct expression signature that was characterized by increased gene fusions as well as increased gene fusion–induced neoantigen open reading frames. The latter served as rationale for exploring the susceptibility of those tumors with higher neoantigen burden could respond to alternative lines of therapy. Also in keeping with known susceptibility to checkpoint inhibitors, is an inflammatory milieu suggesting a "hot" tumor microenvironment, which is known to be more amenable to immune-based therapies, in particular checkpoint inhibitors. As such, the investigators found activation of cancer inflammatory gene sets in CDK12-mutant tumors (**Fig. 2**). More importantly, one patient who was treated with anti-PD-1 checkpoint inhibitor and had a PSA response following 4 cycles of drug, also had membranous and cytoplasmic staining of CD3 in addition to a radiographic response. As such, these results suggest that CDK12 may represent a potential biomarker in tumors with elevated neoantigen burden and that may benefit from checkpoint blockade. There are ongoing clinical trials in different clinical states: NCT04104893, a phase II study exploring activity and efficacy of pembrolizumab in veterans with mCRPC with either mismatch repair deficiency or CDK12 inactivation, and NCT03570619, a phase II trial using ipilimumab and nivolumab combination therapy followed by nivolumab monotherapy in patients with mCRPC harboring loss of CDK12 function, respectively, among others to further explore this hypothesis.

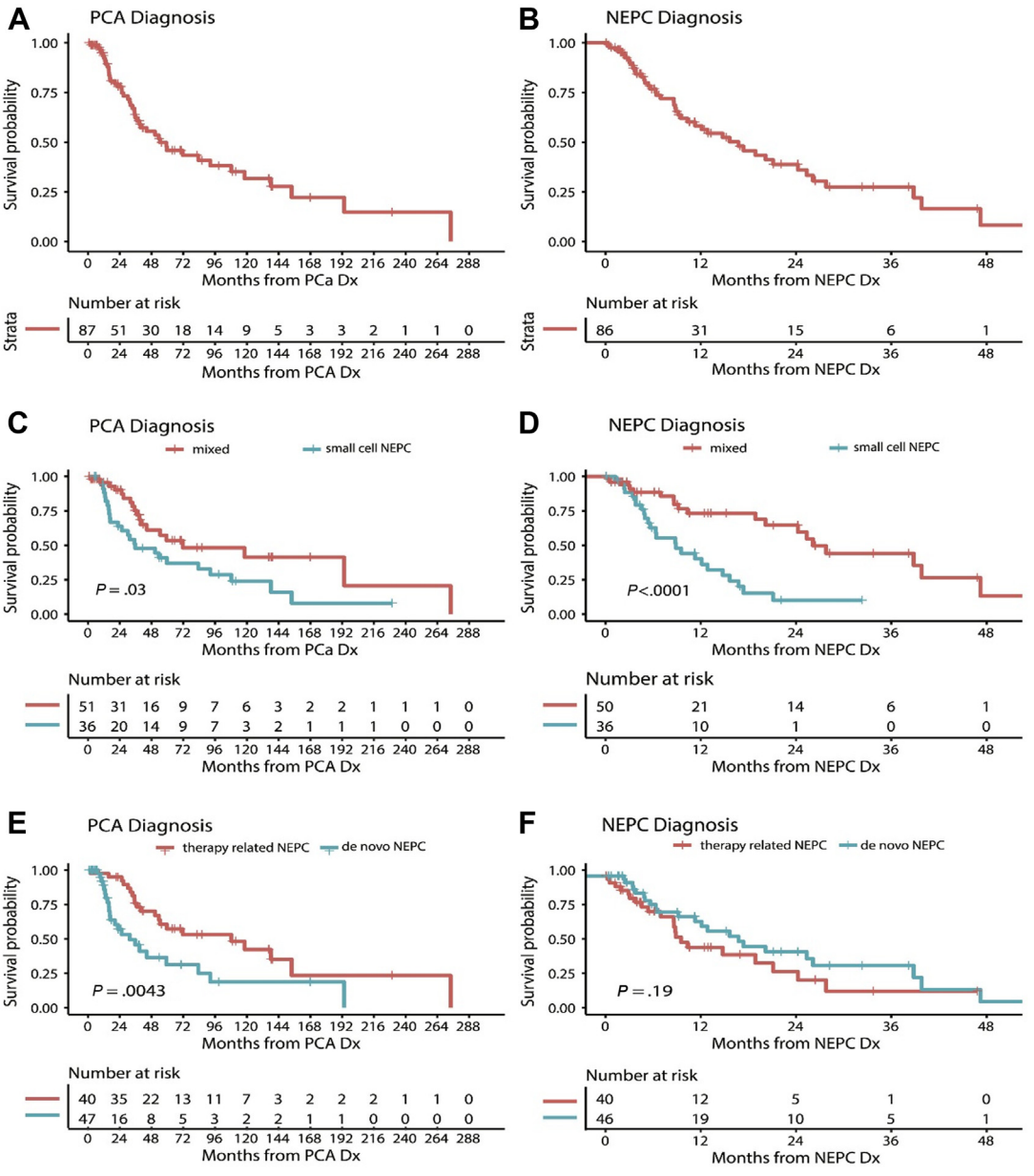

Fig. 1. OS in a cohort of patients with neuroendocrine prostate cancer showing multiple histologic patterns with neuroendocrine disease (NEPC). (*A*) OS from diagnoses of adenocarcinoma versus (*B*) diagnosis of NEPC. (*C*) OS of mixed histology. (*D*) Neuroendocrine histology. OS in de novo versus therapy-related NEPC from diagnosis of prostate cancer (*E*) and from diagnosis of NEPC (*F*). Different axes represent different time scales used for (*A*), (*C*), and (*E*) compared with (*B*), (*D*), and (*F*) due to different time intervals between OS from prostate cancer diagnosis and OS from NEPC diagnosis. (*From* Conteduca V, Oromendia C, Eng KW, et al. Clinical features of neuroendocrine prostate cancer. Eur J Cancer 2019; 121:7-18. doi:10.1016/j.ejca.2019.08.011; with permission.)

IMMUNOTHERAPY IN PRIME TIME: THE ROLE OF BIOMARKERS

A number of technology platforms are being implemented to assess peripheral blood and tissue based biomarkers; of these, RNA-sequencing, flow and mass cytometry, and enzyme-linked immunosorbent assay–based assays have been in widespread use.[24] There are still multiple challenges in using immune approaches in patients with mCRPC. It is clear that understanding the genetic background of the tumor and its host is

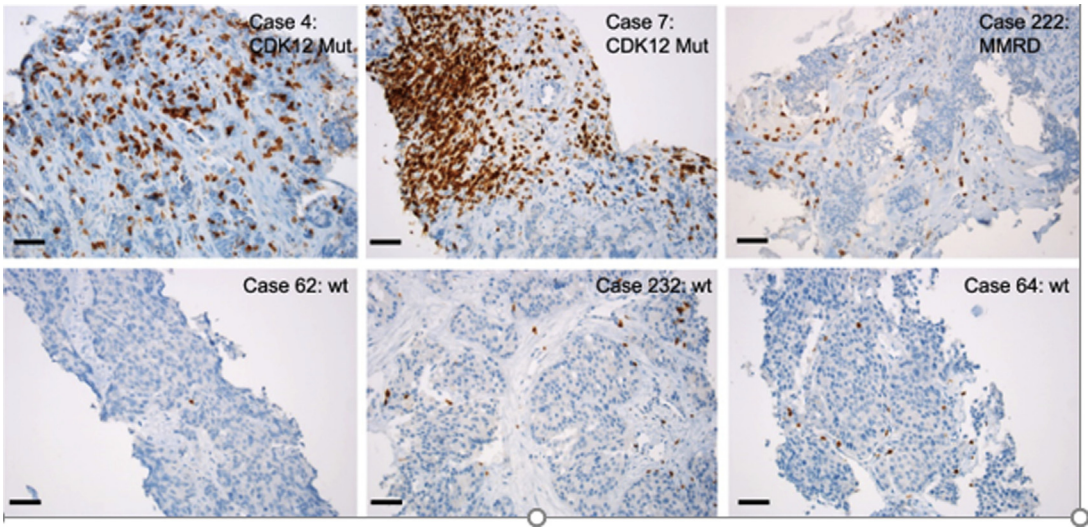

Fig. 2. Immunohistochemistry on formalin-fixed paraffin-embedded tumor sections showing T-cell infiltration by CD3+ cells. Six cases are shown, with 2 showcasing CDK12 mutant (Mut) tumors, 1 mismatch repair (MMR)-deficient tumor, and 3 that are wild type (wt) for CDK12, MMR genes, and homologous repair genes. (*From* Wu Y-M, Cieslik M, Lonigro RJ, et al. Inactivation of CDK12 delineates a distinct immunogenic class of advanced prostate cancer. Cell 2018; 173:1770-1782; with permission.)

highly relevant in certain cases, but at this time, one treatment does not fit all patients. Biomarkers may be in the form of changes in imaging using unique tracers, tumor mutational changes, mutational burden, presence or absence of programmed cell death (PD)-1 or PD-ligand 1 (PD-L1) on tumor or immune cells, circulating tumor cells, or tumor or cell-free DNA; however, biomarkers that are unique to assess changes within the tumor microenvironment or in the peripheral blood have not as yet been well-defined despite multiple efforts. Several solid tumors have relied on the presence of tumor-infiltrating lymphocytes (TILs) to develop and "immunoscore" to determine the amount of immunologic activity that is in situ within the tumor; however, prostate is unique in that it is rare to see TILs either at diagnosis or in the setting of progressive disease. The ratio of T regulatory cells (Tregs)/MDSCs has been explored; CD4+FOXP+CD24^{hi} Tregs have been associated with poor prognosis. In addition, Treg frequency among TILs has been shown to correlate with tumor grade and reduced patient survival in several solid tumors, including breast, melanoma, glioblastoma, and ovarian cancers. What is now observed in multiple clinical trials with checkpoint inhibitors for several solid tumors, such as renal or urothelial cancers, is that the presence or absence of PD-L1 does not seem to impact treatment response. Gnjatic and colleagues[25] have provided guidance from Working Group 4 from the Society of Immunotherapy's Immune Biomarkers Task Force in an attempt to discover host genetic factors, tumor alterations in genes that affect APC function or affect local recruitment of inflammatory cells into the tumor microenvironment. Their work is one of many groups that continue to provide immune monitoring throughout the disease continuum in an effort to determine how to best characterize the immune system's role in disease response. These efforts are to be lauded, as they provide multidisciplinary, multi-institutional viewpoints that allow for greater insight into understanding the layers that govern the immune system's control of disease response.

DISCUSSION

There is a significant thrust toward the further genomic profiling of prostate tumors along the disease continuum, with each new clone likely harboring unique mutations to which novel drugs can be targeted. This does not, however, address the issue as to how to best target the disease in toto, as not all drugs target all sites of disease equally and sometimes not at all. We have come a very long way and are beginning to understand the conditions whereby the immune system can be better engaged with novel therapies. It is clear that no one drug is able to provide complete therapeutic response alone; therefore, continued efforts to combine different classes of agents along with immunologic therapies remain a viable long-term goal for researchers and practitioners alike.

DISCLOSURE

The author has nothing to disclose.

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