Editorial

Is there still an open window in metastatic castration resistant prostate cancer immunotherapy horizon?

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In recent years, immunotherapy (mainly with immune checkpoint inhibitors directed against CTLA-4 or the PD-1/PD-L1 axis) represents the breakthrough of anticancer therapy for several highly immunogenic tumors (melanoma, non-small cell lung cancer, and renal cell carcinoma).

Prostate cancer is a suitable candidate for immunotherapy. The prostate gland lacks of afferent lymphatic, and the seminal fluid has immunosuppressive properties, creating a immunologically privileged microenvironment that favors the escape of tumor cells from immune surveillance. Moreover, the majority of prostate tumors behave like a slow-growing disease, giving time to the immune system to mount a clinically relevant immune response (1).

A further contribution to the high immunogenicity of prostate cancer resides in the abnormal hyper-expression of tumor-associated antigens (TAAs) by prostate cancer cells [including prostate-specific antigen (PSA), prostate-specific membrane antigen (PSMA), prostatic acid phosphatase (PAP), prostate stem-cell antigen (PSCA), cancer/testis antigens (CTAs)], which represent potential target for immunotherapeutic strategies (2,3).

In addition, prostate cancer is marked by a dense inflammatory infiltrate of T-cells [tumor infiltrating lymphocytes (TILs)] both within the tumor and in the surrounded microenvironment (4,5), whose value is not yet entirely understood. Indeed, from one side TILs should participate in host defense mechanisms, recognizing and destroying neoplastic prostate cells. Therefore, high TILs infiltration has been correlated with longer patient survival (6). However, from the other side most of effector TILs are non-active, lacking markers of functional activity (like perforin or IFNγ), being therefore unable to generate an efficient antitumor response (4,7). In contrast to what previously said, several studies suggested a negative prognostic role of TILs in prostate cancer (8), thus investigating the role of TILs represents an important strategy to better understand the relationship between immune system and prostate cancer progression. Furthermore, a substantial contribution to the inability of mounting an efficient immune response that constrains cancer progression is due to the presence of Tregs within the inflammatory infiltrate of prostate cancer tissue. Tregs is a small subpopulation of CD4+/CD25+ and CD8+/Foxp3 T lymphocytes with a negative immune regulatory function (directly via cell–cell contact or indirectly by secreting anti-inflammatory cytokines, like IL-10 ore TGFβ) (9), supposed to have a negative prognostic role in prostate cancer patients (8,10).

Finally, androgen deprivation therapies used for prostate cancer treatment have immunomodulatory effects. Indeed, anti-androgens can reverse thymic involution and promote thymopoiesis (11), promote B-cell proliferation (12), reduce intratumoral infiltration of immunosuppressive Tregs, mitigate tolerance to prostatic antigens (13), increase NK cell infiltrate, and increase T-cell infiltration (mainly CD4+ cells) within prostate cancer tissue (14), suggesting the potential role of combining immunotherapy with hormonal agents to enhance anticancer immune-based treatments (15).

Although very promising theoretically, immunotherapy by increasing immune responses against prostate cancer cells is far from achieving the expected results in clinical practice.

At present, sipuleucel-T (an active cellular immunotherapy, consisting of autologous peripheral-blood mononuclear cells activated and loaded with an immunostimulatory fusion protein—PA2024—containing the prostate tumor antigen prostate acid phosphatase), approved in 2010 for minimally symptomatic or asymptomatic mCRPC patients (16), is the first active immunotherapy vaccine approved for any type of advanced solid cancer. As compared to placebo, treatment with sipuleucel-T determined a survival benefit of about 4 months (mOS 25.8 months in the sipuleucel-T group *vs.* 21.7 months in the placebo group, HR 0.78; 95% CI, 0.61–0.98; P=0.03), and no improvement in PSA response or radiographic progression-free survival (rPFS) (16). However, the population enrolled in the study (good performance status, low disease burden, excellent prognosis), the modest benefit in OS, the difficult access to an apheresis center, and the high costs of this vaccine have limited the spread of sipuleucel-T in clinical practice. In addition, the recent demonstration of a survival advantage with novel hormonal therapies (abiraterone and enzalutamide) and the alpha emitter radium-223, even considering their good safety profile, have further restrict the clinical utility of sipuleucel-T.

Beyond sipuleucel-T, various immune strategies are currently under development, alone or in combination with conventional therapies, including antigen-directed active immunotherapies and monoclonal antibodies (mAbs) against immune checkpoints.

Betraying the expectations, the anti CTLA-4 mAb ipilimumab failed in demonstrating a prolonged survival both in mCRPC patients progressed after docetaxel chemotherapy (17), and in the docetaxel-naïve setting (press release by Bristol-Myers Squibb, July 23, 2015). Several ongoing trials are evaluating the safety and antitumor activity of ipilimumab-based combination strategies, including ipilimumab plus abiraterone (NCT01688492), GM-CSF (NCT01530984), GVAX (NCT01510288), sargramostim (NCT00064129), sipuleucel-T (NCT01832870, NCT01804465), and PROSTVAC-VF (NCT02506114).

Analogously, tasquinimod (an oral quinoline-3-carboxamide derivative with anti-angiogenic properties and tumor growth–inhibiting activity against prostate cancer cells, which target the immunomodulatory protein S100A9 expressed on myeloid-derived suppressor cells of the tumor microenvironment) failed to prolong OS in a randomized, placebo controlled, phase 3 trial in chemotherapy-naïve mCRPC patients (18).

A promising active viral-based immunotherapy under development in the mCRPC setting is the vector-based therapeutic cancer vaccine PROSTVAC, composed of a recombinant poxviral vectors (during the initial priming vaccine) engineered to express PSA and a triad of human T-cell costimulatory molecules (B7.1, ICAM-1, and LFA-3) and a series of fowlpox vectors expressing PSA for subsequent boosts. This virus-vaccine exploits the ability of integrating tumor DNA in the viral genome, and the selective expression of PSA by tumor cells (PSA is therefore the tumor- specific antigen) to stimulate the T-cell antitumor response. The phase 2 randomized placebo-controlled studies of PROSTVAC-VF + GM-CSF in chemo-naïve asymptomatic or minimally symptomatic mCRPC patients showed no improvement in PFS, the primary end point of the study, and biochemical response. However, the vaccine was associated with a survival advantage of about 8.5 months (mOS 25.1 *vs.* 16.6 months; HR 0.56; 95% CI, 0.37–0.85; P=0.0061) (19). An ongoing phase 3 study will evaluate the efficacy of PROSTVAC alone or in combination with GM-CSF in prolonging overall survival in men with few or no symptoms from mCRPC (NCT01322490).

Instead, it has been abandoned the development of GVAX immunotherapy, a vaccine in which genetically modified allogeneic prostate cancer cells express the gene coding for GM-CSF, so as to stimulate dendritic cells and APCs to induce an immune response against prostate cancer cells. The phase 3 trial conduced in symptomatic taxane-naïve CRPC patients, comparing docetaxel in association with GVAX versus docetaxel plus prednisone. The study was prematurely terminated because of an imbalance in deaths (67 in the experimental arm *vs.* 47 in the control arm) due to disease progression. The preliminary analysis demonstrated a survival advantage for the control arm over the experimental arm with GVAX, discouraging further investigations of this vaccine and reinforcing the antitumor activity of corticosteroids in mCRPC (20).

Given these assumptions, it is logical to understand the efforts directed at identifying the immunotherapy that can provide a meaningful survival benefit with an acceptable toxicity profile to a specific cohort of patients with prostate cancer. It is of crucial importance, indeed, not only to

recognize the correct way to stimulate the host immune system against prostate cancer cells, but also to detect the appropriate timing during the disease history where a precise subpopulation of patients might benefit from immunotherapy.

In this landscape, Yoshimura and Colleague presented the results of a randomized phase II trial that compared a personalized peptide vaccine (PPV) to low-dose dexamethasone in patients with chemotherapy-naïve CRPC (with regional lymphadenopathy or metastatic disease), demonstrating significant improvement in PSA-PFS—the primary end-point of the study (22.0 *vs*. 7.0 months; P=0.0076) and OS (73.9 *vs*. 34.9 months; P=0.00084), and delaying the time to initiation of chemotherapy (52.4 *vs*. 23.8 months; P=0.047) (21). Of note, in contrast to other prostate cancer vaccines approved or in development, PPV showed consistent effects not only in prolonging OS but also in tumor response (extending PSA PFS and time to start of chemotherapy).

PPV immunotherapy uses multiple TAAs peptides derived from the tumor cells based on the preexisting host immunity. TAA peptides are recognized by APCs that in turn present them to CD4+ and CD8+ T cells via major histocompatibility complexes (HLA) class I and II molecules, respectively. This interaction results in the induction, maturation, and expansion of antigen-specific cytotoxic T lymphocytes (CTLs), aimed at destroying cancer cells. The basis of this principle is the assumption that initiation of immune boosting of CTLs through peptide vaccination might be more effective than immune priming of naïve T-cells in the induction of prompt and strong immunity. In the study, a maximum of four "reactive" HLA-type specific peptides were chosen for each patient among a repertoire of 24 peptides restricted with HLA-A02, A-24, or A03, based on the evaluation of both anti-peptide IgG levels in plasma and CTL precursors in peripheral blood mononuclear cells (PBMCs), so as to select and vaccinate with peptides against which CTL or peptide-directed antibody existed, therefore making this PPV vaccine an highly personalized therapy. There are additional strengths of this vaccine: the simplicity and cost effectiveness of production of an off-the-shelf vaccine; the increased immunogenicity and the enlarged target population due to the expanded repertoire of 24 peptides compared to a single epitope-based vaccine; the selectivity towards specific TAAs, avoiding to target self-antigens and thus preventing immune-mediated adverse events against healthy self-tissues; the good toxicity profile (22).

Moreover, this study is of particular interest for the remarkable prolongation of OS, even considering the option of crossover for patients in the dexamethasone arm. The acceptability of the control arm with dexamethasone is therefore supported by the historical data of the antitumor and antiangiogenic activity of corticosteroids, but also by the period in which the study was conducted (prior to approval of second-generation anti-androgens, abiraterone and enzalutamide), as well as by the median survival of patients treated with dexamethasone in this study (mOS 34.9 months) that is similar to that reached with abiraterone and enzalutamide in phase 3 pivotal trials in the pre-docetaxel setting (mOS in the treatment arm was 34.7 and 32.4 months, respectively) (23,24).

Interestingly the efficacy and treatment duration of vaccination therapy after failure of dexamethasone (cross-over population) seemed reduced compared to PPV immunotherapy upfront, supposing that the immunosuppressive activity of dexamethasone could limit the effects of the vaccine therapy.

On the contrary, several weaknesses are to be underlined. First, the sample size of enrolled patients was very small (37 patients received peptide vaccinations and 35 received dexamethasone alone), not allowing drawing definitive conclusions. Second, the population was extremely selected for good prognosis, with a good performance status (ECOG PS of 0 or 1), low median PSA (<10 ng/mL), and mostly with bone or node disease and no visceral metastases (in addiction the study did not specify the disease burden). The small subset of patients fulfilling these characteristics justified, at least in part, the long period of accrual (from April 2008 to October 2013).

In conclusion, PPV could represent a promising immune therapeutic option for a specific subset of mCRPC patients. Therefore, it is extremely important not only to validate the OS benefit in a large phase 3 trial, but also to precisely identify the patients and the correct timing to maximize the activity of a vaccine strategy for mCRPC.

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Footnote

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