Immunotherapy for prostate cancer: the next step?

HANNAH RUSH, CLARE GILSON AND SIMON CHOWDHURY

Immunotherapy is showing great promise in the treatment of a wide range of cancers. Using the body’s own immune system to attack tumours is an attractive proposition that has the advantage of being selective with reduced toxicity. In this article the authors provide a comprehensive overview of the current approaches being tested in the treatment of prostate cancer.

Prostate cancer is the most common cancer among men worldwide and one of the leading causes of cancer-related mortality. When diagnosed early, it can be treated effectively with surgery or radiotherapy. However, 5% of patients present with metastatic disease. Despite recent advances in treatment, the average life expectancy for these patients is only 3.5 years.

Androgen deprivation therapy (ADT) has traditionally been the lynchpin of first-line management of metastatic disease. Eventually, all patients treated for metastatic disease will develop castration-resistant prostate cancer (CRPC). Over the last five years, a range of new agents have been found to improve survival in patients with CRPC, including the cytotoxic agent cabazitaxel (Jevtana), anti-androgen drugs abiraterone (Zytiga) and enzalutamide (Xtandi), and sipuleucel-T, the first cellular immunotherapy to receive a licence for solid tumour oncology. Although sipuleucel-T was approved by the American Food and Drug Administration (FDA) in 2010, following an appraisal in 2015, the National Institute for Health and Care Excellence (NICE) has not recommended its use within the NHS in the UK, largely on the grounds of cost.

Recent advances in immunotherapy have been practice-changing in the treatment of melanoma, renal cell carcinoma and lung cancer. It is an exciting therapeutic option, offering the potential for significant...
improvement in patient outcomes, coupled with a more favourable side-effect profile than traditional cytotoxic agents. This review will outline some of the immunotherapeutic approaches currently being evaluated in trials.

WHAT IS IMMUNOTHERAPY?
Preclinical data support the role of immunotherapy in the treatment of prostate cancer. Studies show that prostate cancer stimulates an immune response and that infiltration of certain immune cells within a tumour correlates with patient survival, suggesting the immune system’s key role in controlling cancer growth (Table 1).

Immunotherapy involves stimulating the body’s adaptive immune response against tumour cells, a slower process than the effect of cytotoxic agents. As prostate cancer is relatively slow-growing, there is sufficient time for immunotherapy to produce a response. One advantage in harnessing the immune system in prostate cancer is that the prostate is not a vital organ. Well described tumour-associated antigens (TAAs) have been studied, including prostate-specific antigen (PSA), prostate-specific membrane antigen (PSMA), prostate acid phosphatase (PAP) and prostate stem cell antigen (PSCA). No perfect prostate cancer TAA has yet been discovered.

In addition to the understood mechanism of their therapeutic effect, some established prostate cancer treatments also activate the immune system. ADT enhances immune response against tumour cells, increasing T-cell activation and homing to sites of disease. Chemotherapy has traditionally been thought of as impairing immune response due to lysis of leucocytes; however, there is some suggestion that it may facilitate induction of anti-tumour immunity. For example, docetaxel has been reported to increase the production of pro-inflammatory cytokines and doxorubicin to enhance cytotoxic T-cell anti-tumour immunity. These data suggest that immune activation may play a part in the effectiveness of current therapies and support the development of novel approaches capable of exploiting this further.

IMMUNOTHERAPY AGENTS
Currently, there are two main strategies for harnessing immunotherapy in prostate cancer: vaccination and checkpoint blockade. In the context of treating cancer, therapeutic vaccines aim to stimulate immune cells to recognise malignant cells as foreign, thus initiating an immune attack. Tumours employ inhibitory checkpoint signals to prevent stimulating T-cell activation, thus checkpoint blockade enables the immune response to proceed uninterrupted against tumour cells.

Autologous vaccines
Sipuleucel-T is an autologous dendritic cell infusion. Following leukapheresis, the cells are primed with a fusion protein of the tumour-associated antigen PAP and granulocyte macrophage colony-stimulating factor (GM-CSF), before being infused back into the patient. The primed dendritic cells activate antigen-specific cytotoxic T cells, which target PAP-expressing tumour cells.

Two phase 3, randomised, placebo-controlled trials were initially conducted with a total of 225 patients with metastatic CRPC. Although there was no difference in the primary endpoint of progression-free survival (PFS), a significant 4.3-month median survival difference favoured treatment.

Subsequently, the IMPACT study, a double-blind, placebo-controlled trial, assessing the efficacy of sipuleucel-T in 512 patients with metastatic CRPC, was designed with overall survival (OS) as the primary endpoint. A significant improvement in median OS of 4.1 months was seen, with a 3-year survival of 31% versus 23% with placebo. As in the initial trials, the PFS did not differ between the two groups. Sipuleucel-T was generally well tolerated, with 99% of the patients able to complete the treatment course. The most common side-effects reported were chills, fever and headache. A subgroup analysis demonstrated the greatest effect was seen in patients with a lower baseline PSA, suggesting the treatment may be most beneficial in those with less advanced disease.

One criticism of the trial design was that cells were harvested in both arms of the trial – approximately 90% of each patient’s circulating mononuclear cells were harvested – yet in the control arm these cells were not re-infused. Cell depletion may therefore account for poorer survival in the control arm.

Viral vector–based vaccines
PROSTVAC-VF comprises two recombinant viral vectors, each encoding transgenes

---

**Table 1. Immune markers of prognosis in prostate cancer**

<table>
<thead>
<tr>
<th>Immune markers</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protective immune response</td>
<td>Presence of effector T cells specific to TAAs, including epitopes on the androgen receptor</td>
</tr>
<tr>
<td></td>
<td>Presence of antibodies against NY-ESO-1, a TAA</td>
</tr>
<tr>
<td>Poor prognosis</td>
<td>Increased level of circulating and tumour-infiltrating immunosuppressive Tregs</td>
</tr>
<tr>
<td>Increased risk of recurrence</td>
<td>Infiltration of macrophages after ADT</td>
</tr>
<tr>
<td>TAA, tumour-associated antigens</td>
<td></td>
</tr>
<tr>
<td>NK cell, natural killer cell</td>
<td></td>
</tr>
<tr>
<td>Tregs, T regulating cells</td>
<td></td>
</tr>
<tr>
<td>TGF-β, transforming growth factor beta</td>
<td></td>
</tr>
</tbody>
</table>
for PSA and three immune co-stimulatory molecules. A vaccinia-based vector is used for the initial priming vaccination, followed by six planned fowlpox-based vector boosts. This is intended to activate host dendritic cells, which in turn activate T cells against PSA-expressing cells.

A phase 2, randomised, double-blind, placebo-controlled study of 125 patients with minimally symptomatic CRPC found a significant 8.5-month (25.1 versus 16.6 months) survival advantage in patients treated with PROSTVAC-VF. There was no difference in the primary endpoint of PFS. Common adverse events were fever, nausea, fatigue and injection site reactions. It is not yet clear at which stage of disease PROSTVAC-VF will be most effective; the results of studies evaluating its use in non-metastatic hormone-sensitive prostate cancer are awaited.

Another viral vaccine in early development uses adenovirus type 5 vectors to deliver tumour-associated antigen-coding genes. In a phase 1 trial including 32 patients with metastatic CRPC, 48% had an increase in PSA doubling time and 55% survived longer than predicted.15

Cell-based vaccines
GVAX is an allogenic, whole-cell vaccine consisting of two prostate cancer cell lines transduced with GM-CSF. Two large phase 2 trials, VITAL-1 and VITAL-2, have been conducted. VITAL-1, comparing GVAX with docetaxel and prednisone, was terminated early due to a futility analysis that suggested a low probability of the trial reaching the primary endpoint. VITAL-2, which compared docetaxel and GVAX with docetaxel alone, was terminated due to high mortality in the treatment arm. The increased death rate in the treatment group was not clearly related to increased toxicity. Recent evidence has suggested that GVAX may have a role when given in combination with ADT for hormone-sensitive prostate cancer.

ONY-P1 is another cell-based vaccine comprising three irradiated prostate cancer cell lines. In a non-randomised phase 2 trial, 26 patients with metastatic CRPC received ONY-P1 intradermally, with bacilli Calmette-Guérin as a vaccine adjuvant for the first two doses. A significant delay in PSA velocity was observed in 11 of the 26 patients.18

Personalised peptide vaccines
This approach screens a patient’s immune response against a panel of 31 TAA-peptide epitopes known to be potentially immunogenic in prostate cancer. A small panel of peptides is selected and the patient is vaccinated with them. One phase 2 study involving 42 patients with CRPC, of whom half were resistant and half sensitive to docetaxel, found a non-significant trend towards improved survival amongst the docetaxel-resistant patients compared with historical controls (17.8 versus 10.8 months).19

CTLA-4 checkpoint blockade
T-cell responses depend on a balance between positive and negative co-regulatory signals that are generated within the T cell. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) is an immune checkpoint receptor responsible for suppressing T-cell activation. Ipilimumab is a fully human monoclonal antibody that binds to and inhibits CTLA-4 ligand-driven activation. By overcoming the CTLA-4 mediated suppression, T cells are activated with the potential to ‘take them off the leash’, allowing TAA recognition and elimination.

A phase 3 trial of 799 patients with advanced CRPC that had progressed after docetaxel compared radiotherapy and ipilimumab with radiotherapy and placebo. There was no significant survival difference (11.2 versus 10.0 months).20 Ongoing studies are investigating the use of ipilimumab in earlier stages of prostate cancer.

PD-1 checkpoint blockade
The immune regulatory inhibitor programmed cell death protein 1 (PD-1) is another suppressive immune checkpoint receptor. Tumour cells can express programmed death ligand 1 or 2 (PD-L1 or PD-L2), which interact with PD-1 on T cells, resulting in inhibition of T-cell activation against the cancer. In mouse models, the absence of PD-1 has shown to dramatically delay tumour growth and increase cytotoxic T cells within tumour tissue. A study examining the tumour biopsies of seven patients with prostate cancer found that 90% of the infiltrating CD8+ T lymphocytes had upregulated cell surface expression of PD-1.22

Nivolumab is an anti-PD-1 monoclonal antibody that has recently been approved by the FDA for use in metastatic melanoma. In a phase 1 trial of nivolumab, including 17 patients with metastatic CRPC, no objective response was seen amongst the prostate cancer patients.24 42 patients in the trial, with a mix of solid tumour types, had biopsies assessed for PD-L1 expression. Whilst none of the patients with negative PD-L1 biopsies had a response, 36% of patients with evidence of PD-L1 expression had an objective response to treatment. PD-L1 was the only biomarker to have a significant correlation with response to nivolumab.25

CONCLUSION
Immunotherapy is an exciting and rapidly advancing field that is enjoying renewed interest and some success in prostate cancer. Sipuleucel-T continues to demonstrate durable and well-tolerated
responses in prostate cancer; studies to determine if the impressive results seen with checkpoint inhibitors in other solid tumours can be replicated in prostate cancer are ongoing. Questions remain regarding the efficacy of newer treatments, what constitute optimum sequencing and the potential benefits of combination therapy (see Table 2 for a summary of ongoing trials).

To date, immunotherapy has been investigated predominantly in advanced disease, where the immune system may have been suppressed and impaired by previous treatments, disease burden and associated comorbidities. Immunotherapy could potentially be more effective when administered early in the course of the disease; many current trials are focused on this possibility (Table 2).

We need to better understand the natural history of changes within tumours treated with immunotherapy. According to current methods of measuring PFS, most patients show no response to immunotherapy, yet there is often significant improvement in OS. The Prostate Cancer Clinical Trials Working Group has proposed new criteria for evaluating cytotoxic and non-cytotoxic agents, which include changes in how immune-related responses are assessed.26,27

Studies have assessed whether genetic analysis of tumour cells can provide clues as to who will respond to immunotherapy. New peripheral biomarkers are also being sought to aid in the prediction and measurement of response to treatment, as well as markers that would enable the prediction of toxicity. This would allow targeted therapy for individuals most likely to benefit from immunotherapy, providing a rationale for the use of such high cost treatments and a basis on which truly individualised treatment plans could be formulated.

<table>
<thead>
<tr>
<th>Agents</th>
<th>Population</th>
<th>No. of patients</th>
<th>Phase</th>
<th>Primary outcome</th>
<th>Trial number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sipuleucel-T and enzalutamide</td>
<td>Metastatic CRPC</td>
<td>100</td>
<td>2</td>
<td>Evaluate peripheral immune response</td>
<td>NCT01981122</td>
</tr>
<tr>
<td>Sipuleucel-T and ADT</td>
<td>Non-metastatic prostate cancer with rising PSA</td>
<td>68</td>
<td>2</td>
<td>Measure change in immune response</td>
<td>NCT01431391</td>
</tr>
<tr>
<td>Sipuleucel-T and indoximod</td>
<td>Refractory metastatic prostate cancer</td>
<td>50</td>
<td>2</td>
<td>Immune response to sipuleucel-T</td>
<td>NCT01560923</td>
</tr>
<tr>
<td>PROSTVAC and GM-CSF</td>
<td>Metastatic prostate cancer</td>
<td>1298</td>
<td>3</td>
<td>Overall survival</td>
<td>NCT01322490</td>
</tr>
<tr>
<td>PROSTVAC and enzalutamide</td>
<td>Non-metastatic hormone-sensitive prostate cancer</td>
<td>26</td>
<td>2</td>
<td>Decrease in tumour regrowth rate</td>
<td>NCT01875250</td>
</tr>
<tr>
<td>PROSTVAC and enzalutamide</td>
<td>Metastatic CRPC</td>
<td>76</td>
<td>2</td>
<td>Progression-free survival</td>
<td>NCT01867333</td>
</tr>
<tr>
<td>Adenovirus vaccine ProstAtak as adjuvant with radiotherapy</td>
<td>Localised prostate cancer</td>
<td>711</td>
<td>3</td>
<td>Disease-free survival</td>
<td>NCT01436968</td>
</tr>
<tr>
<td>GVAX and ADT with cyclophosphamide</td>
<td>Localised prostate cancer</td>
<td>29</td>
<td>1 and 2</td>
<td>Assess CD-8 infiltration into prostate cells</td>
<td>NCT01696877</td>
</tr>
<tr>
<td>Ipilimumab and sipuleucel-T</td>
<td>Pre-chemotherapy metastatic CRPC</td>
<td>54</td>
<td>2</td>
<td>Impact of the timing of ipilimumab on immune reponse created by sipuleucel-T</td>
<td>NCT01804465</td>
</tr>
<tr>
<td>Pidilizumab and sipuleucel-T with cyclophosphamide</td>
<td>Advanced CRPC</td>
<td>57</td>
<td>2</td>
<td>Feasibility and immune efficacy</td>
<td>NCT01420965</td>
</tr>
</tbody>
</table>

Table 2. Ongoing trials of immunotherapy agents in prostate cancer
Acknowledgement
Thank you to Dr Sophie Papa for her review and feedback on this article.

Declaration of interests: none declared.

REFERENCES