New horizons for prostate cancer: part 1

DAVID DEARNALEY, CHRISTIAN OTTENSMIEIER, GERHARDT ATTARD AND SIMON CRABB

This report is based on a seminar held during the 9th Annual Meeting of the British Uro-oncology Group in Bristol last September. The workshop reviewed emerging prostate cancer treatment strategies that are predicted to contribute to the changing landscape of prostate cancer management over the coming years. Immunotherapy and developments in radiotherapy are discussed in part 1 of this article, while part 2 will cover androgen receptor inhibition and novel target identification.

IMMUNOTHERAPY IN PROSTATE CANCER

Until recently, research into anti-cancer vaccines was seen as an interesting theoretical pursuit with little potential for clinical application. However, over the past three and a half years, cancer immunotherapy has undergone enormous conceptual changes, and its potential as a legitimate clinical strategy in cancer management is increasingly being recognised. By 2009, individual randomised trials had shown a benefit of immunotherapy in patients with melanoma,1 lymphoma,2 colorectal cancer and lung cancer.3 The major breakthrough came in 2010, with the publication of the IMPACT study showing a 4.1-month overall survival benefit with the dendritic-cell vaccine, sipuleucel-T, in patients with metastatic castrate-resistant prostate cancer (CRPC).4 This led to the first licence for a therapeutic human anti-cancer vaccine, and generated an upsurge in interest into different strategic approaches to cancer immunotherapy.

CD4+ helper T-cells and CD8+ cytotoxic T-cells were identified as the most promising targets for immunotherapy in solid tumours, including prostate cancer (Figure 1). However, the lack of a prolonged survival benefit as well as a number of discrepant results observed with T-cell-targeted immunotherapies, including sipuleucel-T, demand further investigation. Flow cytometric analysis of tumour tissue shows that T-cells in the tumour, but not in the blood, have an exhausted phenotype and express PD1 and TIM3 on the cell surface. In particular, the PD1 receptor/PD1 ligand pair has been shown to have a central role in T-cell exhaustion, offering a potential therapeutic target for cancer immunotherapy with promising early clinical data.5

Vaccination of a transgenic adenocarcinoma of the mouse prostate (TRAMP) model has been shown to offer a significant but marginal survival benefit. The vaccine-specific T-cells were demonstrated to accumulate in the tumour, but have an exhausted phenotype, expressing PD1 on the cell surface.6 Thus preclinical modelling confirms that the future development of immunotherapy for cancer will need to contend with T-cell exhaustion as well as the regulation of T-cells and immunosuppressive effects of the local tumour microenvironment.

Endpoint selection in immunotherapy trials

The effectiveness of a new therapeutic approach to prostate cancer is often evaluated in phase 2 trials by means of prostate-specific
antigen (PSA) monitoring or through analysis of progression-free survival. However, evidence suggests that these approaches may be unsuitable for immunotherapy trials.

In the IMPACT study, overall survival was significantly improved but no effect on PSA progression was observed. This appears to undermine the value of PSA monitoring as a surrogate treatment outcome and calls into question the value of surrogate biomarkers in monitoring disease progression in an immunotherapy setting.

In a further study, a DNA-fusion vaccine encoding for a domain (DOM) from fragment C of tetanus toxin linked to an HLA-A2-binding epitope from prostate-specific membrane antigen was evaluated in recurrent prostate cancer at biochemical failure. Although a T-cell response was detected in 97 per cent of patients, once again there was no objective PSA response. However, PSA doubling time increased significantly from 11.97 months pretreatment to 16.82 months over the 72-week follow-up (p=0.04), suggesting that PSA doubling time might be a surrogate for a lack of progression.

The ACVA study examined the safety and immunogenicity of a DNA-fusion vaccine in carcinoembryonic antigen (CEA)-expressing malignancies (bowel, lung and breast) in 15 patients with measurable disease and 12 patients without radiological evidence of disease but at risk of progression. Interestingly, this study found that a high incidence of gastrointestinal adverse events in vaccinated patients coincided with increased time to clinical and radiological disease progression, longer on-study follow-up, decreases in CEA and a longer duration of positive anti-DOM cellular responses. This suggests, in a notable departure from the traditional approach, that patient adverse events may have potential as a tool for predicting outcome. The link between adverse events and clinical outcomes observed in the ACVA study will be further investigated in a randomised phase 2 study planned later this year.

**Patient selection in immunotherapy trials**

The immune system evidently becomes less competent as cancer progresses, partly as a result of disease progression and partly because of the toll of chemotherapy and radiotherapy regimens. For this reason, immunotherapy is expected to be more effective in early disease. Therefore, trials into cancer immunotherapy are increasingly conducted early in the course of the disease rather than later, challenging the standard way of drug development. The observation that immunotherapy is most likely to show benefit in the setting of a minimal disease burden has initiated the development of a number of clinical trials aimed at testing the efficacy and feasibility of administering immunotherapy regimens, including sipuleucel-T, in the earlier stages of prostate cancer also.

The apparent benefits of immunotherapy have encouraged the development of treatments and combination regimens that result in long-term, immune-mediated responses. However, an important short-term goal will be to identify a means of measuring an objective response to treatment in order to facilitate further research in this area.

**RADIOTHERAPY DEVELOPMENTS IN METASTATIC DISEASE**

Radiotherapy is a proven and available option for the treatment of prostate cancer. The phase 3 ALSYMPCA trial in patients with symptomatic metastatic CRPC showed a significant overall survival benefit in favour of radium-223 (Alpharadin) treatment. The benefit was so pronounced that the study was unblinded early and patients on the placebo arm were offered radium-223 (Alpharadin) treatment. The results of the phase 3 TRAPEZE study investigating docetaxel plus prednisolone versus docetaxel with prednisolone plus either zoledronic acid, strontium-89 or both agents combined are expected soon.

However, as well as offering a benefit when administered systemically, radiotherapy may be delivered focally to target small-volume disease. Local radiotherapy has recently been added as a new arm in the phase 3 STAMPEDE trial in men with high-risk localised or locally advanced hormone-naive prostate cancer. This international, open-label, randomised controlled trial adopted a novel multi-arm, multistage design to assess whether the early...
additional use of one or two drugs (docetaxel, zoledronic acid, celecoxib, zoledronic acid and docetaxel, or zoledronic acid and celecoxib) improves survival in men starting first-line, long-term hormone therapy. Recruitment into the celecoxib arms was stopped in 2012 because of a lack of benefit, and the celecoxib plus zoledronic arm also stopped accrual at the same time. An abiraterone arm was added late in 2011 (Figure 2). Recruitment into the STAMPEDE study is expected to be completed by the end of 2014.

Declarations of interests
The British Uro-oncology Group seminar ‘New horizons for prostate cancer’ was sponsored by Takeda. Takeda selected and briefed the speakers on the content of the session and they were paid an honorarium by Takeda. Takeda has had no editorial control over any publications arising from the meeting. David Dearnaley has attended and received honoraria for advisory boards and served as a consultant for Takeda, Amgen, Astellas Pharma and Succinct Healthcare. Abiraterone acetate was developed at the Institute of Cancer Research, which therefore has a commercial interest in the development of this agent. Christian Ottensmeier has attended and received honoraria for advisory boards, and has received an educational grant for a clinical trial from Bristol Myers Squibb. Gerhardt Attard has received consulting fees from Janssen-Cilag, Veridex and Millennium Pharmaceuticals, lecture fees from Janssen-Cilag, Ipsen, Takeda, Roche/Ventana and Sanofi-Aventis, and grant support from AstraZeneca and Roche/Genentech. He is on the ICR list of rewards to inventors of abiraterone acetate. Simon Crabb has received honoraria for advisory boards for Janssen and Sanofi.

www.trendsinurology.com

REFERENCES