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## PROSTATE CANCER

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### Abstract

The field of prostate cancer treatment and research is finally growing up after many years as the orphan child in oncology. It is sobering to reflect that the first Therapeutic Goods Administration approval of a cytotoxic therapy for metastatic castrate-resistant prostate cancer, docetaxel, occurred less than 10 years ago. No further improvements in the treatment of this condition occurred until the last two to three years. Since then, several new treatments targeting various aspects of prostate cancer biology have shown clinical benefit, including improved survival, and are now entering clinical practice. All of these advances have been made on the basis of better understanding of the unique biology of prostate cancer and its interaction with host tissues and systems. For example, the pivotal role of ongoing signaling through the androgen receptor axis, even in the setting of apparent resistance to manipulation of this pathway, has led to rethinking of long-held dogmas and the development of effective new therapies. Significant advances have also been made in surgical and radiation techniques, and in imaging, that are expected to lead to improved outcomes.

Prostate cancer is the most common non-skin malignancy in western populations and is a frequent cause of cancer deaths in men.<sup>1</sup> Most men diagnosed with prostate cancer have localised disease. Ablative treatments such as prostatectomy or radical radiotherapy lead to excellent cancer outcomes, although morbidity of treatment can

sometimes be substantial. Relapsed or metastatic prostate cancer is usually treated with some form of androgen deprivation, most commonly medical castration using a gonadotrophin releasing hormone agonist with or without an antiandrogen. This treatment is highly effective, but the condition is not curable and over a period of time that

can be highly variable, inevitably develops into metastatic castrate-resistant prostate cancer (mCRPC), the lethal form of the disease.

Docetaxel was the first cytotoxic drug to demonstrate survival benefit in mCRPC and was approved in Australia following two pivotal studies published in 2004.<sup>2,3</sup> Few other options existed for men with mCRPC until 2010. Since that time, several new agents have demonstrated benefit for men with mCRPC, including improved survival and have subsequently been approved by the United States Food and Drug Administration and other jurisdictions around the world. Many of these agents have been developed specifically in the light of better understanding of the biology of mCRPC.

## New approaches

### Androgen receptor (AR)

Signalling through the AR remains critical for many cases of mCRPC, even when conventional methods of androgen deprivation or receptor blockade appear to have failed.<sup>4</sup> Several new agents targeting AR and/or androgen production are now available or under development. Abiraterone acetate (Zytiga®; Janssen) inhibits production of androgens by the testes, adrenals and from within the tumour. Side-effects related to mineralocorticoid excess are mitigated by concomitant prednisone or prednisolone. A pivotal trial showed 36% improvement in the hazard ratio for overall survival and increase in median survival from 11.2 months (placebo plus prednisone) to 15.8 months (abiraterone plus prednisone).<sup>5,6</sup> Secondary endpoints were also all in favour of the experimental arm. A second trial in chemotherapy-naïve mCRPC patients also showed a trend to improvement in overall survival (HR 0.75;  $p=0.01$ ), although this trial may have been unblinded prematurely.<sup>7</sup> Abiraterone acetate is now approved for both indications in the US and in the post-docetaxel setting in Australia.

Another major advance also targeting the AR is the development of new generation AR antagonists such as enzalutamide (MDV3100, Xtandi®, Medivation/Astellas). Enzalutamide competes for ligand binding, impairs translocation of the AR into the cell nucleus, and inhibits binding of the AR to DNA and the recruitment of coactivators.<sup>8</sup> Enzalutamide improves the hazard ratio for survival by 37% (HR 0.63,  $P<0.001$ ) and improves median overall survival (18.4 months v 13.6 months),<sup>9</sup> as well as secondary endpoints. A second trial in chemotherapy-naïve men with mCRPC has completed accrual and results are pending. Enzalutamide is generally well tolerated, with a further potential advantage being the lack of requirement for concomitant corticosteroids.

### Cytotoxic chemotherapy

After docetaxel, this field had been an area of disappointment in prostate cancer until the results of the TROPIC trial comparing cabazitaxel (a semi-synthetic taxane developed for activity against docetaxel-resistant cell lines) to mitoxantrone in the post-docetaxel setting. This trial demonstrated superiority of cabazitaxel in terms of the primary endpoint of overall survival (HR 0.70,  $p<0.0001$ ; median survival 15.1 months v 12.7 months),<sup>10</sup> although toxicity was higher in the cabazitaxel arm. Cabazitaxel is

now approved and reimbursed in Australia for mCRPC post-docetaxel.

### Bone-targeted therapy

Zoledronic acid has been shown to improve skeletal-related event endpoints in clinical trials,<sup>11</sup> although its use is not universal. Denosumab, a fully human monoclonal antibody specific for RANKL, has been shown to be non-inferior to zoledronic acid in men with bone metastases,<sup>12</sup> and superior to placebo in non-metastatic mCRPC (improved time to first skeletal-related event from 25.2 months to 29.5 months [HR 0.85,  $p=0.028$ ]).<sup>13</sup> Osteonecrosis of the jaw occurred at similar rates with denosumab and zoledronic acid.<sup>12</sup>

An exciting innovation in the field of 'bone-targeted' therapy is radium-223 chloride (<sup>223</sup>Ra; Alpharadin®, Bayer). The chemistry of radium is similar to calcium and radium-223 chloride is deposited in bone. Radium-223 is an emitter of alpha particles, providing high energy over a very short path length.<sup>14</sup> It was therefore expected that this intravenously administered radioisotope might provide a useful palliative benefit, together with less marrow toxicity than conventional beta-emitters in current use such as strontium-89 or samarium-153. Radium-223 chloride was shown in a pivotal trial of men with mCRPC after docetaxel to be well tolerated, especially with respect to: marrow toxicity; effectively controlled pain from bone metastasis; and remarkably also improved overall survival compared to placebo (survival HR 0.695, 95% CI 0.552-0.875,  $p=0.00185$ ; median survival 14.0 months for radium-223 compared to 11.2 months for placebo).<sup>15</sup> The precise mode of action remains unclear, but is probably more than a direct anticancer effect; the short path length of alpha particles implies that effects on other cellular targets in bone such as osteoclasts and osteoblasts are involved.

### Immunotherapy

Prostate cancer now holds the remarkable distinction of being the first solid malignancy for which adoptive cellular immunotherapy has shown an advantage. Sipuleucel-T (Provenge®, Dendreon) is an active cellular immunotherapy consisting of autologous peripheral blood mononuclear cells activated ex vivo, with a recombinant fusion protein comprising prostatic acid phosphatase and granulocyte-macrophage colony-stimulating factor.<sup>16</sup> A placebo-controlled trial of men with mCRPC demonstrated improved overall survival (HR 0.78; 95% CI 0.61 - 0.98;  $P = 0.03$ ) and median survival (21.7 months v 25.8 months) compared to placebo, leading to the registration of this therapy in the US. Progression-free survival did not differ between the two arms, however this does not detract from the primary survival endpoint benefit; the discrepancy relates to flawed systems for response evaluation in mCRPC, and the delayed effects of cellular immunotherapy. Other immunotherapeutic approaches are also under development in mCRPC.

### Therapy of localised disease

New treatments are being tested or adopted in efforts to improve treatment of prostate cancer localised to the gland. These include: surgical techniques such as robotic prostatectomy; advances in delivery of radiation, including intensity-modulated and image-guided adaptive radiotherapy; and other ablative techniques such as cryoablation or high-intensity focused ultrasound. Some of these techniques have been adopted in the absence

of evidence showing their superiority to conventional techniques. It remains to be seen whether these new approaches live up to their promise.

## Imaging

The choice of initial therapy for prostate cancer often relates to the confidence of the clinician as to whether the cancer is localised or not. Unrecognised locally advanced or metastatic disease that cannot be resected is currently incurable, and such men might not need to undergo prostatectomy, but perhaps should start other treatment options earlier. Current imaging techniques include CT, ultrasound and MRI, however novel approaches including PET are also being tested.<sup>17</sup> These may allow better selection of men for local therapy and thus improve outcomes.

## Supportive care

The adverse effects of androgen deprivation on bone and cardiovascular health, and the increased risk of metabolic syndrome, were long overlooked by medical oncologists, despite the fact that a large proportion of men with mCRPC will not die of prostate cancer. These men are now living longer, commencing treatment earlier, being treated for longer periods of time, and are receiving therapies that produce profound blockade of AR signalling in the tumour and systemically. The increased non-cancer morbidity and mortality that will inevitably ensue will need to be predicted and managed for each individual man.<sup>18</sup>

## Conclusions

All aspects of the management of prostate cancer, from diagnosis, initial therapy, therapy of advanced disease and supportive care, have undergone fundamental change, especially within the last 10 years. This has already translated into benefits for mCRPC, the lethal form of the disease, and further benefits are likely with improved understanding of the biology of the cancer and the optimal nature and sequencing of therapies. Many new potential therapeutic targets have already been identified.<sup>19</sup> The next 10 years and beyond will no doubt bring further advances and improvement in outcomes.

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