An update on the medical management of prostate cancer

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Over the past decade many advances have been made in the medical management of prostate cancer. Various treatment options are now available to patients, nearly all of which have distinct mechanisms of action that can improve survival in those with progressive metastatic prostate cancer.

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Great advances have been made in the medical management of prostate cancer. Androgen deprivation therapy (ADT) remains the mainstay first-line treatment option in patients with nonmetastatic prostate cancer (together with adjuvant radiotherapy), in those with recurrent disease following definitive treatment and in those with metastatic prostate cancer. Patients who stop responding to ADT develop castrate resistant prostate cancer (CRPC), with docetaxel chemotherapy remaining the standard of care in this setting. In the past five years, a variety of treatment options with distinct mechanisms of action have emerged for progressive metastatic CRPC and have been shown to improve overall survival. The optimal sequence for delivering these agents currently remains unclear. This therapeutic update reviews the main features of the medications available for the management of prostate cancer.

ANDROGEN DEPRIVATION THERAPY

Testosterone is essential for the growth and proliferation of prostatic tumour cells.[1] Testosterone secretion from the testes, the principal source of androgen in men, is regulated by the hypothalamic-pituitary-gonadal axis, as shown in the Figure.

ADT refers to any treatment that results in the suppression of androgen activity. It remains the mainstay first-line treatment option since being first described by Huggins et al in their seminal paper in 1941,[2] and is indicated for:

- nonmetastatic prostate cancer together with adjuvant radiotherapy
- recurrent disease following definitive treatment
- metastatic prostate cancer.

First-line ADT may be accomplished by surgical castration, or treatment with luteinising hormone releasing hormone (LHRH) agonists or antagonists. As discussed later, unpublished results from a recent phase III trial have shown that the addition of docetaxel chemotherapy to ADT as first-line treatment in men with high-volume metastatic disease can improve overall survival

compared with ADT alone. This may change the current standard of care in patients with high-volume metastatic prostate cancer.[3] ADT also includes treatment with oestrogens, steroidal and non-steroidal antiandrogens, and novel drugs such as abiraterone acetate and enzalutamide (Table).

Surgical castration

Surgical castration achieves a significant reduction in testosterone to a level known as the castration level; historically, this was considered to be 1.74 nmol/L (50 ng/dL) but has been recently revised to 0.69 nmol/L (20 ng/dL).[4] Its irreversibility and psychological harm and the innovation of medical ADT has made surgical castration a less popular option, but it remains the gold standard comparison for all other forms of ADT.

Oestrogens: diethylstilboestrol

The oestrogen diethylstilboestrol (DES) acts through the negative feedback loop on the hypothalamic-pituitary-gonadal axis. Although DES has been shown to be as effective as surgical castration,[5] its use has been limited by its cardiovascular and thromboembolic adverse effects,[6,7] and it has been superseded by LHRH agonists as first-line ADT.[8] The recent phase II PATCH trial has shown, however, that DES administration through transdermal patches can reduce its cardiovascular and thromboembolic adverse effects.[9] DES is no longer available in Australia.

LHRH agonists: goserelin, leuprorelin, triptorelin

LHRH agonists are currently the most commonly used form of ADT and have similar efficacy to DES and surgical castration.[5,10] They initially stimulate synthesis of LH and FSH, resulting in a 'testosterone flare', but continuous administration leads to down regulation of LHRH receptors, inhibiting LH and FSH secretion and thus testosterone production. LHRH agonists achieve castrate levels of testosterone within two to four weeks.[11]

The testosterone flare usually presents during the first two weeks of treatment and may worsen the symptoms of prostate cancer, including acute bladder outlet obstruction, obstructive renal failure, increased bone pain and spinal cord compression. Patients at particular risk are those with high-volume symptomatic bony disease. To counter the clinical flare in these patients, antiandrogens should be started one to two weeks before initiation of LHRH agonists and continued for one month in total.

Adverse effects of LHRH agonists include hot flushes, fatigue, reduced libido, osteoporosis and increased risk of diabetes and cardiovascular disease.[12] As a result, it is important to monitor bone mineral density (BMD) periodically, provide dietary advice, encourage weight-bearing exercises where possible and provide calcium and/or vitamin D supplementation. Blood glucose levels and cardiovascular risk factors should also be regularly monitored during treatment.

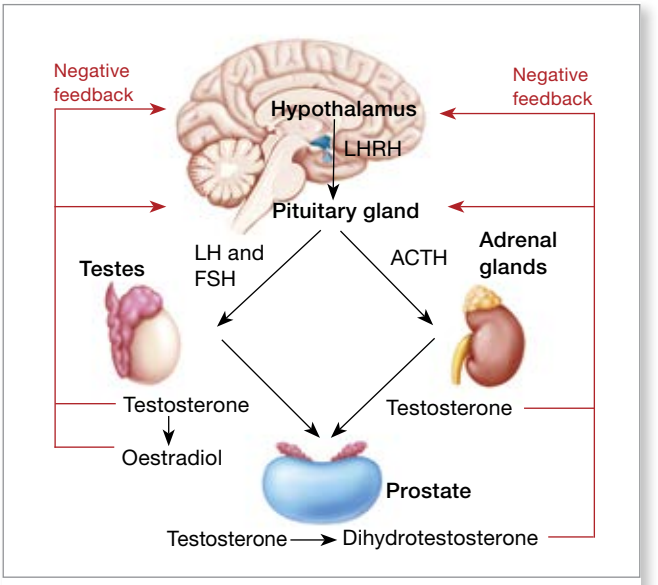

Figure. The hypothalamic-pituitary-gonadal axis. Luteinising hormone releasing hormone (LHRH) secreted by the hypothalamus stimulates the secretion of luteinising hormone (LH) and follicle-stimulating hormone (FSH) and adrenocorticotrophic hormone (ACTH) from the pituitary gland. This in turn stimulates the secretion of testosterone from the testes and adrenal glands. The testes is the primary source of testosterone, with the adrenals contributing 5 to 10% of androgens. Testosterone is then aromatised and converted to oestradiol and they exert a negative feedback on the hypothalamus and pituitary. In the prostate, testosterone is converted by the enzyme 5α-reductase to dihydrotestosterone.

Goserelin, leuprorelin and triptorelin are the LHRH agonists available in Australia and are all listed on the PBS (authority required) for locally advanced or metastatic prostate cancer. Each is delivered as depot injections: goserelin is given one or three monthly; leuprorelin one, three, four or six monthly; and triptorelin one, three or six monthly.

LHRH antagonists: degarelix

LHRH antagonists are a newer class of ADT that bind to pituitary LHRH receptors resulting in a rapid decrease in LH, FSH and circulating testosterone levels. They have been shown to be as effective as, but have several advantages over, LHRH agonists.[13] Compared with LHRH agonists, LHRH antagonists:

- enable testosterone castrate levels and prostate specific antigen (PSA) suppression levels to be reached significantly faster
- do not cause a clinical flare and consequently do not require antiandrogen supplementation
- are recommended in preference in patients with impending spinal cord compression.[13]

Adverse effects include injection-site reactions (mainly with the first dose), sweating and chills. Although long-term data are lacking, due to the suppression of testosterone it is anticipated that degarelix will decrease BMD and increase the risk of diabetes and cardiovascular disease.[12] Counselling on these issues and monitoring, as the case with those taking LHRH agonists, are recommended.

Degarelix is the only LHRH antagonist available in Australia and is listed on the PBS (authority required) for locally advanced or metastatic prostate cancer. Recommended dosing for degarelix is 240 mg subcutaneously for the first dose then 80 mg monthly thereafter. The use of LHRH antagonists in preference to LHRH agonists, however, is limited by the lack of long-term studies and their monthly administration.

Intermittent androgen deprivation *vs* continuous ADT

Intermittent androgen deprivation (IAD) is a treatment option often used after a standardised induction period. The rationale behind IAD is to delay the development of CRPC, improve quality of life and reduce the adverse effects related to long-term ADT. However, systematic reviews have shown that there is no significant difference in overall survival between IAD and continuous ADT and that IAD confers minimal benefit in overall quality of life.[14,15]

ANTIANDROGENS

Short-term use of antiandrogens has an established role to counter the clinical flare associated with LHRH agonists. However, their use as monotherapy and their use in addition to LHRH agonists for complete androgen blockade (CAB) are not the recommended standard of care as they do not improve overall survival.

Steroidal antiandrogens: cyproterone acetate

Cyproterone acetate acts by inhibiting androgen binding to androgen receptors and also has a progestogenic effect resulting in decreased production of testosterone. Steroidal antiandrogen monotherapy is not as effective as LHRH agonist therapy in improving overall survival and thus is not the recommended standard of care.[5,16]

Cyproterone's androgen-related pharmacological side effects include loss of libido, gynaecomastia and breast pain but these side effects are generally well tolerated. Its nonandrogen-related pharmacological side effects include cardiovascular toxicity, thrombosis and hepatoxicity.[17]

Cyproterone is PBS listed (authority required) for the treatment of advanced prostate cancer. The recommended dose for the treatment of hot flushes from LHRH agonist therapy is 50 mg one to three times daily adjusted according to response. The recommended dose for prevention of LHRH agonist-associated clinical flare is 100 mg twice daily and it should be started one to two weeks before initiating LHRH agonist treatment and continued for one month in total. The recommended dosage for monotherapy when LHRH analogues or surgery are ineffective, not tolerated or contraindicated or when oral therapy is preferred is 100 mg twice daily.

Nonsteroidal antiandrogens: flutamide, bicalutamide, nilutamide

Unlike steroidal antiandrogens, the sole action of nonsteroidal antiandrogens is to competitively inhibit androgen binding to androgen receptors, leading to slightly elevated testosterone levels.[18] Nonsteroidal antiandrogens have an established role to counter the clinical flare of LHRH agonists.

There are no comparative studies available for nilutamide monotherapy, and only one underpowered randomised controlled trial has compared the efficacy of flutamide monotherapy with castration, finding no significant different in overall survival.[19] Only high-dose bicalutamide has been shown to improve overall survival in highly selected, well-informed patients with metastatic prostate cancer with a low PSA level. However, this improvement was slight with a median survival difference of only six weeks.[20]

Studies comparing CAB with nonsteroidal antiandrogens versus monotherapy with surgical castration or LHRH agonists have yielded conflicting results.[21-23] Given the minimal, if any, benefit and increased side effect profile shown in these studies, the role of CAB is still debated.

Flutamide, bicalutamide and nilutamide appear to have comparable androgen-related pharmacological side effects (loss of libido, gynaecomastia and breast pain)[24] and, in contrast to steroidal antiandrogens, have a reduced loss of libido effect.[17] They do differ, however, in their nonandrogen-related pharmacological side effects,[25,26] with bicalutamide being the best tolerated of the three.[27] All three are hepatotoxic and regular monitoring of liver enzymes is required, with the highest incidence of hepatotoxicity associated with flutamide. Nilutamide can cause life-threatening interstitial pneumonitis, which is rare for both flutamide and bicalutamide. Nilutamide has the additional unique nonpharmacological side effect of delayed adaptation to darkness and alcohol intolerance.[17]

Bicalutamide, flutamide and nilutamide are listed on the PBS (authority required) for use in metastatic prostate cancer in conjunction with LHRH agonists. Nilutamide is also listed on the PBS (authority required) for use in locally advanced prostate cancer in conjunction with LHRH agonists. Recommended doses to counter the clinical flare of LHRH agonists are flutamide 250 mg two to three times daily, bicalutamide 50 mg once daily and nilutamide 150 mg twice daily. Recommended dosages for the use in CAB are flutamide 250 mg two to three times daily, bicalutamide 50 mg once daily and nilutamide 300 mg once daily for four weeks then 150 mg daily thereafter. The recommended dosage of bicalutamide for monotherapy (off label use) is 150 mg daily.

TABLE. SUMMARY OF MEDICAL TREATMENTS FOR PROSTATE CANCER

Medication	Mode of action	Indications/PBS status*
Androgen deprivation therapy		
LHRH agonists – Goserelin – Leuprorelin – Triptorelin	Continuous administration leads to down regulation of LHRH receptors, inhibiting LH and FSH secretion and thus testosterone production	PBS listed (authority required) for locally advanced or metastatic prostate cancer
LHRH antagonists – Degarelix	Binds to pituitary LHRH receptors resulting in a rapid decrease in LH, FSH and circulating testosterone levels	PBS listed (authority required) for locally advanced or metastatic prostate cancer
Oestrogens – Diethylstilboestrol	Acts via the negative feedback loop on the hypothalamic-pituitary-gonadal axis to reduce testosterone levels	Not currently available in Australia
Antiandrogens		
Steroidal antiandrogens – Cyproterone acetate	Inhibits androgen binding to androgen receptors and has a progestogenic effect, decreasing testosterone production. Counters the clinical flare of LHRH agonists	PBS listed (authority required) for advanced prostate cancer
Nonsteroidal antiandrogens – Flutamide – Bicalutamide – Nilutamide	Inhibits androgen binding to androgen receptors, leading to slightly elevated testosterone levels Counters the clinical flare of LHRH agonists	All three PBS listed (authority required) for mCRPR in conjunction with LHRH agonists; nilutamide additionally listed (authority required) for locally advanced prostate cancer in conjunction with LHRH agonists
Castrate resistant prostate cancer treatment		
Docetaxel	A tubulin-binding taxane	PBS listed for CRCP
Mitozantrone	A cytotoxic doxorubicin analogue	Used off label for mCRCP
New treatment options		
Cabazitaxel	Cytotoxic agent; a tubulin-binding taxane	PBS listed (authority required) for mCRPC post-docetaxel chemotherapy
Abiraterone acetate	Antiandrogen; a selective CYP17 inhibitor that increases mineralocorticoid and decreases glucocorticoid and androgen synthesis	PBS listed (authority required) for mCRPC in patients who failed docetaxel chemotherapy due to resistance or intolerance or in those predicted to be docetaxel intolerant
Enzalutamide	Antiandrogen that inhibits androgen receptor binding and nuclear translocation and transcription	PBS listed (authority required) for mCRPC in patients who failed docetaxel chemotherapy due to resistance or intolerance or in those predicted to be docetaxel intolerant
Radium-223 dichloride	Radiopharmaceutical that acts as a calcium mimetic, targeting new bone growth around bony metastases	Indicated for CRCP with symptomatic bone metastases without visceral metastatic disease. Not listed on the PBS
Sipuleucel-T	Immune therapy that kills prostate acid phosphatase-expressing prostate cancer cells	Not currently available in Australia
Adjuvant medication for metastatic castrate resistant prostate cancer treatment		
Zoledronic acid	Bisphosphonate that inhibits osteoclast-mediated bone resorption	PBS listed (authority required) for bone metastases from CRPC
Denosumab	Human monoclonal antibody that inhibits the RANK ligand, resulting in decreased formation and activity of osteoclasts, thus reducing bone resorption	PBS listed (authority required) for bone metastases from CRPC

ABBREVIATIONS: CRCP = castrate resistant prostate cancer; FSH = follicle stimulating hormone; LH = luteinising hormone; LHRH = luteinising hormone releasing hormone; mCRCP = metastatic castrate resistant prostate cancer; PBS = Pharmaceutical Benefit Scheme. * Refer to the PBS schedule for full details of authority requirements.

TREATMENT OF CRPC

Docetaxel

Nearly all men eventually develop progressive disease after ADT, a stage known as CRPC. It is marked by rising levels of PSA or radiological progression of disease, despite castrate levels of testosterone. Chemotherapy with docetaxel, a tubulin-binding taxane, has been the standard of care for patients with CRPC since being approved by the US Food and Drug Administration (FDA) in 2004 (and in Australia in 2005). However, results from the CHAARTED trial, presented at the American Society of Clinical Oncology (ASCO) Annual Scientific Meeting in June 2014, have shown that commencing docetaxel chemotherapy before the development of CRPC can improve overall survival in patients with high-volume metastatic disease.[3] This was defined as having visceral metastases or four or more bony metastases, including one beyond the pelvis and vertebral column. In this randomised controlled trial, the addition of six cycles of docetaxel chemotherapy to ADT as first-line treatment in metastatic prostate cancer improved overall survival compared with ADT alone by 17 months in those with high-volume metastatic disease. Although the study has not yet been published, this significant benefit in overall survival will likely alter the management of such patients.

Docetaxel is listed on the PBS for the treatment of CRPC, with a recommended dose of 75 mg/m^2 every three weeks combined with prednisone 5 mg twice a day, with up to 10 cycles being given.

Adverse effects of docetaxel include nail changes (nail pigmentation, splinter haemorrhage, subungual haematoma, Beau's lines, acute paronychia and onycholysis), neutropenia, febrile neutropenia, fluid retention and severe hypersensitivity reactions. Premedication with corticosteroids can reduce the incidence and severity of fluid retention and hypersensitivity reactions.

Mitozantrone

Mitozantrone is a cytotoxic doxorubicin analogue initially approved by the FDA for the treatment of acute myeloid leukaemia and later for hormone-refractory metastatic CRPC (mCRPC). Treatment with mitozantrone plus prednisone has been extensively studied and shown to reduce pain and improve the quality of life in men with hormone-refractory mCRPC; however, it does not improve overall survival.[28,29] As a result, the use of mitozantrone has been superseded by docetaxel and several new agents that have been shown to improve overall survival post-docetaxel therapy.

Adverse effects of mitozantrone include cardiac toxicity, which may be acute (arrhythmias), chronic (cardiomyopathy, heart failure) or delayed (arrhythmias, heart failure) as well as myelosuppression, with the white cell count nadir occurring at 10 days and recovery by day 21.

In Australia mitozantrone is used off label for mCRPC; its recommended dosage is 12 mg/m^2 intravenously every three weeks for up to six cycles plus prednisone 5 mg twice daily.

NEW TREATMENT OPTIONS FOR CRPC

In the past five years, five drugs have become available that have been shown to improve overall survival in patients with mCRPC following docetaxel chemotherapy. These include a cytotoxic agent (cabazitaxel), antiandrogens (abiraterone, enzalutamide) and a radiopharmaceutical agent (radium-223). Additionally, abiraterone, enzalutamide, radium-223 and an immune agent, sipuleucel-T, have been shown to improve overall survival in patients with mCRPC pre-docetaxel chemotherapy. Treatment for progressive CRPC remains unclear with no existing guidelines on the exact sequencing for delivering the available treatments.

Cabazitaxel

Cabazitaxel is an antitubulin taxane, like docetaxel, that has been shown to have antitumour activity in docetaxel-resistant tumours. In the TROPIC trial, cabazitaxel plus prednisone was compared with mitozantrone plus prednisone in men with mCRPC post-docetaxel therapy and showed an increase in overall survival of 15.1 months compared with 12.7 months.[30] Cabazitaxel was the first agent shown to improve overall survival in patients with mCRPC in the post-docetaxel setting and was approved by the FDA in 2010 (it was approved in Australia in 2011).

The FIRSTANA trial has recently completed enrolment and will evaluate the use of cabazitaxel in mCRPC in the pre-docetaxel setting. Dosage of cabazitaxel in the TROPIC trial was 25 mg/m^2 intravenously every three weeks plus prednisone 10 mg once daily; however, the current PROSELICA trial is comparing the efficacy and safety of cabazitaxel at doses of 20 mg/m^2 versus 25 mg/m^2.

Adverse effects of cabazitaxel include neutropenia, febrile neutropenia, diarrhoea and peripheral sensory neuropathy.[30] Monitoring for peripheral sensory loss and blood tests prior to each treatment cycle are recommended, in particular full blood counts for neutropenia, urea and electrolytes for diarrhoea and blood sugar levels because of the concomitant use of prednisone.

Cabazitaxel is PBS listed (authority required) for men with mCRPC post-docetaxel chemotherapy when used with prednisone.

Abiraterone acetate

Abiraterone is a selective CYP17 inhibitor that increases mineralocorticoid and decreases glucocorticoid and androgen synthesis. It was approved by the FDA in 2010 (and in Australia in 2012) for use in patients with CRPC post-docetaxel treatment because of encouraging preliminary results in the large phase III COU-AA-301 trial.[31] At final analysis, with a median follow up of 20.2 months, abiraterone plus prednisone *vs* prednisone alone in the post-docetaxel setting was associated with a longer median overall survival of 15.8 months compared with 11.2 months.[32] Abiraterone plus prednisone was also superior to prednisone alone in all secondary endpoints, including time to PSA progression, progression-free survival according

to radiological findings and PSA response rate.

In the follow-up COU-AA-302 trial, abiraterone was investigated for use in patients with mCRPC in the pre-docetaxel setting, with results showing that abiraterone plus prednisone delayed disease progression, pain and functional deterioration compared with prednisone alone.[33] As a result, abiraterone was approved by the FDA in 2013 for use in patients with chemotherapy-naïve mCRPC.

Adverse effects of abiraterone include fatigue, hypokalaemia, peripheral oedema and hypertension. As a result, monthly monitoring of blood pressure, potassium levels and fluid retention is recommended.

Abiraterone is taken 1000 mg orally once daily and must be taken on an empty stomach and in combination with prednisone 5 mg twice daily. It is listed on the PBS (authority required) for mCRPC in patients who have failed treatment with docetaxel because of resistance or intolerance, or in those unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel.

Enzalutamide

Enzalutamide is an antiandrogen that inhibits androgen receptor binding and nuclear translocation and transcription. In the AFFIRM trial, it was associated with a longer median overall survival than placebo (18.4 months *vs* 13.6 months) in men with mCRPC in the post-docetaxel setting.[34] It was also shown to be superior to placebo in all secondary endpoints including PSA response, soft tissue response, quality of life, time to PSA progression, radiographic progression-free survival and time to first skeletal-related event. In the PREVAIL trial, enzalutamide was also shown to decrease the risk of radiographic progression-free survival and overall survival in the pre-docetaxel setting.[35] As a result, the FDA recently approved its use in the pre-docetaxel setting in 2014 (having approved it in the post-docetaxel setting in 2012).

Adverse effects of enzalutamide include fatigue, diarrhoea and hot flushes.

Enzalutamide's dosage is 160 mg orally once daily and no concomitant prednisone is needed. It was listed on the PBS (authority required) in December 2014 for patients with mCRPC who have failed treatment with docetaxel because of resistance or intolerance, or in those unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel.

Radium-223 dichloride

Radium-223 dichloride (Ra-223) is a radiopharmaceutical that acts as a calcium mimetic, targeting new bone growth in and around bony metastases. It kills cancer cells by emitting alpha-particles from the decay of radium-223, leading to double-strand DNA breaks in tumour cells.

In the ALSYMPCA placebo-controlled trial, Ra-223 was administered to patients with mCRPC with symptomatic bony metastases who had previously received or were ineligible for docetaxel chemotherapy.[36] It improved overall survival (14.9 months *vs* 11.3 months for placebo) and prolonged the time to the first symptomatic skeletal event. The survival benefit was maintained regardless of prior docetaxel use and concurrent bisphosphonate use. Ra-223 is the only bone-specific drug associated with a survival benefit and was approved by the FDA in 2013 for the treatment of symptomatic bony mCRPC without known visceral metastases.

Ra-223 was approved in Australia in 2014 but is not currently listed on the PBS. Dosage in the ALSYMPCA trial was 50 kBq/kg with one injection administered every four weeks. Adverse effects include diarrhoea, nausea, thrombocytopenia and neutropenia.

Sipuleucel-T

Sipuleucel-T is the first immune therapy to improve overall survival in patients with asymptomatic or minimally symptomatic mCRPC in the pre-docetaxel setting. It is made in vitro using the patient's own antigen-presenting cells and after reinfusion, the vaccine stimulates the immune system to recognise and kill prostate acid phosphatase (PAP)-expressing prostate cancer cells.

In the IMPACT placebo-controlled trial, chemotherapy naïve patients with asymptomatic or minimal symptomatic mCRPC demonstrated an improvement in overall survival of 25.8 *vs* 21.7 months for placebo.[37] It did not, however, show any benefit in PSA response or progression-free survival.

Adverse effects of sipuleucel-T include fever, chills, fatigue, nausea, headaches and groin pain. It is not available in Australia and its use elsewhere is limited by its high cost.

ADJUVANT MEDICATION FOR MCRPC

Bisphosphonates: zoledronic acid

Most patients with CRPC have bone metastases, which is one of the most debilitating complications. Bisphosphonates, which inhibit osteoclast-mediated bone resorption, can be offered to patients with CRPC with bone metastases to prevent skeletal complications. The largest placebo-controlled trial to date showed that zoledronic acid delays the time to the first skeletal-related event and also reduces the number of skeletal-related events and pathological fractures, thereby improving quality of life.[38]

Adverse effects of zoledronic acid include nausea, vomiting, hypocalcaemia and renal impairment. Although rare, particularly with oral administration, the most serious adverse effect is osteonecrosis of the jaw. To prevent this, patients should be encouraged to maintain good dental hygiene and have regular dental examinations.

Regular monitoring should include calcium, phosphate and magnesium levels as well as renal function. Calcium and vitamin D supplementation should be provided. Recommended dosing of zoledronic acid in CRPC with bone metastases is 4 mg intravenously every three weeks. It is listed on the PBS (authority required) for bone metastases from CRPC.

Denosumab

Denosumab is a human monoclonal antibody that inhibits RANK ligand, resulting in decreased formation and activity of osteoclasts, thereby reducing bone resorption. Like zoledronic acid, denosumab reduces the incidence of skeletal-related events in mCRPC. In a comparative study between the two, time to first on-study skeletal-related event favoured denosumab over zoledronic acid (20.7 months *vs* 17.1 months, respectively) with no difference in overall survival.[39] Hypocalcaemia was more common in the denosumab arm and the risk of osteonecrosis of the jaw was similar between the two groups.

Monitoring should be as for bisphosphonates and, similarly, calcium and vitamin D supplementation should be provided to patients taking denosumab. The recommended dosing in patients with CRPC with bone metastases is 120 mg subcutaneously every four weeks. Denosumab is listed on the PBS (authority required) for bone metastases from CRPC.

CHEMOPREVENTION

5α-reductase inhibitors: dutasteride, finasteride

Although controversial, preventive medication for prostate cancer includes 5α-reductase inhibitors (5-ARIs) such as finasteride and dutasteride. 5-ARIs are primarily used to improve lower urinary tract symptoms secondary to benign prostatic hypertrophy (BPH) by preventing the conversion of testosterone to dihydrotestosterone, a potent cellular androgen that stimulates prostate growth. [40] Both dutasteride and finasteride have been studied as a chemopreventive agent for prostate cancer, and, although they have been shown to decrease the incidence of prostate cancer, an increased rate of high-grade prostate cancer was also observed.[41,42] An estimated one additional high-grade cancer would occur for every three to four lower grade cancers that would be prevented.[43] For this reason, regulatory authorities do not recommend 5-ARIs for chemoprevention in healthy men.

CONCLUSION

The medical management of advanced prostate cancer has evolved significantly over the past decade with a significant increase in treatment modalities available to patients. ADT remains the first-line treatment with options including surgical castration, LHRH agonists and newer LHRH antagonists. The addition of docetaxel chemotherapy to ADT is likely to become increasingly used as first-line therapy in patients with high-volume metastatic disease. Antiandrogens have an established role to counter the clinical flare associated with LHRH agonists; however, their use as monotherapy and in CAB are not the recommended standard of care as they do not improve overall survival.

Progression to CRPC is marked by rising PSA levels or radiological progression of disease, with docetaxel chemotherapy being the standard of care. Several therapeutic options are now available that can improve overall survival in patients with progressive disease pre- or post-docetaxel chemotherapy, including cabazitaxel, abiraterone, enzalutamide, Ra-223 and sipuleucel-T. There is current uncertainty as to the most beneficial sequencing of these medications. MT

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

COMPETING INTERESTS: None.

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