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New developments in metastatic prostate cancer therapy

Manickavasagar T, Gilson C, Chowdhury S, Kirby R. New developments in metastatic prostate cancer therapy.
Practitioner 2015; 259 (1781)21-24

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Practitioner
Medical Publishing Ltd

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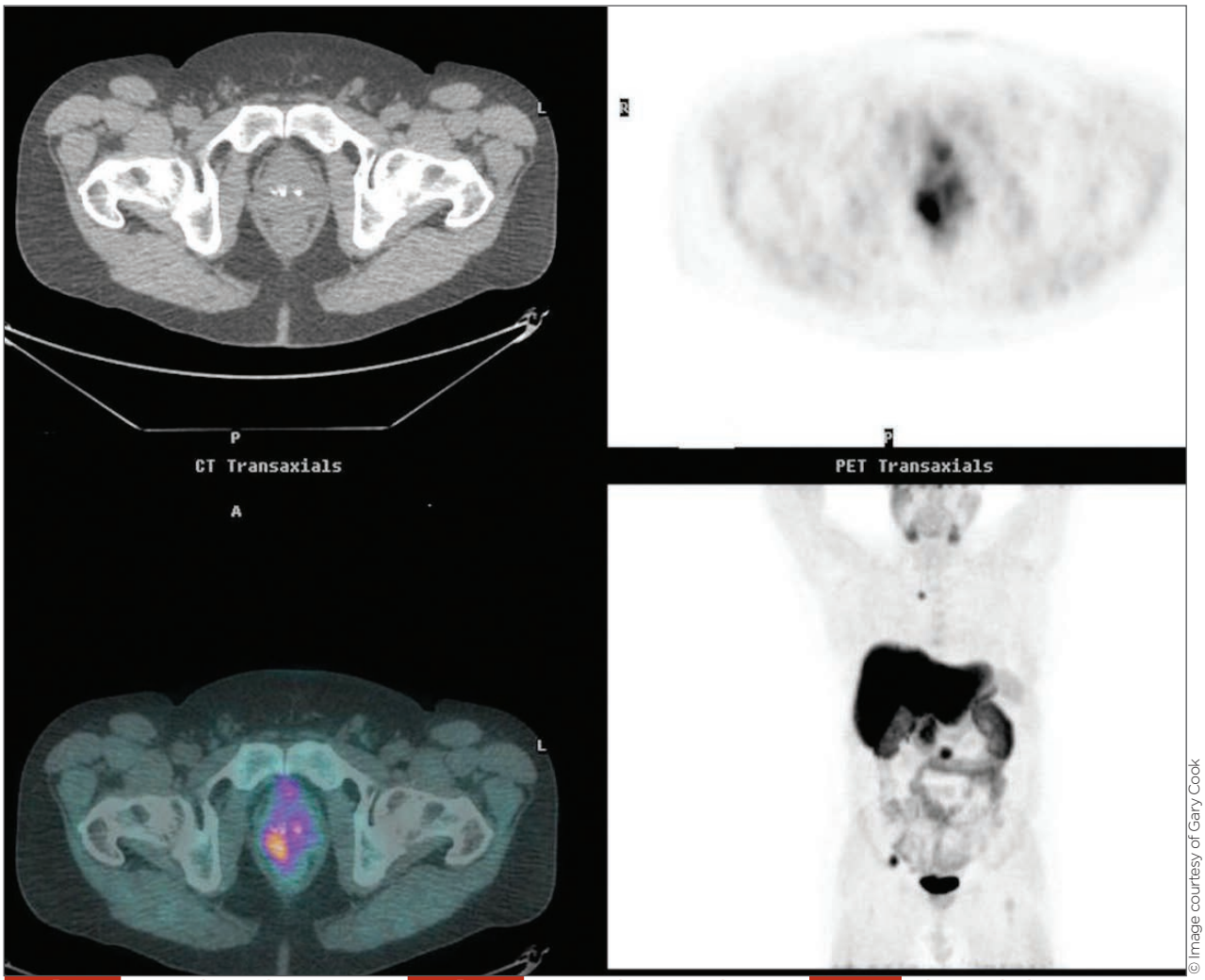

FIGURE 1
18F-choline PET/CT: Abnormal choline in a multifocal primary prostate tumour and three bone metastases affecting the right pelvis, thoracic and lumbar spine

What are the therapy options for metastatic disease?

WHILE METASTATIC PROSTATE CANCER REMAINS A LETHAL AND INCURABLE DISEASE, therapeutic advances over the past few years have led to improvements in survival and quality of life.

Prostate cancer is the most common cancer in men in the UK, accounting for nearly 25% of all male cancer cases. In 2011, 41,736 men were diagnosed with the disease. In the UK, it is the second most common cause of male cancer mortality, with 10,837 deaths in 2012.[1]

The incidence is increasing with age-standardised incidence rates rising by around a sixth in the past decade.[1] Improvements in detection rates and increased awareness of the condition are thought to be the cause.[2,3] However, improvement in survival rates, mainly due to increased diagnosis of earlier stage cancers, has resulted in death rates remaining fairly constant.

What are the risks and benefits of these treatments?

How should patients be monitored?

Nevertheless, metastatic prostate cancer is still commonly a lethal condition. The concept that 'men with prostate cancer die with rather than of their cancer' has been shown to be false.[4]

Many patients still present with metastatic disease. It is estimated that 10-20% of men in the UK present with locally advanced disease and 25-33% of patients treated radically, with either surgery or radiotherapy, will relapse (defined as a PSA rise of > 0.2 ng/ml).[5]

In the past ten years several »

Table 1

Risk factors for early failure of ADT[8,9]

- Distant lymph node metastases
- Visceral metastases
- Bone pain
- Weight loss at presentation
- Poor fitness
- Gleason score ≥ 8
- High PSA (> 500 significant risk)
- Poor PSA response (nadir ≥ 4)
- Younger age

systemic therapies have been developed for metastatic disease. However, the median overall survival remains only 3.5 years for men presenting with metastatic disease.[6]

TREATMENT

Androgen deprivation therapy

Androgen deprivation therapy (ADT) lowers intraprostatic androgen levels resulting in reduced androgen receptor stimulation and increased apoptosis.

The androgen receptor signalling pathway remains the most dominant pathway that has been discovered in solid tumour oncology with almost all patients responding to treatments that target this pathway.

ADT can be carried out either by surgical castration or by blocking the hypothalamic-pituitary gonadal axis using LHRH analogues or antagonists that inhibit LHRH levels resulting in testosterone levels < 50 ng/dl.

The use of LHRH analogues to achieve medical castration has become the gold standard for both locally advanced prostate cancer, combined with radiotherapy, and metastatic disease. ADT is the standard first-line treatment for advanced disease resulting in improvements in symptoms, radiological findings and PSA levels. Response rates to ADT are > 90% and in men with advanced prostate cancer, disease control is achieved for 12-18 months, on average.[7]

Although ADT is commenced by urologists and oncologists ongoing treatment may be continued in primary care or in nurse-led hospital clinics. All healthcare professionals need to be aware of the poor prognostic factors associated with early failure of ADT,[8] see table 1, left.

It is important to monitor these men closely for increasing PSA levels and signs of clinical progression. We see our patients at least once every two months and we advise them to contact us if they develop any symptoms suggestive of progressive disease such as bone pain, lethargy and weight loss.

'It is important to monitor men on ADT closely for increasing PSA levels and signs of clinical progression'

As patients with locally advanced and metastatic disease are living longer some are being treated with ADT for a prolonged period. Common side effects from ADT include fatigue, hot flushes and sexual dysfunction. Screening for dyslipidaemia and diabetes as well as serial measurements of BMD, serum vitamin D and calcium levels are recommended and close communication between primary and secondary care is crucial in providing comprehensive care.[10]

Education of patients and healthcare professionals is vital as many side effects of treatment can be reduced by relatively simple interventions.

Castrate refractory prostate cancer

Ultimately the majority of men with advanced prostate cancer will develop resistance to ADT. Progression of disease despite castrate levels of testosterone is described as castrate refractory prostate cancer (CRPC).

Androgen receptor signalling continues to be a critical pathway, stimulating tumour growth despite castrate levels of androgens. It is however crucial to maintain castrate levels of androgens and ADT treatment should continue in addition to further treatments.

Docetaxel is the standard first-line therapy recommended by international guidelines for patients with symptomatic metastatic CRPC who are suitable candidates for chemotherapy. It was the first agent to show an improvement in overall survival and improved quality of life.[11]

Importantly, a recent trial has shown significant improvement in outcomes in a cohort of men with newly diagnosed metastatic prostate cancer. The ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED), demonstrated that patients presenting with high volume metastatic disease (defined as the presence of visceral metastases and/or 4 or more bone metastases with one outside the axial skeleton), with hormone sensitive disease have a 17 month improvement (32 vs 49 months) in median overall survival when treated with docetaxel. If confirmed, this is practice changing and will mean docetaxel will be used at an earlier stage in the disease.

Table 2

Recent phase III studies in metastatic prostate cancer

Agent	Patient population	Method of action	Trial	Year of publication	Median survival benefit	Additional benefit
Docetaxel[12]	HSPC and high volume disease*	Chemotherapy	CHAARTED	ASCO abstract 2014	17 months	Improved QOL
Abiraterone[13]	CRPC (pre-docetaxel)	AR targeted	COA-AA-302	2013	4.4 months	Reduced pain
Enzalutamide[14]	CRPC (pre-docetaxel)	AR targeted	PREVAIL	2014	2.2 months	NA
Alpharadin[17]	CRPC	Radioisotope	ALSYMPCA	2013	3.6 months	Reduced pain

AR = androgen receptor; HSPC = hormone sensitive prostate cancer; CRPC = castrate resistant prostate cancer; * high volume disease is defined as the presence of visceral metastases and/or 4 or more bone metastases with one outside the axial skeleton

key points

SELECTED BY

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Prostate cancer is the most common cancer in men in the UK, accounting for nearly 25% of all male cancer cases and is the second most common cause of male cancer mortality in the UK. The incidence is increasing with age-standardised incidence rates rising by around a sixth in the past decade. Improvements in detection rates and increased awareness of the condition are thought to be the cause. However, improvement in survival rates, mainly due to increased diagnosis of earlier stage cancers, has resulted in death rates remaining fairly constant.

Metastatic prostate cancer is still commonly a lethal condition. The concept that 'men with prostate cancer die with rather than of their cancer' has been shown to be false. It is estimated that 10-20% of men in the UK present with locally advanced disease. Median overall survival remains only 3.5 years for men presenting with metastatic disease.

The use of LHRH analogues to achieve medical castration has become the gold standard for both locally advanced prostate cancer, combined with radiotherapy, and metastatic disease. Androgen deprivation therapy (ADT) is the standard first-line treatment for advanced disease resulting in improvements in symptoms, radiological findings and PSA levels.

Although ADT is commenced by urologists and oncologists ongoing treatment may be continued in primary care. It is important to monitor these men closely for increasing PSA levels and signs of clinical progression. Common side effects from ADT include fatigue, hot flushes and sexual dysfunction. Screening for dyslipidaemia and diabetes as well as serial measurements of BMD, serum vitamin D and calcium levels are recommended and close communication between primary and secondary care is crucial in providing comprehensive care.

Ultimately the majority of men with advanced prostate cancer will develop resistance to ADT. Docetaxel is the standard first-line therapy recommended by international guidelines for patients with symptomatic metastatic castrate refractory prostate cancer who are suitable candidates for chemotherapy. It was the first agent to show an improvement in overall survival and improved quality of life.

More than 90% of patients with castrate refractory prostate cancer have bone metastases. Radium-223 dichloride is a novel alpha-emitting radiopharmaceutical agent, which mimics calcium and therefore targets bone metastases. It is indicated in patients with metastatic castrate refractory prostate cancer who have symptomatic bone metastases without visceral metastases.

Until recently, there were no treatments showing a survival benefit apart from docetaxel. However, recent trials have shown promising results, see table 2, p22.

Androgen receptor targeted therapy
The first AR-targeted therapy with demonstrable clinical benefit was abiraterone acetate. It is a potent, selective and irreversible inhibitor of CYP17 alpha-hydroxylase and C17, 20-lyase that catalyse two key steps in androgen biosynthesis, thus reducing androgen levels further.[15]

Large clinical trials have shown a survival advantage with abiraterone used either before or after chemotherapy. NICE approval has been gained for post-chemotherapy use. In patients who had abiraterone following docetaxel, there was a 28% reduction in risk of death, with a median time to progression of 8.5 months, hazard ratio (HR) 0.74 (95% CI: 0.64–0.86; P < 0.0001).[15]

The use of abiraterone prior to chemotherapy is increasing in current clinical practice. In this setting, a recent study has shown that abiraterone prolongs overall survival by 4.4 months, 34.7 vs 30.3 months, HR 0.81 (CI:0.70-0.93; P = 0.0033). It also results in significant palliative benefits, including reduction in pain and rates of skeletal events.[13]

Enzalutamide targets the androgen receptor directly. It is a second generation anti-androgen, with high affinity and selectivity for AR binding. Furthermore, it blocks nuclear translocation and reduces recruitment of co-activators.

The initial phase III study of enzalutamide randomised patients with metastatic CRPC to enzalutamide versus placebo in the post-chemotherapy setting.[16] The study was halted prematurely as an interim analysis demonstrated a 4.8 month survival advantage in the active treatment arm. In the pre-docetaxel setting, the PREVAIL study found a 30% reduction in risk of death with enzalutamide compared with placebo, overall survival HR 0.70 (95% CI: 0.59-0.83; P < 0.0001).[14]

Further work is currently underway to determine the sequence in which this treatment is given to ensure the best outcomes for patients.

Radioisotopes
More than 90% of patients with CRPC have bone metastases.[18] Radium-223 dichloride is a novel alpha-emitting radiopharmaceutical agent, which mimics calcium and therefore targets bone metastases. It is indicated in patients with metastatic CRPC who have symptomatic bone metastases without visceral metastases.

In the phase III ALSYMPCA trial, there was a 3.6 month improvement in overall survival, HR 0.70 (95% CI:0.55-0.88; P = 0.00185).[19]

'Radium-223 offers an innovative treatment for metastatic prostate cancer with predominantly bone involvement'

More impressively, it showed palliative benefit, reducing pain, preserving quality of life and delaying the time to first skeletal adverse event by 5.8 months, 15.6 vs 9.8 months, HR 0.66 (95% CI: 0.52-0.83; P < 0.001).[19] This offers an innovative treatment for metastatic prostate cancer with predominantly bone involvement.

THE ROLE OF THE GP

GPs have a key role in ensuring that their patients are referred to appropriate centres and specialist clinicians, and where necessary, are able to get a second opinion.

The best outcomes are most likely to be achieved in specialist centres, treating large numbers of patients and where men with advanced prostate cancer have access to the latest clinical trials and therapies.

'GPs have a key role in ensuring that their patients are referred to specialist centres and clinicians'

Patients with advanced disease should be cared for by a multi-disciplinary team. This should include urology, specialist clinical nursing, oncology, palliative care and specialist pathology and radiology, as well as primary care. Ideally, patients should have access to these specialist »

disciplines within the same unit.

It is vital that the patient, and their GP, have defined points of contact. The key worker may be a specialist nurse, a urologist or oncologist. Direct access to the key worker can be facilitated by phone and email.

As patients live longer with increasing treatment options, education of all the healthcare professionals involved in their care is crucial in ensuring holistic care for this complex disease.

CONCLUSION

The advent of new agents for advanced prostate cancer raises important questions regarding optimal sequencing, patient selection, combination therapy and new toxicities. The CHAARTED study has shown that perhaps using these agents earlier in the disease before castrate resistance has occurred will provide the most benefit and this is the subject of several large phase III studies.

'The treatment of prostate cancer is moving towards personalised care, where therapy will be determined by tumour biology'

The treatment of prostate cancer continues to advance and is moving towards personalised care, where therapy will be determined by tumour biology. An example of this is androgen receptor splice variants, where the ligand binding domain is lost. This is the part of the receptor that ADT, abiraterone and enzalutamide target and is emerging as an important resistance mechanism for these agents. The AR splice variants retain transcriptional activity and new therapies are targeting this part of the receptor.

Advanced prostate cancer, remains an incurable and lethal disease. Innovation continues to provide new hope for our patients with advanced disease, with improved survival while maintaining quality of life.

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