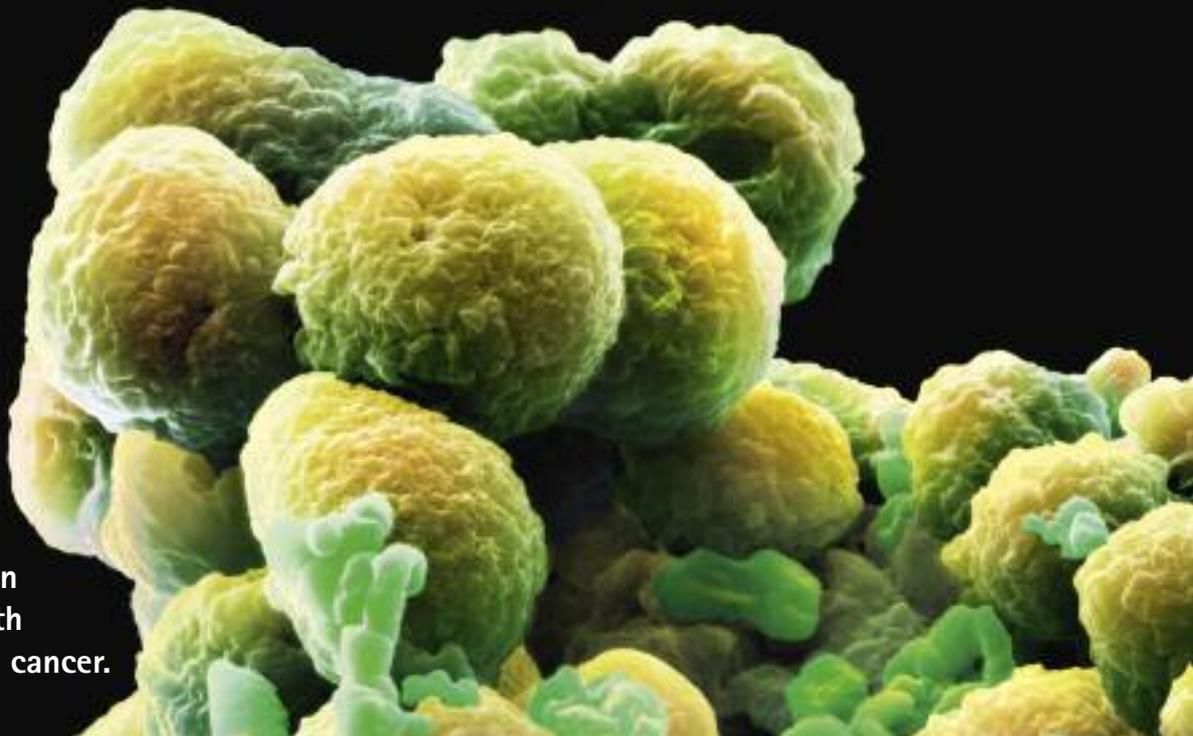


Treatment of metastatic prostate cancer

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The authors review the current therapeutic approaches and consider the many remaining questions and challenges facing clinicians involved in the care of men with metastatic prostate cancer.



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Prostate cancer is the most common male cancer in the UK, with more than 41 000 new diagnoses each year.¹ Prostate cancer is a highly heterogeneous disease. Localised disease may be successfully treated with radical prostatectomy or radiotherapy; however, 25–33% of men treated radically will relapse. Between 10 and 20% present with locally advanced disease, while 5% have metastatic disease at diagnosis (Figure 1).^{2,3} Metastatic disease is an incurable, fatal condition in most and prostate cancer is the second most common cause of cancer-related death in men in the UK.¹

In recent years the management of metastatic prostate cancer has changed

dramatically, with five novel therapies being shown to improve survival since 2011 (Table 1). In spite of this, men with metastatic disease have a median overall survival of just 3.5 years, although this ranges from 1.9 to 7.6 years, highlighting the clinical heterogeneity that exists.⁴

With this changing therapeutic landscape come new toxicities and new clinical considerations (Table 2). Men with metastatic prostate cancer are typically elderly, often with several comorbidities. Their complex needs are best met by multidisciplinary teams involving several specialties, including medical and clinical oncology, urology and palliative care. Involvement of GPs and clinical nurse specialists is crucial and clear channels

VIDEO

Go to the *Trends* website to view an accompanying video by Simon Chowdhury
www.trendsinsenhealth.com/video

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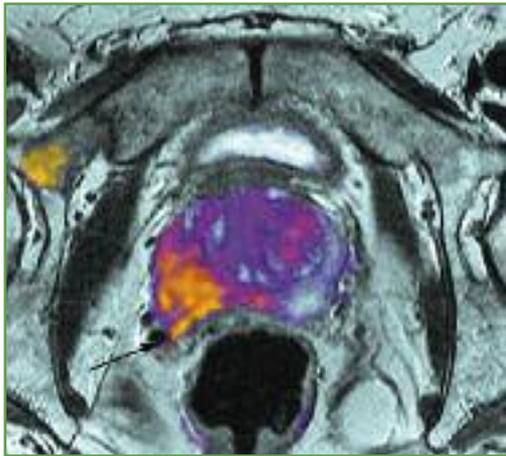


Figure 1. Restriction spectrum imaging MRI image showing high-grade cancer extending from the prostate (purple) into the right seminal vesicle (orange) and a bony metastasis in the right hip (upper left, orange). Image courtesy of David Karow, UCSD

of communication are necessary in order to manage treatment effects such as the potential impact on cardiovascular and metabolic function.

FIRST-LINE TREATMENT

Androgen deprivation therapy

Since first demonstrated by Huggins and Hodges, androgen deprivation remains the mainstay of systemic treatment for both locally advanced and metastatic prostate cancer. This is usually achieved using luteinising hormone-releasing hormone (LHRH) agonists, which are the first line of treatment and are continued during all subsequent therapies.

Androgen deprivation therapy (ADT) is one of the most active therapies in solid

tumour oncology, with response rates of over 90%. In men with high-risk localised or metastatic disease at presentation, ADT alone provides disease control for a median of 11 months.⁴

Recognition of the risk factors for ADT failure is important, with clinical and PSA monitoring recommended at least every 2 months for those at risk of early progression (Box 1). As patients remain on ADT for longer, there is increased awareness of the risks of reduced bone mineral density (BMD), and increased cardiovascular morbidity and mortality. Screening for dyslipidaemia and diabetes, as well as serial measurements of BMD, serum vitamin D and calcium levels are recommended.

Treatment	Trial, year of publication	Comparator	Median overall survival (months)	Additional benefits
Hormone-sensitive metastatic prostate cancer				
Docetaxel	CHAARTED, 2014 ASCO presentation	ADT	High-volume disease: 17.0 (49.2 vs 32.2)	
Docetaxel	STAMPEDE, 2015 ASCO presentations	ADT	10 (67 vs 77) Metastatic patients: 22 (43 vs 65)	
mCRPC pre-docetaxel				
Abiraterone	COU-AAA-302, 2013	Placebo	4.4 (34.7 vs 30.3)	Delayed time to SRE Improved pain Improved QOL
Enzalutamide	PREVAIL, 2014	Placebo	2.2 (32.4 vs 30.2)	Delayed time to SRE Improved QOL
Docetaxel	TAX 327, 2004	Mitoxantrone	2.9 (19.2 vs 16.3)	Improved QOL
mCRPC post-docetaxel				
Abiraterone	COU-AAA-301, 2011	Placebo	4.6 (15.8 vs 11.2)	Delayed time to SRE Improved pain
Enzalutamide	AFFIRM	Placebo	4.8 (18.4 vs 13.6)	Delayed time to SRE
Cabazitaxel	TROPIC, 2010	Mitoxantrone	2.4 (15.1 vs 12.7)	Improved pain
Radium 233	ALSYMPCA, 2013	Placebo	3.6 (14.9 vs 11.3)	Improved pain Delayed time to SRE Improved QOL
ADT, androgen deprivation therapy; mCRPC, metastatic castrate-resistant prostate cancer; SRE, skeletal-related event; QOL, quality of life.				

Table 1. Treatments shown to improve survival in metastatic prostate cancer

Treatment	Side-effects	Monitoring
LHRHa	Fatigue, hot flushes, sexual dysfunction Reduced BMD Increased cardiovascular risk	Vitamin D levels DEXA Modification of cardiovascular risk factors, eg blood pressure control
Abiraterone	Fatigue, hypertension, GI disturbance, deranged LFTs, hypokalaemia, peripheral oedema Steroid associated: insulin resistance, reduced BMD, increased cardiovascular risk	Blood pressure Liver function and electrolytes Diabetic screening in those at higher risk
Enzalutamide	Fatigue, hypertension, breast bud tenderness, insomnia/anxiety	Blood pressure Liver function
Docetaxel	Fatigue, neutropenia, anaemia, peripheral neuropathy, alopecia, pneumonitis	Full blood count Liver function Renal function
Cabazitaxel	Fatigue, neutropenia, diarrhoea, anaemia, haematuria, renal impairment, peripheral neuropathy	Full blood count Liver function Renal function
Radium 233	Anaemia, thrombocytopenia, diarrhoea	Full blood count
LHRHa, luteinising hormone-releasing hormone agonist; BMD, bone mineral density; DEXA, dual-energy x-ray absorptiometry; GI, gastrointestinal; LFTs, liver function tests.		

Table 2. Common treatment side-effects and recommended monitoring

Docetaxel in hormone-sensitive metastatic disease

The chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (CHAARTED) study demonstrated a significant improvement in overall survival with docetaxel given in metastatic hormone-sensitive disease.⁵ The greatest benefit was seen in patients with high-volume disease, defined as visceral metastases and/or four or more bone metastases with at least one beyond the axial skeleton. This group demonstrated a median overall survival advantage of 17 months (49.2 versus 32.2 months; HR 0.60, $p=0.0006$).

Data from the MRC STAMPEDE trial, recently presented at ASCO, again demonstrates an impressive survival advantage when adding docetaxel to ADT in hormone-sensitive advanced prostate cancer. In those with metastatic disease, the median overall survival advantage was 22 months (43 versus 65 months). Benefit was also seen in patients with locally advanced disease in whom failure-free survival was significantly improved. Overall, in all patients with advanced disease, docetaxel delayed the time to relapse by 38%.

This is practice changing in the management of metastatic prostate

Box 1. Risk factors for early failure of androgen deprivation therapy

- Visceral metastases
- Distant nodal metastases
- Bone pain
- Weight loss at presentation
- Poor performance status
- Younger age (<60 years)
- Gleason score ≥ 8
- High PSA at presentation (>500 high risk)
- Poor PSA response (nadir ≥ 4)

cancer and represents a significant advance in patient care. It also raises several questions regarding the effectiveness and tolerability of subsequent therapies post-chemotherapy and the potential role of docetaxel re-challenge in the castrate-resistant setting.

The CHARTED trial demonstrates one way to stratify patients clinically, but the development of predictive biomarkers to help identify patients for whom this approach will benefit most is a crucial next step and focus of ongoing research.

CASTRATE-RESISTANT METASTATIC PROSTATE CANCER

Even after initial disease control with ADT alone, all patients with metastatic prostate cancer will eventually progress in spite of castrate levels of testosterone, termed castrate-resistant prostate cancer (CRPC).

Chemotherapy

Docetaxel was the first treatment to demonstrate a survival benefit in metastatic CRPC (mCRPC) over a decade ago. The TAX327 trial showed a survival advantage compared with the active, but outdated comparator of mitoxantrone (19.2 versus 16.3 months; HR 0.79, $p=0.004$).⁶

While docetaxel remains approved by NICE as the first-line treatment of mCRPC, updated data are required in the era of

androgen receptor (AR) targeted therapies for the management of mCRPC. Current guidelines suggest docetaxel should be considered as first-line treatment over abiraterone or enzalutamide when there are extensive or symptomatic metastases, a rapid PSA doubling time, high Gleason score or a short-term response to primary ADT.⁷

Cabazitaxel is a second-generation microtubule-targeting chemotherapy shown to be effective in patients following docetaxel where resistance or relapse has occurred. The TROPIC study demonstrated cabazitaxel improved overall survival compared with mitoxantrone in patients, 25% of whom had visceral metastases.⁸ Cabazitaxel has recently been reinstated and is once again accessible via the Cancer Drugs Fund for patients in England, providing a further line of treatment in the post-docetaxel setting.

AR-TARGETED THERAPIES

Abiraterone

Abiraterone decreases intratumoral androgen levels through the inhibition of CYP17 alpha-hydroxylase and C17,20-lyase, enzymes responsible for androgen and cortisol production. In large phase 3 studies abiraterone has been shown to improve survival and quality of life when given after docetaxel, and more recently in chemotherapy-naïve patients when it prolongs overall survival by 4.4 months (34.7 versus 30.3 months; HR 0.81; CI 0.70–0.93, $p=0.0033$).^{9,10}

Abiraterone is a well-tolerated oral treatment. Common side-effects include hypertension, fatigue, gastrointestinal disturbance and deranged liver function tests, which are seen in around 10%. Abiraterone is co-prescribed with prednisolone 5mg twice daily, which may have additional benefits including improved pain control, appetite, fatigue and nausea. As abiraterone is increasingly being used prior to docetaxel, patients may receive low-dose steroids for several years.

In addition to ADT, steroids also potentially increase cardiovascular risk and reduce BMD. Monitoring of blood pressure and screening those at higher risk of diabetes is important, which in turn is reliant on good communication between primary and secondary care.

Enzalutamide

Enzalutamide is an oral AR inhibitor, which targets multiple steps in the AR signalling pathway through inhibiting AR nuclear translocation and recruitment of coactivators. Enzalutamide has been shown to improve overall survival when given following docetaxel and in chemotherapy-naïve patients, where it has been shown to reduce the risk of death by 30% (HR 0.70; CI 0.59–0.83, $p<0.0001$).^{11,12}

Additional benefits include a significant delay in the time to first skeletal-related events including fracture or need for palliative radiotherapy, together with improved pain control and quality of life. In contrast to abiraterone, enzalutamide has been shown to be effective in chemotherapy-naïve patients with visceral metastases.

Enzalutamide does not require the co-prescription of steroids and therefore is also preferred where there are contraindications to their long-term use. Importantly, *post hoc* subgroup analysis from the AFFIRM trial demonstrated similar survival benefit in patients above and below the age of 75 years, although clinical experience suggests that older patients are more susceptible to fatigue.¹² This, together with hypertension, are the most common side-effects; gastrointestinal disturbance and breast-bud tenderness are also seen.

The effectiveness of sequential use of abiraterone and enzalutamide is currently being examined in several clinical trials. Outside of a clinical trial, in the UK treatment can be changed only if there is intolerance and within the first 12 weeks of therapy.

RADIOISOTOPES

Radium 223 is a bone-targeted, alpha-emitting radiopharmaceutical and the latest therapy that has been shown to improve survival in mCRPC. In a placebo-controlled trial, radium 223 demonstrated a 3.6-month median survival advantage, but more impressively a nearly 6-month delay in the time to symptomatic skeletal event, defined as bone pain requiring radiotherapy; fracture or spinal cord compression.¹³

Treatment is given as a 4-weekly infusion for 6 months and requires close monitoring, as myelosuppression, particularly anaemia and thrombocytopenia, are common. Interestingly, PSA is usually unaffected, with only 16% demonstrating a PSA decline of 30% or more; response to treatment is therefore assessed clinically and by monitoring alkaline phosphatase.

CHALLENGES AND REMAINING QUESTIONS

Advances in the understanding of AR biology, earlier use of current therapies and innovative new therapeutics are enabling a move away from the therapeutic nihilism that previously surrounded the management of metastatic prostate cancer.

With new therapeutic options come many questions, including the optimum sequencing of treatment, how best to select patients and how to predict and overcome therapeutic resistance. Current challenges in addressing these questions remain the lack of head-to-head comparisons and data derived using outdated comparators, together with the lack of validated biomarkers to predict response and provide prognostic information.

There is a paucity of trial data to address the question of treatment sequencing. However, evidence from subgroup analyses from the COU-AA-301 trial suggests that cross-resistance may

occur between abiraterone and docetaxel, with patients who progressed on docetaxel benefiting less from subsequent abiraterone.¹⁴ The benefit of docetaxel in CRPC was shown prior to AR-targeted therapies and data from a small series of patients receiving docetaxel after abiraterone or enzalutamide suggest docetaxel may be less effective given in this sequence, with a median overall survival of 12.5 months compared with 18.9 months in the TAX327 trial.¹⁵

Small gains in a minority of patients were demonstrated when abiraterone was given following enzalutamide, albeit in two small cohorts where 25–29% of patients were Eastern Cooperative Oncology Group performance status 2.^{16,17} In a series of 35 patients receiving enzalutamide following abiraterone and docetaxel, the median time to progression was just 4 months.¹⁸ Results of ongoing trials are awaited; however, it is clear that predictive biomarkers are urgently needed to inform treatment sequencing, and understanding the mechanisms of resistance is key.

Combination treatments

The increased understanding of the mechanisms of resistance, together with novel therapies with varying therapeutic targets, provides a rationale for treatment combinations, many of which are being evaluated in ongoing clinical trials. The latest arm to be added to the MRC STAMPEDE trial is dual AR blockade with enzalutamide and abiraterone given together with ADT in hormone-sensitive metastatic disease. Combined AR targeting with radium 233 is being investigated in several phase 2 studies. The observation that mutations that may explain taxane resistance affect AR nuclear translocation provides a rationale to combine docetaxel with enzalutamide, which prevents AR translocation and also coactivator recruitment.¹⁹

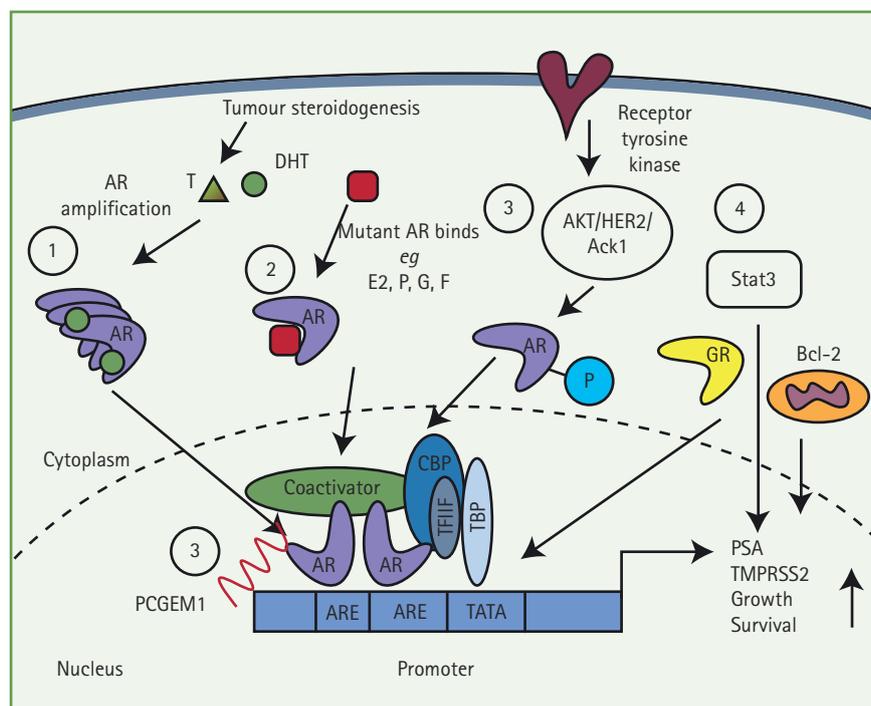


Figure 2. Mechanisms promoting the progression of castration-resistant prostate cancer. (1) Androgen receptor (AR) overexpression coupled with continued tumour steroidogenesis. (2) Promiscuous binding and activation of mutant AR by alternative ligands, such as estrogen (E2), progesterone (P), glucocorticoids (G) and flutamide (F). (3) Ligand-independent mechanisms of AR activation via crosstalk with AKT, HER2, and Ack1 kinases that phosphorylate the AR and via long non-coding RNAs (eg PCGEM1) that bind to the AR to stimulate transcription of AR target genes. (4) AR-independent pathways, in which cancer cell survival and growth are directed by Stat3 signalling or by upregulation of anti-apoptotic Bcl-2. Glucocorticoid receptor (GR) was found to activate a similar set of AR target genes necessary for survival of cancer cells²⁶

Mechanisms of resistance

Advances in the understanding of AR biology have been crucial in exploring mechanisms of therapeutic resistance and represent an important step in attempting to personalise the treatment of prostate cancer (Figure 2). Aberrations in the AR pathways help explain resistance to anti-androgen treatments and over half of patients with CRPC will harbour at least one.²⁰ These can be ligand dependent, such as AR amplification, enabling ongoing prostate cancer cell growth in the context of castrate levels of testosterone. Alternatively, AR mutations can occur, such as splice variants, eg ARV7. These result in truncated AR proteins, which lack a ligand-binding domain and allow ligand-independent activation of the AR pathway

and have been associated with resistance to enzalutamide and abiraterone.²¹

One potential approach, capable of overcoming therapeutic resistance due to mutated AR, is to target post-receptor signal transduction and DNA transcription. Examples of these include BET inhibitors, recently demonstrated to be effective in pre-clinical models of CRPC and antisense oligonucleotides, capable of inhibiting AR-mediated DNA transcription, currently in early phase clinical trials (NCT02122051).^{22,23}

Increased understanding of the interaction between AR and other oncological pathways, such as the PI3K-PTEEN-AKT pathway, provides another rationale

for alternative therapeutic approaches. PTEN loss is seen in around 40% of CRPC patients and is associated with shorter overall survival and earlier treatment failure with abiraterone.²⁴ Dual inhibition of AR and PI3K has been shown to be a promising therapeutic approach in pre-clinical studies, justifying further investigation.²⁵

CONCLUSION

The management of metastatic prostate cancer is changing rapidly and new treatments are enabling men to live longer with a better quality of life. Informed multidisciplinary working is key in the management of longer-term treatment complications and ensuring truly holistic care. The crucial next step is to unpick this heterogeneous disease in order to target therapies appropriately and enable personalised management of prostate cancer, improving care for all men affected by this fatal disease.

Declaration of interests: none declared.

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