Sequencing treatment for metastatic prostate cancer

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In the past 10 years there have been significant advances in the understanding and treatment of metastatic prostate cancer. These include the earlier use of docetaxel chemotherapy, and the use of abiraterone, enzalutamide, radium-223 and cabazitaxel.[1–6] This has led to significant improvements in survival, but has increased the choice and complexity of treatment. In this article, the authors review these advances and look at the sequencing of agents.

In 1941, Huggins and Hodges first demonstrated that prostate cancers are driven by androgens, and that androgen deprivation therapy (ADT) is highly active against prostate cancer.[7] ADT, which lowers testosterone to castration levels, remains the mainstay of systemic treatment. It is still used as an initial treatment for metastatic prostate cancer and will usually continue throughout the duration of all other anti-cancer treatments. ADT is typically a luteinising hormone-releasing hormone (LHRH) agonist that blocks the hypothalamic-pituitary-testicular axis.

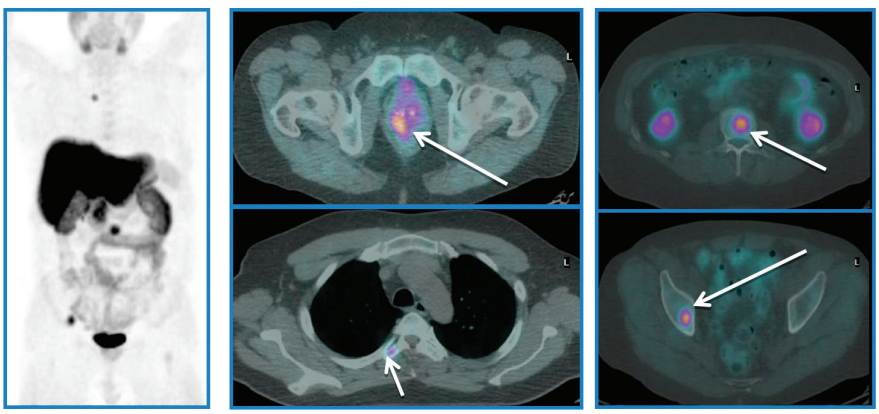

Figure 1. 64-year-old male with newly diagnosed metastatic prostate cancer: presenting PSA 134, Gleason 4+4. PET shows primary tumour uptake and bone metastases. Docetaxel plus androgen deprivation therapy is currently the first-line approach. Images courtesy of Professor Gary Cook, Guy's and St Thomas' NHS Foundation Trust

90% of patients respond to ADT, with a failure-free survival of approximately 45 months.[2]

ADT is usually given as an injection every three months by the patient's general practice, although six-monthly preparations are also available. The occurrence of the 'flare' phenomenon, whereby LHRH agonists can cause a transient increase in testosterone levels resulting in an initial worsening of symptoms, remains controversial.[8] To prevent a potential 'flare', an anti-androgen should be started two weeks prior to initiation of LHRH agonists.

If men present with metastatic disease they are referred to as having metastatic hormone-sensitive prostate cancer (mHSPC) (Figure 1). Once the testosterone level is <50ng/dL on ADT, the patient is referred to as having metastatic castration-resistant prostate cancer (mCRPC).

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CHEMOTHERAPY

Docetaxel

Chemotherapy was first shown to demonstrate a survival benefit in prostate cancer in 2004 in mCRPC, leading to the licensing of docetaxel, a taxane mitotic inhibitor, as a treatment for mCRPC.[9,10] Docetaxel is given intravenously every 21 days for up to 10 doses.

In 2014, the CHAARTED study showed the addition of docetaxel to ADT significantly improved overall survival in mHSPC by around 14 months (58 versus 44 months).[1] The absolute benefit in survival was greater in the subgroup with high-volume disease, as described in Table 1.

In 2015 the results of the STAMPEDE trial were published. This large phase 3, randomised controlled trial compared men with both high-risk locally advanced prostate cancer and metastatic prostate cancer, receiving six doses of docetaxel with ADT, compared to ADT alone.[2] It demonstrated an overall survival benefit of 10 months (from 71 to 81 months) in those receiving docetaxel in addition to ADT. The difference was even greater in the subgroup of patients with metastatic disease, with an overall survival benefit of 15 months (45 versus 60 months). The toxicity profiles in both trials were acceptable.[1,2] In fact, men may tolerate chemotherapy better earlier in their disease course when they are fitter.

In contrast, the results of the GETUG-AFU trial showed that there was no statistically significant survival benefit when giving docetaxel in the hormone-sensitive setting.[11] However, a meta-analysis of 2992 patients from five randomised controlled trials, including CHAARTED, STAMPEDE and GETUG-AFU, showed an absolute improvement in four-year survival of 9% when giving docetaxel in the hormone sensitive setting.[3]

We believe the evidence is compelling and that clinicians should now discuss six cycles of 'upfront' docetaxel with all patients with mHSPC who are fit enough to receive chemotherapy. This means that

Treatment	Trial, year of publication	Comparator	Median overall survival benefit (months)	*p* value
Metastatic hormone-sensitive prostate cancer				
Docetaxel	CHAARTED, 2015	ADT	Whole population: 13.6 (57.6 versus 44.0) High volume metastatic disease:* 17.0 (49.2 versus 32.2)	$p<0.001$ $p<0.001$
Docetaxel	STAMPEDE, 2016	ADT	Locally advanced and metastatic: 10 (71 versus 81) Metastatic disease: 14 (46 versus 60)	$p=0.006$ $p=0.005$
Abiraterone	LATITUDE, 2017	ADT	Metastatic disease: not reached for abiraterone versus 30.4 for ADT	$p<0.001$
Abiraterone	STAMPEDE, 2017	ADT	Overall survival not reached Locally advanced and metastatic: three-year survival 83% versus 76%	$p<0.001$
Metastatic castration-resistant prostate cancer (pre-docetaxel)				
Docetaxel	TAX327, 2004	Mitoxantrone	3 (19 versus 16)	$p=0.004$
Abiraterone (pre-docetaxel)	COU-AAA-302, 2013	Placebo	4.4 (34.7 versus 30.3)	$p=0.003$
Enzalutamide (pre-docetaxel)	PREVAIL, 2014	Placebo	2.2 (32.4 versus 30.2)	$p<0.001$
Metastatic castration-resistant prostate cancer (post-docetaxel)				
Abiraterone	COU-AAA-301, 2011	Placebo	4.6 (15.8 versus 11.2)	$p<0.001$
Enzalutamide	AFFIRM, 2012	Placebo	4.8 (18.4 versus 13.6)	$p<0.001$
Cabazitaxel	TROPIC, 2010	Mitoxantrone	2.4 (15.1 versus 12.7)	$p<0.001$
Radium-223	ALSYMPCA, 2013	Placebo	3.6 (14.9 versus 11.3)	$p<0.001$
*High volume = presence of visceral metastases and/or four or more bone metastases, with at least one beyond the vertebral bodies or pelvis.				

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

patients with metastatic disease should be referred to an oncologist at diagnosis, and be managed within the multidisciplinary prostate cancer team.

Cabazitaxel (Jevtana)

Cabazitaxel is a second-generation microtubule inhibitor, licensed in mCRPC post-docetaxel chemotherapy where relapse has occurred. In comparison to mitoxantrone it has been shown to improve overall survival by 3.4 months (15.1 versus 12.7 months) after prior treatment with docetaxel.[12] Cabazitaxel is generally not as well tolerated as docetaxel and has significant toxicities associated with it, most notably haematological side-effects such as neutropenia and anaemia.[12]

SECOND-GENERATION ANDROGEN RECEPTOR TARGETED THERAPIES

Enzalutamide (Xtandi)

Enzalutamide is an oral second-generation anti-androgen that blocks androgen binding to the androgen receptor, inhibits androgen receptor nuclear translocation, and impairs the androgen receptor binding to DNA, thus preventing gene expression and the growth, survival and proliferation of prostate cancer cells.

The PREVAIL trial, a randomised, double-blind phase 3 trial of enzalutamide versus placebo in the pre-docetaxel setting, showed an overall survival benefit of 2.2 months with enzalutamide versus placebo (32.4 versus 30.2 months respectively, $p<0.001$).[6] In addition, enzalutamide delayed the time to the first skeletal-related event, including fracture and the need for palliative radiotherapy.

Enzalutamide is licensed and NICE-approved in the pre- and post-docetaxel setting. It is generally well tolerated, but the main side-effects patients experience are fatigue, diarrhoea, hot flushes, musculoskeletal pains and headache. In the AFFIRM trial, 5 out of 800 patients in the enzalutamide arm had seizures, and enzalutamide is therefore contraindicated in any patient with a history of seizures.[4]

Abiraterone (Zytiga)

Abiraterone is an androgen biosynthesis inhibitor that inhibits CYP17 (which is expressed in prostatic tumour tissues) and is required for androgen biosynthesis. Abiraterone, like enzalutamide, is a once-daily oral medication, but unlike enzalutamide is given with 5mg prednisolone twice daily.

Abiraterone with prednisolone has demonstrated an overall survival benefit of 4.6 months (15.8 versus 11.2 months) when compared to prednisolone alone in the post-docetaxel setting in metastatic prostate cancer.[5] It has shown a similar survival benefit of 4.4 months when given prior to docetaxel.[8] Side-effects are rare, but include fatigue, fluid retention, hypertension, cardiac disorders, hypokalaemia and liver dysfunction.[5,13]

As patients may be on abiraterone with prednisolone for a significant amount of time, clinicians must address potential long-term complications of steroid use, most notably hypertension, diabetes, weight gain and cardiovascular risk factors.

Abiraterone, like enzalutamide, is licensed and NICE-approved in the pre- and post-docetaxel setting. In 2017, two phase 3 trials demonstrated a survival benefit when combining abiraterone (and prednisolone) with ADT in the hormone-sensitive setting (prior to docetaxel). STAMPEDE, which included men with locally advanced and metastatic disease, demonstrated a three-year survival rate of 83% in the abiraterone/ADT group versus 76% in the ADT alone group.[14] LATITUDE only included patients with metastatic disease, and demonstrated a significantly longer median overall survival in the abiraterone group (not reached versus 34.7 months).[15] As a result, abiraterone has recently been licensed for the treatment of newly diagnosed high-risk mHSPC in combination with ADT.

Abiraterone or enzalutamide?

Although there have been no head-to-head trials of abiraterone and enzalutamide, the efficacy of the drugs appears to be similar.[4,6,13] A decision regarding which drug to choose should be made depending on the patient's comorbidities and the side-effect profile of the drugs. There are insufficient data to support the sequential use of abiraterone and enzalutamide and vice versa.[16–18] Many studies aiming to evaluate the efficacy of this approach have small numbers of patients and are retrospective. Therefore, when treating patients within the NHS, the clinician must choose between one drug and the other. The only indication to switch drug is due to side-effects, and this must be within the first three months of starting treatment.

Radium-223 (Xofigo)

Radium-223 is an alpha-emitting calcium mimetic that selectively binds to areas of increased bone turnover and has a highly localised cytotoxic effect. This minimises the effect on the bone marrow while effectively treating bony metastatic disease. In 2013 the ALSYMPCA trial showed that radium-223 was the first bone-targeted intervention to show an improvement in survival for patients with metastatic prostate cancer.[19]

As well as demonstrating an overall survival benefit of 3.6 months (14.9 versus 11.3 months) in comparison to placebo, radium-223 also increased the time to the first skeletal-related event (*eg* fracture, malignant spinal cord compression) or the need for palliative radiotherapy by 5.8 months. This is likely to have a significant impact on the quality of life for patients affected by metastatic bone disease. The side-effects of radium-223 are rare, but include nausea, anaemia, fatigue, diarrhoea and constipation.

Radium-223 is licensed and NICE-approved for patients who have previously been treated with docetaxel. It is also available

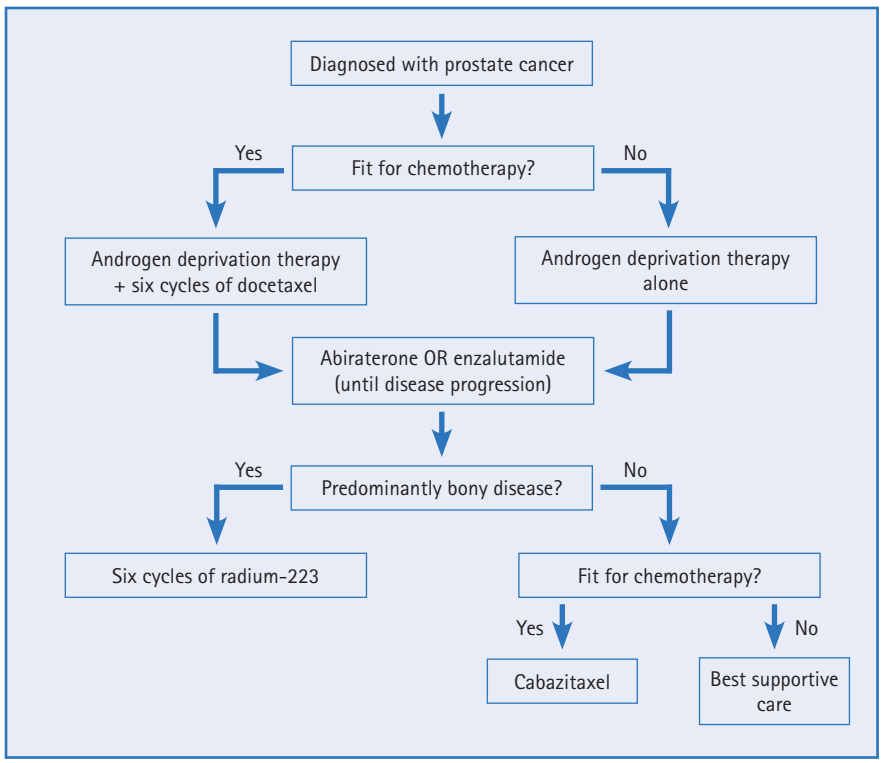

Figure 2. Treatment sequencing in metastatic prostate cancer

via the Cancer Drugs Fund for patients who are unable to take docetaxel or who have declined it. It is only licensed in patients with significant bony disease (two or more bone metastases) and no evidence of visceral metastases.

Radium-223 is given as an intravenous infusion every four weeks for six months in commissioned centres in collaboration with the treating oncologist and nuclear medicine specialists.

SEQUENCING

Figure 2 represents the typical current sequencing of treatments in a newly diagnosed patient with metastatic prostate cancer. Patients should continue ADT throughout all of their treatments and should be considered for clinical trials at all times.

THE FUTURE

Despite significant advances being made in the treatment of metastatic prostate cancer, there are still several unanswered questions. These include drug sequencing, the role of combinations, mechanisms of resistance, and the use of biomarkers to select the best treatment with the lowest toxicity.

Furthermore, trials looking at the combination of different treatments, such as dual androgen-receptor blockade with enzalutamide with abiraterone, are ongoing.[20] Trials are also looking at earlier sequencing of drugs, such as combining enzalutamide with 'upfront' docetaxel.[21] Combinations of drugs may have the potential to overcome mechanisms of resistance and maximise benefit from available drugs.

In future, novel treatments are likely to move beyond those targeting the androgen receptor. For example, it is now recognised that DNA repair abnormalities such as *BRCA2* mutations are frequently found in men with metastatic prostate cancer. The use of poly adenosine diphosphate-ribose polymerase (PARP) inhibitors (such as those used in breast cancer) is likely in men harbouring these mutations in the future.

CONCLUSION

As the number of treatments available for metastatic prostate cancer has increased, treatment has become much more complex. Therefore, patients should be managed in specialist multidisciplinary teams and offered entry into clinical trials that help answer the questions around drug sequencing. General practitioners remain an integral part of this team, from diagnosis to palliation.

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KEY POINTS

- **Androgen deprivation therapy remains the mainstay of initial systemic treatment for hormone-sensitive metastatic prostate cancer**
- **All suitable men with newly diagnosed hormone-sensitive metastatic prostate cancer should be considered for six cycles of docetaxel in addition to androgen deprivation therapy**
- **Abiraterone and enzalutamide have similar efficacy, and the selection of which drug to use is predominantly made on a patient's comorbidities and the side-effect profile of the drug**
- **Patients with predominantly bony disease and without visceral disease should be considered for radium-223**

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