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Chowdhury S, Kirby R. Advances in the treatment of metastatic prostate cancer.
Practitioner 2013– 257 (1760):15-18

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Medical Publishing Ltd

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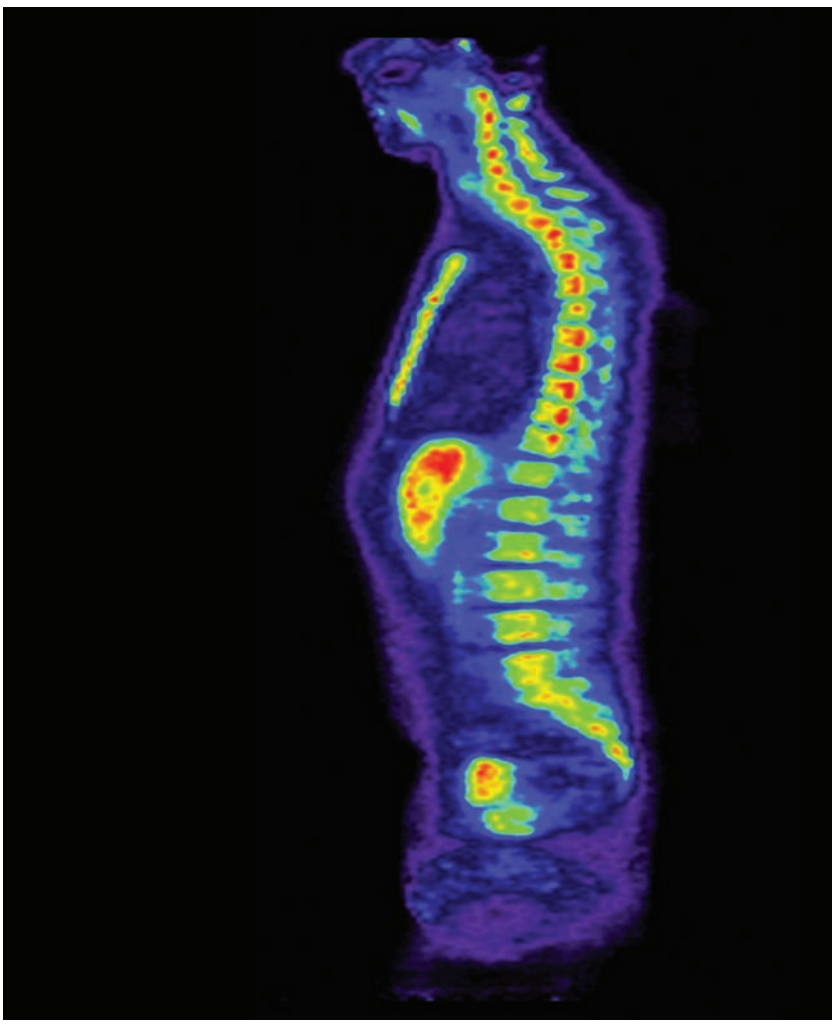
Advances in the treatment of metastatic prostate cancer

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Metastatic prostate cancer: choline PET scan showing widespread bony involvement, including the sternum and vertebrae, and also physiological uptake in the liver

What is the role of androgen deprivation therapy?

How should castrate refractory disease be managed?

How can treatment be tailored to the patient?

PROSTATE CANCER IS THE MOST COMMON CANCER IN MEN IN THE UK. IT ACCOUNTS FOR NEARLY a quarter of all male cancer diagnoses with a total of 40,975 men diagnosed in 2010 and is the second most common cause of male cancer death in the UK, with 10,721 deaths that year.[1]

There has been a large increase in prostate cancer incidence in the UK over the past 20 to 30 years. This is believed to be due to increased rates of detection initially from increased rates of transurethral resection of the prostate (TURP) and subsequently the introduction of prostate specific antigen (PSA) testing in the early 1990s.[2,3] Despite this large increase in prostate cancer incidence, mortality rates have remained relatively constant through improvements in survival. This is the result of increased diagnosis of earlier stage cancers, which can be treated successfully or in some cases require no treatment.

LOCALISED VS METASTATIC DISEASE

Prostate cancer is an extremely heterogeneous disease and although most patients present with localised disease there are still many who have metastatic disease at presentation.

Localised disease is successfully treated by radical prostatectomy or radiotherapy and in some cases low-grade disease may even be managed by active surveillance.

Metastatic disease is, however, commonly a lethal condition and the old adage 'men with prostate cancer die with rather than of their cancer' has recently been shown to be false.[4] Systemic treatment is the cornerstone of management for these men and recent years have seen a revolution in our understanding and subsequent ability to treat this condition. »

Table 1

Selected positive phase III studies in metastatic castrate-refractory prostate cancer

Agent	Method of action	Year of publication	Median survival benefit	Additional benefit
Docetaxel[9]	chemotherapy	2004	2.9 months	Improved QOL
Sipuleucel-T[12]	immunotherapy	2010	4.1 months	NA
Cabazitaxel[11]	chemotherapy	2010	2.4 months	NA
Abiraterone[13]	AR targeted	2011	4.6 months	Reduced pain
Enzalutamide[14]	AR targeted	2012	4.8 months	Improved QOL
Alpharadin[15]	radioisotope	2013*	3.6 months	Reduced pain

AR = androgen receptor; QOL= quality of life * not yet published in full but expected later in 2013

MULTIDISCIPLINARY CARE

The care of the prostate cancer patient with advanced disease should be multidisciplinary. This is likely to involve urology, specialist clinical nursing, oncology, general practice, palliative care and specialist pathology and radiology. It is important that men with prostate cancer are able to access all these areas ideally in one unit and in one or two visits. We have set up our own practices in this way to avoid unnecessary visits for patients many of whom are symptomatic.

'The old adage "men with prostate cancer die with rather than of their cancer" has recently been shown to be false'

To facilitate good communication patients and their GP should have clearly identified points of contact. We believe that the approach where a man with prostate cancer has one or two key workers works best. The key worker is frequently a specialist nurse but can be a urologist or oncologist and we often fullfil this role for our patients. The patient should have direct access to this person and we achieve this by direct phone and email contacts.

We believe that the best outcomes for prostate cancer are in dedicated centres treating large numbers of patients and where data on treatment outcomes are more readily available. For advanced prostate cancer access to the latest clinical trials and therapies is vital as evidenced by the progress seen with such drugs as abiraterone and enzalutamide. These drugs extend life and have significant palliative benefits and until recently were only available in clinical trials.

GPs have a vital role in helping to direct their patients to such centres and such clinicians. For too long doctors and patients shied away from second opinions but we believe that this can significantly improve the care for men with prostate cancer.

New drugs may have a new range of side effects and often these will be managed jointly with GPs. A good example is abiraterone, which commonly causes hypertension. In our practice we have found that patients are best managed using the expertise of GPs who have greater experience than oncologists or urologists in this area.

ANDROGEN DEPRIVATION THERAPY

Prostate cancers are driven by androgens, such as testosterone, which are critical for cancer growth, survival and proliferation.

The Nobel Prize winning research by Huggins and Hodges showed that remission of prostate cancer could be achieved by testosterone deprivation and remains clinically relevant today.[5]

Androgen deprivation therapy (ADT), which is still the mainstay of systemic treatment, effectively reduces intraprostatic androgen concentrations resulting in reduced androgen receptor (AR) stimulation and increased apoptosis.

ADT can be achieved using either surgical castration or medically by blocking the hypothalamic-pituitary-gonadal axis using luteinising hormone releasing hormone (LHRH) analogues or antagonists that inhibit LHRH levels resulting in castrate levels of testosterone.

Medical castration using LHRH analogues has become the gold standard in managing both locally advanced prostate cancer, in combination with radiotherapy, and metastatic disease.

ADT has been established as the standard first-line treatment for advanced disease providing symptomatic, radiological and PSA responses, and is one of the most active systemic therapies in solid tumour oncology. Response rates to ADT are around 90% and the cancer is controlled for an average of 18 to 24 months before signs of progression appear.

'We believe that the best outcomes for prostate cancer are in dedicated centres treating large numbers of patients'

Initiation of ADT in the UK is primarily by urologists and oncologists, which is then continued in the community via general practice or in hospital nurse-led clinics. This results in multiple health professionals sharing responsibility for the care of these patients and monitoring efficacy and toxicity of ADT.

The role of the GP is key and robust channels of communication are needed. It is important that all involved are aware of factors that identify patients in whom ADT is likely to fail earlier.[6] These include patients with:

- Distant lymph node metastases
- Visceral metastases

- Bone pain
- Poor fitness
- Weight loss at presentation
- Gleason score ≥ 8
- Failure to achieve a PSA nadir ≤ 4
- High PSA (the higher the PSA at presentation the greater the risk; we use a level of 500 to identify patients at significant risk)
- Younger age

These patients should be monitored particularly closely for rising PSA and signs of clinical progression. In our practice such patients are seen at least once every two months.

Survival with locally advanced and metastatic disease has increased significantly leading to patients receiving ADT for a prolonged duration. This raises concerns over complications of therapy.

An understanding of ADT toxicities and their management is key to the holistic care of these men.[7] The impact of ADT on endocrine function, metabolism, and cardiovascular and bone health is increasingly recognised.[8] Education of men being treated with ADT and their doctors is key to preventing and managing such complications.

CASTRATE REFRACTORY DISEASE

Eventually most men with advanced prostate cancer become resistant to ADT. This progression of disease despite castrate levels of testosterone used to be called 'hormone refractory', but is now called castrate refractory prostate cancer (CRPC), and is associated with a poor prognosis.

The reason for this name change comes from an increased understanding of cancer biology. Historically, castration-resistant tumours were thought to develop without reliance on the AR.

Recent research has, however, shown that signalling via the AR continues despite castrate levels of androgens. The exact mechanisms remain unknown but supporting evidence for the importance of the AR comes from greater than expected tissue concentrations of androgens in the tumour microenvironment in CRPC. Thus AR signalling remains a critical pathway stimulating tumour growth despite castrate levels of androgens.

For decades systemic treatment options for CRPC were very limited and only provided a palliative benefit. Docetaxel chemotherapy was the first agent to show an improvement in overall survival and improved quality of life.[9]

Until recently, there were no treatments showing a survival benefit post-chemotherapy representing an important area of unmet clinical need. However, there is now hope for patients who progress after chemotherapy with the emergence of several new agents that have been shown to benefit patients, see table 1, opposite.[10]

NEW AGENTS

Second-line chemotherapy

Cabazitaxel is a novel chemotherapeutic agent designed to overcome resistance to docetaxel. The results of a large phase III trial, the Tropic study, showed that cabazitaxel improves survival over another active chemotherapy mitoxantrone.[11]

'There is now hope for patients who progress after chemotherapy with the emergence of new agents'

While the survival advantage was small (15.1 versus 12.7 months) it was statistically significant and against an active comparator. The patient population had very advanced disease (25% visceral disease) and had been heavily pretreated. This study shows that second-line chemotherapy has a place for selected patients.

Immunotherapy

Immunotherapy has recently been shown to have a role in the treatment of CRPC. Sipuleucel-T is a vaccine-based immunotherapy derived from antigen presenting cells which are activated ex vivo with a recombinant fusion protein containing prostatic acid phosphatase, an antigen expressed by prostate cancer cells.

The IMPACT trial (Immunotherapy for Prostate Adenocarcinoma Treatment) showed a statistically significant improvement in survival for sipuleucel-T (25.8 versus 21.7 months).[12] This is the first immunotherapy to show an improvement in survival for advanced prostate cancer.

Sipuleucel-T has a short duration of therapy (1-2 months) and low toxicity and thus a favourable benefit:risk ratio. It provides a novel, albeit expensive, option for the treatment of advanced prostate cancer.

While the expense and complexity of sipuleucel-T currently preclude it from routine use in the UK, trial results suggest that immunotherapy is likely to have a place in the treatment of advanced disease and this is the focus of several ongoing studies.

AR-targeted therapies

The area that has shown the greatest promise, and is already benefiting patients in the UK, comes from the realisation that the AR retains importance in CRPC.

The first AR-targeted drug to show a definite clinical benefit is abiraterone acetate. Abiraterone is a potent, selective and irreversible inhibitor of CYP17 alpha-hydroxylase and C17,20-lyase that catalyse two essential steps in androgen biosynthesis.[13]

Abiraterone markedly decreases levels of androgens in CRPC and initial trials showed promising activity and confirmed that a sub-group of CRPC patients continue to have androgen-driven disease.

A phase III study of abiraterone in metastatic CRPC post-docetaxel has recently shown a significant improvement in overall survival.[13] Abiraterone resulted in a 35% reduction in the risk of death HR 0.65 (95% CI:0.54-0.77; P < 0.0001) and a 36% increase in median overall survival (14.8 vs 10.9 months).

An alternative approach is to target the AR directly. Enzalutamide is a small molecule with high affinity and selectivity for AR binding; it also blocks nuclear translocation and reduces recruitment of co-activators. The phase III study of enzalutamide in the post-chemotherapy setting randomised patients with metastatic CRPC to enzalutamide versus placebo. This trial has recently been stopped as an interim analysis showed a 4.8 month survival advantage.[14]

The results from the abiraterone and enzalutamide trials are truly practice changing and will benefit patients who for too long have had limited active treatment options.

These results show that 'androgen-independent' or 'hormone refractory' disease is neither of these things. Seventy years after Huggins and »

key points

SELECTED BY
Dr Peter Saul
GP, Wrexham and Associate GP Dean for North Wales

Prostate cancer is the most common cancer in men in the UK. It accounts for nearly a quarter of all male cancer diagnoses and is the second most common cause of male cancer death in the UK. Despite a large increase in prostate cancer incidence, mortality rates have remained relatively constant through improvements in survival.

It is an extremely heterogeneous disease and although most patients present with localised disease there are still many who have metastatic disease at presentation. Metastatic disease is commonly a lethal condition and systemic treatment is the cornerstone of management for these men.

Prostate cancers are driven by androgens, such as testosterone. Androgen deprivation therapy (ADT), which is still the mainstay of systemic treatment, effectively reduces intraprostatic androgen concentrations resulting in reduced androgen receptor (AR) stimulation and increased apoptosis. Medical castration using LHRH analogues has become the gold standard in managing both locally advanced prostate cancer, in combination with radiotherapy, and metastatic disease. Response rates to ADT are around 90% and the cancer is controlled for an average of 18 to 24 months before signs of progression appear.

Eventually most men with advanced prostate cancer become resistant to ADT. This is now called castrate refractory prostate cancer (CRPC), and is associated with a poor prognosis. Signalling via the AR continues despite castrate levels of androgens and remains a critical pathway stimulating tumour growth despite castrate levels of androgens. There is now hope for patients who progress after chemotherapy with the emergence of several new agents that have been shown to benefit patients.

The first AR-targeted drug to show a definite clinical benefit is abiraterone acetate. It markedly decreases levels of androgens in CRPC and initial trials showed promising activity. Enzalutamide has a high affinity and selectivity for AR binding, blocks nuclear translocation and reduces recruitment of co-activators. Abiraterone, enzalutamide and other AR-targeted drugs are being studied in clinical trials for patients earlier in their disease history, for example in addition to ADT at first presentation of metastatic disease, where it is likely that greater benefits will be seen.

The best outcomes for prostate cancer are in dedicated centres treating large numbers of patients and where data on treatment outcomes are more readily available. For advanced prostate cancer access to the latest clinical trials and therapies is vital as evidenced by the progress seen with such drugs as abiraterone and enzalutamide. These drugs extend life and have significant palliative benefits and until recently were only available in clinical trials. GPs have a vital role in helping to direct their patients to such centres.

Hodges' initial report, the AR remains an increasingly relevant therapeutic target and an important area for current research.

Abiraterone, enzalutamide and other AR-targeted drugs are being studied in clinical trials for patients earlier in their disease history, for example in addition to ADT at first presentation of metastatic disease, where it is likely that greater benefits will be seen.

CONCLUSION

The management of advanced prostate cancer is changing rapidly with the recent approval of several effective antitumour agents.

With the armamentarium of drugs available it is critical that they are applied appropriately in order to maximise patient benefit and minimise costs.

'With the armamentarium of drugs available it is critical that they are applied appropriately to maximise benefit and minimise costs'

Potential issues including drug-related toxicities and cross-resistance to individual agents after exposure to a prior treatment should be considered.

We are moving away from the era of 'one size fits all' treatment in oncology and it is important that in prostate cancer we embrace this new era. Personalised therapy using state-of-the-art molecular profiling via whole genome sequencing can identify genetic aberrations that inform treatment choices.

There can be few areas of medicine that have been associated with more controversy than prostate cancer or in which treatment options have changed so radically in recent years.

A lot remains to be done to maximise benefit for patients with advanced prostate cancer. However, in these changing times, it is heartening that the benefits that have been seen in localised prostate cancer are now being seen for men with advanced prostate cancer and the prospects for such men have never been better.

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Useful information

Prostate Cancer UK
www.prostatecanceruk.org

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