Managing metastatic prostate cancer

Prostate cancer is one of the most commonly diagnosed malignancies in the west. Most patients with metastatic or recurrent prostate cancer initially respond to androgen deprivation therapy, but almost all eventually progress. This review will focus on current treatment options for metastatic prostate cancer, with a focus on hormonal therapies, chemotherapy and treatment of bony disease, along with biological and targeted therapy.

Prostate cancer is the most frequently diagnosed malignancy among men in industrialized countries (Hsing et al, 2000) In England and Wales 17 000 cases are diagnosed and there are nearly 9000 deaths annually (Landis et al, 1999). This death rate has more than doubled over the last 30 years.

The epidemiology of prostate cancer has given a number of clues as to its aetiology. The incidence of prostate cancer increases with age and varies markedly throughout the world. The countries with the highest incidence include the USA, Canada, Sweden, Australia and France, whereas the incidence in Asian populations is relatively low (Simard et al, 2002). These differences may be the result of genetic factors, but environmental factors also play a part. For example, Japanese male immigrants in the USA have a much higher mortality from prostate cancer compared to those in Japan (Haenszel and Kurihara, 1968) with dietary factors thought to play a significant role (*Table 1*).

Table 1. Proposed risk factors for prostatic cancer

Possible/likely risk factor	Age
	Race
	Premalignant lesion (prostatic intraepithelial neoplasia)
	Affected family member
	Carnivorous diet
	Dietary fat
	Vitamin D
	Sexual habits
Controversial/disproved risk factor	Benign prostatic hyperplasia
	Sexual transmitted disease
	Cigarette smoking
	Alcohol intake
Cadmium exposure	

From Morton (1994)

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Clinical features

The increased public awareness of the symptoms of prostate cancer, along with the introduction of prostate-specific antigen (PSA) testing, has led to a decrease in the incidence of metastatic disease and an increase in early stage disease (Kasamon and Dawson, 2004). Patients with metastatic prostate cancer may be asymptomatic or may present with a number of symptoms. Local symptoms include bladder outflow symptoms, haematuria, haemospermia, back or perineal pain, and renal failure – resulting from chronic retention or local tumour extension around the ureteric orifices beneath the trigone.

Symptoms of distant spread include pelvic lymph node involvement (lower limb swelling) and bony metastases (localized or widespread bone pain, bone marrow infiltration leading to cytopaenia).

Diagnosis and staging

In patients with suspected metastatic prostatic cancer, staging investigations include digital rectal examination to assess the primary tumour stage (*Table 2*), transrectal ultrasound and needle biopsy to determine histology and tumour grade (*Table 3*), PSA, chest X-ray, bone scan and in some patients abdominal and pelvic computed tomography (CT) scan. In patients who have received radical treatment for localized disease, biochemical progression is defined as two consecutive increases in PSA, with a minimum PSA value of 5 ng/ml.

Assessment of response to therapy

One of the problems in assessing response to treatment in patients with metastatic prostate cancer is that many patients do not have measurable disease radiologically. As a result, there has been a lot of variability in the response criteria used among different clinical trials, making direct comparisons difficult.

A consensus panel in 1999 proposed a now widely adopted set of response criteria based on PSA level changes (Bubley et al, 1999). An objective response is defined as a decline in PSA of at least 50% (confirmed by a second PSA value measured 4 or more weeks later) and a radiological response in patients with measurable soft tissue disease. Progressive disease is defined as one or more of the following:

1. Progression of measurable lesion radiologically
2. The appearance of at least one new lesion on bone scan
3. Stable metastases and an increase in PSA of ≥25% (with an increase in the absolute value by at least 5 ng/ml)
4. Increasing PSA and no evidence of metastatic disease.

Treatment options

Hormonal therapy

Luteinizing hormone-releasing hormone agonists or castration

Hormonal therapy is the principal treatment modality for patients with advanced prostate cancer. Historically, this was achieved by surgical castration. However, the current standard treatment is with luteinizing hormone-releasing hormone (LHRH) agonists. These exert their effect by binding to hypothalamic gonadotrophin-releasing hormone (GnRH) receptors with the release of luteinizing hormone (LH) and follicle-stimulating hormone. These peptides are not released from their binding sites and receptor down-regulation occurs with suppression of LH release and testicular androgen synthesis. They are also thought to exert a direct effect at the level of the tumour. LHRH agonists are administered subcutaneously as a monthly or 3-monthly depot preparation. Since these agents initially cause a transient rise in testosterone, their initial use should be covered by an anti-androgen. Typically an anti-androgen is given for 2 weeks before and after the first LHRH agonist injection.

The side effects of GnRH agonists are similar to those of surgical castration, and can include loss of libido, impotence, hot flushes, gynaecomastia, mood disturbance, osteoporosis and anaemia. Their efficacy is also equivalent with respect to response rate and survival with a median response of 12–18 months (Prostate Cancer Trialists' Collaborative Group, 1995). Maximal androgen blockade (MAB) is achieved by the addition of an anti-androgen, such as flutamide or bicalutamide. Randomized controlled trials have shown a survival advantage of around 7 months with combination treatment. However, a meta-analysis which looked at 5-year survival rates has shown that MAB is not more effective than conventional castration alone in hormone-naïve patients (Prostate Cancer Trialists' Collaborative Group, 1995). As the median survival of patients is only 3 years, it would have been more helpful if overall survival had also been reviewed.

Table 2. Tumour, node, metastases classification

T category (local tumour)	TX	Cannot be assessed
	T0	No evidence of primary tumour
	T1	Impalpable, histologically diagnosed
	T1a	Incidental histological finding in <5% of tissue resected at TURP
	T1b	Incidental histological finding in >5% of tissue resected at TURP
	T1c	Tumour identified by needle biopsy (because of raised prostate-specific antigen)
	T2	Palpable tumour confined to prostate
	T2a	Involves one lobe
	T2b	Involves both lobes
	T3	Tumour extends through the capsule
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Invades seminal vesicles
	T4	Fixed or infiltrating
N category (node involvement)	Nx	Nodes cannot be assessed
	N0	No regional nodes metastases
	N1	Regional lymph node metastases
M category (distant metastases)	Mx	Metastasis cannot be assessed
	M0	No metastases
	M1	Metastases present

TURP = transurethral resection of the prostate

Role of continued androgen suppression

Although data are limited, current evidence suggests that in patients who have not had an orchidectomy, continued medical androgen suppression is recommended up to the time that death appears imminent. Manni et al (1988) found that androgen administration as a means of priming prostate cancer cells to increase the efficacy of cytotoxic chemotherapy in hormone-refractory patients, actually shortened survival and often exacerbated symptoms. In addition to this, a retrospective multivariate analysis performed on survival data for 341 patients found that continued androgen suppression was an important predictor for improved survival (Taylor et al, 1993).

Secondary hormonal manipulation

Despite continued androgen suppression most patients will develop progressive disease. Evidence of this includes increasing PSA levels, progressive disease on imaging studies and progression of symptoms. Prognosis for these

Table 3. Grade: Gleason score and association with disease progression

Gleason score*	Differentiation	% likelihood of death from cancer by 15 years
2–4	Well	8
5–7	Moderate	35
8–10	Poor	65

*The Gleason grading system is based on the degree of glandular differentiation. Since prostate tumours exhibit heterogeneity within tissue, two histological areas of the tumour are scored between 1 and 5. The overall scores are then added, to give an overall score between 2 and 10

patients with hormone-refractory prostate cancer (HRPC) is poor, with a median survival of 7–12 months. The evaluation of the mechanisms for resistance to hormone treatment is of great interest, in order to develop new strategies for treatment.

The standard approach for these patients is the addition of an anti-androgen if they are not receiving MAB. These work by competitively binding to and inhibiting the transcriptional activity of the androgen receptor in prostatic tissue. The rationale behind this is that low levels of androgen continue to be produced by the adrenal gland, which can be inhibited by anti-androgen treatment. In a small study involving 50 patients, 54% of those with metastatic HRPC, who had previously been treated with androgen suppression, responded to flutamide (Fowler et al, 1995). Another study found a 15% (2/13 patients) response rate with bicalutamide treatment in patients who relapsed after medical or surgical castration (Scher and Kelly, 1993).

Hormone withdrawal

In a proportion of patients who progress while receiving anti-androgen treatment, hormone withdrawal may be therapeutic, since anti-androgens may paradoxically stimulate the androgen receptor in these tumours. This strategy was first described in 1993 by Kelly and Scher who found that in 10 out of 35 (29%) patients with progressive disease on hormonal treatment, flutamide withdrawal lead to a median decline in PSA of 92% for a median of over 5 months. Although there is no clear evidence that anti-androgen withdrawal prolongs survival in these patients, it is associated with an improvement in clinical symptoms.

Other hormonal manoeuvres

A wide selection of other second-line hormonal therapies have also been tested in HRPC patients. Adrenal androgen inhibition with aminoglutethimide, ketaconazole and/or low-dose corticosteroids produce objective response rates of 10–20%, however, the response is generally less than 6 months and there is no survival benefit. An alternative hormonal manoeuvre is the use of an oestrogen, such as diethylstilbestrol.

Small single institution studies have shown an average response rate of 55%, in patients with rising nadir levels of PSA after androgen deprivation therapy (Malkowicz, 2001). However, cardiovascular toxicity was reported in 10–30% of these patients. This included deep vein thrombosis, myocardial infarction, peripheral oedema and transient ischaemic attacks. The risk of cardiovascular side effects is increased in patients with body weight >75 kg, increased age, and prior history of cardiovascular disease. The administration of low-dose warfarin to these patients has not demonstrated any benefit, however, early data suggest that aspirin reduces the rate of thromboembolic complications to 3–12% (Malkowicz, 2001).

Chemotherapy

Prostate cancer has historically been viewed as a relatively chemoresistant malignancy. Early chemotherapy trials showed response rates of 10–15%, with a small palliative impact on symptomatic patients and no impact on survival (Kasamon and Dawson, 2004). However, newer agents have demonstrated superior responses and are being utilized more in clinical practice.

Mitoxantrone-based regimens

Mitoxantrone is a synthetic anthraquinone drug, which is clinically well tolerated. Owing to its structural similarity to doxorubicin it shares the dose-limiting side effect of cardiotoxicity. Other side effects include nausea, vomiting and myelosuppression. Tannock et al in 1996 published a seminal trial in which symptomatic HRPC patients were randomized between mitoxantrone plus prednisolone *vs* prednisolone alone. They demonstrated a significant benefit in terms of pain scores and analgesic use, but no overall difference in PSA response or survival.

Subsequently, the cancer and leukaemia group B (CALGB) study 9182 confirmed that mitoxantrone and corticosteroid palliated symptoms and delayed time to disease progression, but again failed to demonstrate any survival advantage (Martel et al, 2003). As a result this combination has been approved by the Federal Drug Administration for palliation of bone pain from HRPC. The combination of mitoxantrone and prednisolone *vs* prednisolone alone, in earlier stage asymptomatic HRPC patients, was investigated recently in a phase III trial (Kasamon and Dawson, 2004). Again, the PSA response rates were higher in the chemotherapy arm (48 *vs* 24%) but there were no differences in survival.

Estramustine

Estramustine is a conjugate of estradiol and nitrogen mustard, with hormonal and non-hormonal cytotoxic effects in-vitro. It acts by causing microtubule disassembly and by binding to microtuble-associated proteins, thus inhibiting cell mitosis. Three randomized controlled trials investigating estramustine as a single agent in HRPC (Martel et al, 2003) have shown no benefit in terms of symptom palliation or survival. However, based on in-vitro data suggesting synergy, several studies have evaluated estramustine in combination with other anti-microtubule agents and etoposide. The combination of estramustine with etoposide was particularly attractive since the combination could be administered orally. Phase II studies using this combination have shown PSA responses of 22–58% (Martel et al, 2003), but with significant toxicity. As a result this combination has not been investigated further in phase III studies.

A phase III study has investigated the combination of vinblastine plus estramustine *vs* vinblastine alone, and demonstrated a superior response rate (25.2 *vs* 3.2%) for the combination treatment group but no significant survival advantage. However, the trial was inadequately powered to detect small differences in survival (Martel et al, 2003).

Taxanes

Another group of anti-microtubule agents that have achieved a prominent role in the management of HRPC are the taxanes, especially in light of their synergistic activity and efficacy when combined with other agents such as estramustine.

The Southwest Oncology Group (SWOG) compared docetaxel and estramustine with mitoxantrone and prednisolone, in men with metastatic HRPC. Results of 674 patients showed a survival advantage for the docetaxel group (median survival 17.5 months *vs* 15.6 months; P=0.02) and longer time to progression (6.3 months *vs* 3.2 months; P<0.001), although there was more cardiovascular and gastrointestinal toxicity, and grade 3 and 4 neutropenic fevers. Another recently published randomized trial TAX32 compared two different docetaxel administration regimens with mitoxantrone (with all groups receiving prednisolone). It demonstrated that there was a longer median survival in the docetaxel-treated groups (18.9 months in the group given docetaxel every 3 weeks, 17.4 months in the weekly docetaxel group, *vs* 16.5 months in the mitoxantrone group). The docetaxel arms also achieved an improved PSA (45% and 48% *vs* 32%) and pain response (35% and 33% *vs* 22%) (Tannock et al, 2004). Again the frequency of adverse events was higher in the docetaxel groups. As a result of these significant trials, the National Institute for Clinical Excellence (NICE) is currently reviewing its stand on the use of taxanes in metastatic HRPC.

Isotope therapy and external beam radiotherapy

External beam radiotherapy to bone metastases can provide excellent local pain relief in up to 75% of patients (Martel et al, 2003). It can also help prevent pathological fractures if administered before the cortex is eroded by greater than 50%. In addition, it can benefit patients troubled by urinary obstruction and haematuria, resulting from local progression of prostate cancer.

Bone-seeking β-emitting isotopes such as strontium-89 and phosphorous-32 have been used for the palliation of patients with multiple painful sites of bony metastases. Around 70% of patients reported significant pain relief, with responses lasting 3–6 months. However, prolonged myelosuppression is a significant complication, and can delay or prevent chemotherapy treatment or entry into a clinical trial.

Bisphosphonates

Skeletal complications in metastatic prostate cancer, such as spinal cord compression, pathological fractures and bone pain, are common, since up to 80% of patients have bone involvement, and in addition prolonged androgen suppression can lead to osteoporosis. Bisphosphonates inhibit osteoclast-mediated bone resorption, and are routinely used in the treatment of osteoporosis in postmenopausal women. Although bone metastases in prostate cancer are mainly osteoblastic, there is a minor increase in osteoclastic activity, which is thought to alter the bone microenvironment and favour metastatic deposition.

Until relatively recently, no bisphosphonate has been shown to be of benefit in patients with prostate cancer. An international, multi-centre, randomized placebo-controlled trial of men with HRPC and bony metastases found that 15 months' treatment with the third-generation bisphosphonate zoledronic acid led to a significant reduction in skeletal complications and extended time to the first skeletal complication (Saad et al, 2002). This suggests that zoledronic acid may be useful in preventing bone loss in patients with prolonged androgen suppression. Its role in pain palliation and treatment of bony metastases warrants further investigation.

Investigational therapies

As we understand more about the molecular biology of prostate cancer, the development of targeted therapies with improved efficacy and minimal toxicity has become more of a reality. There is also considerable interest in combining these biological agents with cytotoxic chemotherapy.

Docetaxel and thalidomide

Thalidomide is best known as a potent teratogen that causes dysmelia in humans. It has resurfaced as a potential anti-neoplastic agent, based on its anti-angiogenic properties. As a single agent in HRPC a PSA response was seen in 18% of patients. In light of this, a phase II trial compared docetaxel plus thalidomide with docetaxel alone in 75 patients with chemotherapy-naïve metastatic HRPC. PSA responses were seen in 53% of the combined group compared with 37% in the docetaxel arm (Dahut et al, 2004). There was, however, an increased frequency of venous embolism in the combined treatment group. This appeared to be abrogated when prophylactic low molecular-weight heparin was administered.

Bevacizumab

Bevacizumab is a monoclonal antibody, which targets vascular endothelial growth factor. It has been evaluated in combination with docetaxel and estramustine in HRPC. At time of initial analysis, 79% of patients had a PSA response and median survival had not been reached after 11 months. The CALGB now plan to assess a combination of docetaxel-prednisolone-bevacizumab *vs* docetaxel-prednisolone alone in a randomized trial.

Calcitriol

Docetaxel has also been evaluated in combination with calcitriol, the active form of the steroid hormone vitamin D. It is thought to exert its anti-tumour effects by inhibiting cancer cell proliferation and sensitizing cancer cells to cytotoxic drugs. In a phase II clinical trial, 81% of patients had a 50% reduction in PSA with the combination of docetaxel in combination with weekly high dose calcitriol (Beer et al, 2003). As a result of this data, the Androgen Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere Trial (ASCENT) has been established to compare weekly docetaxel with high dose calcitriol with docetaxol alone.

Other drugs which may show promise in combination with taxane chemotherapy include: atrasentan (an endothelin inhibitor; Smith and Nelson, 2005), G3139 (a BCL-2 anti-sense oligonucleotide), bortezomib (a proteosome inhibitor), and vaccine immunotherapy.

Conclusions

For patients with metastatic prostate cancer, hormonal deprivation with MAB remains the standard first-line treatment. On disease progression, the decision to adopt other hormonal manoeuvres is determined by the patient's symptoms and changes in his PSA levels. Chemotherapy with docetaxel-based combinations has been shown to improve survival in patients with HRPC, and is considered by many to be the new standard of care for these patients. Newer targeted agents in combination with docetaxel have shown promise in phase II trials, however, results from randomized controlled trials are needed to validate these findings. In addition, the improved understanding of the molecular pathophysiology of HRPC should lead to new therapeutic approaches in years to come. BJHM

Conflict of interest: none.

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KEY POINTS

- Luteinizing hormone-releasing hormone agonists, castration and anti-androgens are the first-line treatment options for symptomatic and poor prognosis patients.
- Hormonal withdrawal and second-line hormonal therapies are used for symptomatic patients with progressive disease despite maximal androgen blockade.
- External beam radiotherapy provides local pain relief to bony metastases.
- Zoledronic acid is used to prevent bone loss secondary to long-term androgen deprivation.
- Docetaxel and mitoxantrone chemotherapy offer palliative benefits for patients with hormone-refractory prostate cancer, with docetaxel providing a menian survival advantage of 3 months.
- Investigational therapy with targeted agents alone or in combination may be considered in patients who have failed hormonal treatment.
- Supportive care is important for patients in whom these therapies have failed.