Understanding treatment of prostate cancer

Prostate cancer is the second most common cancer in men worldwide after lung cancer. In 2006, more than 35,000 men in the UK were diagnosed with this cancer. Netty Wood explores its diagnosis and management and highlights the role of screening and treatments.

The prostate is an accessory male sex gland, which is wrapped around the urethra and secretes fluid to form semen. In the UK, prostate cancer is the most common cancer in men, accounting for 24 per cent of all new male cancer diagnoses. However, mortality rates are relatively low, with 70 per cent of patients alive at five years. In fact, many men die with, rather than from, prostate cancer. It is estimated that 215,000 men are living in the UK with a diagnosis of prostate cancer. Although the incidence is increasing, there is no increase in mortality rates. This may be influenced by the introduction of transurethral prostatectomy (TURP), a minimally invasive surgical procedure for removing prostate tissue, and prostate specific antigen (PSA) testing, which have led to the detection of more latent, earlier, slow growing tumours.

Bearing all this in mind, it is likely that pharmacists will encounter increasing numbers of patients with a diagnosis of prostate cancer, so a basic understanding of the disease, the patient’s journey and treatments is important. In addition, prostate cancer is not a topic only for those working in secondary care. Sometimes therapies are initiated in primary care, particularly where GPs write the first prescription following a letter from the consultant, and pharmacists can play a useful role in supporting these patients.

Risk factors

Age is the strongest known risk factor and the condition is rare in men under 50 years. The older the man, the higher the risk, with three-quarters of prostate cancer diagnosis occurring in men over 65 years. Another strong risk factor is family history — men who have a first-degree relative affected with early prostate cancer, have twice the risk of developing prostate cancer and those with two or more first-degree relatives affected with early prostate cancer have approximately a seven- to eightfold increased risk of developing prostate cancer compared with the general population.

The variation of incidence rates globally has led to the suggestion that prostate cancer risk is affected by ethnicity. For example, African American men are 61 per cent more likely to develop prostate cancer than Caucasian men and are nearly 2.5 times as likely to die from it, whereas Asian men generally have a lower risk than the national average. It is uncertain whether this difference is due to genetic susceptibility or exposure to causative environmental factors.

Molecular biology studies have suggested that genetic changes directly related to androgen metabolism can affect the risk of prostate cancer. Furthermore, androgen levels in some populations reflect the risk of prostate cancer — African American men have relatively high androgen levels and Asian men have relatively low androgen levels.

Observational studies have suggested that diets high in saturated fats and red meats, and low in...
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Panel 1: Non-pharmaceutical treatment options

**Watchful waiting/active surveillance** The option of watchful waiting involves an active plan to monitor the patient closely for disease progression without invasive treatment. It is used when an early stage, slow-growing prostate cancer is suspected or when the risks of invasive treatment outweigh the possible benefits.

**Surgery** There are a number of surgical options for prostate cancer treatment, involving removal of the prostate gland (used for tumours that have not spread beyond the prostate) or the testicles (to decrease circulating androgens). Radical prostatectomy is the removal of the prostate gland through an incision in the abdomen wall (retropubic prostatectomy) or the perineum (perineal prostatectomy). Laparoscopic prostatectomy (removal of the gland via small incisions) may be used in an attempt to reduce nerve damage. Side effects of these procedures include loss of urinary control, impotence, infertility and impaired erection and ejaculation.

**Radiotherapy** Radiotherapy can be used instead of or after surgery in early stage prostate cancer. It is also used to treat painful bone metastases in advanced, metastatic prostate cancer (ie, it is used for palliative as well as radical treatment). Radiation treatment can be combined with hormonal therapy for intermediate risk patients. Side effects include diarrhoea, mild rectal bleeding, urinary incontinence and impotence but these tend to improve over time. There are three types of radiotherapy: external beam radiotherapy (EBRT), intensity modulated radiotherapy (IMRT) — both given daily via a linear accelerator (linac) machine over several weeks — and brachytherapy (the permanent implant of 100 small rods containing radioactive material through the skin of the perineum directly into the tumour).

Panel 2: Risk stratification for localised prostate cancer according to risk of recurrence

<table>
<thead>
<tr>
<th>Risk</th>
<th>PSA level</th>
<th>Gleason score</th>
<th>Clinical stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;10ng/ml</td>
<td>6</td>
<td>T1–T2a</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10–20ng/ml or 7</td>
<td>or</td>
<td>T2b–T2c</td>
</tr>
<tr>
<td>High</td>
<td>&gt;20ng/ml</td>
<td>8–10</td>
<td>T3–T4</td>
</tr>
</tbody>
</table>

Panel 3: Localised prostate cancer treatment options

<table>
<thead>
<tr>
<th>Risk</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Watchful waiting</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Watchful waiting, radical prostatectomy, brachytherapy or radiotherapy</td>
</tr>
<tr>
<td>High</td>
<td>If there is a prospect of long-term disease control then prostatectomy or radical radiotherapy (with a minimum of two years’ adjuvant hormonal therapy)</td>
</tr>
</tbody>
</table>

The recommendation for high risk cancer that has spread to the tissues surrounding the prostate (ie, locally advanced cancer), radiotherapy with neoadjuvant and concurrent hormonal therapy for three to six months.

Fruits, vegetables, tomato products and fish can increase the risk of prostate cancer. Obesity has also been suggested as a risk factor for prostate cancer. More frequent ejaculation may reduce the risk of prostate cancer, but this has not been confirmed in larger controlled studies. Infection with the sexually transmitted infections chlamydia, gonorrhoea or syphilis is also suggested to increase the risk.

It has been suggested that the daily use of non-steroidal anti-inflammatory drugs or statins may reduce the risk of prostate cancer.

Screening

Prostate cancer is incurable when diagnosed at a late stage so there is potential benefit in detecting early stage disease. Two tests used to detect the presence of cancer at an early, curable stage are:

- **Digital rectal examination** Internal examination of the rectum by a clinician
- **Prostate specific antigen measurement** The level of PSA, an enzyme produced by the prostate, is measured in the blood

In the US, all men over 50 years (or 45 years if considered at high risk) are offered routine PSA testing but in the UK there is no current screening programme for asymptomatic men. Although this is controversial, the decision is evidence-based. First, there is lack of sensitivity (men with prostate cancer may not have a raised PSA) and lack of specificity (two thirds of men with an elevated PSA level do not have prostate cancer, and this would subject men to unnecessary further investigations). Secondly, there is a lack of consensus about the best treatment for early stage prostate cancer. There is also no evidence that screening reduces mortality, although two large international trials are currently looking into screening.

Presentation, diagnosis and staging

Local symptoms from prostate cancer do not usually manifest until the tissue surrounding the prostate gland is invaded. These include urinary hesitancy, nocturia, incomplete emptying and a diminished urinary stream, which are also signs of benign prostatic hypertrophy. It is less common for men to present for the first time with symptoms of metastatic disease, such as bone pain and anaemia.

Diagnosis is via a transrectal ultrasound (TRUS) biopsy, following a positive DRE or high PSA test, or both. This is the use of sound waves produced by a probe inserted into the rectum to create an image of the prostate to allow biopsy. The aim is to detect prostate cancers with the potential to cause morbidity or mortality. Computer tomography or magnetic resonance imaging scans are only recommended for patients who have high risk cancer and are considering radical treatment.

Staging comprises the Gleason score, a PSA test and the tumour, node, metastases (TNM) system.

**The Gleason score** The Gleason score is based on the microscopic appearance of biopsy tissue, and ranges from 2 to 10, with 10 representing the most abnormal appearance. Cancers with a higher Gleason score are more aggressive and have a worse prognosis.

**The PSA test** Normal PSA levels are considered to be:

- <3.0ng/ml for men aged 50–59 years
- <4.0ng/ml for men aged 60–69 years
- <5.0ng/ml for men aged 70+ years

Higher levels than normal are an indication of prostate cancer.

Author Netty Wood will be available to answer questions online on the topic of this CPD article until 28 November 2009.

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**TNM system** The TNM system describes cancer in terms of the size of the primary tumour (T 1a–4c; where 1a is the smallest), whether lymph nodes are involved (N 0–3; where 0 is non-involvement) and presence of secondary cancer or metastases (M 0–1; where 0 means no metastases).

**Overview of treatment options**
The primary goal of treatment is to prevent mortality and morbidity while keeping side effects to a minimum. There is a lack of good clinical evidence concerning when to use which treatments, and few adequately powered randomised trials comparing the relative effectiveness between the treatments. However in February 2008, the National Institute for Health and Clinical Excellence published clinical guidance on the treatment of prostate cancer, and this article focuses on this. There are five main treatment options for prostate cancer:

- **Watchful waiting** (also known as active surveillance; see Panel 1)
- **Surgery** (see Panel 1)
- **Radiotherapy** (see Panel 1)
- **Androgen deprivation therapy**
- **Chemotherapy**

Most patients will receive one or a combination of these options as their disease progresses.

**Localised prostate cancer** NICE guidance recommends that urological cancer multidisciplinary team meetings should be held to assign a risk category to all men with newly diagnosed localised prostate cancer (ie, contained within the prostate gland). The category is based on risk of recurrence, for which PSA levels, Gleason scores and clinical staging are factors (see Panel 2). This is then used to guide which treatment options are recommended. However, treatment choice should always focus on balancing the goals of therapy with the risks of lifestyle alterations and should be made together with the patient. In particular, the relative risks of loss of sexual function and ongoing continence problems are important considerations.

NICE recommended treatment options according to risk stratification are described in Panel 3.

Patients are followed for five years. Those who “biochemically relapse” (ie, raised PSA) after radical treatment, should be offered hormonal therapy if they have one of the following:

- Symptomatic local disease progression
- Any proven metastases
- PSA levels that double in less than three months

**Metastatic or advanced prostate cancer**
NICE guidance recommends surgery (bilateral orchiectomy) or androgen deprivation therapy (medical castration) or anti-androgen therapy (see Panel 4) for metastatic or advanced prostate cancer. The therapeutic effect of castration was demonstrated in the 1940s, and medical castration is still the mainstay of systemic treatment. However, patients must be informed that there is no long-term evidence of its effectiveness. The figure in Panel 4 shows the mechanisms of action of androgen deprivation therapy.

**Panel 4: Androgen deprivation therapy**
Medical castration removes testosterone that feeds the tumour. Such androgen deprivation is achieved using gonadorelin (also known as gonadotrophin-releasing hormone (GnRH) and luteinising hormone releasing hormone) analogues, GnRH antagonists and anti-androgens.

Gonadorelin is secreted by the hypothalamus and acts at receptors on the pituitary gland, causing it to secrete luteinising hormone and adrenocorticotropic hormone. These act on the testes and adrenal gland, respectively, to increase testosterone levels.

Gonadorelin analogues and GnRH antagonists Gonadorelin analogues and GnRH antagonists have been used in clinical practice since 1985. Considering the mechanisms discussed above, it may not make sense to administer a gonadorelin analogue (i.e., leuprorelin, goserelin, triptorelin or buserelin) because that would increase testosterone but the analogue binds irreversibly to receptors, preventing further activation. Continuous administration therefore inhibits luteinising hormone release. However, on the first administration, the activation of pituitary gland receptors can cause a rise in testosterone. This surge lasts one to two weeks and can cause a tumour flare, which can manifest as spinal cord compression, ureteric obstruction (leading to renal failure) or increased bone pain. Concomitant use of an anti-androgen, started three days before the gonadorelin analogue and continued for three weeks, is recommended to prevent this flare. It should also be noted that if a gonadorelin analogue is not given for a period the receptors become free and the patient is at risk of a further surge in testosterone when therapy is restarted.

Other side effects include sexual dysfunction, gynaecomastia or changes in breast size and hot flushes. Treatment of hot flushes should include synthetic oestrogens (eg, diethylstilbestrol 1–3mg daily).

Anti-androgens Anti-androgens compete with testosterone for the androgen receptor on the prostate gland. As well inhibiting the tumour flare discussed they are used for monotherapy in prostate cancer. Cyproterone and flutamide are licensed for monotherapy in metastatic prostate cancer refractory to gonadorelin analogue therapy. Doses for tumour flare and monotherapy are similar. Bicalutamide can also be used as an adjunct to other therapy. Side effects include reduced sexual drive and potency and inhibited gonadal function.

Patients who are treated with bicalutamide monotherapy should be informed of the adverse impact on overall survival and gynaecomastia, but that they are likely to retain sexual function. In patients who do not maintain satisfactory sexual function, bicalutamide should be stopped. Patients starting long-term monotherapy should receive prophylactic radiotherapy to both breast buds within the first month of treatment. If radiotherapy is unsuccessful in preventing gynaecomastia, weekly tamoxifen (20mg daily) can be considered.
Panel 5: Chemotherapy

Chemotherapy is only used in advanced hormonal refractory disease. The aim is to improve symptoms, prolong life and slow progression of the disease. Chemotherapy regimens that have been used to treat prostate cancer include those based on mitoxantrone, estramustine and docetaxel. Docetaxel has become the gold standard.

The TAX 327 clinical trial compared two docetaxel schedules with mitoxantrone and prednisone (the previous standard chemotherapy regimen). The median survival for the three weekly docetaxel was 18.9 months compared with 16.5 months in the mitoxantrone arm and 17.4 months in the weekly docetaxel. Progression free survival was not reported.4

The SWOG 9916 clinical trial compared docetaxel plus estramustine with mitoxantrone plus prednisone. Median survival for the docetaxel arm was 17.5 months compared with 15.6 months in the mitoxantrone arm. The median time to progression was 6.3 months in the docetaxel and estramustine arm and 3.2 months in the mitoxantrone and prednisone arm.6

In 2006 NICE recommended docetaxel, within its licensed indications, as a treatment option for men with hormone-refractory prostate cancer within specified restrictions.4 Hypersensitivity can occur as a response to docetaxel itself or, more commonly, its polysorbate 80 vehicle. Premedication with steroids to prevent a reaction is, therefore, important.

Other chemotherapy regimens are not recommended by NICE for prostate cancer but mitoxantrone is used for patients who cannot tolerate docetaxel or who fall outside NICE guidance and is also used as the standard arm in many trials. Mitoxantrone with prednisone improves quality of life in men with advanced, hormone-refractory prostate cancer, but it does not improve survival.1

Chemotherapy regimens used in practice include:

- Mitoxantrone 12mg/m² iv on day 1 and oral prednisone 5mg twice daily continuously (21-day cycle)
- Docetaxel 60mg/m² iv on day 2 plus estramustine 280mg orally three times a day on days 1 to 5, with dexamethasone 60mg in three divided doses before docetaxel (21-day cycle)
- Docetaxel 75mg/m² iv on day 1, in combination with prednisone or prednizone 5mg orally twice daily continuously (21-day cycle)

Side effects of chemotherapy include a potential loss of ejaculation and fertility so sperm storage should be offered. For erectile dysfunction, the patient should be offered phosphodiesterase type 5 (PDE5) inhibitors. If these fail or are contraindicated, the patient can be offered vacuum devices, intraurethral inserts or penile injections, or penile prostheses. If urinary function is compromised, then access to specialist continence services should be arranged.

All patients with advanced prostate cancer should be encouraged to participate in local clinical trials if these are available.

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist’s CPD portfolio.

1. Check that patients given a gonadorelin analogue for the first time or after a break have also been given an anti-androgen to prevent tumour flare.
2. Should men with prostate cancer and hypogonadism have consulted their GP.
3. Ensure men buying herbal products sold for benign prostatic hyperplasia have consulted their GP.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

Cancer-related care multidisciplinary team with a view to seeking an oncologist or specialist palliative care opinion, or both, as appropriate.

Treatment options to be considered, according to NICE, are:

- Dexamethasone 0.5 mg daily for palliation of symptoms
- Radiotherapy for painful bone metastases
- Bisphosphonates for painful bone metastases when other treatments have failed
- Strontium-89 for painful bone metastases (This a beta-emitting radioactive isotope which is given intravenously and is taken up preferentially in bone metastases.)
- Chemotherapy (see Panel 5)

Bone metastasis affects more than 80 per cent of patients with advanced prostate cancer. Bisphosphonates (infusions of zoledronic acid or disodium pamidronate are often used) can be used for the palliation of symptoms such as pain and skeletal events. However they do not influence disease progression or patient survival.

Future strategies More research comparing the different treatment options in each stage of the disease is required to determine a more defined treatment strategy. With the increased understanding of the mechanisms responsible for prostate cancer and the development of hormone resistant prostate cancer, I imagine that the development of targeted therapies will soon follow, leading to a change of focus for the treatment of prostate cancer.

References