The management of metastatic prostate cancer

Bruce Turner and Lawrence Drudge-Coates

ABSTRACT
Bone is the most common site for metastatic deposits in men with prostate cancer. Metastatic bone disease is a catastrophic complication which can cause problems such as skeletal-related events, hypercalcaemia, anaemia, spinal cord compression and signifies that the malignant process is incurable. It is important that nurses managing a caseload of patients which includes individuals with, or at risk of, metastatic bone disease are aware of the potential complications and management so that a comprehensive patient assessment can be undertaken and early intervention implemented to reduce the impact on the patient and carers.

Key words: Metastatic prostate cancer • Bone metastases • Bone disease • Bisphosphonates • RANK Ligand • Pain management • Osteoporosis • Hormone therapy

INTRODUCTION
Prostate cancer has emerged as the most common cancer in men with 35 000 new diagnoses in the UK [Cancer Research UK (CRUK), 2009a], 301 500 and 185 985 new diagnoses, respectively, in the European Union and USA annually (Ferlay et al., 2007; Centers for Disease Control and Prevention, 2009). Although advances in the diagnosis and treatment of prostate cancer have dramatically improved survival, a significant amount of men continue to die of this disease. The majority of Western European and American countries have a relatively similar death rate from prostate cancer with nearly 29 000 deaths annually in the USA (Centers for Disease Control and Prevention, 2009). Each year in the UK just more than 10 000 men die from prostate cancer: a 5-year death rate of 30% (CRUK, 2009b). For the average hospital in the UK, which serves a population of 250 000–500 000 people there will be 100–200 new prostate cancer diagnoses annually of which some 20–40% of men will present with metastatic disease (Coleman, 1997).

Bone metastases are the most common metastatic deposits in men with prostate cancer (Hatoum et al., 2008) and occur in 85–100% of men with advanced disease (Desai et al., 2007). Metastatic bone disease is a catastrophic complication, which can cause problems such as skeletal-related events (SREs), hypercalcaemia, anaemia, spinal cord compression and signifies that the malignant process is incurable (Coleman, 1997; Mundy, 2006). Besides bone, prostate cancer may metastasize to any organ, but most commonly it affects distant lymph nodes, lung, liver, brain and skin. Clinical examination, chest X-ray, ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) scans are appropriate methods of investigation, but only if symptoms suggest the possibility of soft-tissue metastasis (Heidenreich et al., 2009).

In addition to bone metastases, patients taking long-term hormone therapy are at risk of developing osteoporosis. Osteoporosis is one of the most prevalent long-term sequelae of cancer therapy (Hawkins, 2006) known as cancer therapy-induced bone loss (CTIBL). Hormone manipulation to decrease serum testosterone levels with agents, such as luteinizing hormone releasing hormone (LHRH) agonists and antiandrogens, has proven to be an effective treatment for prostate cancer and many patients with locally advanced prostate cancer and the majority of patients with metastatic prostate cancer will be receiving a form of hormone manipulation therapy, which is known to accelerate bone loss but possibly to a lesser extent than subcapsular orchidectomy (Daniell et al., 2001).

It is of utmost importance that nurses managing patients with metastatic prostate cancer are aware of the complications and management of bone...
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metastases to ensure the patient has a high level of care that is proactive and aimed at helping to reduce the burden of this problem and by identifying and managing complications promptly and effectively and initiating prophylactic treatment where appropriate. The aim of this article is to educate and inform nurses caring for patients with metastatic prostate cancer regarding the importance of bone health and the complications and management of bone metastases.

BONE
Physiology of normal bone
The average skeleton is made up of 206 bones and constitutes about one-fifth body weight (Parker, 2007). The skeleton is compartmentalized into two main parts: the axial skeleton consisting of the skull, ribs, sternum and vertebrae and the appendicular skeleton consisting of the bones of the upper and lower limbs and the hips. The skeletal system is responsible for providing support, protection, movement, storage of minerals and growth factors, particularly calcium and phosphorous, haematopoiesis (red blood cell production), which occurs in the bone marrow in many bones and triglyceride (fat) storage (Marieb and Hoehn, 2009).

Bones undergo a constant process of resorption and formation which is a balanced sequence known as bone remodelling (Figure 1). Cells which break down bone for resorption are called osteoclasts and cells which form (build) bone are called osteoblasts. In the normal adult skeleton formation and resorption are closely coupled whereby osteoclast activity occurs before osteoblastic activity.

There are four distinct steps in the bone remodelling process.

RESORPTION
Osteoclast precursors release a variety of small proteins that act as chemical messengers between various parts of the immune system (cytokines) and growth factors, which bind to osteoclast receptors, leading to osteoclast activity. Osteoclasts remove bone mineral and matrix (hard bone material), creating and erosion cavity for the rebuilding of new bone (3–4 weeks).

REVERSAL
Mononuclear cells such as lymphocytes prepare the bone surface for new osteoblasts to begin building bone.

FORMATION
Successive waves of osteoblasts synthesize an organic matrix to replace reabsorbed bone and fill the cavity with new bone (3–4 months).

RESTING
The bone surface is covered with lining cells which provide protection. A resting period ensues with little cellular activity until a new remodelling cycle begins. Healthy bone is important for body function and it is apparent how a disruption to its normal working mechanism can affect the individual. Disruption in the homeostasis of bone can occur as a direct result of the cancer cells that metastasize and grow in the bone [cancer-induced bone disease (CIBD)] or as an indirect result of cancer treatment causing weakening of the bone (CTIBL). This article deals with CIBD.

METASTATIC BONE DISEASE
Pathology and pathogenesis of skeletal metastases in prostate cancer
Why prostate cancer cells have an affinity to metastasize to bone remains unclear (Desai et al., 2007), but some studies have shown, for example, that highly invasive prostate cancer cells have elevated levels of osteoponin (Oates et al., 1996), which is both a chemo-attractive and cell attachment factor (Chabas, 2005) and helps tumour cells to metastasize and grow. Tumour cells in bone marrow secrete paracrine factors that stimulate osteoclasts, leading to osteolysis and consequent disruption of normal bone metabolism (Hatoum et al., 2008).

Complications of bone metastases
Bone metastases are a common cause of morbidity in patients with prostate cancer. SREs such as bone pain, pathological fracture, hypercalcaemia (Scher and Chung, 1994) vertebral instability, vertebral
Diagnosis of bone metastases
An early sign of bone metastases may be a raised alkaline phosphatase (ALP) measurement. ALP is usually undertaken as part of the liver function test and raised levels can be seen in cholestasis from any cause. Circulating ALP is also derived from bone and raised levels can be seen in osteomalacia, Paget’s disease and bone metastases (differentiation from cholestasis is made by the absence of rise in serum gamma-glutamyl transferase (γ-GT) (Ballinger and Patchett, 2000). Prostate cancer patients with a raised ALP should be considered for further evaluation to exclude metastatic disease as it is raised in about 70% of patients with bone metastases (Wolff et al., 1999).

The need for reliable serum markers to improve the pretreatment staging of patients with prostate cancer has long been recognized but at present, prostate-specific antigen (PSA) is the marker of choice. A pretreatment serum PSA level > 10 ng/mL has been found to be the single most important indicator of metastatic disease, with a positive predictive value of 100% (Rana et al., 1992).

Bone lesions may be diagnosed by a variety of imaging modalities but radionuclide bone scan (bone scintigraphy) remains the gold standard method for detecting bone metastases (Gerber and Chodak, 1991). Bone scan is performed as a baseline assessment at initial staging for men thought to be at risk of metastatic disease or those who develop signs or symptoms of bone metastases later in their treatment pathway. However, bone scans may not detect micrometastases and MRI scanning may detect bone lesions up to 6 months before they are apparent on bone scan (Buscombe, 2008). False-positive results may be obtained in recent bone trauma, degenerative disease or Paget’s disease, particularly in the ribs (Buscombe, 2008). The bone scan mechanism of uptake is directly related to blood flow and degree of osteoblastic activity (Drudge-Coates, 2006).

The metastatic disease load at diagnosis can be a predictor of outcome: the Soloway et al. (1988) grading of bone metastases at diagnosis is one of the easiest methods of predicting outcome with metastatic disease (Buscombe, 2008) (Tables 1 and 2).

Pal et al. (2008) suggest that bone scan is omitted in asymptomatic men who have a PSA <20 ng/mL; however, in practice as bone scans are usually readily available and are cheap to perform the threshold is usually lower (Oyen et al., 2001) but is not required if the PSA is <10 (Cook and Fogelman, 2001). They are usually undertaken with a Gleason score of ≥3 + 4 = 7, when there is bone pain (Buscombe, 2008) and when there is raised ALP regardless of the PSA level (Heidenreich et al., 2009).

Plain X-ray was traditionally the first imaging test performed when a patient presented with symptoms suggestive of metastatic disease but the use is now limited with bone scan more favoured. Plain X-ray correlation is sometime suggested for further analysis of isolated lesions diagnosed on bone scan, particularly those of the spine and ribs where degenerative disease is common (Buscombe, 2008). If the plain X-ray fails to provide differentiation then an MRI scan or even bone biopsy may be required Heidenreich et al., 2008). In addition, some patients may be diagnosed with metastatic disease in the pelvis or lumbar spine when the prostate is being staged with MRI scan. In this case it would remain routine practice to perform a bone scan to assess the whole spine as there may not be simply an isolated lesion.

<table>
<thead>
<tr>
<th>Table 1 Soloway grade</th>
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<tbody>
<tr>
<td>Grade scan</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
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<table>
<thead>
<tr>
<th>Table 2 Survival by Soloway grade</th>
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<tbody>
<tr>
<td>Soloway grade</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2–4</td>
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</table>
MANAGEMENT

Lifestyle
Although lifestyle modifications will not cure bone metastases or reverse the risk of osteoporosis in patients with prostate cancer they will help to maintain bone density. Optimum calcium intake is achieved through a well-balanced diet but calcium and vitamin D supplements are recommended for patients with a restricted diet (Royal College of Nursing, 2005). Regular weight-bearing exercises such as brisk walking (also provides vitamin D exposure), aerobics or running are also important to help maintain bone health and should be recommended three times a week for a period of 20 min (Royal College of Nursing, 2005).

Pain
Although bone pain is the most common symptom of metastatic bone disease some patients may initially be pain free for a period of time. It is suggested that the pain in metastatic bone disease is one of the most difficult types of cancer pain to treat (Drudge-Coates, 2006); thus, it is important that all patients are routinely screened for the presence, absence and intensity of pain. A descriptive pain assessment should be performed for patients with pain, including assessment for likely aetiology and functional impairment (Dy et al., 2008). Pain is particularly distressing for the patient and can increase their dependency on others.

A multidisciplinary approach to pain management is usually most effective and a combination of systemic and local treatments may be required (Sarafini, 2001). Analgesia should be offered in accordance with the World Health Organisation cancer pain relief programme (Figure 2).

In addition, patients should be educated regarding pain management and should be offered breakthrough opioids if appropriate. The side effects of analgesia should be actively managed such as laxatives in patients receiving opioids (Dy et al., 2008) or consideration of proton pump inhibitors in patients receiving non-steroidal anti-inflammatory medication. It is also important that the patient’s response to analgesia is reviewed regularly.

SYSTEMIC MANAGEMENT OPTIONS FOR METASTATIC PROSTATE CANCER
Charles Huggins won the Nobel Prize in medicine in 1966 for establishing the relationship between testosterone and prostate cancer growth. Since then the majority of patients who have metastatic prostate cancer will be offered a form of hormone manipulation therapy with LHRH agonists, antagonists, antiandrogens, oestrogen or subcapsular orchidectomy.

Although the use of hormone therapy is indicated in other stages of prostate cancer (Table 3), long-term hormone therapy is recommended for patients

Table 3 Indications for hormone therapy in the stages of prostate cancer (adapted from Heidenreich et al., 2009)

<table>
<thead>
<tr>
<th>Hormonal therapy</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic and symptomatic</td>
<td>To palliate symptoms and reduce the risk of potentially catastrophic sequelae (e.g. spinal cord compression, pathological fractures, ureteric obstruction)</td>
</tr>
<tr>
<td></td>
<td>Even without randomized control trials this remains the standard of care</td>
</tr>
<tr>
<td>Metastatic and asymptomatic</td>
<td>Immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related sequelae</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>Immediate castration to improve cancer-free survival</td>
</tr>
<tr>
<td>Locally advanced and treated with radiotherapy</td>
<td><strong>High risk</strong></td>
</tr>
<tr>
<td></td>
<td>Combined and prolonged androgen deprivation therapy</td>
</tr>
<tr>
<td></td>
<td><strong>Low risk</strong></td>
</tr>
<tr>
<td></td>
<td>Up to 6 months of androgen deprivation therapy</td>
</tr>
<tr>
<td>Antandrogen (short-term administration)</td>
<td>To reduce the risk of ‘flare’ in patients who receive an LHRH agonist</td>
</tr>
<tr>
<td>Antandrogen (long-term monotherapy)</td>
<td>Primary monotherapy as an alternative to castration in patients with locally advanced disease</td>
</tr>
<tr>
<td></td>
<td>No place in localized disease as primary treatment modality</td>
</tr>
<tr>
<td></td>
<td>No clear recommendations as neoadjuvant treatment</td>
</tr>
<tr>
<td>Bilateral orchidectomy</td>
<td>Might be the most cost-effective form of ADT, particularly if used before patient is symptomatic</td>
</tr>
</tbody>
</table>

**ADT**, androgen deprivation therapy.
Table 4  Hormonal agents used in the management of prostate cancer

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
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<tr>
<td>Oestrogen agonists:</td>
<td>Suppresses secretion of LHRH (inhibits LH, inhibits testosterone synthesis)</td>
</tr>
<tr>
<td>Diethylstilboestrol</td>
<td></td>
</tr>
<tr>
<td>LHRH agonists:</td>
<td>Suppresses secretion of LHRH (inhibit LH, inhibit testosterone)</td>
</tr>
<tr>
<td>Leuprorelin</td>
<td></td>
</tr>
<tr>
<td>Goserelin</td>
<td></td>
</tr>
<tr>
<td>Triptorelin</td>
<td></td>
</tr>
<tr>
<td>LHRH antagonists:</td>
<td>Direct inhibition of LHRH with no agonist properties</td>
</tr>
<tr>
<td>Degarelix</td>
<td></td>
</tr>
<tr>
<td>Abarelix</td>
<td></td>
</tr>
<tr>
<td>Antiandrogens:</td>
<td>Suppresses testosterone by feedback effects at the pituitary and hypothalamus</td>
</tr>
<tr>
<td>Steroidal</td>
<td></td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td></td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td></td>
</tr>
<tr>
<td>Non-steroidal</td>
<td>Competitively inhibit binding of androgens in target tissue</td>
</tr>
<tr>
<td>Bicalutamide</td>
<td></td>
</tr>
<tr>
<td>Flutamide</td>
<td></td>
</tr>
<tr>
<td>Nilutamide</td>
<td></td>
</tr>
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</table>

(Adapted from Patterson et al., 2002). LH, luteinizing hormone; LHRH, luteinizing hormone releasing hormone.

LHRH is a hypothalamic decapeptide secreted in a pulsatile manner which stimulates the secretion of follicle-stimulating hormone and luteinizing hormone which in turn help to release inhibin and testosterone from Sertoli and Leydig cells, respectively. LHRH agonists initially stimulate the secretion of luteinizing hormone and follicle-stimulating hormone causing a tumour flare (that is prevented by giving the patient antiandrogen cover) and subsequently blocks the down-regulation of LHRH receptors. The suppression effect of luteinizing hormone synthesis leads to inhibition of testosterone synthesis (Wilson and Crawford, 2008).

LHRH antagonists

Although the mode of action of LHRH antagonists is similar to LHRH agonists, the former reduces the release of luteinizing hormone and follicle-stimulating hormone after the first dose, thus working to reduce testosterone levels more quickly than LHRH agonists. In addition to this, the antagonists do not cause an initial stimulation of hormones; therefore, there is no risk of tumour flare and antiandrogen is not required at initiation of therapy. In the initial development of LHRH antagonists, there was a risk of serious allergic reaction and anaphylaxis (Amling and Moul, 2005). With newer generation drugs, such as Degarelix which has been available in the UK since 2009 modifications to the structure of the drug during development, have ensured that the risk of anaphylaxis is reduced due to lower histamine releasing potential (Mason, 2009). The role of LHRH antagonists as an option for hormone manipulation in patients progressing on LHRH agonists or other hormones is yet to be shown. As the testosterone levels reduce so quickly after the administration of LHRH antagonists they may initially emerge as the treatment of choice in patients who present with a very high PSA, bone pain or signs suggestive of active or impending spinal cord compression.

Antiandrogens

Androgens mediate their action through the androgen receptors which are found in abundance in male genital tissue including prostate. Prostate cancer cells rely on androgens for growth and to avoid apoptosis. Antiandrogens block the androgen receptors so that testosterone cannot exert its effect on the target tissue. As circulating serum levels of testosterone are maintained some of the physiological effects of testosterone withdrawal are avoided.

Oestrogen

Diethylstilboestrol is rarely used as a treatment for prostate cancer due to the potential side effects with advanced and metastatic prostate cancer (NICE, 2008a; Heidenreich, 2009). The role of hormone therapy in this setting is to prolong life and palliate symptoms (Miller et al., 2009); the disease is stabilized in >80% of patients (d’Ancona and Debruyne, 2005). However, hormone therapy usually loses its ability to control tumour growth after an average of 2 years due to a multitude of molecular mechanisms that allow tumour growth when there is only a minimal concentration of androgens (Berthold et al., 2008). At this stage, the patient can be given a different type of hormone therapy or a combination of medications (Table 4). Although men will initially benefit from this hormonal manipulation ultimately the disease becomes hormone refractory (Berthold et al., 2008) and does not respond to hormone therapy. Conventional management of non-organ confined prostate cancer continues to evolve and over the past several years further treatment options have emerged.

LHRH agonist therapy

LHRH agonists have become the preferred means of achieving testosterone suppression in the treatment of advanced prostate cancer. When first developed LHRH agonist treatment required daily subcutaneous injections but now one, three and more recently, six monthly depot injections have become available (Schulman et al., 2007).
which can include fluid retention, arterial and venous thrombosis (BNF, 2008) but continues to be used by some oncologists when the patient progresses after several hormone manipulations (Malkowicz, 2001). Additionally, Serrate et al. (2009) have shown that diethylstilboestrol has a significant effect by reducing the PSA in patients whose PSA is increasing following docetaxel chemotherapy and suggest this as an option in this group of patients.

**Bisphosphonates**

Bisphosphonates play an indisputable role in preventing skeletal complications secondary to metastases, both reducing the onset and rate of occurrence (Coleman, 2000). Bisphosphonates have become part of the standard therapy for patients with metastatic prostate cancer to reduce SRE, reduce bone pain, analgesic consumption and improved quality of life (Coleman, 2000).

Bisphosphonates are synthetic analogues of an endogenous regulator of bone turnover called pyrophosphate. They bind readily to the bone matrix and therefore concentrate in the bone (Adami, 1997). All bisphosphonates are characterized by a phosphorous–carbon–phosphorous (P-C-P) containing central structure, which promotes their binding to the mineralized bone matrix (Coleman, 2000) and they inhibit the action of osteoclast activity (Russell and Rogers, 1999). This family of synthetic drugs vary in clinical activity and potency and the very potent bisphosphonate zoledronic acid (Zometa®) remains the only licensed product for use in prostate cancer in the UK. Zoledronic acid induces osteoclast apoptosis and inhibits protein prenylation (BAUS, 2005) the process by which molecules attach to a protein. In addition to this, it is postulated that zoledronic acid also inhibits osteoclast maturation, mature osteoclast cell function (Evans and Braidman, 1994) inhibit tumour cell dissemination and a reduced the ability for tumour cells to invade and adhere to bone matrix (Bossier et al., 2000).

Zoledronic acid is administered intravenously every 3–4 weeks in patients with metastatic prostate cancer and the dose is titrated depending on the creatinine clearance which is calculated using the Cockroft–Gault formula:

\[
\text{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times 1.23}{\text{creatinine (μmol/L)}}
\]

Bisphosphonates have the drawback of being administered intravenously, may cause renal toxicity and the rare complication—osteonecrosis of the jaw.

**RANK ligand inhibitors**

RANK ligand is one of a number of molecules which have been shown to regulate osteoclast maturation, differentiation and survival and is a key mediator in the pathogenesis of a broad range of skeletal diseases (Body et al., 2006). The drug Denosumab is a fully human monoclonal antibody to RANK ligand and was initially developed to treat patients with skeletal diseases mediated by osteoclast activity (Body et al., 2006) such as in the case of prostate cancer patients with bone metastases. Studies have shown that urinary markers such as urinary NTX are normalized more frequently in patients receiving Denosumab compared to those with intravenous bisphosphonates and patients experienced fewer SREs than those receiving intravenous bisphosphonates (Fizazi et al., 2009).

In a phase III placebo-controlled trial in men with non-metastatic prostate cancer on androgen deprivation therapy, Denosumab produced statistically significantly greater increases in bone mineral density (BMD) at the lumbar spine and non-vertebral sites compared with placebo. Additionally, these men experienced less than half the incidence of new vertebral fractures when compared with those receiving placebo, and fewer non-vertebral fractures (Saad et al., 2009).

Denosumab will become available in the next few years for use in the clinical setting. It has the advantage of being a subcutaneous injection and is not associated with the possible side effects of intravenous bisphosphonates. Additionally, Denosumab has the advantage of being completely cleared over a relatively short period of time and it may be the first bone agent to halt focal erosions and osteolysis (Schwarz and Ritchlin, 2007).

**Cytotoxic chemotherapy**

Historically prostate cancer was considered to be chemo-resistant with poor results from mitoxantrone chemotherapy. However, Docetaxel (Taxotere®) chemotherapy with a corticosteroid has now become a standard treatment for hormone resistant prostate cancer (Figure 3) (Serrate et al., 2009) by the majority of oncologists. Two large randomized studies demonstrated that this treatment prolongs survival and also improves time-to-disease progression, pain control and PSA response, as compared with mitoxantrone and prednisone (Petrylak et al., 2004; Tannock et al., 2004).

The TAX 327 study showed an increase in survival to an average of 18.9 months with a significant number of patients alive after 3 years follow up (Berthold et al., 2008); >30% of men had a quantifiable decrease in pain scores and >40% of men had at least a 50% reduction in serum PSA (Tannock et al., 2004). Due
The European Association of Urology state that hormone resistant prostate cancer can be defined as:

1. Castrate serum levels of testosterone
2. Three consecutive rises of PSA 2 weeks apart resulting in two 50% increases over the nadir
3. Antiandrogen withdrawal for at least 4 weeks
4. PSA progression despite secondary hormonal manipulations
5. Progression of bone or soft tissue lesions

(Heidenreich et al, 2008)

Figure 3 Definition of hormone resistant prostate cancer.

to the success of Docetaxel chemotherapy, it is recommended that it is offered to all men with hormone resistant metastatic prostate cancer with a Karnofsky performance status of $\geq 60\%$ (NICE, 2008b). Despite the encouraging results of chemotherapy, the time at which to initiate treatment remains controversial (Heidenreich et al., 2009). Historically cytotoxic treatment has been initiated at the final stage of treatment but now many pioneers of this advocate the use of Docetaxel before oestrogens. In this setting, the patient maintains a better performance status, can be treated aggressively and the use of diethylstilboestrol remains an option when the disease progresses following cytotoxic treatment (Serrate et al., 2009).

Bilateral subcapsular orchidectomy

The removal of testicular tissue where testosterone is produced was widely practiced before the introduction of hormone therapy and the effects are the same. Unlike hormone therapy, however, the results are irreversible. Medical castration has become favoured over surgical castration. Surgical castration may be of particular value in patients who are non-compliant with treatment or where economic reasons are important (Nargund, 2008) and in situations where the side effects, such as those on the cardiovascular system, are thought to put the patient at particular risk. NICE (2008b) recommends that bilateral subcapsular orchidectomy continues to be offered to all men with metastatic prostate cancer in the UK.

LOCAL TARGETED TREATMENT OPTIONS FOR METASTATIC PROSTATE CANCER

Surgery

A pathological fracture is one which has occurred in bone which is abnormal or diseased. Although pathological fracture can occur in any bone it most commonly affects the spine, subtrochanteric region of the femur and the humeral shafts (McRae, 2006). Without treatment union of a fracture seldom occurs at the site of a bone tumour, thus surgical intervention is commonly required whereby internal fixation with a pin and cement is undertaken by the orthopaedic surgeon (Marco et al., 2000). In some cases, the patient may initially present with a pathological fracture and thus with very advanced disease.

Radiotherapy

External beam radiotherapy is extremely effective in treating localized bone pain in patients with metastases (Dy et al., 2008) and one fraction has been shown to be as effective as many (Hartsell et al., 2005). Eleven randomized trials were identified in the published literature that compared single versus multifraction radiotherapy for bone metastases. Pooled analysis of these trials suggested that single fraction radiotherapy was as effective as multifraction radiotherapy in controlling bone pain. However, there were more bone fractures in patients treated by single fraction radiotherapy, and they received further treatment sessions more often than those receiving multifraction radiotherapy (Sze et al., 2004). One benefit of localized pain treated with radiotherapy is that opioid analgesics can routinely be omitted after treatment. External beam radiotherapy also has a role in treating pathological fracture: if the tumour is responsive to radiotherapy healing may occur with appropriate splintage but will be very slow (McRae, 2006).

Radioisotopes

The two radioisotopes, strontium-89 and samarium-153, can partially or completely decrease bone pain in up to 70% of patients, but should not be given too late when the pain is intractable. Early use can give rise to myelosuppression making subsequent chemotherapy more difficult (Heidenreich et al., 2004). Access to radioisotopes is limited in some centres.

SPINAL CORD COMPRESSION

Spinal cord compression occurs when metastases in the epidural space or the vertebral bodies cause compression of the spinal cord and its blood supply resulting in ischaemia and occurs in around 5–10% of patients with metastatic prostate cancer affecting the vertebral column (Chan and Richards, 2008). Metastatic spinal cord compression (MSCC) is a clinical emergency; it must be recognized early and patients at risk should be educated to recognize
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the warning signs (Heidenreich et al., 2009). In the UK every cancer network should ensure that appropriate services are commissioned and in place for the effective diagnosis, treatment, rehabilitation and ongoing care of patients with MSCC and there should be an MSCC co-ordinator with whom patients can be discussed within 24 h (NICE, 2008a).

Symptoms
The symptoms of spinal metastases are similar to those of bone metastasis at other sites and include pain in the thoracic or lumbar spine; progressive lumbar spinal pain; severe unrelenting spinal pain, spinal pain aggravated by straining, localized spinal tenderness or spinal pain preventing sleep (NICE, 2008a). Patients who develop any of the following neurological symptoms suggesting spinal cord compression should be discussed with the MSCC co-ordinator immediately and treated as an emergency:

- Radicular pain
- Limb weakness
- Difficulty walking
- Sensory loss
- Bladder or bowel dysfunction
- Signs of spinal cord or cauda equina compression on imaging.

(NICE, 2008a).

Management of MSCC

Once suspected, high-dose corticosteroids must be given and an MRI performed as soon as possible; if urgent treatment is required and MRI is not available (out of hours) at the referring hospital the patient should be transferred to a unit with 24-h capability (NICE, 2008a). The care of patients should be determined by a senior clinical advisor such as a clinical oncologist or spinal surgeon who has experience and expertise in treating these patients.

According to NICE (2008a), the patient should be nursed flat with the spine in neutral alignment until spinal and neurological stability are ensured: log rolling techniques and a slipper bed pan should be used. Once any spinal shock has settled the patient can gradually sit in a 60 degree position over 3–4 h. If the blood pressure is stable and there is no significant increase in pain or neurological symptoms unsupported sitting and mobilisation can ensue but if symptoms worsen the patient should return to a position where they reverse (NICE, 2008a).

Unless contraindicated, the patient should be given a loading dose of at least 16 mg dexamethasone as soon as possible following assessment and this should be continued whilst further treatment is planned (NICE, 2008a). The patient should be given appropriate analgesia and bisphosphonate therapy initiated (NICE, 2008a). A systematic neurosurgery consultation should be planned to discuss a possible decompression (George et al., 2008); otherwise, external beam radiotherapy is the treatment of choice (Heidenreich et al., 2009).

HYPERCALCAEMIA
Calcium homeostasis is a highly regulated process involving the co-ordinated efforts of the skeleton, kidney, parathyroid glands and intestine (Clines and Guise, 2005). Cancer can alter this homeostasis indirectly by producing endocrine factors causing hypercalcaemia or directly via skeletal destruction as in bone metastases (Clines and Guise, 2005). Although rare in prostate cancer hypercalcaemia (Corrected Calcium >2.6 mmol/L) is a potentially life-threatening complication of neoplastic disease (or cytotoxic chemotherapy). In most solid tumours, hypercalcaemia is the result of bone metastases, but osteolysis from tumour production of prostaglandins has been reported (Zeman and Siroky, 2004). The differential diagnosis includes primary hyperparathyroidism, immobilization, vitamin D intoxication, thiazine diuretic use and sarcoidosis (Zeman and Siroky, 2004).

The symptoms of hypercalcaemia include general malaise, depression, bone pain, abdominal pain, nausea and constipation. Calcium deposition in the renal tubules may cause polyuria and nocturia. A corrected calcium >3.5 mmol/L is a medical emergency; symptoms include dehydration, clouding of consciousness and a risk of cardiac arrest (Ballinger and Patchett, 2000).

Management
If the patient is taking calcium supplementation this should be stopped for a period of time and the patient should be questioned to ensure an overdose of supplementation has not inadvertently occurred. Monitoring of the serum calcium should ensue.

The bisphosphonate zoledronic acid has shown superior results in reducing hypercalcaemia by suppressing osteolysis (Neville-Webbe and Coleman, 2003) compared to other bisphosphonates and has the additional benefit of being administered in only 15 min.

In the emergency situation where a patient presents with stupor or coma saline diuresis with rapid intravenous infusion of normal saline can be effective as the presentation of a large sodium load to the renal tubules enhances calcium excretion (Zeman and Siroky, 2004).
CONCLUSION
Although the management of metastatic prostate cancer remains palliative in nature, it is with current therapies and ongoing advances in treatment that the clinical course of patients with metastatic bone disease has inevitably been prolonged. Subsequently, this has been accompanied by significant morbidity, including severe pain, often requiring radiotherapy in addition to existing analgesia, pathological fractures and spinal cord and/or nerve root compression, with often catastrophic effects for the individual and their quality of life, and additionally, family and carers.

It is perhaps because of the complexities of the patient’s clinical needs, and the ability to tackle clinical challenges that many urology nurse specialists/practitioners find themselves managing increasing numbers of men with metastatic disease. It is therefore essential that they have a greater awareness of the complications to be able to meet the ongoing patient needs, if they are to lessen the morbidity related effects for their patients. It is ultimately the ability of such nurses to be proactive in their diagnosis and management of potential complications that will have the greatest impact on patient outcomes. In addition, their role as practitioners will be further strengthened in acknowledging the treatment approaches provided by a multidisciplinary approach that integrates the treatment of the cancer, symptom management and rehabilitation that will ultimately ensure optimal care.

In acknowledging these important issues that authors believe that this paper will add significantly to the nursing knowledge to help address such complex clinical problems in men with metastatic prostate cancer.

WHAT IS KNOWN
• Metastatic prostate cancer can be a devastating disease.
• Bone is the most common site for metastatic deposits.
• Patients taking long term androgen deprivation therapy are at increased risk of osteoporosis.

WHAT THIS PAPER ADDS
• A review of the currently literature on this disease process.
• Explores the use of hormone therapy, bisphosphonates, RANK Ligand inhibitors and cytotoxic chemotherapy.
• Promotes an active approach to the care of this group of patients.

REFERENCES
The management of metastatic prostate cancer. *Journal of Clinical Oncology; 27*: 15s, abstract number 5056.


