Challenges in the management of metastatic prostate cancer

A significant number of men with prostate cancer will be elderly. Although some of the issues they face will be the same as their younger counterparts, they will also have their own unique set of issues such as concerns about the practical aspects of their disease.

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Prostate cancer is the commonest cancer in men in the UK with over 35,000 new cases diagnosed each year with peak incidence between the ages of 70 and 75 years.¹ There has been a significant (50%) increase in incidence over the past 10 years that relates to increased detection through prostate specific antigen (PSA) testing and histological diagnoses following surgical treatment of benign prostatic hypertrophy.²

Overall five-year survival rates remain favourable at approximately 70% and an estimated 215,000 males are living with the disease in the UK.¹ Many of these men are cancer survivors who have received radical treatment and remain in remission. Others have locally advanced or metastatic disease at presentation and are receiving treatment to achieve long-term control of their disease. Unfortunately those with advanced disease can experience significant morbidity either from disease progression or secondary to treatment.

A significant number of men with prostate cancer will be elderly. Although some of the issues they face will be the same as their younger counterparts, they will also have their own unique set of issues such as concerns about the practical aspects of their disease.³⁻⁵ Older patients are known to present later with cancer, thus vigilance is required among healthcare professionals dealing with elderly men who may not present with typical symptoms or be reticent in volunteering them. Elderly patients may also have pre-existing issues that need to be taken into consideration, such as functional status, comorbidities, polypharmacy and social support. These should be borne in mind when communicating with patients with prostate cancer and planning their management.

Bone metastases are common in advanced disease. As survival improves, an increasing number of patients will be living with them and experience major associated complications. This article will therefore focus on the pathogenesis, clinical features, impact and management of bone metastases in prostate cancer.

Complications

It is estimated that bone metastases occur in up to 80% of patients with hormone-resistant prostate cancer.⁶ Bone lesions from prostate cancer typically appear sclerotic on imaging due to increased osteoblast activity in reaction to metastatic deposits, commonly affecting the vertebral bodies, ribs, pelvis, proximal femur and humerus.⁷

Without adequate treatment, over half of patients experience debilitating complications such as severe pain, spinal cord compression and pathological fractures.⁸ These complications along with addition of chemotherapy, radiotherapy
or surgery to bone for the management of bone metastases are termed skeletal related events (SREs). On average, a patient experiences their first skeletal related event 10 months after being diagnosed with metastatic prostate cancer. In addition to a reduction in health related quality of life in individual patients, SREs lead to increased duration and frequency of hospital stays and a resultant increased cost per patient. Prevention of SREs should therefore be a priority and is discussed in more detail later in this article.

**Pain**

Bone pain causes debilitation and increased dependency on healthcare professionals and carers, leading to a reduction in the patients’ quality of life. Effective analgesia is essential, but it is frequently difficult to achieve. Pain from bony metastases in prostate cancer has also been shown to have a negative impact on mortality.

**Pathological fractures**

Pathological fractures occur in approximately 22% of patients, frequently affecting vertebral bodies and proximal ends of long bones. The propensity for fracture is secondary to the pathogenesis of bone metastases. Osteoclastic recruitment and differentiation lead to bone destruction followed by inappropriate osteoblastic deposition, resulting in low bone strength and potential collapse. The risk of fractures is further increased by androgen deprivation therapy, which reduces bone mineral density.

Patients suffering a pathological fracture secondary to prostatic bony metastases are known to have an increase in all-cause mortality. Treatment involves surgical fixation plus or minus radiotherapy.

**Spinal cord compression**

Spinal cord compression occurs in 3–5% of patients with advanced malignancy. Worryingly 23% of cases occur in those without evidence of metastatic spread to bone.
a prior diagnosis of cancer. Early signs of impending cord compression include worsening pain (often aggravated by coughing or sneezing), point tenderness of the spine, impaired mobility and radiculopathy. Delays in presentation, diagnosis and treatment can lead to development of established cord compression, potentially resulting in paraplegia or quadriplegia and loss of sphincter function with subsequent physical and psychological morbidity and increased mortality.

Despite the fact that spinal pain and neurological symptoms may precede paraplegia by two to three months, approximately 50% of patients are unable to walk by the time of diagnosis. The key to preservation of function is early diagnosis and treatment, be it surgical decompression in the case of a solitary level of compression or palliative spinal radiotherapy. It is important that clinicians educate patients regarding the signs and symptoms of cord compression.

Management

Analgesia

Analgesia is a cornerstone of treatment but bone pain can be difficult to control with standard analgesia, and progressive symptoms often require radiotherapy. Some older patients may not tolerate the analgesics commonly prescribed to manage their pain, such as non-steroidal anti-inflammatories and opiates.

Hormonal manipulation

In the majority of cases, progression of prostate cancer is stimulated by endogenous testosterone. In the absence of testosterone, prostate cancer cells undergo apoptosis with consequent reduction in the secretion of prostate cancer markers and alkaline phosphatase. Treatment options, particularly in metastatic disease, therefore aim to reduce levels of testosterone or modulate response to it.

Castration has remained the gold standard in the management of advanced disease with response rates in the region of 80%. It can be achieved surgically following orchidectomy or medically with leuteinising hormone releasing agonists (LHRHs), such as goserelin (Zoladex) and leuprorelin (Prostap SR), which switch off testosterone production through negative feedback inhibition. As well as reducing disease progression, androgen deprivation therapy improves bone pain, urinary symptoms, and performance status. A comparison of orchidectomy and goserelin demonstrated that they were equivalent but LHRH analogues are the preferred castration option and is the mainstay of initial treatment.

Despite improvement in survival outcomes and effective palliation of symptoms, LHRH agonists can cause morbidity, especially in elderly patients, and therefore good communication of these side effects is essential on commencement of therapy. Side effects include hot flushes, fatigue, weight gain, dyslipidaemia, mood disturbance, osteoporosis, loss of libido and erectile dysfunction. This may have an effect on compliance, and psychological support is essential for a patient cohort who may not readily discuss these issues during consultations.

The initial duration of response to androgen deprivation therapy is about 12–18 months. On progression an option is combined androgen blockade with the non-steroidal anti-androgens, such as bicalutamide and flutamide, which have response rates of approximately 75%. In responders, duration of effect can be up to 11 months. Should the patient show further disease progression, options include switching anti-androgen therapy or withdrawal of the anti-androgen, which produces a response in up to 25% of patients with a median duration of five months.

Hormone-resistant prostate cancer (HRPC) is defined as evidence of disease progression following hormone manipulation on the background of castrate levels of testosterone. This includes radiological progression or two consecutive rises in PSA of at least 5 ng/ml (measured at least two weeks apart). At this stage, significant morbidity and mortality can develop and therefore treatment options should be tailored to focus on improving quality of life. The androgen receptor is considered to remain active on cancer cells and consequently LHRH agonists are continued. Subsequent options include addition of the synthetic oestrogen diethylstilboestrol, which exhibits high PSA response rates in androgen independent disease. It is contraindicated in those with a history of thromboembolism and is associated with tender gynaecomastia and fluid retention. Physiological doses of corticosteroids can also be used and act by suppression of ACTH with subsequent reduction in adrenal androgen levels.

In advanced prostate cancer, preventing the development and
progression of bone metastases, as well as their associated complications, is a priority. As patients become resistant to first-line treatment and develop symptoms, a number of systemic and local treatments are available.

**Radiotherapy**
External beam radiotherapy provides a simple, cost effective treatment option for local control of pain and should be considered in all patients with symptomatic bone metastases. It is delivered in specialist radiotherapy centres. Response to treatment is in the order of 40-70% with complete responses seen in up to 25%. Onset of pain relief may be within two days but can take up to six weeks with sustained response for up to six to seven months. The treatment is associated with low toxicity and often only requires a single planning visit and can therefore be considered for patients with poor performance status.

In the setting of spinal cord compression (SCC) or cauda equina, palliative radiotherapy is aimed at treating soft tissue disease in the spine to preserve and improve neurological function and pain. Following commencement of high-dose steroids with onset of symptoms or signs of SCC, radiotherapy should ideally be delivered within 24 hours of a diagnostic MRI if neurosurgical intervention is not indicated. Patients who exhibit a good response may be amenable to re-treatment although the requirement for this is greater when a single fraction of radiotherapy is administered rather than multiple fractions over successive days.

**Chemotherapy**
One of the main systemic options in men with HRPC is chemotherapy. In metastatic disease, docetaxel is licensed in combination with prednisolone, and patients receive up to 10 three-weekly cycles. As well as an improvement in overall survival and reduction in measurable disease, there is an improvement in quality of life outcomes. The TAX 327 trial found that 35% of patients experienced a significant reduction in pain following treatment. There still remains the perception that chemotherapy is a toxic option in the elderly. In reality this chemotherapy can be offered to those in their 80s and is tolerated to good effect provided their performance status is >2 (based on The Eastern Cooperative Oncology Group Performance Status). Rates of severe toxicity are low with the major side effects being fatigue, diarrhoea, nausea, alopecia, nail changes and sensory neuropathy which are largely well tolerated. Second-line chemotherapy is an option if disease progresses following first-line treatment. Mitoxantrone (Onkotrone) has been given as second-line treatment in the past. However the recently reported TROPIC study has demonstrated a survival advantage with cabazitaxel (Jevtana) when compared with mitoxantrone in this setting and is now licensed for second-line chemotherapy in hormone-refractory prostate cancer.

**Bisphosphonates**
The role of bisphosphonates in hormone-refractory metastatic prostate cancer remains controversial. In contrast to breast cancer and multiple myeloma, several randomised placebo controlled trials of early generation bisphosphonates such as etidronate, clodronate and pamidronate failed to demonstrate an improvement in bone pain from metastatic disease when compared with placebo. Additionally there was no reduction in the frequency of SREs.

Saad et al subsequently conducted a placebo controlled trial using a third generation bisphosphonate, zolendronic acid (Zometa). It was administered intravenously three weekly at a dose of 4 mg. The results demonstrated that zolendronic acid improved pain scores, reduced the incidence of SREs and delayed their onset. The effect was more pronounced if zolendronic acid was commenced prior to the onset of pain; in early bone disease; or following an initial SRE with a continued benefit observed for up to two years.

**Biological agents**
In HRPC, bone metastases are associated with RANK-L mediated osteoclast activation with consequent bone destruction, tumour proliferation and SREs. Denosumab (Prolia) is a fully humanised monoclonal antibody that specifically targets and inhibits RANK-L mediated activation and has been developed for use in bone metastases. Recent results from a phase III trial comparing it directly with zolendronic acid in metastatic prostate cancer have demonstrated superiority of denosumab in delaying and preventing SREs with no significant increase in toxicity. Given the ease of administration, efficacy compared...
with bisphosphonates and tolerability, denosumab is likely to have a significant role in the future of metastatic prostate cancer.

Radioisotopes
Radioisotopes such as strontium-89 and samarium-135 can be administered for refractory bone pain in men with a limited number of bone metastases. They are administered intravenously and concentrate in areas of active bone formation, emitting radiation directly to cancer cells. Response rates range from 40% to 95%, with onset of action between one and four weeks and duration of response up to 15 months. This option is best in those with limited skeletal involvement, good patient performance status, prognosis greater than three months and osteoblastic lesions. They can cause neutropenia and thrombocytopenia but these are generally mild and reversible.

More recently phase 2 results for the α emitter Radium-223 (alpharadin) in men with symptomatic bone metastases from metastatic HRPC have been promising. Compared with placebo, it demonstrated a significant reduction in bone ALP concentrations with an increase in time to progression and median overall survival. There was minimal myelotoxicity and is currently the subject of a multinational phase 3 trial.

There is evidence for improved response rates in combination with chemotherapy and current trials are ongoing as to whether chemotherapeutic combination improves survival.

Conclusion
Prostate cancer is a common disease affecting a significant number of elderly men. Complications include bone metastases that have potentially devastating consequences. A number of treatment options are available that aim to control disease progression, palliate symptoms and importantly prevent complications of bone metastases. The choice of management will depend on individual patient and disease factors.

References are available online and from the editorial office

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