Prostate cancer is the most common malignancy in men, with 40,000 new diagnoses each year in the UK. This disease usually affects men aged 65 years and over, and there is a higher incidence and mortality in men of black African-Caribbean ethnic origin.

Most cases at diagnosis are confined to the prostate gland and may be treated with either radical prostatectomy or radiotherapy (external beam or brachytherapy), or may be suitable for an observational approach termed active surveillance. However, once prostate cancer has metastasised, it is incurable by conventional approaches and the main goal of treatment is to prolong survival, maintain quality of life and palliate symptoms. Prostate cancer commonly spreads to the bones and pelvic/abdominal lymph nodes, and less commonly to visceral sites such as liver or lung. Morbidity and mortality often results from bone involvement, with debilitating pain, spinal cord compression, pathological fractures and bone marrow failure.

In recent years we have seen major advances in the options for systemic therapy for men with advanced incurable disease that achieve the main goals of treatment. This article will summarise these and focus on the role for the recently licensed radiopharmaceutical radium-223 (Xofigo, Bayer).

**Systemic therapy options for advanced prostate cancer**

Prostate cancer is an androgen receptor dependent tumour and androgen-deprivation therapy (ADT) remains the backbone of treatment for advanced disease. ADT is achieved with medical (luteinising hormone-releasing hormone agonist or antagonist injections) or, much less commonly, surgical (bilateral orchidectomy) castration. Eighty per cent of patients respond to this approach.

When this fails to control the disease, combined androgen blockade, by the addition of androgen receptor antagonists such as bicalutamide, can offer prostate specific antigen (PSA) responses and clinical benefit in 30%-35% of patients.

Despite a high response to ADT, most patients will inevitably become androgen-independent at a median of 12 to 30 months after castration. This was previously referred to as ‘hormone refractory’ but is more correctly termed castration resistant prostate cancer (CRPC) as we now recognise that the androgen receptor remains critical and central to the disease at all stages in almost all patients. Castration resistance may be defined as a rising PSA despite castrate levels of serum testosterone, and in patients with metastatic disease, this is usually followed by radiological and symptomatic progression. Once the patient reaches this stage of the disease, the median survival is 9-30 months. Recent evidence indicates the latter end of this range is becoming more common and it appears that most patients will now spend more time in a castrate resistant state, in part due to recent introduction of novel therapies.

During the past decade, there has been a significant transformation in the management of patients with metastatic castration resistant prostate cancer (mCRPC). With a better understanding of the disease biology, it has led to recent development of new therapies that are helping men to live longer and enjoy a good quality of life. These systemic therapies include anti-androgen therapy, immunotherapy, cytotoxic chemotherapy and bone-targeted therapy. Table 1 summarises the key clinical trials for the new agents currently available for men with mCRPC.

**The role of radium-223 in the CRPC therapeutic armamentarium**

Radium-223, an α emitter, is the most significant development in bone-targeted therapies. In simple terms, it mimics calcium (residing in the same column of the periodic table) and so it preferentially targets areas of increased bone turnover such as bone metastases. α particles have a high linear energy transfer, which induces double-strand DNA breaks to adjacent cells resulting in cytotoxicity. However they have the advantage of a very short penetration range (<100μm), thereby limiting toxicity to adjacent normal tissue and, critically, to the bone marrow. In addition, a half-life of 11.4 days results in an agent for which the practical aspects of shipping to end users, storage and disposal, while not negligible, are at least relatively straightforward.

Radium-223 is given intravenously as six doses (50kBq/kg) on a four-weekly basis. At four hours post-injection, approximately 60% of the injected radioactivity is present in the bones. Excretion is primarily via the faecal route and 63-76% of radioactivity is eliminated from the body within seven days. There is little concern of exposure to the public due to the limited γ emission. As a result, outpatient based treatment with relatively simple requirements for patient education are possible.

A phase III randomised trial compared radium-223 with placebo in 921 men with progressive mCRPC with two or more bone metastases without visceral metastases. It showed an improvement in the primary endpoint of OS in favour of the radium-223 group (14.9 months vs 11.3 months; hazard ratio 0.70; 95% CI, 0.58 to 0.83; p<0.001). There was also benefit with respect to a number of important secondary endpoints including the time to first symptomatic skeletal event (15.6 vs 9.8 months; hazard ratio 0.66 (95% CI, 0.52-0.83); p<0.001), time to either PSA or alkaline phosphatase progression and improvement in measurements of quality of life. Adverse events were lower in the treatment group compared to the placebo group with no difference in severe haematological toxicity. In general this was a well-tolerated intervention.

**Introduction**

Prostate cancer is an androgen receptor dependent tumour and androgen-deprivation therapy (ADT) remains the backbone of treatment for advanced disease. ADT is achieved with medical (luteinising hormone-releasing hormone agonist or antagonist injections) or, much less commonly, surgical (bilateral orchidectomy) castration. Eighty per cent of patients respond to this approach.

When this fails to control the disease, combined androgen blockade, by the addition of androgen receptor antagonists such as bicalutamide, can offer prostate specific antigen (PSA) responses and clinical benefit in 30%-35% of patients.
Currently, the use of radium-223 can be considered pre or post-docetaxel for symptomatic bone metastases without visceral metastases. Radium-223 is FDA approved and the European Expert Consensus Panel advised that radium-223 could be considered for symptomatic bone metastases in mCRPC. At the time of writing, radium-223 is available in England through the Cancer Drugs Fund and is being considered by the National Institute for Health and Care Excellence (NICE).

**Conclusion**

The number of effective treatment options for mCRPC has increased over recent years. Clinicians now face the new challenge of identifying the best sequence of agents for individual patients and how to combine these therapies in a rational way to maximise survival and minimise toxicity.

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