Advanced prostate cancer: advancing patient care

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This report is based on a series of regional meetings and a seminar held during the 9th Annual Meeting of the British Uro-oncology Group. The meetings reviewed optimal management of patients with advanced prostate cancer in the context of full multidisciplinary team involvement. Developments in drugs for advanced disease were covered, following which presentations and case discussions were used to look at the future of surgery and palliative care options for this patient population.

THE FUTURE OF ADVANCED PROSTATE CANCER: DRUGS IN THE PRE-CHEMOTHERAPY SETTING

Following many years during which the only option available for the management of advanced castrate-resistant prostate cancer (CRPC) was docetaxel, physicians now find they have effective alternatives in this patient population. The potential roles of two agents that have recently reported benefits for the group of patients with advanced CRPC in the pre-chemotherapy setting, abiraterone acetate (Zytiga) and radium-223 dichloride (Xofigo), are considered below.

Abiraterone acetate

Abiraterone acetate, a novel androgen biosynthesis inhibitor, was approved by the Food and Drug Administration for late-stage prostate cancer in 2011. The phase 3 COU-AA-302 trial, conducted in 1088 patients with asymptomatic or mildly symptomatic metastatic CRPC in patients not treated with docetaxel chemotherapy, showed a significant benefit in terms of radiographic progression-free survival and a trend towards overall survival for abiraterone and prednisolone compared with prednisolone alone. Secondary endpoints were also strongly favourable towards abiraterone (Table 1).

The positive results reported provide a strong rationale for the use of abiraterone in the pre-chemotherapy space. Abiraterone is awaiting a NICE technology review in this clinical setting. In the meantime, abiraterone for chemo-naïve patients can be accessed through the Cancer Drugs Fund in England.

Radium–223 dichloride

Radium-223 dichloride is a first-in-class alpha-emitting pharmaceutical that targets bone metastases with high-energy alpha-particles of short range (<100μm).

The ALSYMPCA trial showed a highly significant overall survival benefit for radium-223 dichloride (p<0.0001) compared with control in patients with symptomatic CRPC and bone metastases. Importantly, the therapy was found to be equally effective in terms of overall survival whether it was administered in the pre- or post-docetaxel setting. Furthermore, fewer patients had a deterioration (≥2 points) in the Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) in the radium-223...
group compared with control at week 12 and 24, while the time to ECOG PS deterioration (≥2 points) was significantly delayed by radium-223 (p=0.003; HR=0.62; 95% CI, 0.46–0.85). Radium-223 has just received a UK licence approval but is not yet generally available on the NHS. In advance of the NICE and Scottish Medicines Consortium appraisals, radium is expected to be available through the Cancer Drugs Fund in England very soon.

Agents such as radium-223 and abiraterone are likely to have a significant role in the pre-chemotherapy setting in the future, and the contribution of certain other emerging therapies, such as enzalutamide (Xtandi), tasquinimod and cabozantinib (to name but a few) has yet to be determined. Further, it is not yet clear how the emerging agents will ultimately be used in relation to one another. Although it is possible to predict likely treatment protocols, this will undoubtedly be influenced by financial considerations and capacity issues. Access to emerging and highly effective therapies must be addressed as a matter of urgency.

MEETING THE UNMET NEED IN CRPC: DRUGS, SURGERY OR PALLIATIVE CARE?
Recent data show that, although the incidence of prostate cancer is rising globally, mortality rates have remained relatively consistent over the past decade (Figure 1). The resulting sharp rise in the number of patients living with prostate cancer, coupled with the ageing population, has real implications in terms of healthcare resources. Prostate cancer patients will increasingly rely on a combination of drugs, surgery and palliative care, and a clear strategy to deliver the appropriate care to individual patients will need to be developed. The aims and expectations at the stages of prevention, survival and palliation will need to be clearly defined.

The National Audit of Cancer Diagnosis in Primary Care showed that for acute presentations, 3.9 per cent of prostate cancer patients present with lower urinary tract symptoms. The most common symptoms at acute presentation include bone pain, incontinence and urine retention. Encouragingly, 61.4 per cent of patients with prostate cancer present at the organ-confined stage, with 15.6 per cent presenting after local spread and 14.0 per cent with distant metastases.

The management of CRPC must address the commonly associated urological problems, as well as incorporate further lines of androgen deprivation therapy, bone-targeted approaches, chemotherapy, and other novel modalities of treatment. This combination of approaches is highly resource intensive and costly. In a study of the final year of life of 226 men with CRPC, 46 per cent had prostate cancer-related complications, while 85 interventions were required. The commonest adverse events in the final year of life in men dying of advanced prostate cancer are those of lower urinary tract symptoms, renal failure, anaemia and bone pain, with almost half of men developing at least one of these.

CRPC commonly presents with a range of complications including lower tract symptoms and dysfunction, upper tract obstruction, cord compression, marrow failure, lymphoedema, rectal obstruction/infiltration, pain and psychological dysfunction. Management of this variety of complications requires a multidisciplinary approach, and drugs, surgery and palliative care all have a vital role to play.

ADVANCE CARE PLANNING IN ADVANCED PROSTATE CANCER
The current focus on developing new drugs and surgical techniques in advanced prostate cancer, and the pressure to extend survival even by a few weeks or months, has tended to mean that end-of-life care can be somewhat overlooked, and not afforded the effort or resources that it deserves. However, end-of-life management is arguably the most important care that a patient will receive, and has an immeasurable impact, not only on the patient’s own comfort but also on the experience of his family and friends.

It can be challenging to recognise the appropriate stage at which to involve end-of-life planning into a patient’s management. One approach is to consider whether you believe your patient is likely to survive another year. If you feel they are not likely to survive a year, important questions about end-of-life priorities should start to be asked. This is also an appropriate stage at
The rapid pace of drug developments has led to the need for effective communication between GPs, limited resources and acceptance of patient preferences.

Urological symptom management requires the involvement of a multidisciplinary team. Important considerations about where an individual prefers to die, as well as where they would prefer to die, need to be addressed. Sometimes, patients express a desire to die at home, and this may require considerable advance planning to ensure that the appropriate care and facilities are in place. Inviting involvement from a palliative care specialist at the appropriate time is beneficial.

At this stage, the medical team should start discussing how the patient and family wish to proceed over the coming months. Palliative care should begin to be considered, even if patients prefer to remain uninformed. It is important to establish the preferences of the individual patient and family so that the appropriate approach can be adopted, while appreciating that preferences often change with time.

Important considerations about where an individual would like to be looked after, as well as where they would prefer to die, need to be addressed. Many patients express a desire to die at home, and this may require considerable advance planning to ensure that the appropriate care and facilities are in place. In some cases, patients express a wish to travel a considerable distance, or even return to a country of origin, for their final weeks. In this case, considerable administrative tasks will probably need to be fulfilled. Wherever a patient chooses to die, it is important to ensure that he will have access to the necessary care and drugs.

At this stage, the medical team together with the palliative care team should start to discuss how the patient and family wish to proceed over the coming months. Some patients prefer to know full details about their illness and prognosis, while others prefer to remain uninformed. It is important to establish the preferences of the individual patient and family so that the appropriate approach can be adopted, while appreciating that preferences often change with time.

It is also vital to consider the needs of family members who may be left behind. Often when an individual dies, all the support and resources that were afforded to the patient are immediately withdrawn, and a bereaved partner or relative can find themselves completely alone. Plans should be put in place to ensure that a partner, particularly if elderly or otherwise infirm, should be looked after in the first days and weeks after bereavement.

Although consideration of these issues may sometimes seem very difficult, it is important that they are addressed in a timely manner. Ultimately, the aim of these measures is to ensure a better quality of death and adequate care for those left behind.

**Declaration of interests**

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**REFERENCES**


