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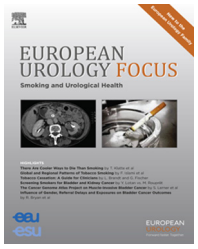

Platinum Priority – Review – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Charting Recent Progress and Challenges in Metastatic Castration-resistant Prostate Cancer: Is There an Optimal Treatment Sequence?

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Abstract

Context: Recent developments in the treatment of metastatic castration-resistant prostate cancer (mCRPC) have led to uncertainty about the optimal sequence of agents.
Objective: To review and assess treatment options and sequence in patients with mCRPC.
Evidence acquisition: To identify data on the optimal use of approved treatments, we searched PubMed for studies on the use of recently approved agents for men with mCRPC published before March 2015. Phase 3 and other key studies were included in the review of efficacy and safety. In this review, we offer our critical interpretation of potential treatment sequences for drug use in the light of our clinical experience.
Evidence synthesis: Since 2004, the treatment landscape for mCRPC has changed dramatically following the approval of docetaxel, abiraterone acetate, enzalutamide, cabazitaxel, denosumab, and radium-223 chloride. To date, only small-scale studies have been undertaken that provide evidence on the sequencing of these treatments. Ideally, randomised, prospective studies would evaluate different sequence options thoroughly so that physicians could make evidence-based decisions, but the number of new agents makes this impractical. When deciding which treatment to prescribe, physicians will need to use the available evidence combined with their own clinical judgement. The potential for cross-resistance between taxanes and hormonal therapies and the possibility that patients might not be suitable for aggressive therapies in later lines should be taken into account. Prevention of complications associated with bone metastases should also be a key consideration because of the major impact these events have on quality of life and healthcare costs.
Conclusions: The recent approval of numerous new agents has resulted in considerable improvements in outcomes for patients with mCRPC. Further studies determining the optimal treatment algorithm, in addition to open discussion of best practice among physicians, are required to ensure patients obtain the maximum possible benefit from their treatment.
Patient summary: In recent years a large number of new treatment options have been approved for use in men with prostate cancer. In the absence of clinical trials assessing the use of one option versus another in specific patient groups, it is important to review the currently published evidence to try to understand patients receive the best treatment options in the correct order.
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1. Introduction

In 2004, the treatment landscape in castration-resistant prostate cancer (CRPC) changed substantially when docetaxel, which prolongs overall survival (OS) in men with metastatic CRPC (mCRPC) [1], was approved in the USA. Since then, more treatment options have been approved for use in Europe in patients with mCRPC. These include five agents with a proven survival benefit: the chemotherapy agent cabazitaxel, two hormonal therapies, abiraterone acetate and enzalutamide, and the radiopharmaceutical radium-223 chloride (Ra-223) [2–6]. In addition, the bone-targeted agent denosumab has been approved to treat bone metastases in patients with mCRPC. The immunotherapy sipuleucel-T was approved in Europe in 2013 but had its approval withdrawn in May 2015 for commercial reasons at the request of the market authorisation holder [7]. It is, however, still available in the USA [8] and so has been included in this review.

Numerous phase 3 trials (Table 1) have investigated the efficacy of these new agents. However, the introduction of these agents over a short period of time has led to uncertainty about their optimal sequence of use. When determining the most effective treatment strategy, efficacy and safety profiles and patient characteristics all play key roles (Box 1, Fig. 1). Herein, we review peer-reviewed evidence on the efficacy and safety of available therapies and treatment sequences.

2. Evidence acquisition

PubMed was used to identify studies published in English on the use of docetaxel, abiraterone acetate, enzalutamide, sipuleucel-T, cabazitaxel, zoledronic acid, denosumab, and Ra-223 in men with mCRPC published before March 2015 using the following terms: docetaxel, abiraterone acetate, MDV 3100, enzalutamide, sipuleucel-T, cabazitaxel, zoledronic acid, denosumab, Ra-223, and mCRPC. Phase 3 studies were reviewed to provide efficacy and safety information. Data from earlier phase studies were included where necessary to highlight key issues relevant to clinical practice. To provide evidence for the optimal sequencing of these agents, a wider range of studies were included; however, only robust data (in the opinion of the authors) were assessed (Table 2). This report offers our critical interpretation of potential treatment sequences in light of our clinical experience.

3. Evidence synthesis

3.1. First-line treatment

3.1.1. Chemotherapy

Docetaxel was the first agent that was found to extend OS in patients with mCRPC [1,9]. Docetaxel is approved by the US Food and Drug Administration and the European Medicines Agency for use with prednisone or prednisolone in patients with mCRPC [10,11]. Subanalyses of the TAX327 study that compared docetaxel and mitoxantrone revealed that pain, visceral metastases, anaemia, and bone scan progression are all risk factors that predict clinical outcomes. Patients with multiple risk factors had worse OS ($p < 0.0001$) and were significantly less likely to have a prostate-specific antigen (PSA) decrease of 30% and a measurable disease response than patients with few risk factors [12]. There were no significant differences in hazard ratios for docetaxel versus the control arm across the risk groups; however, the OS benefit with docetaxel was greatest for patients with 0–1 risk factors [12].

3.1.2. Immunotherapy

Several therapies are available for patients whose disease has progressed on androgen deprivation therapy (ADT). Sipuleucel-T is an option for patients with asymptomatic or mildly symptomatic disease and works by priming the immune system to recognize and kill prostate cancer cells via ex vivo autologous peripheral blood mononuclear cells. These cells have been cultured with granulocyte–macrophage colony-stimulating factor fused to the prostatic acid phosphatase prostate cancer antigen. Antigen-presenting cells are activated by the granulocyte–macrophage colony-stimulating factor–prostatic acid phosphatase protein and induce an immune response upon reintroduction into the patient [13].

In the phase 3 IMPACT study, sipuleucel-T provided a median OS benefit of 4.1 mo over placebo in men with asymptomatic or mildly symptomatic mCRPC [14]. Pre-specified subgroup analyses revealed that patients with low disease burden derived the greatest benefit from this treatment [15]. However, there was a delay before the survival curves for the two study arms diverged, and sipuleucel-T treatment did not delay disease progression compared with placebo [14]. Therefore, it is not an appropriate treatment for patients with symptomatic or rapidly progressing disease. Furthermore, the cost of such treatment needs to be considered. Biomarker research [16] may help predict which patients will respond, thereby improving the cost-effectiveness of sipuleucel-T therapy. In the meantime, if sipuleucel-T marketing authorisation is restored, patients with asymptomatic or mildly symptomatic disease would be eligible for treatment, in line with the recruitment criteria for the phase 3 trial [14].

3.1.3. Androgen receptor inhibitors

Despite becoming refractory to conventional ADT, many tumours retain a dependence on androgens and respond to alternative methods of androgen deprivation. Abiraterone is an inhibitor of CYP17, an enzyme required for androgen biosynthesis [17]. Abiraterone is indicated in combination with prednisone or prednisolone for men with asymptomatic or minimally symptomatic prostate cancer following disease progression on ADT. The pharmacokinetics of abiraterone are affected by food intake and the drug must be taken in a fasting state [17]. A luteinising-hormone-releasing hormone analogue should also be administered concomitantly with abiraterone in patients who have not been surgically castrated.

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