British Journal of Medical and Surgical Urology (2011) 4S, S9—S13

ELSEVIER

British Journal of
Medical & Surgical
Urology

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ORIGINAL ARTICLE

Metastatic castrate-resistant prostate cancer: New landscape, new challenges

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KEYWORDS
Prostate cancer;
CRPC;
Chemotherapy;
Metastatic prostate cancer

Summary Just 5 years after docetaxel was recommended by the National Institute for Health and Clinical Excellence as the standard of care for metastatic castrate-resistant prostate cancer, a novel taxane—cabazitaxel—has been licensed in Europe and the USA for a similar indication. It is authorised for use in patients whose disease progresses after docetaxel, for whom it has been shown to provide a survival benefit over current palliative strategies. However, it is not the only new treatment for this population of patients. The hormonal agent abiraterone has also been licensed in the USA, and is expected to receive a European licence later this year, the sipuleucel-T vaccine has been approved in the USA, and other agents are on the near horizon. While these advances are undoubtedly welcome, much thought will need to be given to their optimal use in terms of patient selection, the timing/sequencing of treatment, and to the design of the prostate cancer treatment paradigm. It will also be important to consider the impact that new agents will have on healthcare spending and capacity.

Introduction

Historically, patients with metastatic castrate-resistant prostate cancer (mCRPC)—defined as progression of disease despite control of serum testosterone to below castrate level [1]—have had a poor outlook. Early studies of hormonal and cytotoxic therapies at this stage of the disease demonstrated, at best, only modest improvements in duration or quality of life [2,3]. Many patients had long periods of cancer progression, with an escalating need for symptom control before ultimately succumbing to the disease.

However, recent years have seen not only an improved understanding of the mechanisms of castration resistance, but also the development of new approaches to drug treatment for mCRPC, bringing about clinically meaningful improvements in overall survival and quality of life for these patients. An early landmark was the publication of data showing that docetaxel-based chemotherapy provided a survival advantage versus mitoxantrone-based

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1875-9742/$ — see front matter © 2011 Published by Elsevier Ltd on behalf of British Association of Urological Surgeons.
doi:10.1016/j.bjmsu.2011.05.003

chemotherapy for men with mCRPC [3,4]. In 2006, docetaxel was approved for use in mCRPC by the National Institute for Health and Clinical Excellence (NICE) [5]. (The background to the emergence of docetaxel-based chemotherapy for mCRPC is discussed in detail elsewhere in this supplement: Payne et al., S2—S8.) Recently, further treatments have emerged for mCRPC. The novel taxane cabazitaxel has already been licensed in Europe and the USA for use in mCRPC post-docetaxel, the hormonal agent abiraterone is licensed in the USA for the same indication, and further options for the treatment of mCRPC are on the way.

Professional education and a re-evaluation of service provision will be key to making the best use of the full range of established, new and emerging treatments, and to ensuring every patient has timely access to the drugs that are most appropriate for his management. It is only in relatively recent years, with the establishment of docetaxel-based chemotherapy, that the focus of mCRPC management has started to shift from GPs and palliative-care practitioners towards oncologists and urologists with a specialist interest in urological malignancies. Challenging the perception that 'nothing can be done' for these patients will continue to be an essential part of the mCRPC landscape.

This article considers the new and emerging treatments that offer a survival advantage for patients with mCRPC, and the implications that they may have for the prostate cancer treatment paradigm.

Novel therapies

Cabazitaxel

When NICE recommended docetaxel for the treatment of mCRPC [5], there was no other chemotherapy agent licensed in the UK for prostate cancer at any stage. Only one course of docetaxel was recommended, and there was known to be a risk of patients developing resistance to docetaxel and certain other taxane drugs [6]. However, a novel taxane—cabazitaxel—has since been formulated to avoid the pitfalls of taxane resistance, and indeed it has shown activity in cell lines resistant to docetaxel and paclitaxel [7—9]. Crucially, it has also demonstrated activity in patients with mCRPC in phase II [8,9] and phase III [10] clinical trials. On the basis of this evidence, cabazitaxel-based chemotherapy is now licensed in the USA (since June 2010) and Europe (since March 2011) for the treatment of patients with mCRPC who have previously received a docetaxel-containing regimen.

Data from the phase III TROPIC trial—a randomised, open-label study of cabazitaxel versus mitoxantrone (both with prednisone or prednisolone) in patients with mCRPC previously treated with docetaxel—were published in 2010 [10]. At the final analysis, after a median follow up of 12.8 months, the improvement in median overall survival was 15.1 months with cabazitaxel (95% confidence interval [CI], 14.1—16.3 months) versus 12.7 months with mitoxantrone (95% CI, 11.6—13.7 months). A total of 755 patients were included in the analysis, with 1:1 randomisation. The toxicity profile of cabazitaxel was acceptable; notably only 8% developed febrile neutropenia. Furthermore, the study authors and those of a commentary article [11] that accompanied the TROPIC report point out that toxicity can be minimised through optimal supportive care and patient education.

Of note, the TROPIC study included a large proportion (25%) of patients with visceral metastases, and hence a poor prognosis [10]. At present, an expanded-access programme for cabazitaxel in patients with mCRPC who have received prior docetaxel is established in the UK, and is expected to provide useful follow-up data.

Abiraterone acetate

In vivo studies, including phase II clinical trials, suggest that mCRPC can remain dependent on androgen receptor signalling, even in the presence of castrate testosterone levels [12—15]. Abiraterone acetate is an inhibitor of CYP17, an enzyme that reduces androgen synthesis in peripheral sources, for example, adrenal and intratumoral production [15].

In 2010, interim results were reported from a multinational, randomised, double-blind, placebo-controlled, phase III study of abiraterone, including almost 1200 patients with progressive disease after receiving docetaxel-based chemotherapy [15]. Patients were randomised 2:1 to abiraterone plus prednisone or placebo plus prednisone. There was a median overall survival difference of almost 4 months (14.8 months versus 10.9 months; $p < 0.0001$) in favour of abiraterone versus placebo, and the toxicity of the study drug was acceptable. Significant improvements were also seen for time to prostate-specific antigen (PSA) progression, radiographic progression-free survival and PSA response rates (38% versus 10%; $p < 0.0001$). Following these findings, the study was unblinded and patients in the control group were offered abiraterone.