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Review

Optimal management of metastatic castration-resistant prostate cancer: Highlights from a European Expert Consensus Panel ☆

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Abstract The exponential growth of novel therapies for the treatment of metastatic castration-resistant prostate cancer (mCRPC) over the last decade has created an acute need for education and guidance of clinicians regarding optimal strategies for patient management. A multidisciplinary panel of 21 European experts in mCRPC assembled for comprehensive discussion and consensus development, seeking to move the field forward and provide guidance and perspectives on optimal selection and sequencing of therapeutic agents and monitoring of response to treatment and disease progression. A total of 110 clinically-relevant questions were addressed and a modified Delphi method was utilised to obtain a consensus. The panel reached a consensus on several important issues, providing recommendations on appropriate phase III clinical trial end-points and optimal strategies for imaging and monitoring of bone metastases. Guidance regarding selection and sequencing of therapy in patients with newly diagnosed or progressive mCRPC is emphasised, including the use of novel bone-targeted agents, chemotherapy, androgen receptor pathway-targeted agents and immunotherapy. The impact of drug resistance and prostate-specific antigen flare on treatment decisions was also addressed. Ultimately, individualised therapy for patients with mCRPC is dependent on continued refinement of clinical decision-making based on patient and disease characteristics. This consensus statement offers clinicians expert guidance on the implementation of recent advances to improve patient outcome, focusing on the future of prostate cancer care.

1. Introduction

Despite continued advances, prostate cancer claims the lives of over 70,000 men in the European Union (EU) each year [1]. Although docetaxel has been established as the standard of care for progressing patients with metastatic castration-resistant prostate cancer (mCRPC) who are able to tolerate this agent, it is now clear that this agent could not be universally used [2–4]. Intense research and a better understanding of the pathophysiology of the disease have resulted in the development of new drugs that are now making their way into the clinic.

Since 2004, we have learned that the androgen receptor (AR) could be further manipulated by novel hormone therapy (i.e. abiraterone acetate and enzalutamide), that the patient immune system could be enlisted to fight the cancer (sipuleucel-T), that novel chemotherapy active against docetaxel-resistant cells could be used (cabazitaxel), and that the bone microenvironment could more effectively be targeted to delay skeletal complications (i.e. denosumab) or even increase overall survival (OS) ($^{223}RaCl_2$ — radium 223 dichloride [Ra223]) [5–13]. Clinical trials have compared these new drugs either to placebo or outdated comparators and there is no head-to-head comparison between these agents. As a result, the need for individualised therapy is widely recognised and treating physicians are left with difficult choices and few available solid determinants.

Against the backdrop of these novel therapeutic developments, a panel of European experts convened with the following objectives:

1. To examine appropriate end-points for current and future clinical trials in mCRPC.
2. To assess the role of imaging in diagnosing metastases and monitoring response to therapy.
3. To discuss the importance of patient phenotype in therapeutic decision-making.
4. To review the role of novel bone-targeted radiopharmaceuticals, chemotherapy, immunotherapy and AR pathway-targeted agents.
5. To evaluate current opinion regarding the most appropriate sequencing of available therapies for mCRPC.

2. Methodology

The European Consensus Panel was held on 7th September 2013 in Nice, France, and consisted of 21 experts with extensive experience in the field of prostate cancer (Appendix A). The format of the consensus conference was modelled after that of the very successful St. Gallen Early Breast Cancer Consensus Conference organised biannually by Professors H.-J. Senn and A. Goldhirsch [14]. A modified Delphi method was used to obtain a consensus and a consensus threshold of 70% was agreed upon. Participants considered a series of 110 questions, completing a baseline questionnaire prior to any discussion. The experts then shared their assessment of topics by answering specific questions during the conference. Guided by the moderator, the panel debated any conflicting viewpoints, followed by another opportunity to vote on the same question. The process continued until