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Expert opinion on first-line therapy in the treatment of castration-resistant prostate cancer

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ABSTRACT

Treatment of metastatic castration-resistant prostate cancer (mCRPC) has been revolutionized in recent years. It is well known that androgen receptor is still active in most patients with disease progression and serum testosterone levels <50 ng/dL. Moreover, further hormonal maneuvers, either through decreasing androgen levels (abiraterone) or by targeting the androgen receptor (AR) pathway (enzalutamide), prolong survival. In addition, a new cytostatic able to overcome docetaxel resistance, cabazitaxel, and the radioisotope radium 223 have been incorporated to the armamentarium of mCRPC.

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mCRPC is not only a heterogeneous tumor, it changes over time developing neuroendocrine features or selection of clones resistant to hormonal maneuvers. In addition, the multiplicity of current treatments, make it necessary to design algorithms that help the specialist to choose the most appropriate treatment for a particular patient. The lack of randomized trials comparing face to face the different available options limit the scope of this review. In this article, the authors describe the prognostic factors for first line therapy in patients with mCRPC, and propose a treatment algorithm for mCRPC based on the levels of scientific evidence available and, if not available, on the consensus between medical professionals. Finally, the panel discuss how to define progressive disease in the setting of mCRPC and treatment with targeted therapies.

1. Introduction

The management of metastatic castration-resistant prostate cancer (mCRPC) has undergone a radical change in recent years with the development of new therapies targeting AR—abiraterone (AA) and enzalutamide (ENZ)—a new taxane able to overcome docetaxel resistance—cabazitaxel (CBZ)—and a radioisotope, radium 223. They have all shown to prolong overall survival (OS) in patients with mCRPC progressing after docetaxel-based chemotherapy (Fizazi et al., 2012; Scher et al., 2012; de Bono et al., 2010; Parker et al., 2012). In addition, AA and ENZ have also achieved OS benefits in chemo-naïve minimally symptomatic patients, in which only one immunotherapy—sipuleucel-T—had previously done so (Ryan et al., 2014; Anon, 2013a; Kantoff et al., 2010). Still, 10 to 20% of patients are primarily refractory to either AA or ENZ (Ryan et al., 2014; Anon, 2013a). Adequate characterization of those patients would avoid undesirable delays of potentially more successful therapies.

In 2004, the combination of docetaxel and prednisone was first able to demonstrate a survival benefit in mCRPC patients and it is considered the standard of care (SOC) (Petrylak et al., 2004; Tannock et al., 2004), although there is no a clear consensus for the optimum timing to be initiated (Anon, 2012, 2013b,d; Horwich et al., 2013). Besides docetaxel, in first line therapy, physicians in charge of patients with mCRPC have available three treatments for which there is strong evidence of survival as well as QoL benefit, with a favorable benefit-risk profile: AA, ENZ, and radium 223 (for patients with predominantly bone metastases). Because of this, the classification of pre-docetaxel and post-docetaxel setting is old fashion nowadays. Guidelines should contemplate therapy with a first line therapy, either docetaxel, radium-223, AA or ENZ, and subsequent second and third-line therapies. Discussion with the patient and into multidisciplinary teams about the best therapy for patients progressing under castrate levels of testosterone is imperative, incorporating a more modern classification between asymptomatic and symptomatic patients (Scher et al., 2015a).

In order to perform clinical trials in more homogeneous groups of patients, the Prostate Cancer Trials Working Group (PCWG2) established 5 clinical subgroups ranging from a patient with local progression (subtype 1) to a metastatic patient with visceral involvement (subtype 5) (Scher et al., 2008). The PCWG2 recognizes the absence or presence of symptoms as a prognostic factor, but not as a stage of progression of the disease itself (Scher et al., 2008). The classification's final aim is to define patient groups in which treatment intervention should have low toxicity —because of excellent prognosis and asymptomatic disease—or groups where a higher level of toxicity could be acceptable due to symptomatic disease and poor prognosis. The pivotal studies of AA and ENZ in chemo-naïve patients included asymptomatic patients where a low toxicity profile seems a prerequisite to establish a new therapy (Ryan et al., 2014; Anon, 2013a). Otherwise, a new concept emerges from the ALSYMPCA study, where radium 223 was compared to placebo in symptomatic patients with only or predominantly bone metastases that had received chemotherapy, refused chemotherapy or were considered "not suitable for chemotherapy", a term that should be better defined (Parker et al., 2012).

The importance of including chemotherapy in the management of mCRPC despite the number of new therapeutic options is enhanced after the publication of the results from the CHAARTED—ECOG 3805 study, wherein patients with high tumor burden, early introduction of docetaxel still in the hormone-sensitive disease setting, provided a benefit in survival. In this trial, patients defined as with high tumor burden (defined by present of visceral metastases, or presence of extra-axial bone metastases) receiving docetaxel plus androgen deprivation therapy had a median survival of 49.2 months *vs* 32.2 in patients receiving only androgen deprivation therapy. Although a similar trial previously published was negative, the GETUG trial, there are subtle differences between the CHAARTED and GETUG trials in terms of trial design and patient population recruited that may lead to different clinical outcomes, including the CHAARTED trial patients with far advanced disease (Sweeney et al., 2014; Gravis et al., 2013).

A third trial, STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy), have communicated evidence of the benefit in terms of overall survival of adding docetaxel in the hormone-sensitive setting for patients either with advanced locoregional or metastatic disease (James et al., 2015). Since 2005, more than 6500 men with prostate cancer were recruited making STAMPEDE the largest randomized study to date. The addition of new therapies as well as a change in the standard of care for this growing cancer population can be expected from this study that is still ongoing in the UK.

Four were the therapies analyzed in the study and 2962 the hormone-naïve prostate cancer patients assigned to either of the following groups: SOC with androgen deprivation therapy for at least three years and radiation therapy for eligible patients; SOC with six cycles of docetaxel; SOC with zoledronic acid for two years; and SOC with both docetaxel and zoledronic acid. The addition of zoledronic acid to hormonal therapy, either alone or with docetaxel, did not improved survival in comparison to SOC with docetaxel alone. On the other hand, the addition of docetaxel showed an improvement in survival from 43 months to 65 months in men with detectable metastatic disease (61% of the 2962 men included in the analysis). The overall survival in the docetaxel arm (after a median follow-up of 42 months) was 77 months (24% improvement) in comparison to 67 months of the standard of care arm. The time to relapse of the docetaxel arm also showed an increase by 38% in all the patients.

These results will lead to a change in the current metastatic prostate cancer therapy towards the early introduction of docetaxel to patients with hormone sensitive disease. Moreover, the meaning of these results may also influence the management of hormone-refractory disease since the benefit of the early introduction of chemotherapy surpasses the benefit of chemotherapy in more advanced disease.