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Management of metastatic castration-resistant prostate cancer: A focus on radium-223
Opinions and suggestions from an expert multidisciplinary panel

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ABSTRACT

Radium-223, a calcium mimetic bone-seeking radionuclide that selectively targets bone metastases with alpha particles, is approved for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) and symptomatic bone metastases. In patients with mCRPC, treatment with radium-223 has

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been associated with survival benefit, regardless of prior docetaxel use, and also has a positive impact on symptomatic skeletal events and quality of life. Radium-223 is best suited for patients with symptomatic mCRPC and bone-predominant disease and no visceral metastases, and may lead to better outcomes when given early in the course of the disease. An expert multidisciplinary panel convened in Milan, Italy to review the current best-evidence literature on radium-223 and to convey their personal expertise with the use of radium-223 and identify possible strategies for best practice. This article summarizes the best available evidence for the use of radium-223, discusses the essential role of the multidisciplinary team in delivering effective treatment for mCRPC, clarifies pre- and post-treatment evaluation and monitoring, and outlines future scenarios for radium-223 in the treatment of men with MCRPC.

1. Introduction

Prostate cancer (PC) is the most frequently diagnosed cancer affecting men in the USA (Siegel et al., 2016) and Europe (Ferlay et al., 2013), and the second most frequent cause of cancer-related death. Although local treatments, such as radical prostatectomy, external radiotherapy, and brachytherapy allow definitive disease eradication, approximately 35% of patients will develop distant metastases (Bubendorf et al., 2000): in this case, androgen deprivation therapy (ADT) provides good disease control even in the long term. Unfortunately, many, if not all, men will eventually experience disease progression while on ADT, leading to a clinical state referred to as metastatic castration-resistant prostate cancer (mCRPC) (Scher et al., 2011). In recent years, a number of different therapeutic options have been developed for the management of prostate cancer, with substantial increases in survival of patients with mCRPC.

The availability of several active agents allows clinicians the unprecedented opportunity to tailor their choice according to the characteristics of each patient for each treatment line, but at the same time represents a challenge to define the optimal therapeutic sequence for the individual patient. Owing to the evolution of the therapeutic scenario, the complex evaluation process of the patient during his therapeutic path and the variability in clinical aspects of the disease a multidisciplinary approach it is of paramount importance in order that patients receive the best treatment options at the appropriate time.

The present paper presents the opinions and recommendations of an expert multidisciplinary panel on radium-223 convened in Milan, Italy to summarize the best available evidence for the use of radium-223, to discuss the role of the multidisciplinary team, to clarify pre- and post-treatment evaluation, and to outline future scenarios for radium-223 in the treatment of men with MCRPC.

2. Therapeutic scenario in mCRPC

From the beginning of this century, the therapeutic landscape of mCRPC has dramatically changed due to the introduction of several new agents that have significantly improved overall survival (OS). Docetaxel was the first agent to demonstrate a significant benefit over mitoxantrone in prolongation of the OS of patients with mCRPC (Tannock et al., 2004). For several years, no further therapies were approved, while in 2010 a new taxane, cabazitaxel, showed improved survival in patients who had received previous treatment with docetaxel (de Bono et al., 2010). Moreover, novel endocrine therapies such as abiraterone acetate and enzalutamide have shown survival benefits in both chemo-naïve and docetaxel-pretreated patients (Beer et al., 2014; de Bono et al., 2011; Ryan et al., 2013; Scher et al., 2012). Finally, an innovative radiopharmaceutical agent, radium-223, has also been shown to be associated with increased survival in mCRPC patients, regardless of previous docetaxel administration (Parker et al., 2013).

As a consequence, the current availability of a range of agents may allow their sequential use with the aim of achieving a cumulative benefit in survival; unfortunately, the efficacy of these newer treatments progressively decreases when they are administered later in the progression of mCRPC when patients have been exposed to other agents. Such reduced activity is to be expected, as it also occurs in others tumor types when a specific drug is administered in a subsequent treatment line, and the potential mechanisms of cross-resistance are emerging (Antonarakis et al., 2014, 2015; Thadani-Mulero et al., 2014). Furthermore, the toxicity profiles of chemotherapeutic drugs are quite different compared to either new hormonal agents or radium-223. Thus, the availability of several active agents provides clinicians with an unprecedented opportunity to tailor the therapeutic choice to the individual characteristics of the patient for each line of treatment, but at the same time presents a challenge in defining the optimal therapeutic sequence for a particular patient (Caffo et al., 2016).

3. The role of the multidisciplinary team

According to the European Partnership for Action Against Cancer (EPAAC), a multidisciplinary team should manage new and recurrent cancer patients from diagnosis onwards, providing evidence-based treatment respectful of the preferences and needs of the patient, while responding to treatment-induced needs and monitoring the patient during and after treatment (European Partnership Action Against Cancer Consensus Group et al., 2014). The collaboration of experienced health professionals is the best means of delivering multimodal treatments that require quality, continuity and individualization of care, and consideration of the physical, functional, psychological, and financial needs of patients. It is also essential to pay careful attention to the organization and dynamics of the multidisciplinary team and to coordinate all the members in the successful management of cancer patients during all phases of the disease (Boyle et al., 2005; Fleissig et al., 2006; Kagan, 2005; Ko and Chaudhry, 2002; Sidhom and Poulsen, 2006).

A multidisciplinary team for prostate cancer patients should be composed of urological surgeons, radiation oncologists, medical oncologists, pathologists, imaging specialists, experts in nuclear medicine, psychologists, and social workers, as well as nurses with special training in urologic diseases, experts in rehabilitation, experts in supportive and palliative care, geriatricians, and urologists with special training in sexual rehabilitation (Valdagni et al., 2011, 2015). These individuals have specific roles depending on the disease state of the patient and, in order for the team to be effective and efficient, the members should be organized with regards to the different phases of the disease and associated treatments.

The availability of new drugs and treatment modalities, the sequencing of treatments, and the emerging role of physicians such as imaging specialists and experts in nuclear medicine have been identified as crucial issues in the management of prostate cancer (Renzulli et al., 2015; Valdagni et al., 2015). As there is now a wide