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EDITORIAL

Nuclear medicine and the revolution in the modern management of castration-resistant prostate cancer patients: from ^{223}Ra-dichloride to new horizons for therapeutic response assessment

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Prostate cancer (PC) is the most common neoplasm in men in Western countries, and approximately 10 – 20 % of patients with PC will develop castration-resistant disease (CRPC) [1]. More than 90 % of men with metastatic CRPC have radiological evidence of bone metastases, which are a major cause of decreased quality of life, morbidity, treatment costs and mortality [2]. CRPC is considered an incurable condition, with a median survival of less than 2 years [3].

Nuclear medicine has been profoundly involved in the management of PC patients, particularly for those with metastatic disease. First, there has been increasing interest in some radiopharmaceutical agents able to specifically target the bone or the cancer, and second a new therapeutic radiation-based strategy able to provide survival advantages beyond palliative effects has recently been introduced. These "new" options open the door to a multidisciplinary approach involving strong cooperation between nuclear medicine physicians and other specialists including oncologists, radiation oncologists and urologists, that will allow the development and implementation of diagnostic and therapeutic strategies in patients with PC. This is the most efficient way to guarantee that professionals and structures are available to offer care at all stages to patients with PC, taking into account both the optimized current strategies and futures updates and modifications [4].

Until a few years ago, the therapeutic instruments of nuclear medicine in the management of PC consisted of some beta-emitting agents for the treatment of bone metastases, such as ^{82}Sr, ^{153}Sm and ^{188}Re, that demonstrate only a palliative effect in patients with extensive skeletal disease. ^{223}Ra-dichloride (Xofigo®) is the first targeted α-emitting radiopharmaceutical agent approved for the treatment of patients with metastatic CRPC that has been shown to improve overall survival, and also to delay skeletal-related events (SREs) and better control of bone pain. It selectively binds to areas of increased bone turnover, thus producing nonrepairable double-stranded DNA breaks [5, 6], with a potent cytotoxic effect [7–9]. ^{223}Ra has a relatively low haematological toxicity profile compared with β emitters [5, 10]. The short range of α particles (100 μm, less than ten cell diameters) and the high linear energy transfer (27.4 MeV) produce a strong effect in a restricted area, limiting damage to adjacent tissues [10]. After injection, ^{223}Ra immediately accumulates in the skeleton, with minimal observed uptake by other organs. Clearing is mostly by fecal excretion, with 52 % of ^{223}Ra in the bowel 24 h after administration and no evidence of reabsorption. Urinary elimination is only 5 % [10–12]. There are no known drug interactions with ^{223}Ra [13] and no dose modification is required in elderly or unfit patients.

The overall survival benefit and safety profile of ^{223}Ra have been documented in the phase III ALSYMPCA trial, a randomized, double-blind, placebo-controlled, multinational study comparing the efficacy and safety of ^{223}Ra plus best standard of care with placebo plus best standard of care in CRPC patients with symptomatic bone metastases (two or more) and no evidence of visceral disease [8, 14]. A total of 921 patients were enrolled, distributed in two arms (^{223}Ra,

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n=614 and placebo n=307), and stratified according to previous docetaxel use, baseline total ALP level (<220 vs≥220 U/L), and current bisphosphonate use. ^{223}Ra treatment resulted in a 30 % reduction in the risk of death versus placebo. Median overall survival was 14.9 months with ^{223}Ra and 11.3 months with placebo (hazard ratio, HR, 0.70, 95 % CI 0.58 – 0.83; p<0.001). The effect of ^{223}Ra on overall survival was consistent across all patient subgroups. Moreover, the median time to first symptomatic SRE was longer with ^{223}Ra than with placebo (15.6 vs. 9.8 months; HR 0.66, 95 % CI 0.52 – 0.83; p<0.001) [8]. Observed adverse events were generally less severe in patients receiving ^{223}Ra than in those receiving placebo, being mostly related to the disease itself. The main toxicities were minor gastrointestinal side effects and mild neutropenia and thrombocytopenia [8]. Grade 3/4 thrombocytopenia was more common in patients receiving ^{223}Ra previously treated with docetaxel (9 %) than in those with no prior docetaxel (3 %) [15]. Furthermore, a greater extent of disease at baseline (six or more metastases or superscan) was associated with increased risk of grade 2–4 anaemia (HR 1.52, 95 % CI 1.17 – 1.97; p=0.002) [16]. Among patients receiving concomitant external beam radiotherapy, adverse events remained low [16]. At the end of a 3-year follow-up period, there were no reports of acute myeloid leukaemia, myelodysplastic syndrome or new primary bone cancer [17]. International guidelines recommend ^{223}Ra as a first-line treatment option in patients with metastatic CRPC, both before and after docetaxel treatment [3, 7, 18, 19].

In the last 5 years, the treatment landscape for patients with metastatic CRPC has rapidly changed. Besides ^{223}Ra, new hormonal, cytotoxic and immunotherapeutic drugs have been shown to improve overall survival in large randomized trials. The new agents seem suitable in the majority of patients with metastatic CRPC, due to their favourable toxicity profile. While a few years ago in most patients with CRPC the approach to management would have been watchful waiting and supportive care only, now patients are probably going to spend most of their life on treatment, and clinicians are more keen also to deliver new treatments for asymptomatic patients. Multiple new therapeutic options and new combination strategies are under evaluation. In particular, the non-overlapping mechanisms of action of ^{223}Ra and other available drugs in CRPC indicate a potential benefit from their concomitant or sequential use, with no increase in toxicity burden [20]. Preliminary data from the Expanded Access Program suggest that concomitant administration of ^{223}Ra and new-generation antiandrogens is safe and well tolerated [20, 21]. Currently, several clinical trials are evaluating the safety and efficacy of ^{223}Ra combined with abiraterone acetate (NCT02043678) and enzalutamide (NCT02194842).

The recent impressive development of novel treatment and diagnostic strategies in metastatic PC has raised some questions about the modality for the assessment of therapy response. In patients with bone metastases from CRPC the ideal goal of response assessment is the early identification of biology and architectural changes of bone disease after the start of therapy. The detection of these changes with biochemical markers and standard imaging modalities is challenging. RECIST criteria consider bone metastases as nontarget lesions [22]. Notably, radiological assessments were not scheduled in the ALSYMPCA trial. According to the recent PCWG3 criteria [21] and the St. Gallen Consensus Conference [23], the benefit examined throughout clinical evaluation and pain scores should represent the most important criteria of response to treatment. Nevertheless, the integration of clinical response, bone biomarkers such as ALP, morphological imaging (CT and multimodal MRI) and metabolic techniques targeting bone (bone scan and ^{18}F-fluoride PET/CT) can provide reliable information. Prostate-specific antigen alone is not an adequate instrument to assess the clinical outcome. However, bone scan can also be misleading, due to the bone flare phenomenon that can falsely indicate progression of disease, and according to PCWG3, it should be postponed to the end of treatment [24].

In this setting, nuclear medicine today offers different radiopharmaceutical options for the detection of metastatic PC. They can be arbitrarily divided in two main subsets: bone targeting agents (^{99m}Tc-phosphonate and ^{18}F-fluoride) and cancer targeting agents (^{11}C/^{18}F-choline, ^{18}F-FDG, ^{68}Ga-PSMA, ^{18}F-FACBC, ^{11}C-acetate and ^{18}F-bombesin), although some of these are still considered experimental and therefore not applicable in clinical practice. Many questions remain unresolved; for example, the choice of radiopharmaceutical agent on the basis of disease phase and the right balance between cost and benefit. Moreover, CT and MRI are still valuable tools used in many clinical trials. Current clinical guidelines suggest the use of CT and bone scan to monitor response to therapy in patients with skeletal disease, although some guidelines, such as the National Comprehensive Cancer Network (NCCN version 1.2015 [25]), recommend to add radiolabeled choline PET/CT to bone scan or 18F-Fluoride PET/CT. It is clearly time to consider updating clinical guidelines. On the other hand, large and well-conducted prospective clinical trials are mandatory before these radiopharmaceutical agents can be used routinely. In conclusion, the developments discussed above are an example of multidisciplinary work in which nuclear medicine physicians play an important role. We are sure that this contribution can soon open the door to fundamental achievements in the management of metastatic PC.

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