World Journal of Radiology

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DOI: 10.4329/wjr.v8.i10.816

World J Radiol 2016 October 28; 8(10): 816-818
ISSN 1949-8470 (online)
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FIELD OF VISION

Radium-223 and metastatic castration-resistant prostate cancer: All that glitters is not gold

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Author contributions: Aprile C wrote the manuscript; Aprile C, Persico MG, Lodola L and Buroni FE collected the material and discussed the topic.

Conflict-of-interest statement: Nothing to declare.

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Manuscript source: Invited manuscript

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Received: April 30, 2016
Peer-review started: May 3, 2016
First decision: July 6, 2016
Revised: August 4, 2016
Accepted: August 27, 2016
Article in press: August 29, 2016
Published online: October 28, 2016

Abstract

After being approved by the National Drug Agency in several countries, Radium-223 (Ra-223) is gaining wide acceptance in the treatment of bone metastatic castration resistant prostate cancer. The exact mechanism of action remain unclear: The established model of direct alpha-particle irradiation from the remodelling bone surface, where Ra-223 accumulates, surrounding the tumor foci can explain a lethal effect only on metastatic microdeposits, but not on higher tumor burden. According to the "pre-metastatic niche model", it is likely that Ra-223 targets several non-tumoral cell types of the tumor microenvironment involved in the complex mechanism of cancer bone homing and colonization. A deeper insight into this hypothetical mechanism will lead to a more accurate dosimetric approach and to find optimal sequencing and/or combination with the other therapeutic options.

Key words: Radium-223; Bone metastases; Castration resistant prostate cancer; Tumor microenvironment; Pre-metastatic niche model

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Core tip: Radium-223, possible perspectives for a more effective use in bone metastatic castration resistant prostate cancer.

Aprile C, Persico MG, Lodola L, Buroni FE. Radium-223 and metastatic castration-resistant prostate cancer: All that glitters is not gold. *World J Radiol* 2016; 8(10): 816-818 Available from: URL: http://www.wjgnet.com/1949-8470/full/v8/i10/816.htm DOI: http://dx.doi.org/10.4329/wjr.v8.i10.816

COMMENTARY ON HOT TOPICS

Several therapeutic options have been shown to be clinically effective in treating metastatic castration resistant prostate cancer (mCRPC), albeit real efficacy of treatment is very difficult to establish due to a substantial

lack of head-to-head comparison trials. Radium-223 (Ra-223), an alpha-emitting radiopharmaceutical, prolongs overall survival (OS), delays symptomatic skeletal events and improves quality of life compared to placebo treatment, in patients with CRPC and symptomatic bone metastases without visceral involvement, regardless of prior docetaxel use[1,2].

The calcium mimetic alpha emitter ion Ra-223 forms complexes with hydroxyapatite in bone areas where turnover tissue is increased as in primary bone tumours and metastases. Unlike other therapeutic bone seekers, such as beta minus emitters Sr-89 or ^{153}Sm-EDTMP, Ra-223 has a high linear energy transfer (LET 80 keV/μm) leading to a high frequency of lethal double-strand DNA breaks in nearby cells[3].

The short path length of alpha particles is less than 100 μm, less than a 10 cell diameter and has an *in vitro* killing effect in tumor cells, osteoblasts and osteoclasts.

In vitro data demonstrates that the lethal effect is not cell type specific, is effective on multidrug resistant cells, induces G2 arrest and causes a dose-dependent inhibition of osteoclast differentiation[4-6].

The efficacy of Ra-223 has been demonstrated *in vivo* in animal models, indicating a significant antitumor effect in experimental skeletal metastases in nude rats[4], increased survival in a mouse model of breast cancer metastases, more pronounced if associated with zoledronic acid or doxorubicin[5].

These physical and biological data explain why Ra-223 is the first-in-class commercially available alpha emitter in the treatment of bone metastases. Results from a Phase Ⅲ trial called ALSYMPCA confirmed the clinical efficacy of the radiopharmaceutical in a large cohort of bone mCRPC[7]. However the mechanism of action remains unclear.

The most simplistic model that alpha emission acts directly on surrounding tumor cells is commonly accepted, even though its short path length can kill only a few tumor cells lines, much as the outer layers of an onion. Dosimetric considerations of this model indicate that the estimated absorbed dose in a 250 μm radius sphere decreases steeply from about 65 Gy at 5 μm from the surface to 0 Gy at 70 μm, assuming a Ra-223 concentration of 0.67 Bq/mm^2 on the surface[8]. In such a way, Ra-223 could deliver a lethal dose to small foci of cancer cells or micrometastases, while the dose to larger ones are likely to be ineffective.

Data from the ALSYMPCA trial indicate a significant decrease in PSA, regarding tumor burden and alkaline phosphatase (ALP) activity, the latter being a marker of bone turnover that correlates with the progression of bone metastases. The classical model cannot fully explain the therapeutic effect of Ra-223 in the presence of a large tumour burden in bone. Current treatment such as abiraterone targets cancer cells directly, while docetaxel acts indirectly on rapidly proliferating tissue. At present, only sipoleucel-T, whose mechanism of action involves the immune system, acts differently. Further questions remain to be answered as to why PCa displays an increased predilection for bone and why it induces an osteoblastic response. Just over a century ago, Paget proposed the "Seed and Soil" hypothesis. More recently, Lyden's laboratory[9] defined the "pre-metastatic niche model", where the remodelling of metastatic distant site occurs earlier than tumor cells detach from the primary site. Therefore the interaction between host and tumor or, in other words, the tumor microenvironment, may answer the above questions.

In a recent innovative paper Ganguly *et al*[10] reviewed the specific processes involved in the seeding and development of PCa bone metastases. Integrins, extracellular proteases and transient epithelial-mesenchymal transition can promote PCa progression, invasion and metastasis, just as chemotactic cytokines, adhesion molecules and bone derived signals can explain homing, colonization and osteoblastic characteristics. According to this model, many non-tumoral cell types could be the target of lethal alpha emission from Ra-223 leading to a "curative" effect, while the beta minus emission from Sr-89 and ^{153}Sm-EDTMP can obtain only a palliative effect.

Albeit preliminary, there is PET evidence indicating acute metabolic changes in large metastatic deposits after Ra-223 therapy, with a dramatic drop of uptake either of ^{18}F-choline[11] or ^{68}Ga-PSMA[12] in responders accompanied by a reduction of PSA and ALP. This effect cannot be explained by the classical mechanism of action where only a limited number of tumour cells can be hit, but rather by an effect on the microenvironment including vessels and stroma, inducing tumor regression.

The "niche model" could explain why the preventive administration of Ra-223 before cancer transplant in mice decreases the tumor burden and increases life expectancy[5]. In addition, Ra-223 uptake in the bone microenvironment surrounding metastatic foci is roughly the same in both osteolytic and osteoblastic tumours, opening new perspectives in the treatment of other cancer types[6].

Cancer cells with stem-cell like characteristics survive as non-proliferating (dormant) in close proximity to active bone multicellular units. They can survive after most therapeutic approaches including androgen deprivation and they start to proliferate receiving the appropriate signal from the stroma. Assuming that Ra-223 emissions act more likely and more efficiently on the microenvironment, they could have a role in the dormancy stage, inhibiting the metastatic growth.

It is quite surprising that basic research on Ra-223 was not oriented to study the effect of radiation to the cells involved in the niche model (homing, dormancy and proliferation) and the role of radiation to the vascular endothelium. In fact it is well known that Ra-223 accumulation did not correspond to bone volume or surface area but to local blood vessel density[6].

Median OS gain in the ALSYMPCA trial is 3.6 mo. Since 2010 six new agents have been approved for mCRPC, including chemotherapeutic agent, newer hormonal agents as enzalutamide and arabiterone, immune

therapy and bone-targeted agents as denosumab. However the Ra-223's OS gain is far to be optimal, as well as for the above mentioned agents. The main Health Technology Assessments, taking into account the cost per Quality Adjusted Life Years, concluded that Ra-223 therapy is not cost effective[13].

The integration of Ra-223 into the management of mCRPC with other currently available therapeutic options is likely to further improve OS[2,10]. This leads to further questions as to whether treatment should be started earlier in the course of mCRPC, a disease which frequently lasts several years, which is the best sequence of drugs or whether a combined therapy would be more effective than a sequential therapy[14].

The non-overlapping mechanism and the high safety profile of Ra-223 would potentially allow new combination strategies with the novel innovative drugs, moving from symptomatic high-volume bone disease to an earlier phase of asymptomatic low-volume bone disease and extending its use in the visceral disease phase if, as usually occurs, bone is involved[15].

These questions require a deeper insight into Ra-223's mechanism of action at the microenvironment level, thus allowing a more accurate dosimetric approach beyond activity/weight criteria.

ACKNOWLEDGMENTS

Authors wish to thank Professor Karen Susan Doyle for the language revision of the paper.

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P- Reviewer: Kang TW, Vlachostergios PJ, Xia SJ **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Li D

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