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Review Article

^{223}Ra-dichloride in castration-resistant prostate cancer (CRPC) with bone metastases: a still unexplored resource

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Abstract

Metastatic skeletal disease is the cause of considerable morbidity in patients with advanced Castration-Resistant Prostate Cancer (CRPC). It is considered that bone metastasis is the most common cause of cancer-related pain. In recent years, the safety and efficacy of palliation of painful bone metastases in patients with castration-resistant prostate cancer (CRPC) has been demonstrated in many clinical studies using ^{223}Ra-dichloride. It is our belief that therapy with ^{223}Ra-dichloride is intended to be used as a first approach in the case of multiple bone metastases from CRPC, in absence of visceral metastases, not to miss the opportunity to attack the lesions with high doses, calculated pre-therapy, tailored patient per patient, for each lesion. Administered Xofigo® doses higher of those currently used are recommended and for more than six cycles, also considering the increased OS found in many cited works.

Introduction

Prostate cancer is the most common non-dermatological cancer in males and ~~is~~ the second most common cancer in men worldwide [1].

About 10% of patients present bone metastases already at presentation. Almost all patients dying of prostate cancer have skeletal involvement [2].

Several authors have attempted to correlate skeletal metastatic involvement and its extent with survival in patients with advanced prostate cancer. One of these authors developed a system based on the number of lesions identified by bone scintigraphy, noting that it was predictive of survival [3]. On average, a patient with metastatic disease will undergo some skeletal-related event every 3-6 months [4].

Metastatic skeletal disease is the cause of considerable morbidity in patients with advanced cancer. It is considered that bone metastasis is the most common cause of cancer-related pain [5].

The destruction of bone by metastatic disease reduces its carrying capacity and initially involves micro-fractures, which cause pain. The fracture of a long bone or the epidural extension of the tumor in the vertebral column causes most of the disability. Another consequence of bone metastases is represented by the compression of the spinal cord which is a medical emergency. When that is suspected urgent assessment and treatments become necessary [6]. Weakness and/or paralysis are the consequences of spinal cord compression in most patients. The most frequent symptom in 70 patients with spinal cord compression secondary to breast cancer was motor weakness (96%) followed by pain (94%), sensory disturbance (79%) and disturbing sphincter (61%). Ninety-one percent of patients had at least one symptom for 1 week; those walking before therapy (96%) maintained walking ability. In those who are unable to walk, 45% have recovered ambulation, with radiotherapy and surgery equally effective. Median survival was 4 months. Back pain was found to be a frequent symptom in patients with advanced cancer and in 10% of cases it is due to vertebral column instability [5].

^{223}Ra-dichloride therapy

The use of analgesics, external beam radiotherapy and systemic therapy with radionuclides are some of the therapeutic approaches for bone metastases and their associated effects.

For patients with multiple skeletal metastases, targeted systemic palliative therapy with suitable radiopharmaceuticals has emerged as a particularly attractive and efficient treatment modality [7-9].

The main challenge in the palliative treatment of bone pain by using radiopharmaceuticals able to focus on the lesions is to provide an adequate dose of ionizing radiation to the bone lesion, at the same time minimizing the dose to healthy bone sites and adjacent tissues. Radiopharmaceuticals used for therapy are those containing radioisotopes that emit beta and alpha particles and Auger electron [10]. Usually the range of β^- particles is up to several millimeters in the tissue, this can cause the crossfire irradiation of cells adjacent to the target tumor. α particles have, in contrast to beta, a typical penetration range of less than 100 μm [11,12]. Auger electrons (electrons of typical energy around 20-100 keV) have short penetration ranges from several nanometers to micrometers [13]. During the research of radiopharmaceuticals ideal for palliative treatment of bone metastases, other characteristics should be considered in addition to the physical properties of different radionuclides. It should be assessed whether its properties are susceptible to radiochemical procedures and the costs of radionuclide production and feasibility should be determined [9]. In order to help with the determination of the appropriate therapeutic dose to be administered and to facilitate treatment monitoring, it would

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also be useful for the radionuclide used for the palliative treatment of bone metastases to enable in vivo imaging [7,12,14].

The first radioisotope to be evaluated for palliative treatment of bone metastases was ^{32}P and its first clinical use dates back to 1941[15]. In the clinical setting for alleviation of bone pain was also used 89 Sr and it was approved by the FDA for clinical use in 1993 [16].

More recently 153 Sm, which was approved by the FDA for clinical use in 1997, was one of the most commonly used radionuclides for palliative treatment of bone metastases in routine clinical practice [17,18].

A newly introduced alpha emitter radioisotope is ^{223}Ra-dichloride, which acts as a calcium-mimetic accumulating in areas of increased bone turnover, thus having as target bone metastases.

In recent years, the safety and efficacy of palliation of painful bone metastases in patients with castration-resistant prostate cancer (CRPC) has been demonstrated in many clinical studies using ^{223}Ra-dichloride (Xofigo®, Bayer HealthCare). For patients with CRPC and bone metastasis $^{223}RaCl_2$ is becoming a new standard of care due to significantly improved overall survival and very low toxicity [7,19-26]. In fact, compared to beta radiation, a greater biological effectiveness is due to the high linear energy transfer (LET) of alpha radiation, causing the rise of cytotoxicity which is independent of dose rate, cell cycle growth phase, and oxygen concentration [12,27]. Due to an increase in life expectancy in patients treated with $^{223}RaCl_2$ than that of patients in the placebo group, an effect not previously registered for other available radiopharmaceuticals [28], ^{223}Ra-dichloride can be used as a systemic treatment strategy for patients with CRPC who develop bone metastasis, both as first-line and as rescue therapy.

Some authors reported that patients treated with ^{223}Ra-dichloride and a concomitant bone-targeting agent (BTA) appeared to have longer time to first skeletal-related events (SREs) than those treated without a concomitant BTA [29]. In another work the same authors shaw that alkaline phosphatase (ALP) dynamics and overall survival (OS) show some changes in metastatic castration-resistant prostate cancer (mCRPC) patients treated with ^{223}Ra: ALP decline was associated with longer OS and time to first SREs [30].

After stating the utility of SPECT/CT for dosimetry determination in Targeted Radionuclide Therapy [31], we assessed that with appropriate programs fixed therapy dose administration of β-emitters radionuclide, can be implemented with no enhance of side effects [18].

Treatments with $^{223}RaCl_2$ are associated with low rates of both haematologic and non-haematological adverse events, using the standard administration program. It is therefore legal to think that, based on appropriate dosimetric evaluations, it is possible a dose escalation for treatments with $^{223}RaCl_2$, taking care not to increase the side effects [32].

If it is planned to increase the administered dose, one of the major concerns is radiation-induced myelotoxicity. no grade 4 toxicities, and infrequent grade 3 toxicities have been observed in past studies [19,20]. These outcomes may be better understood by means of mycrodosimetry. The percentage of cells that received a potentially toxic absorbed dose, (2 or 4 Gy) as a function of the average absorbed dose over the marrow cavity was determined and in a previous study was showed that: (1) the cellular absorbed dose has a heterogeneous distribution strongly dependent on the position of the cell within the marrow cavity, (2) increasing the average marrow cavity absorbed dose (by increasing the administered activity) results in only a small increase in potential marrow toxicity (i.e. the number of cells receiving more than 2 or 4 Gy) for a range of average marrow cavity absorbed doses from 1 to 20 Gy [33].

In conclusion, in the presence of persistence of the disease, in particular if in locations different from those visible before the $^{223}RaCl_2$ therapy and in absence of significant side effects, it is right to schedule a continuation of therapy with Xofigo®, by administering further cycles at the same dosage, or at higher dosages [34]. Applying a dosimetric methodology able to calculate the absorbed dose for a specific lesion, on each individual patient, it may be outlined a dose to be administered, already before therapeutic cycles [32, 35]. Having been demonstrated that there is a good correlation between the diagnostic images with ^{99m}Tc-MDP and those obtained after therapeutic administration of $^{223}RaCl_2$, dosimetry lesion by lesion can be easily performed using the first of the six ^{223}Ra-dichloride therapeutic doses as a tracer dose for scintigraphy and comparing it with the pre-therapy one performed after administration of ^{99m}Tc-MDP [32,35,36].

Furthermore, it is our belief that therapy with ^{223}Ra-dichloride is intended to be used as a first approach in the case of multiple bone metastases from CRPC, in absence of visceral metastases, not to miss the opportunity to attack the lesions with high doses, calculated pre-therapy, tailored patient per patient, for each lesion. Administered Xofigo® doses higher of those currently used are recommended and for more than six cycles, also considering the increased OS found in many cited works.

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