BJRS

BRAZILIAN JOURNAL
OF
RADIATION SCIENCES
10-02 (2022) 01-12

Reviewing therapy with radioisotopes for pain bone metastasis and its possible evolution

Silva D.C.[1], Meyer R.J[2]

[1]Physicist, mastering of postgraduate program Processos Interativos dos Órgãos e Sistemas, Health Science Institute, Federal University of Bahia.[2]Titular Professor of Health Science Institute, UFBA. Salvador, Bahia, Brazil Postal Code 40110-100. dcoirosilva@gmail.com

ABSTRACT

Introduction: The therapy with radioisotopes is widely used, its beginnings were focused on thyroid pathologies treatments. Over the years, the radiopharmaceuticals and/or radioisotopes have had their usage increased, to be used on painful bone metastasis. Material and Methods: A bibliographic search was conducted in the major health Science basis to evaluate what the therapies have to offer for patients in this condition. Results: Currently there are only two available materials in Brazil, the ^{153}Sm that is national production, and ^{223}Ra, that is imported. Outside Brazil we can find a variety of materials that have already been approved by the Sanitary Organization in other countries, even though we are not authorized to use them due to Brazilian Regulation and production issues. Conclusion: Besides the diversity of materials that could be used, dosimetry systems must be implemented in order to have a more efficient treatment and to have an accurate administrated activities to patients.

Keywords: Radiopharmaceuticals. Radioisotope. Metastasis. Bone

ISSN: 2319-0612
DOI: https://doi.org/10.15392/bjrs.v10i2.2011
Submitted: 2022-02-12
Accepted: 2022-04-04

1. INTRODUCTION

The therapy using radioisotopes has always been widely used in medicine, one of the first composites is the ^{131}I (Iodine 131), Beta emission particles (β) and Gamma emission (ɣ). The first record is from 1941, when it was used for hyperthyroidism treatment at Massachusetts General Hospital [1].

According to Costa[2], bone metastasis is one of the most regular secondary cancers, more commonly coming from breast and prostate cancer disease. These cases report mobility impairments, functional independence, and decreased quality of life for patients. Narenda Nair[3] evaluated the use of ^{32}P(Phosphorus 32) compared with ^{89}Sr(Strontium 89) in 31 individuals with bone metastasis related to the bone pain relief; in this paper some bone marrow functions were decreased, showing a more severe plaquettes toxicity in P32 than Sr89, being considered a breakthrough in (β) particles emission (beta).

In 2014, Pandit-Taskar [4] has described the alpha therapy with ^{223}Ra (Radium 223) to be effective, efficient, and safe for prostate cancer patients resistant to castration, useful for pain control, also and more important, declining events related to the skeleton and increase of survival.

Kolesnikov-Gauthier[5] has presented effectiveness analysis as well as a security study about using ^{153}Sm(Samarium 153 – EDTMP), stating that this is an active radiopharmaceutical for pain relief, safe and well tolerated by patients with severe pain from bone metastasis, improving quality of life.

Ajit S. Shinto[6], in 2018, has presented the possibility of a radioisotope that is a beta emission particle (β) and gamma emission particles (ɣ), efective for pain therapy from bone metastasis, also improving the patient's quality of life, proving to be a real theranostic.

Jörgen Elgqvist[7] has talked about TAT (Target Alpha Theraphy) the use of alpha particles in therapies, quoting the possibility of using radioactive elements with complex decay, such as ^{225}Ac.

In 2020, Mareike Roscher[8]has related the use of nanogenerator systems, using ^{225}Ac (Actinium 225) and ^{227}Th(Thorium 227) radioisotopes, crucial for new chelators development for this therapy to be applied to medical clinic.

2. MATERIALS AND METHODS

The current study was carried based on a bibliographic search on Medline/Pubmed, Lilacs and Science Direct base, using the following descriptors in Portuguese, and the corresponding in English: bone metastasis treated with radiopharmaceuticals, painful bone metastasis treated with radiopharmaceuticals, bone metastasis treated with radioisotopes and painful bone metastasis treated with radioisotopes.

The time horizon covers the period from 2010 to 2020. Previous publications were also viewed, due to its historical importance, as per chart below.

The results indicate the need of further broadening of this theme.

3. RESULTS AND DISCUSSION

Following, the number of publications found in this research.

Table 1 – Distribution of publications without relation between them.

Descriptor	Quantity
Cancer	1.865.892
Bone metastasis	17.836
Bone pain	52.765
Bone pain treatment	31.632
Radioisotopes	41.574
Radiopharmaceulticals	41.110

When making the relevant association in terminology, the result was the following.

Table 2 - Publications with applied associations

Descriptors association	Quantity
Cancer and bone metastasis	16.687
Cancer and bone metastasis and bone pain	1.956
Cancer and bone metastasis and bone pain and treatment	1.634
Cancer and bone metastasis and bone pain and radiopharmaceultical treatment	105

The publications were selected by the thematic approach, as follow.

Table 3 – Publication distribution according to the bone metastasis origin.

Bone metastasis origin	Percentage
Prostate	64%
Breast	22%
Prostrate and breast	8%
Other sites	6%

In this revision, six technical books were used, whose agenda regarded the following subject: radiation detection, orthopedics, nuclear physics fundamentals, radiology protection, bone metastasis management and radiation dosimetry.

About official documents, the search has included publication from the following institutions: World Health Organization (WHO), National Health Surveillance Agency (ANVISA), Nuclear Energy National Commission (CNEN) and National Cancer Institute – Brazilian Health Ministry (INCA-MS), as following related:

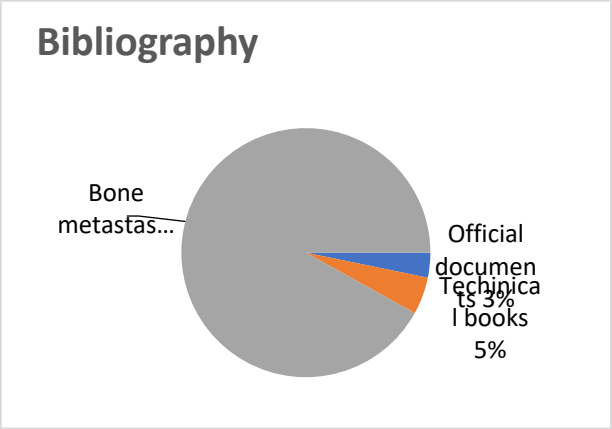

Figure 1 – Used material distribution

For treatment it is possible to use the radioisotope in its original form, or in radiopharmaceutical form, which contains two components a radionuclide and a pharmaceutical.

The value of a radiopharmaceutical is shaped by the features of these two components[9]. The ^{131}I radioisotope (iodo-131), evaluated and used in clinical since 1941 because of beta particles emission (β) and gamma radiation emission (ɣ) is considered the first Nuclear Medicine theranostic compound.

According to Ballinger[10], the theranostic definition has involved the diagnostic compound administration, that has the following function:

(1) Establish the position or studied disease state, as a substitute for a potential therapeutic agent with similar chemical properties;

(2) Examine its biodistribution as predictive effects outside the target (adverse) from potential therapeutic agent;

(3) Assist to determine the ideal therapeutic dosage or the activity to be administered, based on the anticipated tumoricidal dosage, measured in the tumor área (i.e.dosimetry), and /or

(4) Monitor treatment response.

In mid-1992, a discussion started about activity to be administered for diagnostic and/or therapeutics purposes for each patient, forwarding the issue of individualized dosimetry, considering the medicine principles in this modality.

According to Lyra[11], the main characteristics for a choice suitable radionuclide for therapeutics usage must be associated to the follow:

a) Decay characteristic and bioquemical reactivity;
b) Desired half-life is between few hours and several days;
c) The emitted particles of radiation should have an appropriate linear energy transfer (LET)
d) High radionuclide purity;
e) High radiochemical purity and high specific radioactivity;
f) Prolonged retention of the radiopharmaceutical in the tumor while the uptake in normal tissue should be kept at the lowest levels.

According to Saha[9], the linear energy transfer is the average amount of energy lost per unit track length in tissue by a particular type of radiation.

In Ahmadzadehfar[12], the following radioisotopes are presented to be used in the painful bone metastasis treatment.

Table 4: Radioisotope and physical properties

Isotope	Emission type	Physical Half-life (days)	Maximum energy β particle (MeV)	Maximum energy ɣ (MeV)	Maximum tissue penetration (mm)
^{32}P	β	14,3	1,709	x	8,5
^{89}Sr	β – γ	50,5	1,5	0,909	7
^{153}Sm	β – γ	1,9	0,8	0,103	4
^{186}Re	β – γ	3,7	1,07/3,93	0,137	5
^{188}Re	β – γ	0,7	2,12	0,188	10
^{177}Lu	β – γ	6,7	0,498	0,208 /0,113	1,8
^{223}Ra	α	11,4	0,154/5,97	0,27	0,1

Source: Translation and adaptation from Ahmadzadehfa. (β -beta particle: α -alfa particle e γ - gamma radiation)

We can observe that except for ^{32}P (that is only a beta particles emitter), the other items would be candidates to be theranostics, because part of the therapy is done with particles and part of diagnostic is done with gamma radiation emission, which would allow to have scanning of image systems.

The requirements for optimal bone-targeting radiopharmcaeuticals are:

(1) Selective uptake and prolonged retention in metastatic bones with a high metastatic-to-normal bone uptake ratio;

(2) Rapid clearance from nonskeletal sites and fast excretion into urine or feces;

(3) Biodistribution that can be estimated by imaging modalitites such as bone scans;

(4) Simple production process, good radiochemical stability, and clinical availability;

(5) Cost-effectiveness;

(6) Low toxicity and few side effects;

(7) Radiation safety for patients and nuclear medicine staff;

(8) Clinically proven therapeutic effects of reduced analgesic use and bone pain palliation and/or survival benefits.

The following chart presents various approved radiopharmaceuticals for clinical usage by some regulatory agencies in some countries, as well as the Brazilian territory with ANVISA (National Health Surveillance Agency) approval.

Radiopharmaceutical	Korea MDS	US FDA	EU	ANVISA
^{32}P-Orthophosphate	NA	NA	NA	NA
^{89}Sr- Dichloride	A	A	A	NA
^{186}Re- HEDP	NA	NA	A	NA
^{188}Re- HEDP	NA	NA	NA	NA
^{153}Sm-EDTMP	NA	A	A	A
^{177}Lu- EDTMP	NA	NA	NA	NA
^{223}Ra- Dichloride	A	A	A	A

Source: Translated and adapted from Choi[13] (2018) [NA (not approved); A (approved)]

The approach of using radiopharmaceutical treatment for cancer patients presents benefits over the current existing options; there is already a list of 30 new developing compounds, some of them already commercially cleared, and others in pre-clinical stage 3[14].

The ability of getting images and quantitatively characterize the probable biological result from radiopharmaceutical treatment, via treatment planning and dosimetry, is a unique and very strong aspect from this treatment perspective.

Roscher[15] has given a radioisotope analysis, like ^{225}Ac and ^{227}Th, in which they have presented a series of radioactive decay called atomic in vivo nanogenerators whose decay are shown below.

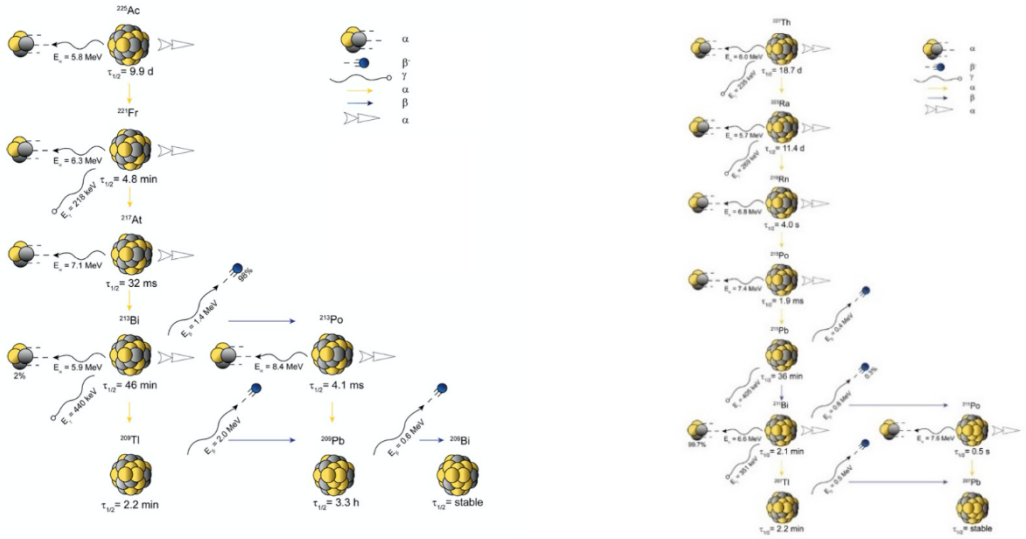

Figure 2. Radioactive decay scheme . Source: Adapted from Roscher e collaborators[16]

It should be emphasized that for these radioisotopes to be used, more specific chelating must be studied, maintaining its properties with the daughter isotope, because only then the therapy will be effective. It has been a widening field, whose development is dependent of a multidisciplinarity concerned issues.

According to Graves[16], there are various platforms that assist on dosimetry measurement for each patient, based on MIRD (Medical Internal Radiation Dose) and the Voxelwise method. Both depend on acquired images from Nuclear Medicines machines, that will supply with:

a) Image activity quantification;

b) Registration of images across time;

c) The modeling or fitting of physical properties, either activity or dose rate, as a function of time;

d) Segmentation of organs or regions of interest.

Each step introduces substantial uncertainty for final dosimetry. It is recommended to try and combine both current techniques into one practice in clinical usage. Cada uma dessas etapas introduz incerteza substancial na dosimetria final. Recomenda-se ainda que seja realizado um esforço de juntar as duas técnicas atuais em uma única prática no uso clínico.

According to Dash[17], even though the radioisotopes therapies have been well established for more than three decades, there are still some barriers for the extensive use, such as:

a) Lack of knowledge and awareness of referring practioners, misconceptions concerning the potential toxicity of treatment and the lack of health policy support.

b) Limited acceptance of new radiopharmaceuticals by referring physicians.

c) Because of the lack of licensing to administer radiopharmaceuticals, most medical oncologists have to refer patients to radiation oncologists and/or nuclear medicine physicians to enable treatment.

d) The much smaller market for radiopharmaceuticals compared to that of other generic drugs.

e) Limitations on the availability of radionuclide of required quality amenable for clinical use.

f) Early forms of radiopharmaceuticals such as ^{32}P and ^{89}Sr were associated with side effects, such as myelosuppression. Because of the lingering concern of potential delayed myelosuppression medical oncologists reserve radiopharmaceutical treatment for late-stage cancer patients.

g) There are also limited clinical data indicating the benefits and acceptability of radiopharmaceuticals when used in combination with contemporary oncology treatments with potentially overlapping toxicity profiles.

h) The cost of treatment is not just the acquisition cost of the radiopharmaceuticals; rather than the entire process required for administration in an appropriate environment. Lack of financial incentive to medical oncologists treating patients constitutes an impediment that does not support progress since most oncologists are not reimbursed for radiopharmaceutical administration. The requirement for an approved hospital to offer nuclear medicine/radiology service for the

administration of radiopharmaceuticals emerged as a barrier since medical oncologists are not licensed for reimbursement for these procedures, in contrast to office-administered treatments such as chemotherapy.

5. CONCLUSION

The therapy with radioisotopes and/or radiopharmaceuticals is in broader evolution in Medicine[17]. It is notice as well that various requirements must be fulfilled for a radiopharmaceutical product is allowed to be used in the medical clinic, both as sanitary reasons as production and distribution issues[18-20].

It is evident that we are walking the path to offer treatments for patient with radioisotopes and/or radiopharmaceutical based products more efficient and with less side-effect, as well as the improvement of life quality for people with cancer disease.

We realize the development necessity for effective and easy-to-use dosimetry systems, so that the therapeutic planning is more and more successful.

We cannot find a standard model for dosimetry Measurement, which indicates there are still more to be worked, because the current algorithms make the measurements, but the machines must be well calibrated, since the images come from them.

REFERENCES

1. V. Ralph McCready. Radioiodine – the success story of Nuclear Medicine. **Eur J Nucl Med Mol Imaging** (2017) 44:179–182

2. Luis Costa & Xavier Badia & Edward Chow et all. Impact of skeletal complications on patients' quality of life, mobility, and functional Independence. **Support Care Cancer** (2008) 16:879–889

3. Narendra Nair, Relative Efficacy of 32P and 89Sr in Palliation in Skeletal Metastases. **J NucI Med**1999.40:256 a 261

4. Neeta Pandit-Taskar, Steven M. Larson et all, Bone-Seeking Radiopharmaceuticals for Treatment of Osseous Metastases, Part 1: Therapy with 223Ra-Dichloride**. J Nucl Med** 2014; 55:268–274

5. Hélène Kolesnikov-Gauthier, Nathalie Lemoine, Emmanuelle Tresch-Bruneel et all. Efficacy and safety of 153Sm-EDTMP as treatment of painful bone metastasis: a large single-center study. **Support Care Cancer** DOI 10.1007/s00520-017-3885-3.

6. Ajit S. Shinto, Madhava B. Mallia, Mythili Kameswaran, et all. Clinical utility of 188Rhenium-hydroxyethylidene-1,1-diphosphonate as a bone pain palliative in multiple malignancies. **World J Nucl Med**. 2018 Oct-Dec; 17(4): 228–235.

7. Jörgen Elgqvist,SofiaFrost, Jean-Pierre Pouget,PerAlbertsson. The potential and hurdles of targeted alpha therapy – clinical trials and beyond. **Frontiers in Oncology** January 2014 | Volume 3 | Article 324

8. Mareike Roscher , Gábor Bakos and Martina Benešová. Atomic Nanogenerators in Targeted Alpha Therapies: Curie's Legacy in Modern Cancer Management. **Pharmaceuticals** 2020, 13, 76.

9. G.B. Saha**, Fundamentals of Nuclear Pharmacy**, Springer International Publishing AG 2018 (paperback).

10. Ballinger JR. Theranostic radiopharmaceuticals: established agents in current use. **Br J Radiol** 2018; 91

11. Maria E. Lyra, Maria Andreou, Antonios Georgantzoglou et all. Radionuclides Used in Nuclear Medicine Therapy – From Production to Dosimetry. **Current Medical Imaging Reviews**, 2013, 9, 51-75 51.

12. Hojjat Ahmadzadehfar, MD, MSc , Markus Essler, MD , Kambiz Rahbar, MD , et all Radionuclide Therapy for bone metastases utility of scintigraphy and PET imaging for treatment planning**. PET Clin**. 2018; 13:491–503).

13. Joon Young Choi. Treatment of Bone Metastasis with Bone-Targeting Radiopharmaceuticals. **Nuclear Medicine and Molecular Imaging** (2018) 52:200–207

14. George Sgouros , Lisa Bodei , Michael R. McDevitt et all. Radiopharmaceutical therapy in cancer: clinical advances and challenges. **Nat Rev Drug Discov** 19, 819 (2020)

15. Mareike Roscher, Gábor Bakos, Martina Benešová. Atomic Nanogenerators in Targeted Alpha Therapies: Curie's Legacy in Modern Cancer Management. **Pharmaceuticals** 020, 13, 76;

16. Stephen A. Graves, PhD, and Robert F. Hobbs, PhD. Dosimetry for Optimized, Personalized Radiopharmaceutical Therapy**. Semin Radiat Oncol** 31:37−44.2020

17. Ashutosh Dash, Tapas Das, and Furn F. (Russ) Knapp Jr. Targeted Radionuclide Therapy of Painful Bone Metastases: Past De- velopments, Current Status, Recent Advances and Future Directions**. Current Medicinal Chemistry**, 2020, 27, 3187-3249

18. Diretrizes básicas de proteção radiológica. **Norma CNENNN3.01 Resolução 164/14Março/2014**

19. Requisitos de segurança e proteção radiológica para serviços de medicina nuclear. **Norma CNEN NN 3.05 Resolução CNEN 159/13 dez./2013**

20. **Resolução-RDC No 64, de 18 de dezembro de 2009. ANVISA**