LUMEN ET VIRTUS

Lutetium-specific prostatic membrane antigen (luPSMA) treatment for metastatic castration- resistant prostate cancer

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ABSTRACT

Introduction: Cancer is one of the leading causes of death globally, with the majority of cases occurring in low-income countries. There are more than a hundred types, divided into sarcomas and carcinomas. Prostate cancer is the most common cancer among men and is usually asymptomatic. Treatment depends on the stage of the disease and may include surgery, hormone therapy, and radiation therapy. In advanced stages, new treatments such as the radiopharmaceutical LuPSMA are investigated to improve patients' quality of life. Objective: To analyze the efficacy of treatment with the radiopharmaceutical LuPSMA in patients diagnosed with metastatic prostate cancer through a literature review. Methodology: An exploratory-descriptive literature review with a qualitative approach was conducted, based on books and scientific articles. Data collection took place between 2019 and 2024, including complete and relevant documents on the topic, without language restriction, and excluding irrelevant, duplicate, or incomplete materials. The databases used were LILACS, SciELO, and PubMed, using the descriptors "Prostate Neoplasms," "Lutetium," and "Positron Emission Tomography combined with Computed Tomography" in Portuguese and English, added by the boolean operator "AND". Results: A total of 189 articles were found, of which only 30 were selected, after reading the titles and abstracts, according to the inclusion criteria, showing that theranostics with LuPSMA presents significant results in the quality and survival of patients with mCRPC. Conclusion: The results showed that LuPSMA significantly increased overall survival and progression-free survival compared to standard treatment, while being well tolerated with manageable adverse effects. However, there are uncertainties about the therapeutic response and prognosis in patients with low PSMA expression, indicating the need for further research. The study has contributed to imaging and oncology, offering new perspectives on alternative therapies for metastatic cancer and serving as a basis for future investigations into imaging-guided radionuclide therapies.

Keywords: Prostate Neoplasms, Lutetium, Positron Emission Tomography combined with Computed Tomography.

INTRODUCTION

Cancer is the second most common cause of death worldwide, with the majority of them, approximately 70%, in middle- and low-income countries. In 2018 alone, cancer claimed an average of 9.6 million victims. It can be defined as the uncontrolled growth of malignant cells,which can be developed by genetic predispositions, ethnicity, and external factors, such as: lifestyle, diet, smoking, and alcoholism (PAHO, 2020). Science knows more than a hundred types of cancers, at first they can be divided into two large groups, these are: sarcomas, when they arise in connective tissues, and carcinomas that originate from epithelial tissues, which, inturn, cover most organs (Brasil, 2023).

Among carcinomas, prostate cancer can be mentioned as the most common adenocarcinoma among men (Brasil, 2023). Carcinomas receive the prefix "adeno" when theyaffect glands, in this case, the prostate, an exclusively male organ that is part of the genital system. This type of cancer is considered elderly, since almost 80% of cases affect men from the age of 65; this statistic can be explained by the fact that it is a slow-developing cancer, sinceit can take up to 15 years for the tumor to reach 1cm³, remaining unnoticed for years and possibly being discovered later than expected, being in the metastatic phase, for example (Brasil, 2023).

Most individuals with prostate cancer are diagnosed asymptomatic, with ProstateSpecific Antigen (PSA) being one of the most important tests, as well as digital rectalexamination; other patients may have urinary obstruction, pain located in the prostate region, and, if in the metastatic phase, pain in the bones, even causing fractures (Straub *et al*., 2023). The treatment will be chosen depending on the clinical characteristics of the individual, and surgery and Transurethral Resection (TR) may be performed in localized tumor, association with hormone therapy in locally advanced tumor, androgen blockade or surgical castration in cases of metastasis (Farolfi *et al*., 2019).

Traditional treatments may not present significant results in the metastatic phase, sincethe latest protocols aim to improve the quality of the end of life of these individuals, as there isno reduction in tumors. Thus, it is necessary to know how the Lutetium-Prostatic Membrane Antigen (LuPSMA) radiopharmaceutical can help in the treatment of patients with metastatic prostate cancer.

METHODOLOGY

This was an exploratory-descriptive bibliographic study with a qualitative approach andthese data were used for the elaboration of the scientific article. According to Gil (2022): bibliographic research is developed based on material already prepared, consisting mainly of books and scientific articles, that is, it is the one in which the theoretical survey of a given subject is carried out from the collection of information about what different authors report onthe subject.

A study has an exploratory nature when it involves a bibliographic survey, interviews with people who have had (or have) practical experiences with the researched problem and analysis of examples that stimulate understanding. It also has the basic purpose of developing,clarifying and

modifying concepts and ideas for the formulation of subsequent approaches. Thus, this type of study aims to provide greater knowledge for the researcher about the subject,so that he can formulate more precise problems or create hypotheses that can be researched byfuture studies (Gil, 2022).

According to Gonçalves (2003), descriptive research records, analyzes, classifies and interprets the observed facts, often establishing relationships between them. As for the approach, this study is qualitative. Minayo (1994) describes that qualitative research is one whose concern of the researcher is not directed to the quantitative profile of the data, but ratherto the value of the information that can be collected, correlating the phenomena and variables to reality, in order to understand this experience in deeper dimensions, encompassing creativityand directing to the construction of scenarios and new perspectives within the same reality.

Data collection was based on a bibliographic survey carried out through research carriedout on scientific productions on the proposed theme, from 2019 to 2024.

The inclusion criteria for the selection of content were those published in full accordingto the theme, documents, regulations, regulations of health entities on the theme, articles, without language restrictions. The exclusion criteria were articles that were not relevant to thetheme, duplicate materials, incomplete materials, debates, reviews, abstracts, and materials notavailable in full. The literature search was carried out in the following databases: Latin American and Caribbean Literature in Health Sciences (LILACS), the Virtual Scientific*Electronic Library Online* (SciELO) and *the National Library of Medicine* (PubMed). It is noteworthy that the LILACS database was consulted through the Virtual Health Library (VHL).The searches were performed using the Health Sciences Descriptors (DeCS) of the Regional Library of Medicine (Bireme): Prostate Neoplasms, Lutetium and Positron Emission Tomography combined with Computed Tomography, in Portuguese and English with the aid ofthe Boolean operator "AND".

The methodology used in this study began with the careful selection of keywords in DeCS (Health Sciences Descriptors), followed by searches in several indexed databases, including PubMed, Virtual Health Library (VHL) and SciELO. Using both the selected keywords and their alternative terms, tables were prepared containing all the pertinent articles related to the searches with the corresponding descriptors and alternative terms in each databaseconsulted. Duplicate articles were eliminated in each table, and a selection by title relevance was conducted. After this screening, the selected articles were submitted to the reading of the abstracts, and those that met the established relevance criteria were included for exhaustive reading.

For the comprehensive analysis of the selected articles, four axes of discussion were identified, which were outlined based on the specific objectives of the study and transformed into guiding questions. Such questions guided the reading of the selected articles, providing a conceptual framework for the critical and in-depth analysis of the information contained in them. The answers

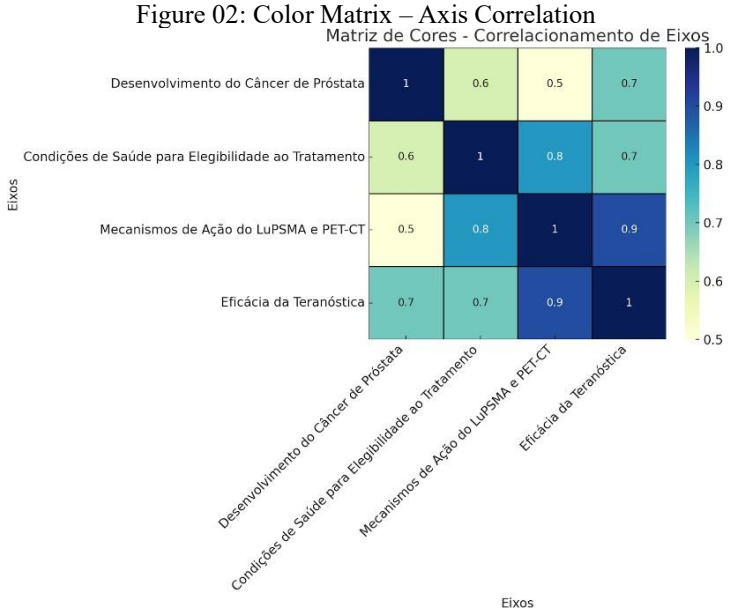
obtained for each question, from the exhaustive reading of the articles, constituted the basis for the writing of the results and the conduction of the discussion, thus enriching the analysis and interpretation of the data. This structured and meticulous methodology provided a systematic and reasoned investigation of the relevant literature,reinforcing the validity and robustness of the results presented in this scientific study.

RESULTS AND DISCUSSION

To carry out this final course work, 189 articles were found, already unifying those found in different databases and excluding duplicates, using the descriptors "Prostate Neoplasms", "Lutetium" and "Positron Emission Tomography combined with Computed Tomography" in Portuguese and English, associated by the Boolean operator "AND", in the PubMed and LILACS databases, being LILACS consulted through the VHL. In the SciELO database, no studies were found using the descriptors used. Having the articles in a table, afterreading the titles and abstracts, a total of 30 relevant scientific articles on LuPSMA treatment for mCRPC were selected and analyzed, the inclusion criteria adopted involved articlespublished between 2019 and 2024, without language restrictions, and focused mainly on the presentation of results of the proposed theranostics. Studies that did not meet the established relevance criteria or that were not fully available were excluded.

A color matrix was generated to present the correlation between the four axes discussedrelated to mCRPC and LuPSMA treatment in conjunction with PET-CT (Figure 02). The strongest correlations observed are between the mechanisms of action of LuPSMA and PET- CT and the efficacy of theranostics (0.9), suggesting that the efficacy of treatment is highly dependent on how these mechanisms work. In addition, health conditions for treatment eligibility show a high correlation (0.8) with the mechanisms of action of LuPSMA and PET- CT and with the efficacy of theranostics (0.7), indicating that the health of patients is highly relevant to the efficacy of these mechanisms.

Figure 02: Color Matrix – Axis Correlation



Source: Prepared by the author.

PHATOPHYSIOLOGY OF PROSTATE CANCER

Prostate cancer is defined as a neoplasm originating in the tissues of the prostate and isthe second most commonly diagnosed neoplasm in the male population worldwide (Avila *et al*., 2024). This type of cancer develops when cells in the prostate, a gland of the male reproductive system, begin to grow in an uncontrolled way influenced by genetic, hormonal, and environmental factors, resulting in malignant tumors that can spread to other parts of the body (Vlachostergios *et al*., 2021; Karimzadeh *et al*., 2023; Neubauer *et al*., 2024).

Genetic and epigenetic alterations play a crucial role in the malignant transformation of prostate cells, affecting the mechanisms of regulation of cell growth and apoptosis (Zang *et al*.,2019; Farolfi *et al*., 2019). Generally, prostate cancer develops slowly and may not cause symptoms for many years. When symptoms do occur, they may include difficulty urinating, blood in the urine or semen, pain in the pelvic region, and pain during ejaculation (Straub *et al*.,2023).

Metastatic castration-resistant prostate cancer (mCRPC) is established in patients with suppressed testosterone levels <50 ng/dL and at least one of the following criteria: biochemical progression, defined as an increase in PSA in studies spaced at least one week apart, with two increases of 50% above the nadir value, and with PSA >2 ng/mL, or radiological progression with two or more new lesions on bone scan or soft tissue lesions (Suman *et al*., 2019; Sartor *etal*., 2021; Avila *et al*., 2024). This condition poses a significant challenge in treatment, as cancercells become less responsive to traditional androgen deprivation (ADT) therapies (Seifert *et al*.,2023).

Therapy for prostate cancer, especially in advanced stages, involves a combination of approaches, including surgery, radiation therapy, and hormone therapy. In cases of mCRPC, radioligand therapy using Lu-177-PSMA-617 (LuPSMA) has shown efficacy, working in

conjunction with Positron Emission Tomography combined with Computed Tomography(PET-CT) to monitor disease progression and response to treatment (Seifert *et al*., 2021).

MAIN HEALTH CONDITIONS FOR THE PATIENT TO BE ELIGIBLE FORTREATMENT

Patients eligible for LuPSMA treatment must be adults, have mCRPC and symptoms ofbone metastasis, have undergone all previously recommended and approved therapies such as antiandrogen therapy and chemotherapy, and have failed effective regular treatments (Beyersdorff *et al*., 2021). It is essential to be in good health, patients with clinically significantimpaired medullary, hepatic or renal function are not eligible for treatment (Zang *et al*., 2020; Burgard *et al*., 2023; Avila *et al*., 2024). In addition, patients must have an ECOG performancestatus of 0 to 2 and a life expectancy of at least six months (Sartor *et al*., 2021; Karimzadeh *et al*., 2023).

Before starting treatment with LuPSMA, patients should undergo a staging through PET-CT with [68Ga]Ga-PSMA-11, with reassessment after two cycles of LuPSMA (Burgard *et al*., 2023; Neubauer *et al*., 2024). It is necessary for these patients to have a significant expression of PSMA, detected through imaging tests, such as PET-CT, to ensure the effectiveness of the therapy, since the local binding of the ligand in the tumor is essential to administer the radiation dose correctly (Zang *et al*., 2020; Beyersdorff *et al*., 2021; van Golen;Vogel; Lam, 2023; Burkett *et al*., 2023).

Eligibility is further determined by appropriate laboratory parameters such as PSA, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and C-reactive protein (CRP)levels, which help monitor treatment response and overall patient health (Kafka *et al*., 2024). Careful assessment of the patient's overall health and the absence of coexisting severe medicalconditions are essential to ensure that treatment is safe and effective, providing a better qualityof life and potentially extending survival (Seifert *et al*., 2023; Violet *et al*., 2019).

MECHANISMS OF ACTION OF LuPSMA IN CONJUNCTION WITH PET-CT

A radionuclide can be stabilized by a chelator, a cage, or a covalent bond, and then coupled to a vector by means of a ligand molecule. This vector connects to a specific moleculartarget, allowing visualization of the target for diagnosis or treatment, as well as enabling targeted delivery of radiation therapy to the desired site. Alternatively, a free radionuclide ion can be used, under certain conditions, to reach tumors or cancer cells (Figure 01).

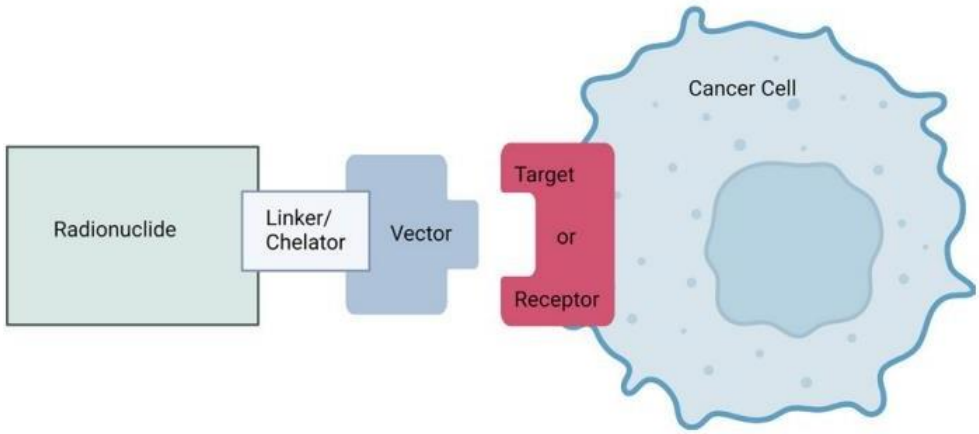
Prostate-specific membrane antigen (PSMA) is a transmembrane protein that is highly expressed in most prostate carcinoma cells, offering a starting point for diagnosis and therapy.PET-CT with [68Ga]Ga-PSMA-11 allows diagnosing and staging prostate cancer, identifying tumor lesions that express PSMA and determining the extent of the disease (Kamaldeep *et al*.,2021; van

Golen; Vogel; Lam, 2023; Avila *et al*., 2024). This assessment is crucial for selectingpatients and for assessing response to LuPSMA treatment.

In the theranostic in question, LuPSMA is a radiopharmaceutical that binds to PSMA expressed on tumor cells. After administration, it will emit beta radiation, destroying PSMA- positive cancer cells, preserving the surrounding healthy tissues, in addition to emitting a smallamount of gamma radiation, enabling imaging research of the cells marked by PET-CT. (Georgakopoulos; Bamias; Chatziioannou, 2023; van Golen; Vogel; Lam, 2023).

PET-CT, as it allows visualizing the precise location of the radiopharmaceutical in thebody and quantifying the PSMA capture of tumors, will be used for diagnosis, staging, patientselection, and treatment follow-up (Burkett *et al*., 2023; Neubauer *et al*., 2024).

Figure 01: Radionuclide therapy regimen



Source: Burkett et al., 2023.

THERANOSTICS EFFICACY

The efficacy of theranostics, which includes the use of LuPSMA in conjunction with PET-CT, is promising for the treatment of mCRPC. The use of PSMA-PET-CT to guide patientselection for radionuclide therapy allows for a personalized approach with proven and potentially more effective diagnostic utility, and its application in the detection of biochemicalrelapses demonstrates a significant change in treatment plans and improved clinical outcomes (Luining *et al*., 2022; Chandran; Figg; Madan, 2022; Georgakopoulos; Bamias; Chatziioannou,2023).

The mechanism of action of radionuclide therapies is characterized by a highly selectiveeffect on the tumor, with often low toxicity. Treatment of prostate cancer with radium dichloride(Ra-223) was the first radionuclide therapy to show survival benefit; however, due to its mechanism of action, it is not effective in visceral metastases or large lymph node metastases.In contrast, LuPSMA targets all tumor locations and has an excellent combination of survival benefits with few side effects (Kamaldeep *et al*., 2021; van Golen; Vogel; Lam, 2023).

Retrospective and prospective studies have demonstrated a significant reduction in PSAlevels and a positive response in a substantial percentage of patients treated with LuPSMA. Yadav et al. (2020) report that in one study, after 2 to 3 months of the first therapy, more than 50% decline in PSA was observed in 32.2% of patients, and this proportion increased to 45.5%by the end of the evaluation. The disease control rate was 77%, and the median overall survival was 14 months. Phase III trials are further investigating the efficacy and role of this therapeuticapproach in the management of mCRPC (Beyersdorff *et al*., 2021).

In 2021, the VISION study, an international phase III study of 831 patients with mCRPCwho progressed after antiandrogen therapy and chemotherapy, showed that LuPSMA provided significantly higher overall survival, longer progression-free survival compared to standard care, as well as emotional functionality and reduction of symptoms such as fatigue and pain (Zang *et al*., 2019; Iravani *et al*., 2020; Sartor *et al*., 2021; van Golen; Vogel; Lam, 2023; Burkett *et al*., 2023; Burgard *et al*., 2023; Karimzadeh *et al*., 2023; Seifert *et al*., 2023; Neubauer *et al*., 2024; Avila *et al*., 2024).

Therapy was well tolerated, with haematological adverse effects such as anaemia and thrombocytopenia being the most common but generally manageable. The efficacy of therapy was correlated with treatment dose, with higher doses resulting in higher PSA response rates and disease control, although this was also associated with a higher risk of hematologic toxicity(Zang *et al*., 2020).

However, there is still an unresolved clinical question about identifying the patients with mCRPC who will benefit from LuPSMA therapy. The efficacy of theranostics depends on the expression of PSMA measured by PSMA-PET-CT, it is still unclear to what extent this expression can predict therapeutic response and predict overall survival, and a meticulous evaluation of imaging results is necessary to adjust treatment (Seifert *et al*., 2020; Seifert *et al*.,2021). There is a need for therapies with a different target that are better tolerated, as not all current therapies are effective or suitable for patients with mCRPC, and effective therapies mayalso increase toxicity over time (van Golen; Vogel; Lam, 2023).

CONCLUSION

The results indicate that LuPSMA provided significantly higher overall survival and longer progression-free survival compared to standard treatment, being a well-tolerated therapywith manageable adverse effects. However, some limitations have been identified, such as uncertainty about the therapeutic response and prognosis of overall survival in patients with low PSMA expression, which suggests that future research should consider methods for the efficacy of this treatment in patients with low PSMA expression.

In conclusion, this study contributed to the fields of imaging and oncology, offering new perspectives on alternative therapies, especially in cases of metastatic cancer. It is hoped that the findings presented here will serve as a basis for future investigations that seek to deepen theknowledge about radionuclide therapies guided by imaging tests.

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