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Prostate Cancer, Castration-Resistant Prostate Cancer (CRPC), Radium-223 Dichloride Injection for Bone Metastasized Prostate Cancer

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Abstract

Purpose: The purpose of this paper is to discuss the most important facts about prostate cancer, its treatments and efficacy, the type of prostate cancer that does not improve with hormonal therapy (Castration-Resistant Prostate Cancer-CRPC), and the recently approved Radium-223 dichloride targeted therapy for CRPC that has metastasized to bones. Prostate cancer is the third most common malignancy diagnosed worldwide and the most common malignant disease in men. Also, the incidence of prostate cancer varies between regions. So it's important to have a proper understanding of all above points to prevent the further development and spread of cancer and improve the cure rate. **Design:** The paper begins by discussing what prostate cancer is, the risk factors, clinical manifestations, and the treatments for prostate cancer. It covers the clinical manifestations, pathology, screening (cancer biomarker Prostate Specific Antigen, Digital Rectal Examination—DRE, prostate biopsy, and imaging) and treatments for prostate cancer. The paper then delves into the main treatment methods for prostate cancer, including how Castration-Resistant Prostate Cancer (CRPC) differs from normal prostate cancer after hormone suppression therapy. Additionally, it discusses the effectiveness of the recently introduced Radium-223 dichloride injection as a radiation-targeted therapy for treating CRPC that has metastasized to bones. This section covers the properties of radium-223 dichloride injection, its pharmacokinetics, pharmacodynamics, absorption and volume of distribution, half-life, metabolism, route of elimination, clearance, toxicity, adverse effects, and mechanism of action at the tumor site. It also discusses preclinical studies related to radium-223 dichloride injection and its effectiveness in treating CRPC patients with bone metastasis. **Conclusion:** Prostate cancer is a common

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cancer that can be treated with surgery or hormonal therapy. However, if the cancer progresses despite hormonal therapy, Radium-223 dichloride injection can be used as a radiation target therapy to treat patients with CRPC and symptomatic bone metastases. This treatment kills tumor cells in bones and reduces associated pain with minimal damage to surrounding normal tissue. However, the metastatic disease cannot be cured and can only offer palliation for the patient. **Suggestions:** Based on the facts, Radium-223 target therapy is effective in treating and providing palliation for cancers. It is suggested to further develop the usage of radiation target therapy and to test the safety and efficacy of more than 6 injections of Radium-223 dichloride and its combination with currently used chemotherapy drugs for bone metastasized CRPC. This paper aims to contribute to future research designs related to cancer therapies using radiation and to design new studies and practical implementations, especially regarding the usage of radium-223 dichloride.

Keywords

Prostate Cancer, Castration-Resistant Prostate Cancer, Radium-223 Dichloride

1. Introduction

Prostate cancer is a common form of cancer, with over 95% of cases being adenocarcinomas. 95% of remaining 5% consist of transitional cell carcinomas and remaining are neuroendocrine carcinomas, or sarcomas [1]. This discussion will focus on adenocarcinomas due to their high incidence compared to other types of prostate cancer.

Prostate adenocarcinoma is a malignant proliferation of prostatic glands and is the third most common cancer diagnosed worldwide [2] [3] [4]. It is also the most common malignant disease in men and the second most common cause of cancer-related deaths in men [3]. The incidence of prostate carcinoma varies between regions and is greatly affected by PSA (Prostate Specific Antigen) testing and related screening programs. Therefore, it is important to understand what prostate carcinoma is, the risk factors associated with it, and the available treatments. This discussion will also cover the most recently introduced radiation therapy using Radium-223 dichloride injection for bone metastasized prostate cancer.

2. What Is Prostate Cancer

Prostate cancer occurs when a prostatic cell becomes cancerous due to gene change, leading to neoplastic proliferation and the development of prostate cancer. The exact cause of these gene change is unknown, but risk factors for prostatic adenocarcinoma include advanced age, race (African Americans > Caucasians > Asians), and a diet high in saturated fats (obesity) [3].

Prostatic carcinoma usually arises in the postero-peripheral region of the

prostate gland and does not typically produce urinary symptoms early on. It is often clinically silent in the early stages until the tumor grows and spreads from the postero-peripheral region to the central peri-urethral region of the prostate gland, causing obstruction. So the symptoms are commonly noted during the advanced stage when the tumor starts to compress the urethra [3] [5].

2.1. Clinical Features during Advanced Stage

- Difficulty in urinating (problems in starting and stopping urine stream);
- Decreased force of urination;
- Frequent urination;
- Impaired bladder emptying with increased risk of infection and hydronephrosis; When tumor creates an obstruction in peri-urethral region it impairs bladder emptying and results in fluid buildup in the bladder. This leads to fluid backup in the kidneys. As this fluid can't be drained out, the fluid accumulated in kidneys, known as hydronephrosis.
- Hypertrophy of bladder wall smooth muscles and increased risk of bladder diverticula;

When bladder emptying impaired due to obstruction in peri-urethral region, the bladder will press against the obstruction and the smooth muscles of the bladder wall undergo hypertrophy. Additionally, the high pressure generated by the bladder as it pushes against the obstruction could result in diverticula of the bladder wall.

- Blood in semen and slight hematuria;
- Bone pain and Pain or discomfort in pelvic area (if cancer metastasized to the bones).

The growth of prostatic tumor cells is androgen dependent and is related to the dihydrotestosterone (DHT). Testosterone is converted in to DHT by 5alpha reductase, and these DHT acts on androgen receptors of prostatic tumor cells, resulting in prostatic tumor cell hyperplasia. Therefore, the tumor will grow and spread rapidly if testosterone and DHT are present.

2.2. Screening

- The screening for prostate cancer begins at the age of 50 years with Digital Rectal Examination (DRE) and serum Prostate-Specific Antigen (PSA) test [3].

PSA is a protease produced by the epithelia of the prostate. It is increased in patients with prostate cancer because it damages to the crypt structure of the prostate, but the normal serum PSA increases with age (**Table 1**) due to Benign Prostatic Hyperplasia [6] (2.5 μg/L for ages between 40 - 49 years and 6.5 - 7.5 μg/L for ages above 70 years). If the serum PSA level 2.5 μg/L or less than 4 μg/L, the patient is reasonably safe, but if serum PSA level is more than 4 μg/L the patient should be more concerned and should have further tests for early diagnosis of prostate carcinoma. A serum PSA > 10 μg/L is highly worrisome at any age (**Table 2**). As cancer makes bound PSA, decreased % free-PSA is suggestive of cancer [3].

Table 1. Age specific normal serum PSA levels.

Healthy males of age (years)	Serum PSA (μg/L)
40 - 49	2.5
50 - 59	3.5
60 - 69	5.0
70 - 79	6.5
80 - 89	7.5

(Courtesy of Oxford Handbook Clinical Medicine 2006).

Table 2. Normal PSA levels with age.

Indication	PSA Levels
Safe to permissible limits	0 - 2.5 μg/L
Reasonably safe	2.6 - 4 μg/L
Suspicious	4 - 10 μg/L
Dangerous	>10 μg/L

(Courtesy of Oxford Handbook Clinical Medicine 2006 and Fundamentals of Pathology 2016).

▪ **Prostatic biopsy** is required to confirm the presence of carcinoma. It cannot be assumed that the patient has cancer based solely on high PSA levels and abnormal DRE results. Therefore, if there is sufficient clinical suspicion, a prostatic biopsy must be performed before considering prostate removal. In a cancerous prostate biopsy using H&E stain, small, invasive glands that infiltrate the prostatic tissue and prominent nucleoli in glandular cells are typically observed (**Figure 1**) [3]. Additionally, for further confirmation of prostate cancer, immunohistochemistry can be performed using an antibody to detect a specific antigen in prostatic cancer cells in the tissue sample (**Figure 2**).

The grading of the Prostatic cancer is done using the Gleason grading system, which is totally based on architecture [1] [3] and does not consider nuclear atypia [usually abnormal nuclear changes are seen in malignancy]. In this grading system multiple regions of the tumor are assessed because architecture varies from area to area. Therefore, tumor's common patterns within the cancer scored from 1 - 5. Finally, two distinct areas scored and added together to get the final score (2 - 10), with a higher score suggesting a worse prognosis.

▪ **Imaging**

The Transrectal Ultrasound (TRUS) is useful for evaluating tumor volume and guiding biopsy needles in to the peripheral zone and other specific areas such as base, apex and the transition zone of the prostate. An intravenous urogram reveals urinary retention or distal ureteral obstruction. A chest X-ray may reveal uncommon lung metastases, but more often shows typical osteoblastic metastases in the thoracic spine or ribs. An abdominal X-ray may reveal metastases in the lumbosacral spine or ileum. A CT scan of the pelvis may show an enlarged prostate and large pelvic or para-aortic lymph nodes. MRI test is more helpful in pelvic staging of prostate cancer than CT scan [1].

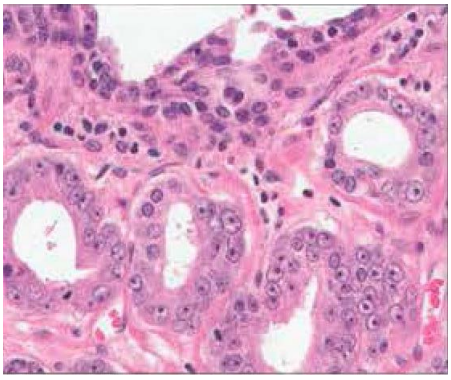

Figure 1. Prostatic adenocarcinoma H & E Stain (Courtesy of Fundamentals of Pathology 2016).

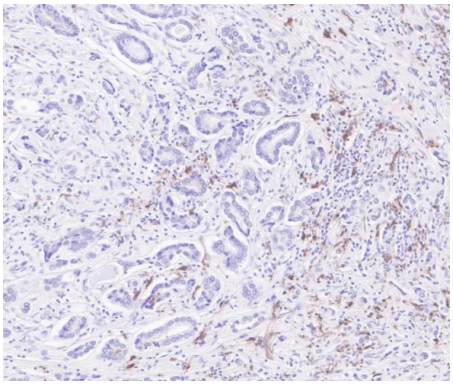

Figure 2. Immunohistochemistry of 50 years old prostatic adenocarcinoma patient (Author's compilation).

• Prostate cancer commonly spreads to the lumbar spine or pelvis, resulting in osteoblastic metastases [will get sclerotic lesions on the bone] that present as low back pain and elevated serum alkaline phosphatase, PSA, and prostatic acid phosphatase (PAP) [3]. These manifestations are not seen in localized disease, and this bone metastasized clinical stage of prostate cancer cannot be cured.

2.3. Treatment and Prognosis

Prostate adenocarcinoma presents in different stages, each with its own clinical findings. Stage A (T1) adenocarcinoma presents no physical signs, nonpalpable and is typically only diagnosed when prostate tissue is removed during treatment for symptomatic bladder outlet obstruction caused by benign prostatic hyperplasia, or when it is found by an elevated PSA. Stage B (T2) or higher disease is characterized by a hard nodule on the prostate that can be felt during rectal examination (**Table 3**) [1]. In over 60% of these cases, the cancer causes obstructive symptoms, urinary retention, or urinary infection. Previously, 50% of patients presented with evidence of metastases (weight loss, anemia, bone pain, acute neurologic deficit in the lower limbs), but due to early diagnosis, fewer than 20% of patients present in this way currently [1].

Table 3. Treatment and prognosis of prostate cancer related to tumor stage.

Conventional stage	TNM stage	Clinical Manifestations	Treatment	Fifteen Year Survival (%)
A1	T1a	Non palpable tumor, low grade cancer, <5% of prostate involved (Incidental finding at prostatectomy)	Observation	Normal
A2	T1b	Non palpable tumor, high grade cancer or >5% of prostate involved, or both (Incidental finding at prostatectomy)	Total prostatectomy with pelvic lymphadenectomy	30 - 45
B1	T2a	Localized nodule, 1 - 1.5 cm in diameter in one lobe	Total prostatectomy with pelvic lymphadenectomy	50 - 60
B2	T2b	Tumor > 1.5 cm in diameter or more than one lobe	Total prostatectomy with pelvic lymphadenectomy	35 - 45
C	T3, T4	Periprostatic extension	Radiation with or without pelvic lymphadenectomy	20 - 30
D	N+ Or M+	Pelvic lymph node involvement or distant metastasis	Hormonal therapy (LHRH/antiandrogen) when symptomatic. Irradiation for isolated bone pain	0 - 10

(Courtesy of text book of Surgery by Lawrence W. Way, Gerard M. Doherty, Chen Xiaoping).

Patients with Stage A1 (T1a) have a prognosis like patients without adenocarcinoma of the prostate and only require observation. Patients with clinical stage A2 (T2b), B0, B1 (T2a), or B2 (T2b) lesions are curable with total prostatectomy (Table 3), but patients with grossly positive pelvic lymph nodes are not candidates for this procedure. Patients with Stage C cancer (periprostatic extension) is treated with androgen deprivation therapy with GnRH analogs and radiation therapy (external beam pelvic radiation), but when the lesion is large, palliation is the only expected outcome [1].

Metastatic disease cannot be cured, but significant palliation can be offered by hormone suppression therapy. Patients in whom hormonal therapy has failed can be treated by inhibiting adrenal androgen production with aminoglutethimide or ketoconazole, or by short-term relief of bone pain with oral corticosteroids. Palliation can also be offered by radiation therapy for symptomatic bone lesions, as well as local irradiation for an obstructing or bleeding prostate tumor [1]. The newly introduced Radium-223 dichloride injection is a bone-seeking radioisotope that offers palliation to the patient.

Briefly, treatments for prostate cancer include:

- Prostatectomy for localized disease;
- Hormone suppression therapy/Androgen deprivation therapy (ADT) for advanced disease;

Advanced disease is treated with hormone suppression to reduce testosterone and DHT,

- Prostate cancer is androgen dependent. Therefore, continuous GnRH analogs (example; leuprolide) will shut down the hypothalamus which reduces the

LH and FSH (androgens) production from anterior pituitary gland and reduce testosterone production as a result. Therefore, the ability of prostate cancer to thrive will be reduced.

• In addition, Flutamide can be used as a competitive inhibitor at the androgen receptor.

• If hormone suppression therapy failed aminoglutathimide or ketoconazole can be used as inhibitors of adrenal androgen production.

▪ Radiation therapy (external beam pelvic radiation);

The radiation therapy can be given with hormone suppression therapy when the lesion is smaller and not metastasized.

▪ Bone seeking radioisotope Radium-223 dichloride targeted therapy;

• Radium-223 dichloride is used for metastasized disease that has progressed despite hormone therapy, offering palliative care.

• Ra-223 dichloride 55 kBq/kg of body weight at 4 week intervals for a total of 6 injections over the course of treatment [4] [7] (safety and effectiveness of more than 6 injections have not been studied).

• NOTE: prohibited in combination with Arbitron acetate and prednisolone. (Before treatment: should have full blood count assessed to make sure the patient is well enough to receive the treatment, and blood must be administered to patient at baseline before each dose of the drug. After treatment: should have full blood count assessed and monitored in regular basis as radiation therapy may cause myelosuppression) [7].

3. Radium-223 Dichloride

Radium-223 dichloride, also known by the product name Xofigo (**Figure 3**) [4] [7] [8], is a radiopharmaceutical agent used to treat patients with Castration-Resistant Prostate Cancer (CRPC) with symptomatic bone metastases and no known visceral metastatic disease [4]. Castration-resistant prostate cancer is defined by disease progression despite hormone therapy/androgen deprivation therapy (ADT) and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases (such as pelvic lymph node involvement or distant metastases like bone metastases). In other words, castration-resistant prostate cancer means it hasn't responded to treatments that lower testosterone levels. The chemical structure of Radium-223 dichloride is shown below (**Figure 4**) and it is also known as Radium Ra-223 dichloride.

Average molecular weight: 293.92 [9];

Approved by FDA (Food and Drug Administration) in May 2013 [10];

Approved in china on 26th Aug 2020 [7];

Brand name Xofigo, formerly called Alpharadin, Not an OTC (Over The Counter) [7];

Radium 223 dichloride is a Small molecule type targeted therapy agent (**Figure 5**) [10].

Figure 3. Xofigo (Author's compilation).

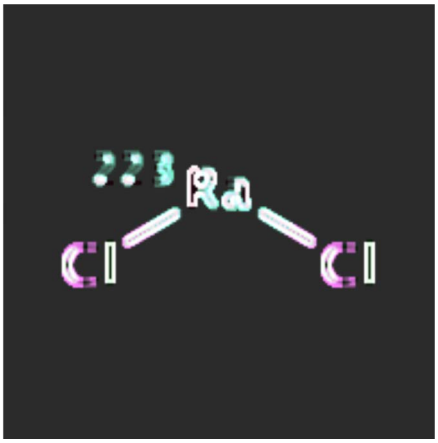

Figure 4. Chemical structure of Radium-223 dichloride (Author's compilation).

3.1. What Is Targeted Therapy?

Targeted therapy is a highly effective cancer treatment that specifically targets proteins that control the growth, division, and spread of cancer cells, unlike other treatments that directly kill the cancer cells [10]. This treatment is designed based on a better understanding of DNA changes and proteins that contribute to the development and spread of cancer.

There are various types of agents used in targeted therapy, including small molecules, monoclonal antibodies, angiogenesis inhibitors, apoptosis inducers, and hormonal therapy (**Figure 5**). Medical experts will test your tumor to determine if it contains targets for the treatment drugs to be used in targeted therapy. This process, known as biomarker testing, helps in choosing the most effective treatment for your cancer. You may need to undergo a biopsy for biomarker testing.

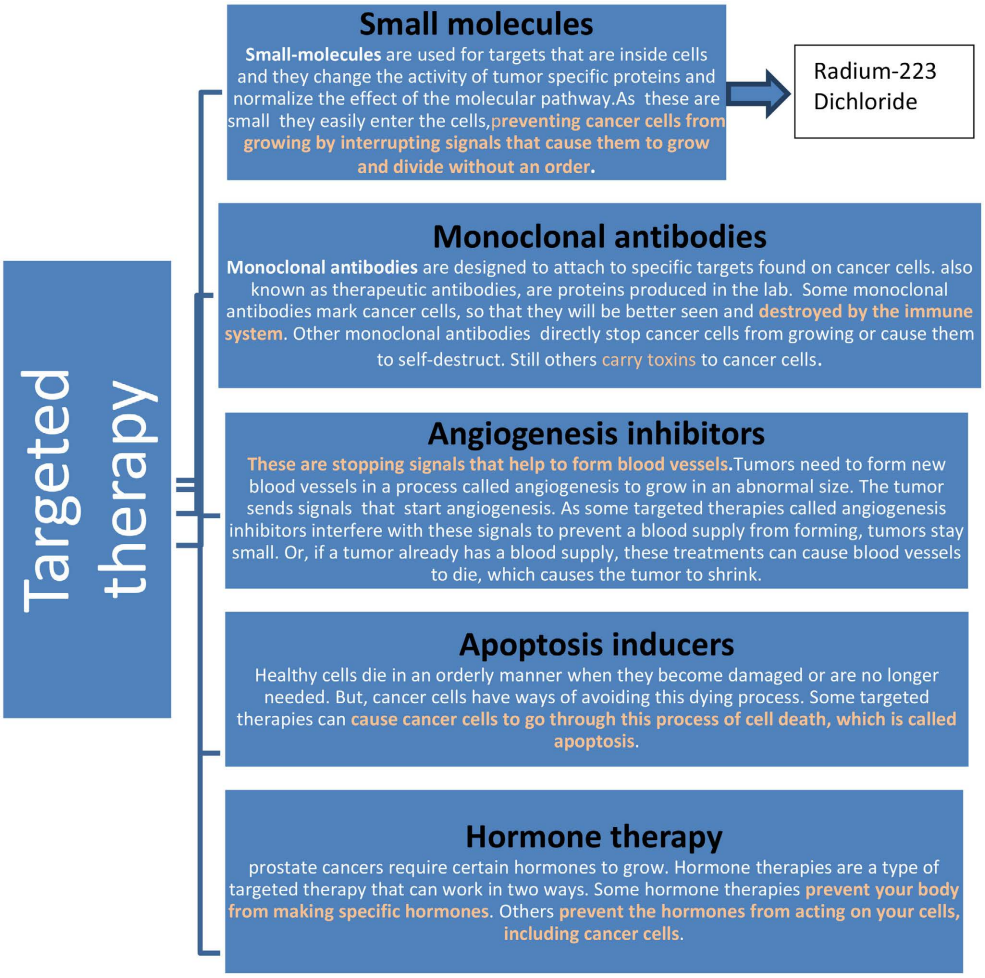

Figure 5. Types of Targeted therapy (Courtesy of Radium-223 dichloride-National Cancer Institute) https://www.cancer.gov/about-cancer/treatment/drugs/radium-223-dichloride.

3.2. How Does Radium-223 Dichloride Targeted Therapy Work against Cancer?

Radium Ra 223 Dichloride is a radiopharmaceutical containing the radioisotope radium-223 that emits short-range but high linear energy alpha-particles. As a cation, radium mimics calcium and binds to hydroxyapatite [4] [11], a bone mineral found in areas of active bone formation or high bone turnover [10] (Removal of old bone and laying down of new bone) as seen in bone metastases. Bone metastases can cause severe bone pain and symptoms like pathologic fractures and spinal cord compression, or myelosuppression [4]. After intravenous administration of Radium 223 chloride, its ability to accumulate in bones and emit alpha particles can reduce the bone pain and improve the quality of life for the patient. ^{223}Ra decays via six short-lived daughter nuclides in to the stable lead isotope ^{207}Pb (**Figure 6**) [4]. The total energy emitted is 28.2MeV, of which 95.3% is from alpha emission, 3.6% from beta and 1.1% from gamma emission [4]. So the radioactive alpha-particles in radium-223 act on bone metastases and deliver radiation with higher biological effects to a more localized area, in-

ducing high frequency double-strand DNA breaks in tumor cells (**Figure 7**) [4], killing the tumor cells and reducing the pain they cause. Also, since the alpha particle path range is short (<100 μm), it may minimize damage to the surrounding normal tissue [4].

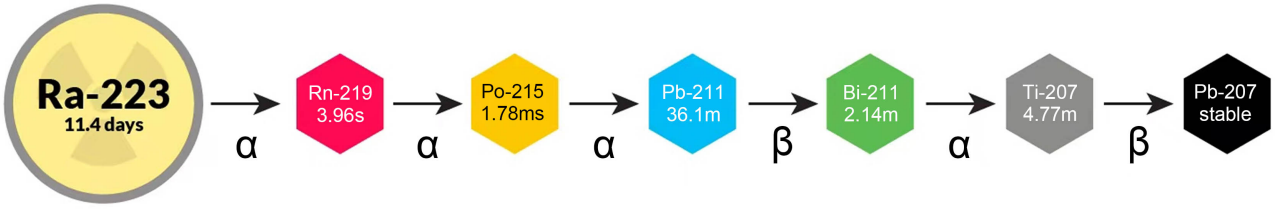

Figure 6. ^{223}Ra decay (Author's compilation).

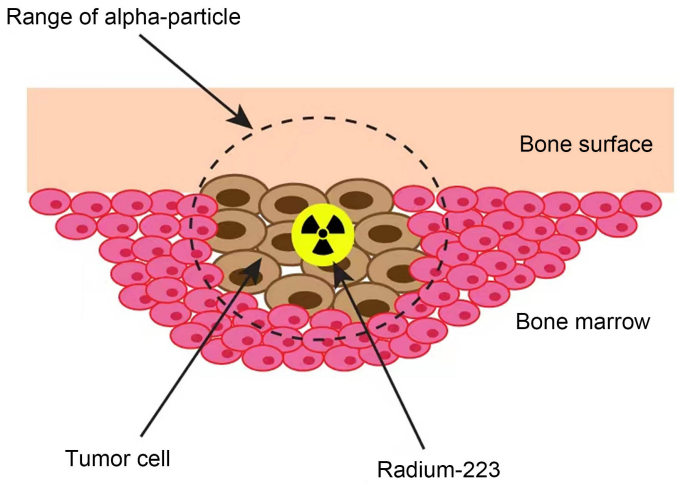

Figure 7. Mechanism of action of 223Ra at tumor site (Author's compilation).

3.3. Preclinical Studies

Preclinical studies related to Radium-223 dichloride [4] [12] [13] have demonstrated that Radium 223 dichloride has a definite skeletal affinity and has an antitumor effect with a relatively low toxicity on bone marrow. More recently in a large randomized phase III trial ALSYMPCA (ALpharadin in SYMPtomatic prostate CAncer), patients with castration-resistant prostate cancer (CRPC) and bone metastasis received six cycles of 50 kBq/kg of radium 223 dichloride in 4-week intervals. In these men, radium 223 dichloride improved the median overall survival by 3.6 months when compared to the placebo group [4] [7] [12] [13]. Collectively, these results suggest that radium 223 dichloride is a promising candidate for managing bone metastases in patients with CRPC.

3.4. Properties of Radium-223 Dichloride

3.4.1. Pharmacodynamics

Physiologically, Radium-223 Dichloride prevents the growth and spread of bone cancer by killing the associated bone cancer cells [4].

3.4.2. Mechanism of Action

Radioisotope radium-223 mimics calcium and binds to hydroxyapatite, which is a bone mineral found in areas of high bone turnover as seen in bone metastases. It emits short range but high linear energy alpha particles [4] [11]. The high energy damages bone cancer cells by introducing double-stranded DNA breaks. This leads to cell death and prevention of the spread of the bone cancer cells with minimal impact on nearby non-cancerous cells.

3.4.3. Pharmacokinetics

After Radium 223 dichloride is administered intravenously (I.V) it is rapidly removed from the blood and absorbed by organs and tissues such as bone surfaces and red marrow [4] [7]. Intake of radium either by inhalation or ingestion (^{224}Ra or ^{226}Ra in sulphate form), radium gradually enters blood stream and transferred to all parts of the body and absorbed especially by the bone surfaces and red marrow [4]. The absorbed doses of organs can be estimated via imaging data of the patients [4]. The pharmacokinetic behavior of radium in the blood stream that is administered either by injection or ingestion shows similar.

3.4.4. Absorption and the Volume of Distribution

Since Radium Ra 223 Dichloride is administered I.V., the bioavailability should be 100%. The volume of distribution was not quantified, but after 24 hours, there is less than 1% radium-223 remaining in the blood [4]. The rest of the radium-223 dose is distributed to bones (50% - 60% of the radioactive dose after 4 hours of post-injection) intestine and to fewer organs. Up to 7% of radium-223 dose uptake in liver after 7 hours of post-injection and 2% uptake in kidney after 2 hours of post-injection. No other organs were found to have significant uptake [4].

3.4.5. Protein Binding and Metabolism

Radium-223 does not undergo metabolism because it is a radioisotope that decays. But there is negligible plasma protein binding.

3.4.6. Route of Elimination

Radium-223 excretion is mainly through the feces (50% after 3 days of post-injection) and a less extent in the urine (2%) [4]. Also the elimination rate of radium-223 from the intestines is variable due to the high variability of intestinal transit rates among patients [4]. Therefore there could be more intestinal radiation exposure in patients with slower intestinal transit rates, but the significance of this in relation to toxicity is not known.

3.4.7. Half Life

The half-life of Radium-223 is relatively long at 11.4 days [4].

3.4.8. Clearance

The plasma clearance rate of radium-223 is very fast. According to preclinical studies 2 hours after injection about 2.5% of the injected dose remained in the plasma and after 24 hours of post-injection less than 1% remained [4].

3.4.9. Toxicity

Radium Ra 223 Dichloride is contraindicated in women who are pregnant, lactating or are of child bearing age due to high potential for fetal harm [7]. The effectiveness of radium-223 on fertility and reproductive function has not been studied. Other side effects include several hematological abnormalities, peripheral edema, nausea, vomiting, and diarrhea.

3.4.10. Side Effects

Side effects of the radium-223 dichloride intravenous solution include [8] [10]:

- Hematologic abnormalities (Anemia 93%, Lymphocytopenia 72%, leukopenia 35%, Thrombocytopenia 31%,Neutropenia 18%);
- Gastrointestinal issues (Nausea, Diarrhea, Vomiting);
- Skin problems (Erythema);
- Renal failure and impairment (around 3%);
- Other: Peripheral edema, Dehydration.

4. Summary

Prostate cancer is caused by a gene change with an unknown etiology, and risk factors include advanced age, race, and a diet high in saturated fats. The growth and spread of prostate cancer cells are accelerated by the presence of testosterone and DHT. The cancer is clinically silent in the early stages, but patients will experience urinary symptoms in the advanced stages due to compression in the peri-urethral region of the prostate gland. Screening for prostate cancer involves DRE and serum PSA levels, with a prostatic biopsy for confirmation.

Treatment for localized prostate cancer involves prostatectomy, while hormone suppression therapy is used for advanced disease. Radium-223 dichloride injection (recently introduced) is used for radiation therapy if the disease progresses despite hormone therapy and metastasizes to the bones. This treatment is currently being used for castration-resistant prostate cancer patients with symptomatic bone metastasis and no known visceral metastatic disease, to kill the tumor cells and reduce the pain they cause.

5. Discussion

The facts suggest that prostate cancer is a dangerous carcinoma if it moves beyond the prostate gland. If the cancer is localized, it is curable by surgical treatment, but the use of the treatment is limited to those with a reasonable life expectancy. Additionally, if the cancer has metastasized, it cannot be cured, and only palliative care can be offered. Therefore, annual DRE and serum PSA monitoring for all men over 50 years of age, and for those over 40 years of age with a positive family history in a first-degree relative (father, brother) or African Americans, can improve the cure rate. Preclinical studies suggest that Radium-223 dichloride can be effectively used to treat and provide palliative care for prostate cancer patients with bone metastases, killing cancer cells and relieving pain with minimal damage to surrounding normal cells. Because, Radium is a

radiopharmaceutical that emits short-range but high linear energy α-particles, which can kill cancerous cells with minimal damage to surrounding normal cells. This article contributes to the knowledge of medical researchers, for further research or practical implementation related to cancer therapies using radiation. It is especially relevant for researchers studying the use of radium-223 dichloride injection for patients with castration-resistant prostate cancer (CRPC) with symptomatic bone metastases and no known visceral metastatic disease. Further research is needed to be establish to test the safety and effectiveness of more than 6 injections of radium-223 dichloride for a patient, the combination of radium-223 dichloride with currently used chemotherapy drugs for bone metastasized CRPC, the effectiveness of radium-223 on fertility and reproductive function, and the extent of intestinal radiation exposure in patients with slower intestinal transit rates. This article aims to inspire medical researchers to design further studies on radium-223 dichloride.

6. Conclusion

Prostate cancer is a common cancer diagnosed worldwide. Localized cancer can be surgically removed, while advanced disease can be treated with hormonal therapy. Radium-223 dichloride can be used for patients with castration-resistant prostate cancer and symptomatic bone metastases, offering palliative care by killing tumor cells and reducing pain with minimal damage to surrounding tissue. The metastatic disease cannot be cured, and can only offer palliation for the patient. Radium-223 dichloride treatment should be done under the supervision of medical experts, considering the specific medical conditions of patients.

Declaration

The drug information in this article is meant to be educational and is not a substitute for medical advice. The information may not cover all possible uses, actions, interactions, or side effects of these drugs, or precautions to be taken while using it. Please consult your health care professional for more information about your specific medical condition and the use of these drugs.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Way, L.W., Doherty, G.M. and Chen, X.P. (2003) TextBook of Surgery. Eleventh Edition, McGraw-Hill Companies, New York.

[2] Giona, S. (2021) The Epidemiology of Prostate Cancer. Exon Publications, Brisbane. https://doi.org/10.36255/exonpublications.prostatecancer.epidemiology.2021

[3] Sattar, H.A. (2016) Fundamentals of Pathology. Medical Course and Step 1 Review. Pathoma LLC.

[4] Höllriegl, V., Petoussi-Henss, N., Hürkamp, K., *et al.* (2021) Radiopharmacokinetic Modelling and Radiation Dose Assessment of ^{223}Ra Used for Treatment of Metastatic Castration-Resistant Prostate Cancer. *EJNMMI Physics*, **8**, Article No. 44. https://doi.org/10.1186/s40658-021-00388-1

[5] Burnand, K.G., Black, J., Corbett, S.A. and Thomas, W.E.G. (2015) Brow's Introduction to the Symptoms & Signs of Surgical Disease. CRC Press, Taylor & Francis Group, Boca Raton.

[6] Longmore, M., Wilkinson, L.B. and Rajagopalan, S.R. (2006) Oxford Hand Book of Clinical Medicine. Oxford University Press, New York.

[7] Radium Chloride [223 Ra] Injection Fluid—Institute for Energy Technology/[223Ra] Pharmacokinetic, Pharmacological Action /Toxicology/. https://drugs.dxy.cn/pc/drug/xaxcv3pMtcmTvPlvTvx04g

[8] Drugs.com (2023) Radium 223 Dichloride/Xofigo Side Effects. https://www.drugs.com/sfx/xofigo-side-effects.html

[9] ScienceDirect (2023) Radium Chloride Ra 223. https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/radium-chloride-ra-223

[10] NCI (National Cancer Institute) (2013) Radium 223 Dichloride. Research Results and Related Resources, Targeted Cancer Therapies, Radiopharmaceuticals: Radiation Therapy Enters the Molecular Age, Drug Label Information. https://www.cancer.gov/about-cancer/treatment/drugs/radium-223-dichloride

[11] Nilsson, S. (2014) Alpha-Emitter Radium-223 in the Management of Solid Tumors: Current Status and Future Directions. *American Society of Clinical Oncology Educational Book. American Society of Clinical Oncology. Annual Meeting*, 152-159. https://doi.org/10.14694/EdBook_AM.2014.34.e132

[12] Nilsson, S., Cislo, P., Sartor, O., Vogelzang, N.J., Coleman, R.E., O'Sullivan, J.M., Reuning-Scherer, J., Shan, M., Zhan, L. and Parker, C. (2016) Patient-Reported Quality-of-Life Analysis of Radium-223 Dichloride from the Phase III ALSYMPCA Study. *Annals of Oncology: Official Journal of the European Society for Medical Oncology*, **27**, 868-874. https://med.wanfangdata.com.cn/ https://doi.org/10.1093/annonc/mdw065

[13] Parker, C., Nilsson, S., Heinrich, D., Helle, S.I., O'Sullivan, J.M., Fossa, S.D., *et al.* (2013) Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer. *The New England Journal of Medicine*, **369**, 213-223. https://doi.org/10.1056/NEJMoa1213755