South Russian Journal of Cancer. 2024. Vol. 5, No. 4. P. 6-13
https://doi.org/10.37748/2686-9039-2024-5-4-1
https://elibrary.ru/ohijav
ORIGINAL ARTICLE

Intravenous radionuclide therapy with radium chloride [223Ra] in patients with bone metastases from castration-resistant prostate cancer

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ABSTRACT

Purpose of the study. Assessment of clinical safety and effectiveness of radium-223 in patients with bone metastases from castration-resistant prostate cancer.
Patients and methods. The study involved materials on 15 patients with bone metastases from castration-resistant prostate cancer aged 58–81 years, with the mean age of 67.2 ± 6.5 years, who were examined and received full treatment with 6 intravenous injections of radium-223 chloride [223Ra] at the National Medical Research Centre for Oncology. Most patients (73.3 %) showed ECOG 1 performance status. Pain syndrome before the treatment was registered in 12 (80 %) patients.
Results. Evaluation of the tolerability of radium chloride did not show hematological reactions such as anemia and thrombocytopenia. One patient had grade II intestinal toxicity after the 3rd injection managed with medication. Assessment of indirect signs of the treatment effectiveness demonstrated that 6 people showed an increase in PSA during treatment, while alkaline phosphatase levels were within normal range indicating no bone destruction. 8 of 12 patients with pain syndrome showed its relief during the therapy. The following results were obtained during a follow-up examination after 3 months in 15 patients who received the full treatment course: stabilization in 8 patients; improvement in 4 patients with decreased metabolic activity and lower numbers of metastatic foci; progression with the appearance of new metastatic foci in the bones in 3 patients.
Conclusion. Radium chloride showed good results in the treatment of patients with bone metastases from castration-resistant prostate cancer. Low toxicity and improvement in the quality of life by pain relief make this treatment technique promising.

Keywords: castration-resistant prostate cancer, bone metastases, radium chloride [223Ra], quality of life

For citation: Kit O. I., Maksimova N. A., Gusareva M. A., Shevchenko A. N., Zinkovich M. S., Ilchenko M. G., Boyko K. P., Faenson A. V., Dimitriadi S. N., Rozenko L. Ya. Intravenous radionuclide therapy with radium chloride [223Ra] in patients with bone metastases from castration-resistant prostate cancer. South Russian Journal of Cancer. 2024; 5(4): 6-13. https://doi.org/10.37748/2686-9039-2024-5-4-1, https://elibrary.ru/ohijav

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Compliance with ethical standards: the ethical principles presented by the World Medical Association Declaration of Helsinki, 1964, ed. 2013, were observed in the work. The study was approved by the Committee on Biomedical Ethics at the National Medical Research Centre for Oncology (extract from the protocol of the meeting No. 7 dated 08/08/2022). Informed consent was received from all participants of the study.

Funding: this work was not funded

Conflict of interest: Kit O. I. has been the member of the editorial board of the South Russian Journal of Cancer since 2019, however he has no relation to the decision made upon publishing this article. The article has passed the review procedure accepted in the journal. The authors did not declare any other conflict of interest

The article was submitted 01.12.2023; approved after reviewing 12.10.2024; accepted for publication 30.10.2024

Южно-Российский онкологический журнал. 2024. Т. 5, № 4. С. 6-13
https://doi.org/10.37748/2686-9039-2024-5-4-1
https://elibrary.ru/ohijav
3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Применение внутривенной радионуклидной терапии радия хлоридом [223Ra] у пациентов с костными метастазами кастрационно-резистентного рака предстательной железы

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РЕЗЮМЕ

Цель исследования. Оценка клинической безопасности и эффективности применения радия-223 у пациентов с костными метастазами кастрационно-резистентного рака предстательной железы (РПЖ).

Материалы и методы. В исследование включены сведения о 15 пациентах с костными метастазами кастрационно-резистентного РПЖ в возрасте от 58 до 81 года, средний возраст 67,2 ± 6,5 года, обследованных и получивших полный курс лечения из 6 внутривенных радиотерапий препаратом радия хлорида [223Ra] на базе ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации. Функциональное состояние большей части пациентов (73,3 %) соответствовало 1 по шкале ECOG. Перед началом лечения болевой синдром отмечался у 12 (80 %) пациентов.

Результаты. При оценке переносимости радия хлорида было отмечено отсутствие гематологических реакций, таких как анемия и тромбоцитопения. У одного пациента была отмечена кишечная токсичность II степени, которая появилась после 3-го введения и была медикаментозно купирована. Оценка косвенных признаков эффективности проведенного лечения: у 6 человек за время лечения был отмечен рост простатического специфического антигена (ПСА), при этом показатели уровня щелочной фосфатазы находились в пределах нормы, что может говорить об отсутствии костной деструкции. У 8 из 12 человек с болевым синдромом наблюдалось его снижение уже на этапе терапии. У 15 пациентов, получивших полный курс лечения, при контрольном обследовании через 3 месяца были получены следующие результаты: у 8 человек – стабилизация процесса, у 4 человек – улучшение в виде снижения уровня метаболической активности и уменьшение количества метастатических очагов, у 3 пациентов отмечено прогрессирование заболевания с появлением новых метастатических очагов в костях скелета.

Заключение. Радия хлорид показал хорошие результаты в терапии пациентов с костными метастазами кастрационно-резистентного рака предстательной железы. Низкие уровни токсичности и возможность улучшить качество жизни за счет снижения выраженности болевого синдрома позволяют говорить о перспективности данной лечебной методики.

Ключевые слова: кастрационно-резистентный рак предстательной железы, метастазы в кости, радия хлорида [223Ra], качество жизни

Для цитирования: Кит О. И., Максимова Н. А., Гусарева М. А., Шевченко А. Н., Зинькович М. С., Ильченко М. Г., Бойко К. П., Фаенсон А. В., Димитриади С. Н., Розенко Л. Я. Применение внутривенной радионуклидной терапии радия хлоридом [223Ra] у пациентов с костными метастазами кастрационно-резистентного рака предстательной железы. Южно-Российский онкологический журнал. 2024; 5(4): 6-13. https://doi.org/10.37748/2686-9039-2024-5-4-1, https://elibrary.ru/ohijav

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Комитетом по биомедицинской этике при ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации (выписка из протокола заседания № 7 от 08.08.2022). Информированное согласие получено от всех участников исследования.

Финансирование: финансирование данной работы не проводилось

Конфликт интересов: Кит О. И. является членом редакционной коллегии журнала «Южно-Российский онкологический журнал» с 2019 г., но не имеет никакого отношения к решению опубликовать эту статью. Статья прошла принятую в журнале процедуру рецензирования. Об иных конфликтах интересов авторы не заявляли

Статья поступила в редакцию 01.12.2023; одобрена после рецензирования 12.10.2024; принята к публикации 30.10.2024

INTRODUCTION

Prostate cancer (prostate cancer) ranks second in the structure of cancer incidence in the male population and is one of the leading causes of cancer mortality in the world [1, 2]. Its share is 15.1 % in the structure of the incidence of malignant neoplasms in the male population in Russia [1]. Over 10 years, the increase in Russia amounted to 41.69 %, so in 2021, the incidence of prostate cancer almost doubled compared to 2011 and reached 59.24 per 100,000 population [1]. The mortality rate in Russia from prostate cancer remains high, in 2021 it is 19.03 per 100,000 population, an increase of 23.87 % over 10 years [1]. In Russia, up to 50 % of patients suffering from prostate cancer are already treated with advanced stages III–IV of the disease, metastatic cancer accounts for up to 18.1 % of patients [3, 4]. It is generally accepted for patients with prostate cancer to undergo hormonal treatment in the form of maximum androgenic blockade, including pharmacological castration. The development of resistance to the therapy leads to the progression of the disease with a fatal outcome. According to literature data, castration-resistant prostate cancer (CRPC) develops within 5 years of treatment in 10–20 % of patients. Currently, the issue of finding methods to overcome castration resistance remains relevant, since the appearance of bone metastases, the generalization of the process is accompanied by a significant deterioration in the quality of life of patients and an increase in overall mortality rates from prostate cancer [2, 5].

The property of radium chloride [223Ra] to competitively bind to bone hydroxyapatites makes it possible to use it as an osteotropic radiopharmaceutical therapy (RPT) in the presence of metastatic foci in skeletal bones associated with increased bone mineralization [6]. Radium chloride [223Ra] is an approved drug for the treatment of CRPC with direct effects on foci in metastatic bone lesions. Radium-223 is recognized as the drug of choice in patients with CRPC in the presence of bone metastases of the 1st and subsequent lines of therapy according to the recommendations of the European Association of Urologists (high degree of recommendation) [6, 7] and the National Cancer Control Network (1st level of evidence) in 2020. Since radium chloride therapy [223Ra] the presence of visceral metastases is a contraindication to its use, it should be used as early as possible before their appearance. When radium chloride [223Ra] is prescribed for the diagnosis of bone metastases, the results of osteoscintigraphy are of fundamental importance, which does not require the use of additional research methods such as CT or MRI [6, 8].

The purpose of the study was to evaluate the clinical safety and efficacy of radium-223 in patients with bone metastases of castration-resistant prostate cancer.

MATERIALS AND METHODS

The study included 15 patients who received therapy with the drug "Xofigo" radium chloride [223Ra] at the National Medical Research Centre for Oncology. The average age of the patients was 67.2 years (ranged from 58–81 years). The objective status of the majority of patients on the ECOG scale corresponded to 1 (73.3 %) [9]. Patients were assessed for pain intensity before treatment and before each course of radiotherapy using a visual analog pain scale (VAS) [6]. VAS is a straight-line segment 10 cm long. Its beginning corresponds to the absence of pain – "there is no pain", and the end point reflects excruciating unbearable pain – "unbearable pain". The line can be either horizontal or vertical. The patient was asked to make a mark on it corresponding to the intensity of the pain he was experiencing at the moment. The distance between the beginning of the segment ("there is no pain") and the mark made is measured in centimeters and rounded to the whole. Each centimeter on the line corresponds to 1 point. At a mark of up to 2 cm, the pain is classified as mild, from 2 to 4 cm – moderate, from 4 to 6 cm – severe, from 6 to 8 cm – the strongest and up to 10 cm – unbearable. At the time of initiation of therapy, pain syndrome of varying severity was noted in 12 patients (80 %). Radium-223 was received as 1st-line therapy by 4 patients (26.7 %), 2nd-line – 7 people (46.6 %), 3rd-line – 4 patients (26.7 %). All patients received a full course of radiotherapy – monthly intravenous injections of radiopharmaceutical radium chloride [223Ra] for 6 months in the required volume [9]. In total, 90 patients underwent intravenous radiotherapy with radium chloride [223Ra].

Radium chloride solution [223Ra] is a radium solution in ionic form with an activity of 1100 kBq/ml. The specific activity of radium-223 is 1.9 MBq/ng.

The half-life of radium is 223 11.4 days. At the stages of the decay of radium-223 to stable lead, alpha, beta and gamma particles are emitted with an alpha radiation energy value of 95.3 % (energy range 5.0–7.5 MeV), 3.6 % beta radiation (energy range 0.45–0.49 MeV) and 1.1 % gamma radiation (energy range 0.01–1.27 MeV) [10] Being a competitor of calcium, radium-223 selectively affects bone metastases in prostate cancer, forming a complex compound with the bone mineral hydroxyapatite. The therapeutic effect is because of alpha particles, which have a cytotoxic effect on tumor cells and microenvironments (osteoclasts, osteoblasts). The high energy of radium chloride alpha particles (80 keV/μm) and the low range of action – less than 100 μm (less than 10 cell diameters) make treatment safe with minimal damage to healthy tissues [10, 11].

Due to its good tolerability and minimal side effects, the treatment of bone metastases with radium isotope does not require special preparations. The main amount is excreted through the intestines and about 5 % of the drug is excreted by the kidneys. For these reasons, on the day of administration, we recommended using products that do not have an irritating effect on the intestinal mucosa and immediately before administration, we recommended drinking about 1 liter of water to reduce the load on the urinary system. And, a few days before the introduction of the isotope, it was recommended to stop taking drugs containing calcium or vitamin D because of the possibility of its interaction with calcium and phosphates [10, 12].

The method of therapy: a full course of radium chloride treatment [223Ra], consisting of 6 injections of the isotope with an interval of 28 days, is designed for six months. Before each course of treatment, we monitored blood counts [10, 13]. The drug was administered intravenously slowly, at the rate of 55 kBq/ kg, through a peripheral or central venous catheter.

We calculated the required dose of activity using the formula: the patient's body weight (kg) × 55 (kBq/kg) = activity (kBq), then the required volume of RPT was determined by the formula: activity (kBq)/ (1100 kBq/ml × radioactive decay coefficient) = volume of the drug (ml). The activity in the vial at the date of administration was calculated using the formula: 6600 kBq × decay factor = activity in the vial on the day of administration (kBq), then the activity in the unopened vial was measured and the required volume of the drug was collected into a syringe. The activity in the syringe was measured and the drug was administered intravenously slowly. After administration, the dose rate of photon radiation was determined at 1.0 meters from the patient's body with the injected RPT activity at the exit from the unit, which should not exceed 3 mSv/h (NRB-99). The measured doses of photon radiation in all patients were within the acceptable standard parameters, on average 0.83 mSv/h.

After intravenous radiotherapy of radium chloride [223Ra], the patient was provided with the necessary protocols and medical documents with recommendations on the peculiarities of behavior, considering radiation safety standards.

STUDY RESULTS

A full course of treatment (6 injections of radium-223) was performed in 15 patients. Radium-223 showed low levels of toxicity, so hematological reactions (anemia, thrombocytopenia) were not observed in any patient. The level of alkaline phosphatase was within the normal range before and during treatment. In 6 patients (40 %), an increase in PSA levels by more than 100 % was noted during treatment, which, according to the literature, is not a reliable indicator of progression and does not require a change in the line of therapy [10]. One patient (6.6 %) had grade 2 intestinal toxicity after the 3rd administration, which was medically stopped and did not recur. Of the 12 patients with pain syndrome, 8 (66.6 %) had a decrease after 3–4 intravenous radiotherapy sessions with radium chloride [223Ra]. So, before the start of radiotherapy, 2 patients (16.6 %) noted pain by 8 on the scale, 4 people (33.3 %) gave 7 points, 3 patients (25 %) gave 6 points, 2 (16.6 %) – 5 points and 1 (8.3 %) – 4 points. After completing 6 courses, all patients assessed a decrease in pain intensity by almost two times (Fig. 1).

In patients who received a full course of treatment, the following results were obtained during a control examination after 3 months: stabilization of the process in 8 people (53.3 %), improvement in 4 people (26.6 %) in the form of a decrease in metabolic activity and a decrease in the number of metastatic foci, and only 3 patients (20 %) revealed the progression of the disease in the form of the appearance of new foci.

A clinical example

Patient R., born in 1962, presented with castration-resistant prostate cancer sT2cN1M0, st.IV, after hormonal and radiation therapy, progression (bone metastases), bisphosphonate therapy and 6 courses of systemic radionuclide therapy (Ra 223), cl. gr. 2.

From the anamnesis: during a routine examination, an increase in PSA to 75 ng/ml was noted in June 2019. Prostate biopsy of G. A. No. 7243–7254 moderately differentiated adenocarcinoma, Gleason index 7 (4 + 3) was concluded on 06/20/2019. In magnetic resonance computed tomography from 07/04/2019: lesion of both lobes of the prostate gland without the tumor leaving the capsule, internal iliac lymph nodes on the right side up to 3 cm. Osteoscintigraphy dated 07/15/2019 showed no scintigraphic signs of osteodestructive changes in the bones of the skeleton. Hormonal therapy in the amount of maximum androgenic blockade for 12 months was administered. PSA on 07/12/20 was 0.230 ng/ml. From 08/10/2020 to 09/04/2020, the course of conformal remote radiation therapy to a total focal dose (TFD) of 75 Gy per area of the prostate gland and seminal vesicles, up to TFD 50 Gy per pelvic area. MRI from 04/22/2021 showed MR-signs of hyperplasia of the prostate gland transitional zone. The presence of index foci was not revealed. The focus in S1 of the sacrum (possibly mts) requires dynamic

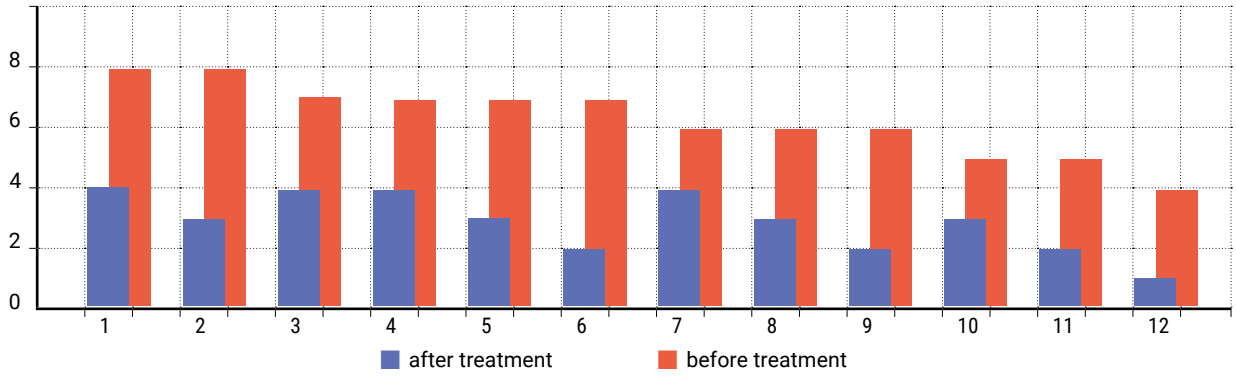

Fig. 1. Results of pain intensity assessment before and after 6 courses of intravenous radiotherapy with radium chloride [223Ra]

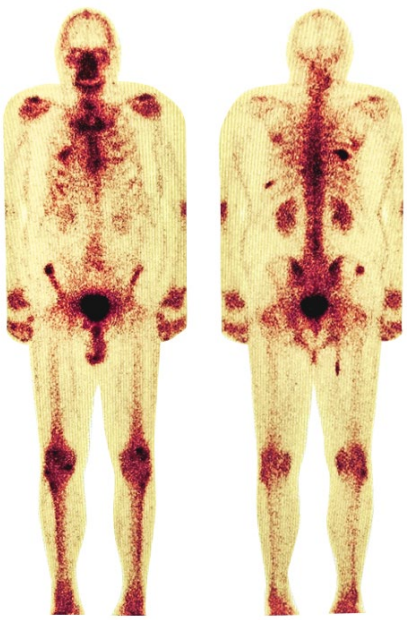

Fig. 2. Bone scintigraphy before the treatment

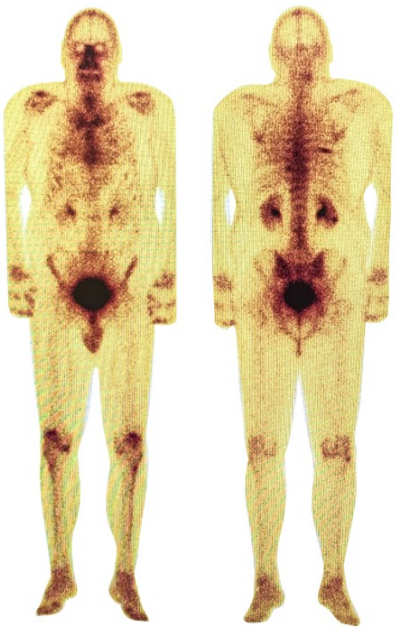

Fig. 3. Bone scintigraphy after the treatment

control. Osteoscintigraphy (05/07/2021): there is a pronounced uneven distribution of radiopharmaceutical (RPT) with signs of focal lesion: 7 ribs on the right – 45 %, 9 ribs on the left – 55 %, iliac root 70 %. Hormonal therapy and bisphosphonates were prescribed. SCT (06/02/2022) showed lung tissue without foci. The intrathoracic lymph nodes were not enlarged. There is no data for visceral metastases. There is no ascites. Retroperitoneal lymph nodes are not enlarged. Metastatic lesion of the 7th rib on the right. Osteoscintigraphy (06/07/2022) revealed signs of local osteodestructive changes in the projection of 7 ribs on the right – 48 %, 9 ribs on the left – 35 %, right iliac bone – 64 % (Fig. 2.). There was a complaint of pain in the pelvic bones. From 07/28/2022 to 12/13/2022, at the National Medical Research Centre for Oncology, the patient underwent 6 courses of systemic radionuclide therapy sessions with radium chloride [223Ra]. The patient tolerated treatment adequately, no toxic reactions from the treatment were observed. According to laboratory studies, there was an increase in PSA throughout the course.

Total PSA on 07/25/2022 was 2.07 ng/ml; on 08/23/2022–3.65 ng/ml; on 09/19/2022–6.55 ng/ml; on 10/14/2022–8.03 ng/ml; on 11/11/2022–8.5 ng/ml; on 12/9/2022–9.54 ng/ml. After the third administration, there was a significant decrease in the severity of the pain syndrome, after the sixth administration, only minor discomfort was noted. Osteoscintigraphy dated 01/26/2023 showed scintigraphic signs of local osteodestructive changes in the bones of the skeleton, in projection of the 7th rib on the right (18 %), and the right ilium (16 %) (Fig. 3).

As we can clearly see there is a pronounced positive shift.

CONCLUSION

Even though it is too early to talk about statistically significant conclusions, a number of positive aspects related to radium chloride 223Ra therapy can already be noted. First, a decrease in the severity of pain syndrome and, as a result, an improvement in the quality of life in patients with bone metastases of castration-resistant prostate cancer. A low degree of severity of adverse and toxic reactions was noted, which is important, since most patients are elderly people with severe concomitant pathology. The results obtained using objective research methods are comparable with the data of domestic and foreign authors and indicate the prospects of this therapeutic technique.

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