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Review Article

Prospects for the Clinical Use of Radionuclide Therapy for Castrate-resistant Metastatic Prostate Cancer with ^{177}Lu-PSMA

Roytberg GE[1], Plotkin M[2] and Sharkhun OO[1]*

[1]*Pirogov Russian National Research Medical University, Moscow, Russia*

[2]*The Vivantes Institute for Nuclear Medicine, Berlin, Germany*

***Corresponding Author:** Roytberg GE, Pirogov Russian National Research Medical University, Moscow, Russia.

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Abstract

Despite the improvement of diagnostic methods and the introduction of prostate-specific antigen monitoring, the incidence of advanced forms of prostate cancer in Russia remains high. Long-term hormonal therapy often leads to tumor adaptation and further progression of the disease, the development of castrate-resistant prostate cancer, the complications of which significantly worsen the quality of life and adversely affect overall survival rates. Over the past 3 years along with the introduction into clinical practice of numerous drugs for the treatment of such forms of the disease, new types of palliative peptide receptor radionuclide therapy have been developed in particular, using the isotopes Lutetium-177, Radium-223, Actinium-225 etc. Currently therapy with ^{177}Lu -PSMA is experimental in nature, as the drug has not yet been approved for clinical use by either European or American drug control agencies. However, the results of studies published to date are encouraging for the future clinical applications of ^{177}Lu-PSMA therapy. The results of prospective studies conducted in the last 2-3 years will be crucial for the future of this method.

Keywords: Prostate; Cancer; Radionuclide; Lutetium

Introduction

In the structure of the incidence of malignant neoplasms of the male population of Russia, prostate cancer ranks second after lung tumors. Despite the improvement of diagnostic methods and the introduction of prostate-specific antigen (PSA) monitoring, the incidence of advanced forms of prostate cancer in Russia remains high. As of 2019 metastatic stage IV prostate cancer was diagnosed in 18.9% of patients at the time of diagnosis.

For the treatment of metastatic prostate cancer, a combination of radiation and drug therapy is most often used. Hormone therapy is carried out during the entire period of the patient's illness. As a result of prolonged suppression of testosterone, the tumor adapts to this condition and further progression of the disease occurs. Castrate-resistant prostate cancer (CRPC) is characterized by an increase in PSA levels and/or signs of radiological progression against the background of ongoing hormone therapy. The features of the CRPC are the presence of bone metastases in the dominant number of patients (up to 90%), often causing a number of complications (pain, pathological fractures, spinal cord compression, decreased mobility), leading to a deterioration in the quality of life [1]. In addition, the development of bone metastases negatively affects overall survival rates. Prostate cancer metastases to visceral organs are diagnosed in approximately 10% of patients with CRPC [2].

Over the past 3 years numerous drugs have been approved and put into clinical practice for the treatment of progressive CRPC. At the same time there are metastatic and non-metastatic CRPC, for which there are different treatment regimens. In parallel with the development of drug therapy, new types of palliative radionuclide therapy were developed – therapy of bone metastases

with Radium-223 (^{223}Ra), therapy with the isotope Lutetium-177 (^{177}Lu) – prostate-specific membrane antigen (PSMA), as well as PSMA therapy using the isotope Actinium-225 (^{225}Ac). This review is devoted to the prospects for the use of ^{177}Lu-PSMA in metastatic CRPC.

Accumulated experience in therapy with ^{177}Lu-PSMA (a brief review of the literature)

One of the molecular markers of prostate cancer is PSMA, which is a type II transmembrane protein with glutamate-carboxypeptidase activity, fixed in the cell membrane of prostate epithelial cells [3]. At the same time, the chemical properties of the PSMA molecule made it possible to label it as a therapeutic isotope ^{177}Lu (beta and gamma emitter) and a positron emitter Galium-68 (^{68}Ga), which provided the possibility of theranostics using positron emission tomography (PET/CT), targeted peptide receptor radionuclide therapy (PRRT) and scintigraphic control. The high expression of the PSMA in malignant prostate tumors and its activation in metastatic and hormone-refractory carcinomas allowed the development of new radiopharmaceuticals (RPh) for effective targeted PRRT. At the same time, the low level of PSMA expression in healthy tissue minimizes the radiation load on healthy tissues.

Therapy with ^{177}Lu-PSMA was developed in 2010 at the Heidelberg Clinic (Germany), where ^{177}Lu-PSMA-617 was synthesized for the first time [4]. The first reports on the clinical application of the method were published in 2015 [5]. The first bicentric experimental study showed a convincing biochemical response (a decrease in PSA levels by more than 50%) in 5 out of 10 patients, while no serious side effects were observed [6]. Early dosimetric data published in January 2016 showed that the radiation load on critical organs (kidneys, salivary glands) is moderate, which indicated an acceptable level of RPh radiotoxicity [7].

The subsequent the German Multicenter retrospective Study involving 145 patients involved 13 university clinics in Germany [8]. In total, 248 cycles of therapy with ^{177}Lu-PSMA-617 (a dose of 2-8 GBq per cycle) were carried out within the framework of this study. In total grade III - IV hematotoxicity was observed in 18 of 145 patients (12.4%): severe leukopenia in 1 patient (0.7%), anemia in 11 patients (7.6%), thrombocytopenia in 2 patients (1.4%) and a combination of these blood changes in 4 patients (2.8%). Dry mouth was observed in 8% of patients (5.5%). The evaluation of the effectiveness of therapy was based on the analysis of the further course of cancer in 99 patients (the average follow-up period was 16 weeks): the biochemical response after the completion of 4 cycles of therapy was 45.5% (44 patients), and the PSA response was observed in 40% of patients after the first cycle of therapy.

The preliminary publication of the results of the randomized phase II «TheraP» trial showed very encouraging results of PRRT with ^{177}Lu-PSMA-617 [9]. This study evaluates the effectiveness of ^{177}Lu-PSMA-617 in the case of disease progression after docetaxel in comparison with the drug cabazitaxel in metastatic CRPC. Observation of patients in both groups for 13 months showed that in the group of patients who received ^{177}Lu-PSMA-617, the PSA-PFS index (survival without PSA increase) was significantly higher compared to the group who received kabacitaxel (HR 0.69). In addition, significantly better biochemical control was observed in the group with ^{177}Lu-PSMA-617: a decrease in PSA levels by 50-66% versus 37% in the group of patients who received cabazitaxel. At the same time, a lower level of toxicity was observed in the group of patients who received ^{177}Lu-PSMA-617.

In addition to ^{177}Lu-PSMA-617 another RPh with similar radiopharmaceutical properties ^{177}Lu-PSMA-I&T (imaging and therapy) is successfully used for the treatment of prostate cancer [10]. Both PSMA-617 and PSMA-I&T can be labeled with ^{68}Ga or Fluoro-18 (^{18}F) positron emitters which makes it possible to use them within the framework of theranostic algorithms.

Assessment of the prospects for the development of therapy with ^{177}Lu-PSMA in the next 5 years taking into account current clinical studies

Currently therapy with ^{177}Lu-PSMA is experimental in nature, since the drug has not yet been approved for clinical use by either the European or American pharmaceutical control agencies (EMA, FDA). Nevertheless, the results of the studies published to date inspire optimism about the future possibilities of clinical application of therapy with ^{177}Lu-PSMA. The results of prospective studies conducted in the last 2-3 years will be crucial for the future of this method.

Vision research

To date the most important study is an international prospective randomized phase III study on the use of ^{177}Lu-PSMA-617 in the progressive, metastatic, castrate-resistant stage of prostate cancer, conducted by Novartis Concern [11]. Preliminary results of the study were published at the ASCO Congress in June 2021. The study involved 831 patients. The patients were selected from a total group of 1,179 patients who underwent screening. Before being included in the study, patients were previously treated with systemic therapy with one of the drugs from the taxane group (docetaxel or cabazitaxel) and one of the new generation antiandrogenic drugs (enzalutamide or abiraterone). The course of therapy consisted of 4-6 cycles with an interval of 6 weeks, a dose of 7.4 GBq ^{177}Lu-PSMA-617 per cycle. Randomization was carried out according to the 2:1 scheme. At the same time 551 patients received ^{177}Lu-PSMA-617 and 280 patients received supportive therapy ("best supportive care" without chemotherapy, without ^{223}Ra). The main endpoint of the study was the indicator "overall survival" (OS). The study showed a statistically significant difference between the groups: the overall survival in the group of patients who received ^{177}Lu-PSMA-617 was 15.3 months, and in the group of patients who received maintenance therapy, 11.3 months. The difference between the groups of 4 months was statistically significant (HR = 0.62; $p < 0.001$). The assessment of the indicator "progression–free survival" (PFS) also showed a statistically significant difference of 5.3 months (HR = 0.40; $p < 0.001$). Since the patients of the comparison group were treated not with one of the approved drugs, but with the "best supportive therapy", the results of the study favorable for ^{177}Lu-PSMA cannot prove its superiority over other drugs approved for clinical use for systemic therapy, so therapy with ^{177}Lu-PSMA-617 (preliminary designation of the Novartis company's commercial product Vipivotide tetraxetan®) in the case of clinical admission expected at the end of 2022 is likely to remain in the last line of the treatment algorithm for CRPC.

The TheraP study is a randomized phase II trial in the progressive metastatic castration-resistant stage of prostate cancer, which compares ^{177}Lu-PSMA with cabazitaxel in patients who have received docetaxel in the past. It is planned to include 200 patients who should be in a physical condition that allows carbazitaxel therapy. After 1:1 randomization either treatment with 10 cycles of carbazitaxel or therapy with a maximum of 6 cycles of ^{177}Lu-PSMA-617 (8.5 GBq/cycle) is performed. The main endpoints are the biochemical response (reduction of PSA by more than 50%) and progression-free survival (PFS). Preliminary (very encouraging) results were published at the ASCO Congress in 2020 [9]. It was found that the PSA response rate was 66% in the group of patients who received ^{177}Lu-PSMA-617 and only 37% in the group who received carbazitaxel. In the group with ^{177}Lu-PSMA-617, the number of side effects was significantly lower. If this trend is confirmed in the final evaluation of the study, ^{177}Lu-PSMA-617 will be able to move in the algorithm of therapy for metastatic CRPC and be offered before the appointment of carbazitaxel.

The PRINCE study (PSMA-Lutetium Radionuclide Therapy and Immunotherapy iN Prostate CancEr)

The phase I study tests a combination of pembrolizumab every 3 weeks with 4 cycles of ^{177}Lu-PSMA-617 (8.5 GBq every 6 weeks) in the progressive metastatic castration-resistant stage of prostate cancer after previous therapy with enzalutamide and abiraterone. The main endpoints are the biochemical response of PSA and toxicity. The purpose of this combination therapy is to induce an immunological reaction using radionuclide treatment of the tumor, which should enhance the effect of checkpoint inhibitor pembrolizumab. This may turn out to be a very effective strategy, since prostate cancer is considered immunologically "cold" and therefore insufficiently available for immunotherapy. If the study shows a positive result combination therapy "pembrolizumab + ^{177}Lu-PSMA-617" may be recommended before chemotherapy with docetaxel after progress with enzalutamide or arbiraterone.

The LuPARP trial is a randomized phase I trial in the progressive metastatic CRPC, testing a combination of the PARP inhibitor olaparib with 177Lu-PSMA-617 (7.4 GBq every 6 weeks, 4 cycles) [12].

Now one of the promising direction of PRRT is the tandem therapy of CRPC with ^{177}Lu-PSMA-617 and ^{225}Ac-PSMA-617. The effectiveness of such therapy is enhanced by alpha radiation which causes a double break in the DNA chain. However now there is not enough data on the safety of the treatment [13,14].

Review of indications for therapy with ^{177}Lu-PSMA, taking into account international recommendations

German interdisciplinary S3 level Guide for early detection, diagnosis and therapy of various stages of prostate cancer (Version 5.1, May 2019) claims that patients with castrate-

resistant progressive disease in good general condition can be offered experimental therapy with ^{177}Lu-PSMA based on the recommendation of an interdisciplinary oncological consultation after all recommended treatment options have been exhausted [15]. Patients with castrate-resistant progressive disease in good general condition after chemotherapy with docetaxel should be offered one of the following treatment options, if necessary in combination with symptomatic and supportive therapy (in alphabetical order): abiraterone in combination with prednisolone, cabazitaxel, enzalutamide, radionuclide therapy with ^{223}Ra for bone metastases.

The recommendations of the European Association of Nuclear Medicine (EANM) on the clinical application of therapy with ^{177}Lu-PSMA (August 2019) indicate that the decision to prescribe alternative treatment to a patient (^{177}Lu-PSMA) as a rule goes beyond the competence of a nuclear medicine doctor and should be taken at an interdisciplinary oncological consultation with the participation of specialists in urooncology, nuclear medicine and radiation oncology, taking into account the possibility of standard methods: antiandrogenic deprivation (LHRH agonists/antagonists, abiraterone, enzalutamide), chemotherapy or PRRT with ^{223}Ra [16].

According to the joint Recommendations of the European Association of Urologists (EAU), the European Association of Nuclear Medicine (EANM), the European Society for Radiotherapy and Oncology (ESTRO), the European Society of Urogenital Radiology (ESUR) and the International Society of Geriatric Oncology (SIOG) PSMA-based RFPs labeled with beta-emitting (^{177}Lu or ^{90}Y) or alpha-emitting (^{225}Ac) isotopes can be used for the treatment of metastatic prostate cancer [17].

Currently all these methods should be considered as experimental. It should be emphasized that the Joint Recommendations of the American Urological Association (AUA), the American Society of Radio Oncologists (ASTRO) and the Society of Urooncology (SUO) do not mention treatment using the ^{177}Lu-PSMA [18].

Thus taking into account the principles of individualized medicine, recommendations for the rational selection of patients for PRRT with ^{177}Lu-PSMA include the following indications: 1) the presence of castrate-resistant metastatic prostate cancer; 2) progression after the last systemic therapy; 3) previous therapy with the following drugs: docetaxel, abiraterone and/or enzalutamide, cabazitaxel, ^{223}Ra (XOFIGO), olapirib (in the case of a positive BRCA-1 or BRCA-2 mutation). If there has been progress after therapy with abiraterone in the past, conducting therapy with enzalutamide up to ^{177}Lu-PSMA is according to most oncologists optional and not even rational since there is cross-resistance between these drugs. However there is no general opinion on this issue, the results of the phase II study indicate the effectiveness of enzalutamide even in cases where progress was observed after abiraterone [19]. Therapy with cabazitaxel can be abandoned if severe toxic reactions have been observed during therapy with docetaxel (for example, grade III-IV neutropenia). Therapy with ^{223}Ra should be abandoned if the patient in addition to bone metastases has organ metastases (for example, in the liver or lungs), as well as if there are no pain sensations. Finally, the indication for therapy with ^{177}Lu-PSMA may be situations when, during PET/CT with ^{18}F-PSMA (or with ^{68}Ga-PSMA) reveals increased expression of PSMA in all metastases. However, this point is not sufficiently covered in the published recommendations. The presence of both PSMA-negative and PSMA-positive metastases in one patient is often associated with another metachronous cancer which may be more aggressive than prostate cancer (for example, small cell lung cancer and non-Hodgkin's lymphoma). Contraindications for therapy are unsatisfactory general condition of the patient (ECOG > 2, Karnovsky index < 60%); pronounced myelosuppression (leukocytes < 2.5 x 10^9/l, platelets < 75 x 10^9/l); kidney failure (CKD-EPI < 30 ml/min/1.73m^2); pronounced bilateral obstruction of the urinary tract; severe liver failure (increased liver enzymes > 5 values of the upper limit of the norm); the presence of another malignant tumor requiring myelosuppressive therapy; the presence of prostate metastases requiring local therapy, for example, surgical stabilization of the spine or radiation therapy; fecal incontinence.

Conclusion

Currently, therapy with ^{177}Lu-PSMA is experimental in nature, since the drug has not yet been approved for clinical use by either European or American pharmaceutical control agencies. Nevertheless the results of the studies published to date inspire optimism about the future possibilities of clinical application

of PRRT with ^{177}Lu-PSMA. The results of prospective studies conducted in the last 2-3 years will be crucial for the future of this method.

Bibliography

1. Freedland SJ., *et al*. "Treatment patterns in patients with prostate cancer and bone metastasis among US community-based urology group practices". *Urology* 80.2 (2012): 293-298.

2. Tait C., *et al*. "Quantification of skeletal metastases in castrate-resistant prostate cancer predicts progression-free and overall survival". *BJU International* 114.6b (2014): E70-E73.

3. Israeli RS., *et al*. "Expression of the prostate-specific membrane antigen". *Cancer Research* 54.7 (1994): 1807-1811.

4. Benešová M. "Preclinical Evaluation of a Tailor-Made DOTA-Conjugated PSMA Inhibitor with Optimized Linker Moiety for Imaging and Endoradiotherapy of Prostate Cancer". *Journal of Nuclear Medicine* 56 (2015): 914-920.

5. Kratochwil C., *et al*. "177Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer". *European Journal of Nuclear Medicine and Molecular Imaging* 42 (2015): 987-988.

6. Ahmadzadehfar H., *et al*. "Early side effects and first results of radioligand therapy with (177)Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study". *EJNMMI Research* 5 (2015): 1140259-014-2978-1.

7. Delker A., *et al*. "Dosimetry for (177)Lu-DKFZPSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer". *European Journal of Nuclear Medicine and Molecular Imaging* 4 (2016): 42-51.

8. Rahbar K., *et al*. "German Multicenter Study Investigating 177Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients". *Journal of Nuclear Medicine* 58 (2017): 85-90.

9. Hofman MS., *et al*. "TheraP: a randomized phase 2 trial of ^{177} Lu-PSMA-617 theranostic treatment vs cabazitaxel in progressive metastatic castration-resistant prostate cancer (Clinical Trial Protocol ANZUP 1603)". *BJU International* 124 (2019): 5-13.

10. Weineisen M., *et al*. "68Ga- and 177Lu-Labeled PSMA I&T: Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies". *Journal of Nuclear Medicine* 56.8 (2015): 1169-1176.

11. Morris MJ., *et al*. "Phase III study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION)". ASCO (2021).

12. de Bono J., *et al*. "Olaparib for Metastatic Castration-Resistant Prostate Cancer". *The New England Journal of Medicine* 382.22 (2020): 2091-2102.

13. Kratochwil C., *et al*. " (^{225})Ac-PSMA-617 for Therapy of Prostate Cancer". *Seminars in Nuclear Medicine* 50.2 (2019): 133-140.

14. Khreish F., *et al*. "^{225}Ac-PSMA-617/^{177}Lu-PSMA-617 tandem therapy of metastatic castration-resistant prostate cancer: pilot experience". *European Journal of Nuclear Medicine and Molecular Imaging* 47.3 (2020): 721-728.

15. S3-Leitlinie Prostatakarzinom (leitlinienprogramm-onkologie.de) Version 6.0 | Mai (2021).

16. Kratochwil C., *et al*. "EANM procedure guidelines for radionuclide therapy with ^{177}Lu-labelled PSMA-ligands (^{177}Lu-PSMA-RLT)". *European Journal of Nuclear Medicine and Molecular Imaging* 46.12 (2019): 2536-2544.

17. EAU-EANM-ESTRO-ESUR-SIOG-Guidelines-on-Prostate-Cancer-2020 v4.pdf (uroweb.org)

18. Lowrance WT., *et al*. "Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline PART II". *Journal of Urology* 205 (2021): 22-29.

19. Khalaf DJ., *et al*. "Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial". *Lancet Oncology* 20.12 (2019): 1730-1739.