The importance of ^{177}Lu-PSMA in the treatment of castration-resistant prostate cancer

Význam ^{177}Lu-PSMA v léčbě kastračně-rezistentního karcinomu prostaty

Benderli Cihan Y.

Department of Radiation Oncology, Kayseri City Hospital, Kayseri, Turkey

The importance of ^{177}Lu-PSMA in the treatment of castration-resistant prostate cancer

There are some treatment options for metastatic and castration-resistant prostate cancer, and there is no single standardized treatment protocol today. In this group of patients, the chance of success in the treatment increased with the introduction of abiraterone, enzyalutamide/apalutamide, taxane chemotherapy (docetaxel, cabazitaxel) and immunotherapy (ipilimumab, sunitinib, cabozantinib, or xofigo). Although there was an increase in both disease-free and overall survival, resistance to these drugs developed within 1-2 years. Therefore, the search for new treatments has continued [1–3]. In recent years, ^{223}radium and ^{177}lutetium (^{177}Lu) prostate-specific membrane antigen (PSMA) have been shown to provide effective treatment of metastatic and castration-resistant prostate cancer with the application of radiopharmaceuticals containing ionizing radiation. The use of ^{177}Lu-PSMA treatment, which is a radionuclide treatment, is increasing day by day [4–6].

PSMA is a transmembrane glycoprotein with enzyme functions in the cell. It takes part in cell migration, cell survival and proliferation. Although healthy prostate epithelial cells have low expression, prostate cancer can be found in rates up to 1,000-times. This has made the PSMA molecule a target for radiopharmaceuticals in the diagnosis and treatment of prostate cancer. First of all, radiopharmaceuticals using antibody-mediated carrier molecules have been developed and used limitedly for imaging and treatment purposes. Later, small molecular weight molecules developed from inhibitors of the enzyme component of the molecule were marked with radionuclides such as ^{68}Ga, ^{18}F, ^{44}Sc, ^{177}Lu, 225Ac, ^{211}At and many treatment and imaging radiopharmaceuticals developed in this way quickly entered clinical use and became widespread. ^{177}Lu was the most preferred among these. It is a radionuclide with a half-life of 6.64 days and emits beta and gamma rays. While beta rays from ^{177}Lu decay are used to kill tumor cells, gamma rays are used for patient imaging and dosimetry studies [1–3,7–8].

It is administered intravenously to the patient in the form of ^{177}Lu-PSMA-617 or ^{177}Lu-PSMA I&T radiopharmaceutical. This radiopharmaceutical is collected intensely in the structure and the tumor is treated through the beta rays emitted. Standard activity after the application is 3–8 GBq. This treatment is repeated 4- or 6-times with an average interval of 2 months. With the internal dosimetry calculations to be made before or after the treatment, it is possible to select patients with higher doses or those who may develop toxicity in fixed dose protocols, albeit few [3,4,8,9]. Due to the distribution of radiation within the body; critical organs sensitive to radiation such as kidney, bone marrow and liver take the same dose. These critical organ doses are one of the most important factors affecting the number of treatments. To monitor these side effects, complete blood count, serum creatinine level, alanine aminotransferase, aspartate aminotransferase levels are measured before and after the application of ^{177}Lu-PSMA treatment. Treatment response evaluation is basically performed by monitoring serum alkaline phosphatase, serum prostate specific antigen (PSA) level and PSMA positron emission tomographic (PET) imaging. Although it is generally accepted that PSA level and PSMA PET should be performed after at least two cycles of treatment, there is no consensus about when to evaluate the treatment [1–4].

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.

The Editorial Board declares that the manuscript met the ICMJE recommendation for biomedical papers.

Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.

Yasemin Benderli Cihan, MD
Department of Radiation Oncology,
Kayseri City Hospital
Şeker District, Muhsinyazıcıoğlu
Boulevard, No:77
38080 Kocasinan/Kayseri
Turkey
e-mail: cihany@erciyes.edu.tr

Submitted/Obdrženo: 18. 7. 2020
Accepted/Přijato: 15. 9. 2020

doi: 10.48095/ccko2021151

It has not been approved by the U.S. Food and Drug Administration or the European Medicines Agency for the treatment of ^{177}Lu-PSMA and therefore no formal criteria for patient involvement have been defined. The therapy is currently carried out under retrospective evidence, expert opinion or under local regulations for unproven interventions for patients who have exhausted all treatment options. ^{177}Lu-PSMA treatment is preferred if it is refractory to standard antineoplastic treatments or second-generation antiandrogen treatments or if these treatments cannot be applied and if there is more than 5 metastatic lesions in the ^{68}Ga-PET PSMA imaging. The use of ^{177}Lu-PSMA therapy is based on the last 10 years, and its first use has started in cases where there is no other treatment option [10–13]. With this treatment, biochemical response (more than 50% reduction in PSA) occurred in approximately 43–66% of patients [2–5]. It has been shown to have positive effects on both total survival and disease-free survival, as well as providing severe pain palliation [1,2,4]. In a phase II study in which 30 patients were included, the rate of the decrease in PSA levels by > 50% was found to be 57%. In the same study, the progression-free survival was found to be 7.6 months and the median survival was 13.5 months [10]. In another published study, it was reported that ^{177}Lu-PSMA-617 treatment only reduced PSA, compared to salvage radiotherapy and treatment with abiraterone in lymph node metastatic prostate cancer [6]. In the study conducted by Yadav et al to determine the palliative effect of ^{177}Lu-PSMA treatment in patients with castration-resistant prostate cancer, it was stated that pain and overall quality of life scores were significantly improved with ^{177}Lu-PSMA [7]. In a phase I–II study conducted by Tagawa et al, it was stated that the application of ^{177} Lu-J591 to the fraction in the metastatic castration resistant prostate cancer marked a higher dose administration. Accordingly, it has been reported that overall survival, toxicity, and response to PSA increased at higher doses [8]. In another study, it was stated that hyperfractionated regimens were not superior to fractional application [11].

Meta-analyzes started to be carried out upon the positive reporting of the retrospective study results. Von Eyben et al revealed a meta-analysis of systemic treatment options (such as docetaxel, cabazitaxel, abiraterone and enzalutamide), which are known to prolong survival, and 12 retrospective case series undergoing the treatment with ^{177}Lu-PSMA. In 43% of patients who received ^{177}Lu-PSMA, the maximum PSA reduction after the treatment was ≥ 50%, while the PSA decrease following third line therapy was observed in 21% of patients. It has been reported that it provides better PSA reduction if there are fewer side effects, and it is also the first and only study showing the contribution of ^{177}Lu-PSMA to survival [5].

In another systemic examination and meta-analysis, it has been reported that ^{177}Lu-PSMA is effective and reliable in metastatic castration resistant prostate cancer [7]. In the meta-analysis performed by Kim et al, the first cycle of ^{177}Lu-PSMA-617 radioligand therapy was reported. He stated that after two cycles, two thirds of the patients had a PSA decrease and more than 50% of the PSA reduction was expected. He noted that prolonged survival was observed due to a decrease in PSA [12].

When the literature is examined, published studies are retrospective. There are currently no prospective randomized studies published. Nowadays, a phase III study (VISION Trial) targeting 750 case participation is ongoing. As a result of this study, treatment responses and side effects of ^{177}Lu-PSMA treatment (in which patient groups, when, and at what dosages) will become clearer [13].

As a result, ^{177}Lu-PSMA is one of the new and promising teranostic treatment options in the treatment of metastatic castration resistant prostate cancer. Despite data on its application, efficacy and clinical reliability covering nearly 10 years, there are no phase III studies that have been completed yet. For this reason, it is partly accepted as a treatment method for research purposes and it is applied in accordance with national legislation, taking into account ethical rules. Prospective randomized studies are strongly needed to verify the effectiveness of ^{177}Lu-PSMA with randomized control studies, to investigate its contribution to survival, earlier administration and combinations with other treatments.

References

1. Kulkarni HR, Singh A, Schuchardt C et al. PSMA-Based radioligand therapy for metastatic castration-resistant prostate cancer: the bad berka experience since 2013. J Nucl Med 2016; 57 (Suppl 3): 97S–104S. doi: 10.2967/jnumed.115.170167.
2. Rahbar K, Boegemann M, Yordanova A et al. PSMA targeted radioligandtherapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. Eur J Nucl Med Mol Imaging 2018; 45(1): 12–19. doi: 10.1007/s00259-017-3848-4.
3. Ahmadzadehfar H, Essler M. Predictive factors of response and overall survival in patients with castration-resistant metastatic prostate cancer undergoing 177Lu-PSMA therapy. J Nucl Med 2018; 59(7): 1033–1034. doi: 10.2967/jnumed.118.209270.
4. Rahbar K, Bogeman M, Yordanova A et al. Delayed response after repeated 177Lu-PSMA-617 radioligand therapy in patients with metastatic castration resistant prostate cancer. Eur J Nucl Med Mol Imaging 2018; 45(2): 243–246. doi: 10.1007/s00259-017-3877-z.
5. von Eyben FE, Roviello G, Kiljunen T et al. Third-line treatment and 177Lu-PSMA radioligand therapy of metastatic castration-resistant prostate cancer: a systematic review. Eur J Nucl Med Mol Imaging 2018; 45(3): 496–508. doi: 10.1007/s00259-017-3895-x.
6. von Eyben FE, Kiljunen T, Joensuu T et al. 177Lu-PSMA-617 radioligand therapy for a patient with lymph node metastatic prostate cancer. Oncotarget 2017; 8(39): 66112–66116. doi: 10.18632/oncotarget.19805.
7. Yadav MP, Ballal S, Sahoo RK et al. Radioligand therapy with 177Lu-PSMA for metastatic castration-resistant prostate cancer: a systematic review and meta-analysis. Am J Roentgenol 2019 Aug; 213(2): 275–285. doi: 10.2214/AJR.18.20845.
8. Tagawa ST, Vallabhajosula S, Christos PJ et al. Nanus DMPhase 1/2 study of fractionated dose lutetium-177-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 ((177) Lu-J591) for metastatic castration-resistant prostate cancer. Cancer 2019; 125(15): 2561–2569. doi: 10.1002/cncr.32072.
9. Yadav MP, Ballal S, Tripathi M et al. 177Lu-DKFZ-PSMA-617 therapy in metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. Eur J Nucl Med Mol Imaging 2017; 44(1): 81–91. doi: 10.1007/s00259-016-3481-7.
10. Hofman MS, Violet J, Hicks RJ et al. 177Lu-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol 2018;19(6): 825–833. doi: 10.1016/S1470-2045(18)30198-0.
11. Niaz MJ, Batra JS, Walsh RD et al. Pilot study of hyperfractionated dosing of lutetium-177-labeled anti-prostate-specific membrane antigen monoclonal antibody j591 (177lu-j591) for metastatic castration-resistant prostate cancer. Oncologist 2020; 25(6): 477–e895. doi: 10.1634/theoncologist.2020-0028.
12. Kim YJ, Kim YI. Therapeutic responses and survival effects of 177Lu-PSMA-617 radioligand therapy in metastatic castrate-resistant prostate cancer: a meta-analysis. Clin Nucl Med 2018; 43(10): 728–734. doi: 10.1097/RLU.0000000000002210.
13. Study of 177Lu-PSMA-617 In Metastatic Castrate-Resistant Prostate Cancer (VISION). [online]. Available from: https://clinicaltrials.gov/ct2/show/NCT03511664?term=177lu&rank=9.