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

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

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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, enzalutamide/apalutamide, taxane chemotherapy (docetaxel, cabazitaxel) and immunotherapy (ipilimumab, sunitinib, cabozantinib, or xofogo). 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, $^{225}$Ac, $^{211}$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, serum 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].

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It has not been approved by the U.S. Food and Drug Administration or the European Medicines Agency for the treatment of ¹⁷⁷Lu-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. ¹⁷⁷Lu-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 ¹⁸⁶⁹Ga-PET PSMA imaging. The use of ¹⁷⁷Lu-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 ¹⁷⁷Lu-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 ¹⁷⁷Lu-PSMA treatment in patients with castration-resistant prostate cancer, it was stated that pain and overall quality of life scores were significantly improved in 43% of patients who received ¹⁷⁷Lu-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 ¹⁷⁷Lu-PSMA to survival [5].

In another systematic examination and meta-analysis, it has been reported that ¹⁷⁷Lu-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 ¹⁷⁷Lu-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 randomised studies published. Nowadays, a phase III study (VISION Trial) targeting 750 case patients carried out under retrospective evidence, taking into account ethical rules. Prospective randomized control studies, to investigate its contribution to survival, earlier administration and combinations with other treatments.

References