Perspective on 177Lu-PSMA therapy of metastatic castration-resistant prostate cancer

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Treatment options in patients with metastatic castration-resistant prostate cancer are limited, and consist of chemotherapy with taxanes or hormonal treatment with abiraterone or enzalutamide [1]. These treatments result in a survival benefit of several months.

Prostate cancer cells, and also castration-resistant prostate cancer cells, may overexpress Prostate Specific Membrane Antigen (PSMA). Because of this, compounds that target PSMA were developed for diagnostic imaging and later also for delivering internal radiation to the tumor sites. For diagnostics, 68Ga-labelled PSMA ligands are often used, and for treatment 177Lu-labelled agents can be used. This approach, using the same compound (or a very similar one) for diagnostic imaging and therapy is referred to as “Theranostics”. The only difference between the diagnostic compound and the therapeutic agent is the radionuclide that is used. The principle of theranostics has a history in Nuclear Medicine, dating back to the application of 123I/131I in thyroid disease, and, more recently, somatostatin receptor imaging and therapy with [111In-DTPA]octreotide and [177Lu-DOTA,Tyr3]octreotate (177Lu-octreotate), respectively. Peptide Receptor Radionuclide Therapy (PRRT) with 177Lu-octreotate proved very valuable in patients with metastatic neuroendocrine tumors [2], and a recent randomized controlled trial demonstrated a very significant gain in Progression Free Survival (PFS) for patients treated with PRRT compared to the control patients treated with high-dose somatostatin analogues (PFS not reached vs. 8 months, respectively; Hazard ratio 0.2; expected PFS for the PRRT arm therefore ~40 months) [3]. For this reason, such an approach may also be very promising for prostate cancer patients.

In this issue of the Journal of Nuclear Medicine, Baum et al. report on the toxicity and efficacy of treatment with a 177Lu-PSMA ligand, 177Lu-DOTAGA-(I-y)fk(Sub-KuE), in patients with castrate-resistant prostate cancer [4]. 177Lu-PSMA showed high, specific and rapid uptake in prostate cancer metastases. The long effective half-life in both skeletal and soft tissue metastases, approaching the physical half-life of 177Lu, resulted in a high mean absorbed tumor dose in both bone and lymph node metastases. As for toxicity, only mild and transient xerostomia occurred, due to the radiation dose to the salivary glands. More importantly, no important hematological toxicity occurred. An earlier study on
radioimmunotherapy using the PSMA antibody $^{177}$Lu-DOTA-J591 was limited by myelosuppression in addition to non-hematological toxicity (5). In the patients studied by Baum et al., the serum tumormarker PSA decreased with more than 50% in 62% of patients. With CT a Partial Remission (PR) was found in 20% of patients, and evaluated with $^{68}$Ga-PSMA, PR was observed in 56% of patients. The discrepancy in the evaluation of remission classified as responders by $^{68}$Ga-PSMA PET/CT, but not stand-alone CT, can be explained by the lower sensitivity of stand-alone CT in the assessment of skeletal lesions. An impressive median PFS of 14 months was found.

Other groups, using $^{177}$Lu-DOTAGA-(I-y)fk(Sub-KuE) (also termed “$^{177}$Lu-PSMA I&T”), or other radioabelled PSMA ligands, have also reported very promising results in patients with castrate-resistant prostate cancer, albeit in small patient groups (6-8). Especially the study by Ahmadzadehfar et al. (8), using $^{177}$Lu-DKFZ-617 PSMA, reports similar results to those reported by Baum et al. They analysed retrospectively the early side effects and the response rate in 10 patients. Eight weeks after the therapy, 5 patients (50%) had a PSA decline of more than 50%. No patient experienced any side effect immediately after injection of $^{177}$Lu-PSMA. Hematotoxicity grade 3 or 4 occurred 7 weeks after the administration in one patient.

The data reported by Baum et al. were obtained in patients who were treated under conditions of “compassionate use”. This implies that a control group is lacking. Because of the very encouraging results of $^{177}$Lu-PSMA treatment as reported by Baum et al., it is seems mandatory that this therapy obtains its recognized place in the treatment algorithm of metastatic prostate cancer. This can only be achieved through randomized controlled trials. After all, alternative treatments have been tested that way as well, and authorities and treating physicians will ask for such proof. Also, in many countries reimbursement is restricted to the use of registered pharmaceuticals.

In Nuclear Medicine, it has been customary for decades to use radioactive compounds for diagnosis and therapy that are synthesized locally in house. For instance, PRRT in neuroendocrine tumor patients is performed using several different somatostatin analogues, radiolabeled with different radionuclides. Also, the dosing scheme and dosing interval varies from institution to institution.

In order to get the recognition it deserves, radionuclide therapy, for instance $^{177}$Lu-PSMA therapy, needs to be standardized and tested in randomized trials, like has happened with PRRT with $^{177}$Lu-octreotate in the NETTER-1 trial (3). It implies the involvement of (radio)pharmaceutical companies as manufacturers and sponsors. This is the only way in which radionuclide therapy can establish its role and come to maturity. It may therefore be hoped that we will soon witness the start of randomised controlled trials
with $^{177}$Lu-PSMA ligands in prostate cancer patients. Also, it may be expected that other radionuclide therapies be developed for different oncological patient groups.

References


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