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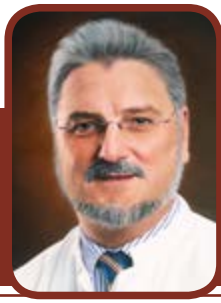

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Navigating the revolution of PSMA radioligand therapy of metastatic prostate cancer: Theranostics experience in over 800 treatments since 2013

177Lu-DOTAGA PSMA I & T: Based on the principles of targeted radionuclide therapy, 177Lu labeled ligands binding specific to PSMA were developed using DOTAGA as chelator (Weineisen M et al. 2015). PSMA radioligand therapy (PRLT) with 177Lu-DOTAGA PSMA ligands was performed in 56 progressive, metastasized, castrate-resistant prostate cancer (mCRPC) patients (Baum et al. 2016). Ga-68 PSMA PET/CT was used for patient selection and follow-up after PRLT. Hematological status, renal function and serum prostate specific antigen (PSA) levels were documented before and after therapy. Dosimetry was performed in 30 patients. 177Lu DOTAGA PSMA small molecule demonstrated very high tumor uptake, rapid blood clearance and fast renal washout resulting in high absorbed tumor doses (median, 3.3 mGy/MBq) as compared to normal organs. All patients tolerated the therapy without any acute adverse effects. Except mild reversible xerostomia in two patients, no long-term side effect was observed. No relevant hematotoxicity or renal impairment occurred. Decrease in PSA was noted in 45/56 (80%) and pain significantly reduced in 33% of patients. In 25 patients, followed up at least 6 months after ≥2 PSMA-RLT cycles, molecular response evaluation (68Ga-PSMA PET/CT) revealed partial remission (PR) in 14, stable disease (SD) in 2 and progressive disease (PD) in 9 patients. Contrast-enhanced CT exhibited PR in 5, SD in 13, and PD in 7 patients. The median progression-free survival was 13.7 months, and the median overall survival was not reached at follow-up of 28 months.

177Lu-PSMA-617: Between April 2013 and June 2018, intention-to-treat analysis was performed in 274 patients (mean age 71 years, mean Gleason score 8) with mCRPC. They received 1 to 11 PRLT cycles (total 824 courses) using 3.5 - 11.7 GBq (mean 6.7 GBq) of Lu-177 labeled PSMA ligand. Previous treatments included surgery, external beam radiation, chemotherapy , androgen deprivation and Ra-223 chloride. The most frequent sites of metastases were bone (n=228 patients), lymph node (209), liver (34) and lungs (36). Ga-68 PSMA PET/CT was used for initial evaluation and therapy response assessment (THERANOSTICS concept). Laboratory parameters included complete blood count, renal and liver function, electrolytes etc. PSA levels were documented before and regularly after therapy.

Any PSA decline was observed in 72 % of all patients, the best response was biochemical complete remission (PSA=0.0 ng/ml). Decrease in PSA by >50% was seen in 53% of cases. Median progression-free survival (according to RECIST 1.1) was 9.8 months. Median overall survival (at 61 months follow-up) was 30.9 months (96 patients deceased). G3-4 hematolo-gical toxicity was observed in <5% of patients and was more frequently associated with previous chemotherapy or Ra-223 treatment. Nephrotoxicity was not observed in any of the 274 patients treated, even if there was only a single functioning kidney present (n=17).

Pain reduced dramatically and the quality of life improved significantly in symptomatic patients (EORTC questionnaire).

In general, the patients tolerated the treatment very well with no severe acute or long-term side effects (observation period 64 months). The most common adverse effect was mild fatigue lasting for a few days after therapy. Radiation

effect on salivary gland function was assessed using dynamic salivary gland scintigraphy before and after PRLT. Using a standardized questionnaire, <5% of patients reported mild dryness of mouth, which was mostly reversible.

First line (de novo) Lu-177 PSMA radioligand therapy was effective in 11 non-castrate metastatic prostate cancer, offering a significant survival benefit. Patients demonstrating a PSA decline of more than 50% after at least two PRLT cycles, lived significantly longer.

Additional treatment with newer antiandrogen agents (Abiraterone or Enzalutamide) in combination with 177Lu PRLT also prolonged survival.

Targeted Alpha radioligand therapy (ART)

The feasibility, toxicity and efficacy of targeted alpha radioligand therapy (ART) in end-stage, metastatic, treatment-resistant prostate cancer, having progressed under Lu-177 PSMA radioligand therapy, were evaluated in a pilot study in 10 patients with Bismuth-213 PSMA-617 (1-2 cycles, 2-4 applications per cycle). Bi-213 (t1/2 46 minutes) was obtained from an Ac-225/ Bi-213 generator (provided by Isotope Technologies Garching (ITM), Munich Germany). The median administered activity of Bi-213 PSMA per cycle was 390 MBq (155 – 623 MBq). All patients tolerated the therapy very well without any acute adverse effects. Decrease in PSA was noted in 43 % of patients. With the administered radioactivities mentioned, no significant acute / subacute toxicity was noted and minor responses could be demonstrated.

Since February 2018, 22 patients have been treated with Actinium-225 PSMA-617 or with a combination of Lu-177 / Ac-225 PSMA (TANDEM-ART). The results are extremely promising and will be presented in more detail.

Conclusions: PSMA Radioligand Therapy with 177Lu-PSMA has been performed since April 2013 in 274 patients (total number of 824 administered treatment cycles). PRLT of mCRPC is feasible, safe (especially no nephrotoxicity as noted without renal protection) and effective with appropriate selection and follow-up of patients by 68Ga-PSMA PET/CT applying the concept of Theranostics (Baum et al. 2015, Kulkarni et al. 2016).

Targeted alpha radioligand therapy using Ac-225 PSMA or TANDEM-ART appears to be extremely promising for Precision Oncology of end-stage metastatic treatment-resistant prostate cancer, progressing after castration, newer hormonal agents, chemotherapy as well as after progression under Lu-177 PRLT.

Randomized clinical trials have now started to confirm the results of this extremely promising new concept of molecular targeted radiotherapy.

Biography

Richard Baum is the Chairman and Clinical Director at the Theranostics Center for Molecular Radiotherapy and Molecular Imaging, Zentralklinik Bad Berka, Germany. He is a renowned Professor of Nuclear Medicine, with several accolades to his credit. He has won numerous awards for his contribution to the field of Nuclear Medicine. He has published over 150 articles in reputed journals and is actively associated with major Nuclear Medicine societies around the world. He was the past president (2013) of the World Association of Radionuclide and Molecular Therapy (WARMTH). His work focusses on Prostate Cancer, Neuroendocrine Tumors, Theranostics and Personalized Medicine.

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