Systemic Radioligand Therapy with ^{177}Lu Labeled Prostate Specific Membrane Antigen Ligand for Imaging and Therapy in Patients with Metastatic Castration Resistant Prostate Cancer

Matthias M. Heck,*,† Margitta Retz,† Calogero D'Alessandria, Isabel Rauscher, Klemens Scheidhauer, Tobias Maurer, Enno Storz, Friederike Janssen, Margret Schottelius, Hans-Jürgen Wester, Jürgen E. Gschwend, Markus Schwaiger, Robert Tauber‡ and Matthias Eiber‡

From the Departments of Urology (MMH, MR, TM, ES, JEG, RT) and Nuclear Medicine (CD, IR, KS, MSchw, ME), Klinikum rechts der Isar (FJ), Technical University of Munich, Munich and Pharmaceutical Radiochemistry, Technical University of Munich (MScho, HJW), Garching, Germany

Abbreviations and Acronyms

CT = computerized tomography

mCRPC = metastatic castration resistant PC

PC = prostate cancer

PCWG2 = Prostate Cancer Clinical Trials Working Group

PET = positron emission tomography

PS = performance status

PSA = prostate specific antigen

PSMA = prostate specific membrane antigen

RECIST = Response Evaluation Criteria In Solid Tumors

RLT = radioligand therapy

Purpose: We report our initial clinical experience with β -emitting ^{177}Lu-PSMA-I&T (^{177}Lu labeled prostate specific membrane antigen ligand for imaging and therapy) for systemic treatment of metastatic castration resistant prostate cancer.

Materials and Methods: Patients with metastatic castration resistant prostate cancer who experienced treatment failure with chemotherapy and novel androgen receptor targeted therapy were treated for 8 weeks with up to 4 cycles of ^{177}Lu-PSMA-I&T. We report safety data, the antitumor response with prostate specific antigen decreases and the radiographic tumor response as well as the clinical outcome with changes in ECOG (Eastern Cooperative Oncology Group) performance status and pain severity.

Results: The first 3 patients were treated with a lower activity of 3.7 GBq in cycle 1. Due to a favorable safety profile the activity was increased to 7.4 GBq in 19 subsequent patients who completed a total of 40 cycles. With the higher activity no grade 3/4 toxicities were observed. The main nonhematological and hematological grade 1/2 toxicities were dry mouth in 7 patients (37%), anemia in 6 (32%) and thrombopenia in 5 (25%). The proportion of patients who achieved a maximum prostate specific antigen decrease of 30% or greater, 50% or greater and 90% or greater was 56%, 33% and 11%, respectively. Combined assessment

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* Correspondence: Department of Urology, Technische Universität München, Klinikum rechts der Isar, Ismaninger Str. 22, 81675 München, Germany (telephone: +49 178 8541282: FAX: +49 4140 4843; e-mail: matthias.heck@tum.de).

† Equal study contribution.

‡ Senior authors.

For another article on a related topic see page 562.

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of bone and soft tissue metastases showed complete remission in 5% of patients, stable disease in 63% and progressive disease in 32%. ECOG performance status improved or was stable in 74% of patients. Of men with bone pain 58% achieved complete resolution or reduced pain.

Conclusions: Radioligand therapy with ^{177}Lu-PSMA-I&T appears to be safe and active in heavily pretreated patients with metastatic castration resistant prostate cancer.

Key Words: prostatic neoplasms; neoplasm metastasis; castration; glutamate carboxypeptidase II, human; lutetium

PROSTATE cancer is the most frequent cancer and the second to third leading cause of cancer death in American and European men.[1–3] In patients treated for metastatic PC the progression from a hormone sensitive state to castration resistance marks a transition to the lethal phenotype of the disease. In recent years several new agents have been approved to treat mCRPC. They include androgen receptor targeted therapies with abiraterone and enzalutamide as well as chemotherapy with cabazitaxel and the radiopharmaceutical ^{223}Ra. Despite these innovations for mCRPC therapy more than 250,000 men still die of PC worldwide each year.[4] Therefore, the development of new therapeutic options represents an urgent medical need.

PSMA is a transmembrane protein that is over expressed in PC cells in comparison to benign prostatic tissue.[5] Most importantly, PSMA expression progressively increases in higher grade cancers, metastatic disease and castration resistant prostate cancer.[6–9] Furthermore, PSMA has a catalytic site in its extracellular domain, which results in its internalization after ligand binding.[10] Subsequently, PSMA has attracted the attention as a potential therapeutic target for RLT of mCRPC.

A variety of selective PSMA ligands for RLT has been developed in recent years.[11] Preliminary results were reported for the PSMA ligand ^{131}I-MIP-1095 (MIP-1095 labeled with ^{131}I)[12] and ^{177}Lu-DKFZ-617 (DKFZ-617 labeled with ^{177}Lu)[13] after treatment with 1 cycle in patients with mCRPC. Consistently, substantial PSA decreases of 50% or greater in 50% to 60% of patients and a favorable safety profile were reported for both radiopharmaceuticals.

Another PSMA ligand that can be used for RLT was introduced by Weineisen et al.[14] It was improved in 2 steps to achieve increased affinity for PSMA on PSMA expressing tumor cell lines (DOTAGA-FFK[Sub-KuE]) and finally to achieve higher internalization capacity (DOTAGA-[I-y]fk [Sub-KuE]).[15] As a theranostic compound this PSMA ligand allows for diagnostic purposes when labeled with ^{68}Ga using PET and for therapeutic purposes when labeled with ^{177}Lu. Subsequently, the PSMA ligand was termed PSMA-I&T for imaging and therapy. Recently, the first application of ^{177}Lu-PSMA-I&T in 2 mCRPC cases was reported.[15] The investigators observed no adverse events and a lasting tumor response after 3 months on imaging, accompanied by a significant PSA decrease. Taken together, these results suggest high potential of ^{177}Lu-PSMA-I&T for RLT of mCRPC.

To our knowledge we report the first standardized results of ^{177}Lu-PSMA-I&T RLT in consecutive patients with mCRPC undergoing up to 4 cycles. Specifically, we assessed the safety profile and antitumor activity of ^{177}Lu-PSMA-I&T.

MATERIALS AND METHODS

All patients provided signed informed consent and were treated under a compassionate use protocol, which was approved by the institutional medicinal ethics committee at Technical University of Munich. The Appendix lists eligibility criteria for ^{177}Lu-PSMA-I&T RLT. Several previous treatment lines were demanded, including novel androgen receptor directed therapy (abiraterone and/or enzalutamide) as well as chemotherapy (docetaxel and/or cabazitaxel). In addition, patients had to be pretreated with or be ineligible for standard therapy with ^{223}Ra because of visceral lesions and/or lymphatic lesions greater than 3 cm. All patients underwent ^{68}Ga-PSMA PET/CT within 4 weeks before treatment initiation, which had to show considerable PSMA expression of all PC lesions to demonstrate high PSMA ligand binding capacity. Anticancer treatment for mCRPC was halted before that.

Treatment Regimen

Synthesis and radiolabeling of ^{177}Lu-PSMA-I&T was performed as reported previously.[14] ^{177}Lu-PSMA-I&T was administered in compliance with The German Medicinal Products Act, AMG §13 2b, and in accordance with the responsible regulatory body (Government of Oberbayern). For potential dose reduction to the kidneys as established for RLT in neuroendocrine tumors an amino acid infusion (2.5% arginine/lysine) was started 30 to 60 minutes before ^{177}Lu-PSMA-I&T administration.[16] For potential reduction of side effects induced by high uptake of ^{177}Lu-PSMA-I&T the salivary glands were cooled and saliva production was stimulated by drops. Intravenous treatment with ^{177}Lu-PSMA-I&T was applied every 8 weeks. Treatment continued to a maximum of 4 cycles in patients with absent radiographic or clinical progression and lack of severe toxicity according to the investigator.