From Compassionate Use to Phase 3 Trial: The Impact of Germany's PSMA-617 Literature

Thomas A. Hope

Department of Radiology and Biomedical Imaging, University of California, San Francisco, and Department of Radiology, San Francisco VA Medical Center, San Francisco, California

Targeted radionuclide therapy has been progressing over decades, and although the approval of ^{177}Lu-DOTATATE brought a new focus on targeted radionuclide therapies, it is the development of prostate-specific membrane antigen (PSMA)–targeted therapeutics that has brought the most attention to the field. The 2017 article by Kambiz Rahbar et al., entitled "German Multicenter Study Investigating ^{177}Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients," was the splash that brought these treatments to the forefront (*1*). This article presented the largest collection of patients treated with ^{177}Lu-PSMA-617 at the time and spawned enormous interest in PSMA-targeted therapy. It was originally published online in October 2016, and the first prospective study using this agent was not published until the article of Hofman et al. came out in May 2018 (*2*). During the intervening 18 months, Endocyte purchased the rights to ^{177}Lu-PSMA-617 and the VISION trial was approved and opened. Without the results presented in the Rahbar article, this fast-paced progress in the field would never have been achieved.

The Rahbar article was a retrospective collection of patients treated under the compassionate-use program at 12 facilities in Germany. How compassionate-use authorization is used to support research is not uniformly implemented, although in the setting of ^{177}Lu-PSMA-617, it is evident that access to this therapy benefits the patient and therefore is following the intention of the law. It is important for a moment to highlight some differences between compassionate use as it is implemented in Germany and the right-to-try law in the United States. With the right-to-try law, a therapeutic agent has to complete phase 1 studies, the manufacturer has to approve its use, and the patient has to have exhausted all available therapies (*3*). In Germany, compassionate use does not have these requirements and is frequently used to perform first-

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For correspondence or reprints contact: Thomas A. Hope, University of California, 505 Parnassus Ave., San Francisco, CA 94143.
E-mail: thomas.hope@ucsf.edu

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German Multicenter Study Investigating ^{177}Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients

Kambiz Rahbar*[1], Hojjat Ahmadzadehfar*[2], Clemens Kratochwil[3], Uwe Haberkorn[3], Michael Schäfers[1], Markus Essler[2], Richard P. Baum[4], Harshad R. Kulkarni[4], Matthias Schmidt[5], Alexander Drzezga[5], Peter Bartenstein[6], Andreas Pfestroff[7], Markus Luster[7], Ulf Lützen[8], Marlies Marx[8], Vikas Prasad[9], Winfried Brenner[9], Alexander Heinzel[10], Felix M. Mottaghy[10], Juri Ruf[11], Philipp Tobias Meyer[11], Martin Heuschkel[12], Maria Eveslage[13], Martin Bögemann[14], Wolfgang Peter Fendler†[6], and Bernd Joachim Krause†[12,15]

*[1]Department of Nuclear Medicine, University Hospital Muenster, Muenster, Germany; [2]Department of Nuclear Medicine, University Hospital Bonn, Bonn, Germany; [3]Department of Nuclear Medicine, University of Heidelberg, Heidelberg, Germany; [4]Theranostics Center for Molecular Radiotherapy and Molecular Imaging, Zentralklinik, Bad Berka, Bad Berka, Germany; [5]Department of Nuclear Medicine, University of Cologne, Cologne, Germany; [6]Department of Nuclear Medicine, Ludwig-Maximilians-University Munich, Munich, Germany; [7]Department of Nuclear Medicine, University of Marburg, Marburg, Germany; [8]Department of Nuclear Medicine, University of Schleswig-Holstein, Campus Kiel, Kiel, Germany; [9]Department of Nuclear Medicine, Charite, University Hospital Berlin, Berlin, Germany; [10]Department of Nuclear Medicine, University Hospital Aachen, Aachen, Germany; [11]Department of Nuclear Medicine, University of Freiburg, Freiburg, Germany; [12]Department of Nuclear Medicine, University of Rostock, Rostock, Germany; [13]Institute of Biostatistics and Clinical Research, University of Muenster, Muenster, Germany; [14]Department of Urology, University Hospital Muenster, Muenster, Germany; and [15]German Society of Nuclear Medicine Göttingen, Göttingen, Germany

^{177}Lu-labeled PSMA-617 is a promising new therapeutic agent for radioligand therapy (RLT) of patients with metastatic castration-resistant prostate cancer (mCRPC). Initiated by the German Society of Nuclear Medicine, a retrospective multicenter data analysis was started in 2015 to evaluate efficacy and safety of ^{177}Lu-PSMA-617 in a large cohort of patients. **Methods:** One hundred forty-five patients (median age, 73 y; range, 43–88 y) with mCRPC were treated with ^{177}Lu-PSMA-617 in 12 therapy centers between February 2014 and July 2015 with 1–4 therapy cycles and an activity range of 2–8 GBq per cycle. Toxicity was categorized by the common toxicity criteria for adverse events (version 4.0) on the basis of serial blood tests and the attending physician's report. The primary endpoint for efficacy was biochemical response as defined by a prostate-specific antigen decline ≥ 50% from baseline to at least 2 wk after the start of RLT. **Results:** A total of 248 therapy cycles were performed in 145 patients. Data for biochemical response in 99 patients as well as data for physician-reported and laboratory-based toxicity in 145 and 121 patients, respectively, were available. The median follow-up was 16 wk (range, 2–30 wk). Nineteen patients died during the observation period. Grade 3–4 hematotoxicity occurred in 18 patients: 10%, 4%, and 3% of the patients experienced anemia, thrombocytopenia, and leukopenia, respectively. Xerostomia occurred in 8%. The overall biochemical response rate was 45% after all therapy cycles (absence warranted to elucidate the survival benefit of this new therapy in patients with mCRPC.

Key Words: prostate cancer; PSMA-617; mCRPC; radioligand therapy

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According to the American Cancer Society, prostate cancer is the most common cancer and second most frequent cause of cancer-related death in men in the United States (*1*). The 5-y survival rate of locally advanced prostate cancer is nearly 100%; however, the rate is significantly lower in the case of metastatic disease (31%) (*2*). Therefore, developing new strategies for diagnosis, imaging, and treatment of metastatic prostate cancer is of major importance.

Prostate-specific membrane antigen (PSMA) is overexpressed in prostate cancer and even more so with increasing de-differentiation or castration-resistant disease (*3*). Radiolabeled ligands targeting PSMA have recently been the subject of numerous studies showing

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in-humans diagnostic and therapeutic studies. The intention of both compassionate use and right-to-try is identical: to provide therapeutic options to patients who have none.

Notwithstanding the limitations of the Rahbar article, the value of ^{177}Lu-PSMA-617 was acknowledged by the Food and Drug Administration, as evidenced by its willingness to allow Endocyte to forgo conventional phase 1 and phase 2 trials before opening the phase 3 VISION study. That decision in most part was based on data such as that presented in the Rahbar article. This article paved the way for what will hopefully become a standard therapy for men with metastatic prostate cancer.

Although targeted radionuclide therapy has been around for decades in nuclear medicine, treatments such as ^{177}Lu-PSMA-617 that were brought to the forefront by the Rahbar article are changing the face of nuclear medicine. The ability to radiolabel small molecules using α- and β-emitters is providing several therapeutic avenues for many cancers. The optimism, based on results such as found in the Rahbar article, has motivated research and investment in numerous new molecules. We as a field look forward to the future advancements in antibodies and small molecules that will help reshape nuclear medicine.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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The major limitation of this study is its retrospective nature. Data were collected in 12 therapy centers, which caused inhomogeneity of available data in terms of follow-up timeline and concomitant medication. Data might be biased by patient selection, loss of follow-up, and undocumented adverse events. Therefore, all inferential statistics are intended to be exploratory (hypotheses generating, as a limitation in all retrospective studies), not confirmatory, and are interpreted accordingly. The primary endpoint for efficacy was based on PSA level. In a retrospective multicenter study, change in PSA is more objective and reliable than imaging follow-up, however, its clinical value remains controversial (*25*).

CONCLUSION

The present multicenter study demonstrates favorable safety and efficacy of ^{177}Lu-PSMA-617 RLT in a large number of mCRPC patients. ^{177}Lu-PSMA-617 RLT might exceed the performance of other third-line systemic therapies reported in the literature. Future prospective phase II/III trials are currently in preparation, to evaluate the potential of this new targeted radioligand therapy especially with regards to improved patient survival.

DISCLOSURE

Uwe Haberkorn is part of the PSMA-617 patent application. No other potential conflict of interest relevant to this article was reported.

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