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Angaben zur Veröffentlichung / Publication details:

Rinscheid, Andreas, Alexander Gäble, Georgine Wienand, Christian Pfob, Alexander Dierks, Malte Kircher, Martin Trepel, Dorothea Weckermann, Constantin Lapa, and Ralph A. Bundschuh. 2023. "An intrapatient dosimetry comparison of 177 Lu-rhPSMA-10.1 and 177 Lu-PSMA-I&T in patients with metastatic castration-resistant prostate cancer." *Journal of Nuclear Medicine* 64 (12): 1918–24. https://doi.org/10.2967/jnumed.123.265970.

An Intrapatient Dosimetry Comparison of ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T in Patients with Metastatic Castration-Resistant Prostate Cancer

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As the use of radioligand therapy moves earlier in the prostate cancer timeline, minimizing the absorbed dose to normal organs while maintaining high tumor radiation doses becomes more clinically important because of the longer life expectancy of patients. We performed an intrapatient comparison of pretherapeutic dosimetry with the novel radiohybrid prostate-specific membrane antigen–targeting radiopharmaceutical ^{177}Lu-rhPSMA-10.1, along with ^{177}Lu-PSMA-I&T, in patients with metastatic castration-resistant prostate cancer. **Methods:** Four consecutive patients with advanced histologically proven metastatic castration-resistant prostate cancer who were scheduled for radioligand therapy were evaluated. Before undergoing therapy, each patient received 1.06 ± 0.05 GBq of ^{177}Lu-rhPSMA-10.1 and 1.09 ± 0.02 GBq of ^{177}Lu-PSMA-I&T at least 7 d apart. For dosimetric assessment, whole-body planar scintigraphy was performed after 5 min, 4 h, 1 d, 2 d, and 7 d. In addition, SPECT/CT images were acquired over the thorax and the abdomen, 4 h, 1 d, 2 d, and 7 d after injection. Dosimetry of the whole body and salivary glands was based on the evaluation of the counts in whole-body planar imaging. Dosimetry of the kidneys, liver, spleen, bone marrow, and tumor lesions (≤4 per patient) was based on the activity in volumes drawn on SPECT/CT images. Doses were calculated using OLINDA/EXM version 1.0. The therapeutic index (TI), or ratio between mean dose of the metastases and mean dose of the kidneys, was calculated for each patient. **Results:** We found the dose to the kidneys to be higher with ^{177}Lu-rhPSMA-10.1 than with ^{177}Lu-PSMA-I&T (0.68 ± 0.30 vs. 0.46 ± 0.10 mGy/MBq); however, ^{177}Lu-rhPSMA-10.1 delivered an average of a 3.3 times (range, 1.2–8.3 times) higher absorbed radiation dose to individual tumor lesions. Consequently, intraindividual comparison revealed a 1.1–3.1 times higher TI for ^{177}Lu-rhPSMA-10.1 than for ^{177}Lu-PSMA-I&T in all evaluated patients. The effective whole-body dose was 0.038 ± 0.008 mSv/MBq for ^{177}Lu-rhPSMA-10.1 and 0.022 ± 0.005 mSv/MBq for ^{177}Lu-PSMA-I&T. **Conclusion:** Using ^{177}Lu-rhPSMA-10.1 can significantly increase the tumor-absorbed dose and improve the TI compared with ^{177}Lu-PSMA-I&T. An improved TI gives the flexibility to maximize tumor-absorbed doses up to a predefined renal dose limit or, in earlier disease, to reduce the radiation exposure to the kidney while still achieving an effective tumor dose. The function of at-risk organs such as the kidneys is being assessed in a prospective clinical trial.

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Key Words: prostate cancer; radioligand therapy; therapeutic index; dosimetry; prostate-specific membrane antigen

J Nucl Med 2023; 64:1918–1924
DOI: 10.2967/jnumed.123.265970

Several prostate-specific membrane antigen (PSMA)–targeted radioligand therapies have recently been developed and are under investigation for patients with metastatic castration-resistant prostate cancer (mCRPC) who have progressed after conventional treatments, such as with novel androgen-axis drugs or chemotherapy. Promising clinical data have been shown with ^{177}Lu-labeled PSMA-I&T and PSMA-617 (*1–3*). Data from the phase 3 VISION trial (*4*) show increased overall survival after treatment with ^{177}Lu-PSMA-617 compared with the standard of care in patients with mCRPC who had progressed after receiving at least 1 novel androgen-axis drug and 1 line of taxane-based chemotherapy in the castration-resistant phase of their disease. ^{177}Lu-PSMA-617 received U.S. Food and Drug Administration approval in May 2022 followed by European Medicines Agency approval in December 2022 (*5*).

The data that exist thus far for ^{177}Lu-labeled PSMA compounds support the general principle that the greater the radiation dose delivered to the cancer, the better the response to treatment. Whole-body SUV_{mean} from pretherapeutic PET correlates with the absorbed dose to tumor lesions (*6,7*), and recent data from a subanalysis of the VISION trial demonstrate that a higher whole-body SUV_{mean} is associated with improved survival (*8*). Additionally, it has been shown that there is a strong correlation between whole-body tumor dose and prostate-specific antigen response (*7*). Therefore, enhancing the absorbed radiation dose to the tumor with new PSMA-targeted radioligand therapies may achieve better clinical outcomes.

The most frequent toxicities reported with ^{177}Lu-labeled radiopharmaceuticals are experienced during the dosing period and include fatigue, pain, dry mouth, dry eyes, nausea, and vomiting (*4*). These are generally reported as of low grade and self-limiting. The predominant grade 3 or 4 toxicities are hematologic and relate to radiation dose delivered to the bone marrow during distribution of the radiopharmaceutical. The deposited radiation can cause or contribute to anemia, neutropenia, and thrombocytopenia.

Over the longer term, a key consideration is the radiation dose delivered to the kidneys and the risk of a delayed radiation

nephropathy. Although the VISION (*4*) and TheraP (*9*) trials captured the short- and medium-term toxicities experienced by subjects undergoing therapy, there is currently no long-term follow-up extending several years after dosing, partly because of the short life expectancy of men with advanced mCRPC that has progressed after several lines of prior therapy. However, studies of this class of therapy in men with less advanced mCRPC (NCT04689828) and hormone-sensitive prostate cancer (NCT04720157) may furnish this information, as it might be expected that the subjects would have a longer life expectancy. The cells of the kidney have a slow turnover, and radiation nephropathy may be observed years after dosing. Complicating the assessment is the fact that a significant proportion of men dying of prostate cancer has progressive renal deterioration in the final year of life, with studies reporting frequencies ranging from 3% to 16% of patients (*10*–*12*). This background rate of deterioration as a result of disease progression presents the potential to mask radiation-induced nephropathy and lead to a lack of attribution of causality. Thus, careful management of the radiation dose absorbed by the kidney is required to minimize the potential for future renal impairment in men with a longer life expectancy or curable disease. The safe renal dose limit, and the impact of individual patient factors, are not currently known. As such, it is imperative that the tumor-to-kidney ratio be considered for any novel PSMA-targeted radiopharmaceuticals for radioligand therapy to maximize the absorbed dose to tumor while also minimizing the impact on the kidneys as a key organ at risk (*13*).

Radiohybrid PSMA-targeted ligands are a new class of radiopharmaceuticals currently under evaluation in prostate cancer diagnosis and treatment. The compounds offer the potential for ^{18}F radiolabeling for use in diagnostic imaging or labeling with α- or β-emitting radiometals for radioligand therapy (*14*). The lead diagnostic radiohybrid PSMA, ^{18}F-rhPSMA-7.3, shows favorable diagnostic performance in the diagnosis of recurrent prostate cancer (*15*,*16*), and preclinical and pretherapeutic dosimetry data from its ^{177}Lu-labeled counterpart show it to be a promising candidate for radioligand therapy (*3*,*17*). The results of a series of preclinical assessments of a further ^{177}Lu-labeled radiohybrid PSMA ligand, ^{177}Lu-rhPSMA-10.1, also show encouraging data (*18*).

Here, we present pretherapeutic dosimetry using a low activity of the radiopharmaceutical ^{177}Lu-rhPSMA-10.1, assessing normal organs and tumor lesions, in an intrapatient comparison with the same activity of ^{177}Lu-PSMA-I&T. This pretherapeutic dosimetric assessment was performed before the first therapeutic cycle of radioligand therapy in patients with mCRPC. Additionally, we present the findings of therapeutic dosimetry during this first treatment cycle in a subset of patients.

MATERIALS AND METHODS

Radiopharmaceutical Preparation and Approval

All reported investigations were conducted in accordance with the Helsinki Declaration and with national regulations. The local institutional review board (review board of the Ludwig-Maximilians-Universität München, Munich, Germany) approved this retrospective dosimetry analysis (permit 22-1011). ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T were prepared in compliance with the German Medicinal Products Act, Arzneimittelgesetz §13 2b, and after informing the responsible regulatory body.

Patients and Pretherapeutic Dosimetry

Four consecutive patients with mCRPC who were previously treated with a spectrum of prostate cancer therapies including surgery, radiation therapy, androgen deprivation, novel androgen-axis drugs, and chemotherapy were included in this retrospective analysis. All patients gave written informed consent to imaging and therapeutic procedures.

Sufficient PSMA expression was confirmed by PET/CT examination using ^{68}Ga-PSMA-I&T in a clinical setting. Sufficient expression was defined according to the inclusion criteria of the VISION trial (*4*). The patients underwent dosimetric investigations with a low activity (1 GBq) of both ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T. To avoid systematic error, in 2 patients the analysis with ^{177}Lu-rhPSMA-10.1 was performed first, and in the other 2 patients the dosimetry began with ^{177}Lu-PSMA-I&T. To determine the potential antitumor effect in relation to the dose delivered to the kidneys as the organ considered to be at greatest risk, the therapeutic index (TI; mean absorbed radiation dose to tumor lesions [≤4 lesions per patient were evaluated] divided by absorbed dose to the kidneys) was determined for both radiopharmaceuticals. Additionally, tumor–to–salivary gland and tumor–to–bone marrow ratios were calculated for each patient.

The relative TI was calculated by evaluating the TI of ^{177}Lu-rhPSMA-10.1 relative to the TI of ^{177}Lu-PSMA-I&T for each patient to determine the radiopharmaceutical with the most preferable distribution. The patient then went on to receive treatment with whichever radiopharmaceutical showed the most favorable TI.

The patients received a pretherapeutic administration of ^{177}Lu-rhPSMA-10.1 (1,065 ± 41 MBq) and ^{177}Lu-PSMA-I&T (1,086 ± 12 MBq), with a period of at least 7 d between the two. The radiopharmaceuticals were delivered by intravenous bolus injection followed by a saline flush. Figure 1 outlines the study conduct and sampling timeline for pretherapeutic comparative dosimetry. Images were acquired on a Discovery NM/CT 670 Pro (GE Healthcare) with use of a medium-energy general-purpose collimator. Planar imaging was conducted 5 min after injection of ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T (patients 1 and 2 had additional planar imaging at 1 h after injection), with further SPECT/CT and planar imaging acquired at 3–4 h, 1 d, 2 d, and 7 d after injection. Estimation of individual-patient absorbed doses for the whole body and key organs (as listed in Table 1) was based on the MIRD schemes, and absorbed organ and tumor doses were calculated using OLINDA/EXM version 1.0 (*19*), except for the salivary glands, for which mass-scaled S values were used from the IDAC-Dose 2.1 software (*20*). The effective dose provided by OLINDA/EXM was corrected using the current tissue-weighting factors from International Commission on Radiological Protection publication 103 (*21*). Further details on the dosimetry methodology are given in Supplemental Appendix A (supplemental materials are available at http://jnm.snmjournals.org) (*22*).

Venous blood samples were collected at 5 min, 3–4 h, 1 d, 2 d, and 7 d after injection, and activity measurements obtained with a calibrated well counter were used to estimate blood clearance over time, with the decay corrected to the time of blood sampling. Patients 1 and 2 had additional blood samples collected at 1 h after injection.

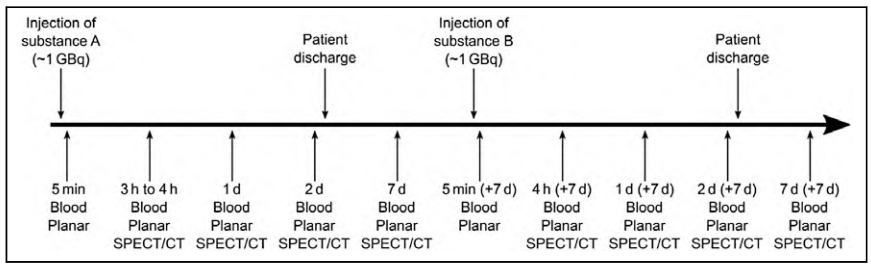

FIGURE 1. Study sampling timeline for pretherapeutic comparative dosimetry.

TABLE 1
Pretherapeutic Absorbed Doses for Normal Organs and Effective Dose for Whole Body

Organ	Pretherapeutic absorbed dose									
	Patient 1		Patient 2		Patient 3		Patient 4		Mean ± SD	
	^{177}Lu-rhPSMA-10.1	^{177}Lu-PSMA-I&T	^{177}Lu-rhPSMA-10.1	^{177}Lu-PSMA-I&T	^{177}Lu-rhPSMA-10.1	^{177}Lu-PSMA-I&T	^{177}Lu-rhPSMA-10.1	^{177}Lu-PSMA-I&T	^{177}Lu-rhPSMA-10.1	^{177}Lu-PSMA-I&T
Adrenals	0.011	0.010	0.020	0.012	0.019	0.014	0.018	0.011	0.017 ± 0.004	0.012 ± 0.002
Brain	0.005	0.007	0.017	0.010	0.017	0.012	0.014	0.008	0.013 ± 0.006	0.009 ± 0.003
Breasts	0.006	0.007	0.017	0.010	0.017	0.012	0.014	0.008	0.013 ± 0.006	0.009 ± 0.003
Gallbladder wall	0.011	0.010	0.020	0.012	0.019	0.014	0.017	0.010	0.017 ± 0.005	0.011 ± 0.002
LLI wall	0.006	0.008	0.018	0.010	0.018	0.013	0.016	0.009	0.014 ± 0.006	0.010 ± 0.003
Small intestine	0.007	0.009	0.019	0.011	0.018	0.013	0.016	0.009	0.015 ± 0.006	0.010 ± 0.003
Stomach wall	0.007	0.009	0.019	0.011	0.018	0.013	0.016	0.009	0.015 ± 0.006	0.010 ± 0.003
ULI wall	0.007	0.009	0.019	0.011	0.018	0.013	0.016	0.009	0.015 ± 0.006	0.010 ± 0.003
Heart wall	0.007	0.008	0.018	0.011	0.018	0.013	0.015	0.009	0.015 ± 0.006	0.010 ± 0.003
Kidneys	1.110	0.543	0.510	0.369	0.443	0.383	0.675	0.554	0.685 ± 0.300	0.462 ± 0.100
Liver	0.177	0.095	0.133	0.079	0.076	0.048	0.110	0.053	0.124 ± 0.043	0.069 ± 0.023
Lungs	0.007	0.008	0.018	0.010	0.017	0.013	0.015	0.009	0.014 ± 0.006	0.010 ± 0.003
Muscle	0.006	0.008	0.018	0.010	0.017	0.013	0.015	0.008	0.014 ± 0.006	0.010 ± 0.003
Pancreas	0.010	0.010	0.020	0.012	0.019	0.014	0.017	0.010	0.017 ± 0.005	0.011 ± 0.002
Red marrow	0.064	0.028	0.042	0.006	0.036	0.023	0.156	0.095	0.074 ± 0.056	0.038 ± 0.040
Osteogenic cells	0.045	0.038	0.073	0.031	0.069	0.049	0.136	0.081	0.081 ± 0.039	0.050 ± 0.023
Salivary glands (planar)	0.350	0.109	0.684	0.185	0.287	0.099	0.415	0.135	0.434 ± 0.175	0.132 ± 0.039
Skin	0.005	0.007	0.017	0.010	0.016	0.012	0.014	0.008	0.013 ± 0.006	0.010 ± 0.003
Spleen	0.080	0.044	0.143	0.086	0.080	0.030	0.036	0.014	0.085 ± 0.045	0.043 ± 0.031
Testes	0.005	0.007	0.017	0.010	0.017	0.012	0.014	0.008	0.013 ± 0.006	0.010 ± 0.003
Thymus	0.006	0.008	0.018	0.010	0.017	0.013	0.015	0.008	0.014 ± 0.006	0.010 ± 0.003
Thyroid	0.005	0.007	0.017	0.010	0.017	0.013	0.015	0.008	0.014 ± 0.006	0.010 ± 0.003
Urinary bladder wall	0.006	0.008	0.018	0.010	0.017	0.013	0.015	0.009	0.014 ± 0.006	0.010 ± 0.003
Total body	0.016	0.013	0.024	0.013	0.021	0.016	0.023	0.014	0.021 ± 0.004	0.014 ± 0.002
Whole-body effective dose (mSv/MBq)	0.036	0.021	0.039	0.019	0.030	0.020	0.048	0.028	0.038 ± 0.008	0.022 ± 0.005

LLI = lower large intestine; ULI = upper large intestine.
Absorbed dose data are mGy/MBq.

Statistics

All continuous data are reported as mean, SD, and range.

Therapeutic Dosimetry of First Treatment Cycle

Therapeutic dosimetry was conducted for 3 of the 4 patients after the first treatment cycle with ^{177}Lu-rhPSMA-10.1, which showed a favorable renal TI in all 3 patients (activity, 7,409 ± 98 MBq; in accordance with the recent guidelines including cooling of the salivary glands for approximately 4 h starting 30 min before administration of the radiopharmaceutical (*23*)). The fourth patient experienced claustrophobia and so did not undergo posttherapeutic dosimetry. Planar imaging and blood sampling were conducted at 5 min, 3–4 h, 24 h, 48 h, and 144–168 h after injection, and SPECT/CT was conducted at 3–4 h, 24 h, 48 h, and 144–168 h after injection. In addition, patient 1 had planar imaging and blood sampling at 1 h after injection and planar imaging, SPECT/CT, and blood sampling at 96 h after injection. Reconstruction and dosimetry evaluations were conducted as per the pretherapeutic dosimetry.

RESULTS

Patients

The clinical characteristics of the 4 patients are presented in Table 2.

Pretherapeutic Dosimetry in Normal Organs

Table 1 presents the pretherapeutic absorbed radiation dose estimates for normal organs. When the organs at risk were considered, the mean absorbed doses in the kidneys were 0.68 ± 0.30 mGy/MBq (range, 0.44–1.11 mGy/MBq across the 4 patients) for ^{177}Lu-rhPSMA-10.1 and 0.46 ± 0.10 mGy/MBq (range, 0.37–0.55 mGy/MBq) for ^{177}Lu-PSMA-I&T. In the bone marrow, the mean absorbed dose was 0.074 ± 0.056 mGy/MBq (range, 0.04–0.16 mGy/MBq across the 4 patients) for ^{177}Lu-rhPSMA-10.1 and 0.038 ± 0.040 mGy/MBq (range, 0.01– 0.10 mGy/MBq) for ^{177}Lu-PSMA-I&T. In the salivary glands, the mean absorbed dose was 0.43 ± 0.18 mGy/MBq (range, 0.29–0.68 mGy/MBq across the 4 patients) for ^{177}Lu-rhPSMA-10.1 and 0.13 ± 0.04 mGy/MBq (range, 0.10–0.19 mGy/MBq) for ^{177}Lu-PSMA-I&T.

Across the 4 patients, the mean whole-body pretherapeutic effective dose was 0.038 ± 0.008 mSv/MBq (range, 0.030–0.048 across the 4 patients) for ^{177}Lu-rhPSMA-10.1 and 0.022 ± 0.005 mSv/MBq (range, 0.019–0.028 across the 4 patients) for ^{177}Lu-PSMA-I&T. These data show the overall ratio of ^{177}Lu-rhPSMA-10.1/^{177}Lu-PSMA-I&T for whole-body effective dose to be 1.7. This ratio ranged from 1.5 to 2.1 across the 4 patients.

No significant difference was observed regarding which dosimetric analysis was first, ^{177}Lu-PSMA-I&T or ^{177}Lu-rhPSMA-10.1.

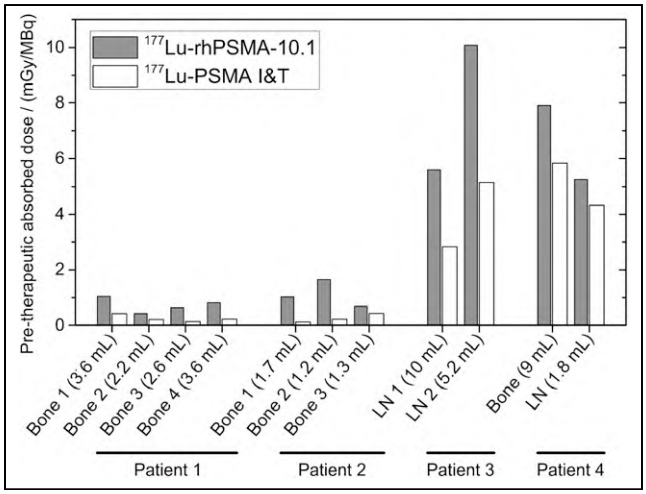

FIGURE 2. Pretherapeutic absorbed doses of ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T in tumor lesions. LN = lymph node.

Pretherapeutic Dosimetry in Tumor Lesions

In total, 11 lesions (8 bone metastases and 3 lymph node metastases) were evaluated across the 4 patients. Figure 2 provides details on the evaluated lesions along with the absorbed doses of ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T in these lesions.

The absorbed dose of ^{177}Lu-rhPSMA-10.1 was higher than the absorbed dose of ^{177}Lu-PSMA-I&T in all lesion types, with the ratio of mean absorbed dose of ^{177}Lu-rhPSMA-10.1/^{177}Lu-PSMA-I&T shown to be 1.77 for all tumors, 1.87 for all bone lesions, and 1.70 for all lymph node lesions. On a per-patient basis, the ratio of mean absorbed dose of ^{177}Lu-rhPSMA-10.1/^{177}Lu-PSMA-I&T for all lesions was 2.92 for patient 1, 4.33 for patient 2, 1.97 for patient 3, and 1.30 for patient 4.

TABLE 2
Patients' Clinical Characteristics

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Prostate-specific antigen at baseline (ng/mL)	0.9	9.9	15.0	20.0
Gleason score	4 + 4 = 8	4 + 5 = 9	3 + 4 = 7	4 + 5 = 9
GFR at baseline (mL/min/1.73m^2)	87.9	>90	79.5	54.0
Prior treatment	RPE, RTx, ADT	ADT, RTx, Doce	RPE, ADT, Doce	RPE, RTx, ADT, Doce, Arb, Enz
Metastatic sites at baseline	Bone	Bone	Bone, lymph node	Bone, lymph node
Prostate-specific antigen 6 wk after first treatment cycle (ng/mL)	0.1	6.4	5.8	1.3

GFR = glomerular filtration rate; RPE = radical prostatectomy; RTx = external-beam radiotherapy; ADT = androgen deprivation therapy; Doce = chemotherapy with docetaxel; Arb = treatment with abiraterone; Enz = treatment with enzalutamide.

TABLE 3
Intraindividual TI for ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T

Patient	^{177}Lu-rhPSMA-10.1			^{177}Lu-PSMA-I&T			
	Mean tumor-absorbed dose	Kidney-absorbed dose	TI	Mean tumor-absorbed dose	Kidney-absorbed dose	TI	TI, 10.1/I&T
1 (4 tumor lesions)	0.73	1.1	0.66	0.25	0.54	0.46	1.4
2 (3 tumor lesions)	1.1	0.51	2.2	0.26	0.37	0.70	3.1
3 (2 tumor lesions)	7.8	0.44	18	4.0	0.38	10	1.7
4 (2 tumor lesions)	6.6	0.68	9.8	5.1	0.55	9.2	1.1

Absorbed dose data are mGy/MBq.

TI

As shown in Table 3, intraindividual comparison of ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T revealed a higher TI for ^{177}Lu-rhPSMA-10.1 in all investigated patients (TI range for ^{177}Lu-rhPSMA-10.1/^{177}Lu-PSMA-I&T, 1.1–3.1) based on kidney uptake. Thus, ^{177}Lu-rhPSMA-10.1 was the preferred radiopharmaceutical for treatment in all investigated patients (Supplemental Fig. 1).

A similar metric was estimated for other at-risk organs (the salivary glands and bone marrow) as shown in Table 4. The data show that the relative TI (TI for ^{177}Lu-rhPSMA-10.1/^{177}Lu-PSMA-I&T) ranged from 0.42 to 1.2 across patients for the salivary glands and from 0.63 to 1.3 for the bone marrow.

Blood Clearance

As shown in Figure 3, the mean radioactivity concentrations of ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T in venous blood samples over the whole evaluation period indicate that both radiopharmaceuticals are rapidly cleared within the first 2 h after injection.

Therapeutic Dosimetry

Posttherapeutic dosimetry was conducted in 3 of the 4 patients. The TI (mean tumor-absorbed dose/kidney-absorbed dose) was calculated individually for each patient (0.73 for patient 1, 2.2 for patient 2, and 16 for patient 3; Supplemental Tables 1 and 2) and shown to be comparable with those determined from the pretherapeutic dosimetry. In addition, a slight decrease in the average dose to salivary glands from 0.43 ± 0.18 mGy/MBq (pretherapeutic, without cooling) to 0.38 ± 0.18 mGy/MBq (therapeutic, with cooling) was observed.

DISCUSSION

Here, we present an intrapatient comparison of the pretherapeutic dosimetry of ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T for radioligand therapy in patients with mCRPC. The results indicate that ^{177}Lu-rhPSMA-10.1 offers an increased absorbed dose to the tumor compared with ^{177}Lu-PSMA-I&T. Moreover, whereas the

TABLE 4
Intraindividual Tumor–to–Organ-at-Risk Ratios for ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T

Parameter	Patient			
	1 (4 tumor lesions)	2 (3 tumor lesions)	3 (2 tumor lesions)	4 (2 tumor lesions)
^{177}Lu-rhPSMA-10.1				
Mean tumor-absorbed dose	0.73	1.1	7.8	6.6
Salivary gland–absorbed dose	0.35	0.68	0.29	0.41
Tumor–to–salivary gland ratio	2.1	1.6	27	16
Bone marrow–absorbed dose	0.064	0.042	0.036	0.16
Tumor–to–bone marrow ratio	11	27	221	42
^{177}Lu-PSMA-I&T				
Mean tumor-absorbed dose	0.25	0.26	4.0	5.1
Salivary gland–absorbed dose	0.11	0.19	0.10	0.13
Tumor–to–salivary gland ratio	2.3	1.4	40	38
Bone marrow–absorbed dose	0.028	0.006	0.023	0.095
Tumor–to–bone marrow ratio	8.9	43	170	53
Tumor–to–salivary gland ratio, 10.1/I&T	0.91	1.2	0.68	0.42
Tumor–to–bone marrow ratio, 10.1/I&T	1.3	0.63	1.3	0.79

Absorbed dose data are mGy/MBq.

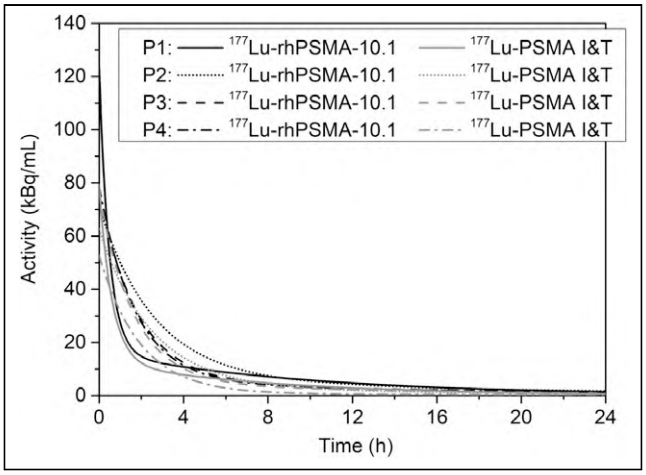

FIGURE 3. Radioactivity concentration of ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T in venous blood samples as function of time. P1–P4 = patients 1–4.

dose to normal organs was increased for ^{177}Lu-rhPSMA-10.1, the overall kidney TI was found to favor ^{177}Lu-rhPSMA-10.1 over ^{177}Lu-PSMA-I&T for all 4 patients evaluated.

Although the dose to the tumor was seen to vary by patient and by lesion, the present study design allows a direct intrapatient comparison of the 2 radiopharmaceuticals. The data showing that ^{177}Lu-rhPSMA-10.1 delivers an average dose across tumors that is up to 4.3 times higher than ^{177}Lu-PSMA-I&T is of clinical relevance based on the observation made with ^{177}Lu-PSMA-617 that greater efficacy is derived from delivery of a higher radiation dose to the tumor (*8*).

^{177}Lu-labeled radiopharmaceuticals are generally well tolerated when compared with chemotherapy, which is a recommended treatment option for patients with progressive mCRPC (*9*); however, the kidneys remain one of the most important normal organs to consider when planning radioligand therapy because of the risk of delayed radiation nephropathy (*24*,*25*). Although the appropriate maximum renal radiation dose for a β-emitting radiopharmaceutical is still unclear and will likely vary from patient to patient (*26*), dosimetry is crucial to determine the expected radiation dose and to predict the overall safety of a radiopharmaceutical. As longer-term safety data are collected for this new class of prostate cancer therapy during the rollout of the newly approved ^{177}Lu-PSMA-617 to many thousands of men, the degree of risk to kidney function will be more accurately quantified and appropriate renal dose limits can be established. The present data show a 1.1- to 3.1-fold difference in the kidney TI of ^{177}Lu-rhPSMA-10.1 relative to ^{177}Lu-PSMA-I&T. This result is of clinical importance because an improved TI gives the option of maximizing tumor-absorbed doses in patients with a significantly shortened life expectancy while enabling them to tolerate a higher kidney-absorbed radiation dose, or, for patients who are earlier in the disease timeline with a longer life expectancy, an improved TI provides the option of reducing the radiation exposure to the kidney while still achieving an effective dose to the tumor.

In addition to the kidneys, the salivary glands are often considered an at-risk organ for PSMA radioligand therapy, although with ^{177}Lu-labeled compounds the toxicity appears to be self-limiting and reversible, and preventative strategies can help minimize the toxic effects (*27*–*29*). The relative TI as measured by tumor–to–salivary gland ratio appeared to favor ^{177}Lu-PSMA-I&T in this experience, although in patient 2 ^{177}Lu-rhPSMA-10.1 was preferred. This likely reflects the difficulty of accurately measuring the salivary gland dose given the anatomic size of the organs and the contouring required on SPECT. By precooling the salivary glands, we were able to observe a reduction in the dose of ^{177}Lu-rhPSMA-10.1 to the salivary glands in the first treatment cycle compared with the pretherapeutic dosimetry. Further study is necessary to determine whether precooling might influence any symptoms experienced by the patient.

The results of the VISION trial indicate that, although rare, bone marrow toxicity is an important consideration for PSMA radioligand therapy (*4*). We found that although the absorbed dose to bone marrow varied greatly from patient to patient, the bone marrow–absorbed doses were greater with ^{177}Lu-rhPSMA-10.1 than ^{177}Lu-PSMA-I&T. However, when measured as a ratio of tumor to bone marrow, the results were mixed, with 2 patients favoring ^{177}Lu-rhPSMA-10.1 and 2 patients favoring ^{177}Lu-PSMA-I&T. Determining the dose to bone marrow can be prone to errors and may be overestimated because of the presence of microscopic tumor lesions in the region of interest, especially in prostate cancer, in which bone is the preferred site of metastasis formation. Additionally, the correlation of bone marrow–absorbed dose and any observed hematologic toxicity is not clear, and the degree to which patients are pretreated with chemotherapy is likely to be a significant factor in the relationship. Nevertheless, dose-limiting bone marrow toxicity, even in the presence of extensive bone metastases, is not common (*17*).

^{177}Lu-rhPSMA-10.1 is the lead compound in a novel class of radiohybrid radiopharmaceuticals with theranostic potential. The encouraging findings of the present study show ^{177}Lu-labeled radiohybrid PSMA compounds to be suitable candidates for clinical translation, and the results of the ongoing phase 1/2 clinical trial of ^{177}Lu-rhPSMA-10.1 in patients with mCRPC (NCT05413850) are eagerly anticipated.

In addition to the technical challenges of dosimetry as discussed above, there are several limitations to the present work. Collection of blood samples might not have been sufficient because blood half-life was as short as 30 min. Dosimetry of small structures is challenging because of spill-out effects. These were in part compensated for by the use of PET to estimate the volume of the lesions and the use of a larger volume of interest to estimate counts. Since the same size of volume of interest was always used for a lesion in SPECT, the comparability of the 2 radiopharmaceuticals was ensured. However, the absolute dose values yield high uncertainties. Additionally, whereas the present study design facilitates a true comparison of the 2 radiopharmaceuticals within the same patient, data are presented for only a small number of patients and further studies are required to confirm our findings. In our series of 4 patients, we performed dosimetry with both ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T, with each compound being injected first in 2 patients. We did not observe any differences depending on the order of the application, any significant therapeutic effects, or a stunning phenomenon. However, it is beyond the scope of this analysis to determine the influence of the dosimetry doses on the first treatment cycle, for which the pretherapeutic doses may still induce a stunning effect.

Moreover, this study does not provide a comparison with the currently approved PSMA-targeted radioligand therapy, ^{177}Lu-PSMA-617. However, a recently published experience comparing the radiation dosimetry of ^{177}Lu-PSMA-I&T and ^{177}Lu-PSMA-617 in a cohort of 138 patients suggests these agents have very similar profiles (*30*). Furthermore, the present study does not determine the

clinical impact of the higher tumor-absorbed radiation doses delivered with ^{177}Lu-rhPSMA-10.1, and future studies will be necessary to confirm whether improved clinical outcomes are possible.

CONCLUSION

This intrapatient comparison shows ^{177}Lu-rhPSMA-10.1 to deliver an increased radiation dose to the tumor compared with ^{177}Lu-PSMA-I&T in patients with mCRPC. In all patients evaluated, a more favorable kidney TI was noted for ^{177}Lu-rhPSMA-10.1 than for ^{177}Lu-PSMA-I&T, yielding the potential to maximize tumor-absorbed doses or to reduce the radiation exposure to the kidneys while still achieving an effective dose to the tumor.

DISCLOSURE

Constantin Lapa reports prior consulting activities for Blue Earth Diagnostics Ltd. (Oxford, U.K.) and Novartis. Ralph Bundschuh is a consultant for, and has received speaker honoraria from, Bayer Healthcare (Leverkusen, Germany) and Eisai GmbH (Frankfurt, Germany). Medical writing support was provided by Blue Earth Diagnostics Ltd. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Is the TI of ^{177}Lu-rhPSMA-10.1 improved when compared with ^{177}Lu-PSMA-I&T in the same patients?

PERTINENT FINDINGS: In mCRPC, pretherapeutic organ- and tumor-absorbed doses are higher for ^{177}Lu-rhPSMA-10.1 than for ^{177}Lu-PSMA-I&T. A more favorable TI was noted for ^{177}Lu-rhPSMA-10.1 in all patients evaluated, suggesting that the use of ^{177}Lu-rhPSMA-10.1 may permit higher absolute tumor doses to be achieved in mCRPC or that, in prostate cancer patients with long life expectancy, the same therapeutic effect might be achieved with a lower absolute kidney-absorbed dose.

IMPLICATIONS FOR PATIENT CARE: Pretherapeutic data indicate favorable properties for ^{177}Lu-rhPSMA-10.1 when compared with ^{177}Lu-PSMA-I&T, and therefore prospective clinical studies are under way to confirm this finding (NCT05413850).

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