Pretherapeutic Comparative Dosimetry of ^{177}Lu-rhPSMA-7.3 and ^{177}Lu-PSMA I&T in Patients with Metastatic Castration-Resistant Prostate Cancer

Benedikt Feuerecker[1–3], Maythinee Chantadisai[1], Anne Allmann[1], Robert Tauber[4], Jakob Allmann[1], Lisa Steinhelfer[1], Isabel Rauscher[1], Alexander Wurzer[5], Hans-Jürgen Wester[5], Wolfgang A. Weber[1,2], Calogero d'Alessandria*[1], and Matthias Eiber*[1,2]

[1]*Department of Nuclear Medicine, School of Medicine, Technical University of Munich, München, Germany;* [2]*Partnersite München, German Cancer Consortium (DKTK), Heidelberg, Germany;* [3]*Department of Radiology, School of Medicine, Technical University of Munich, München, Germany;* [4]*Department of Urology, School of Medicine, Technical University of Munich, München, Germany; and* [5]*Department of Pharmaceutical Radiochemistry, Technical University of Munich, Garching, Germany*

Radiohybrid prostate-specific membrane antigen (rhPSMA) ligands allow for labeling with ^{18}F and radiometals for endoradiotherapy. rhPSMA-7.3 has been designated as a lead compound with promising preclinical data for ^{177}Lu-rhPSMA-7.3, which has shown higher tumor uptake than ^{177}Lu-PSMA I&T. In this retrospective analysis, we compared pretherapeutic clinical dosimetry data of both PSMA ligands. **Methods:** Six patients with metastatic castration-resistant prostate cancer underwent both ^{177}Lu-rhPSMA-7.3 and ^{177}Lu-PSMA I&T pretherapeutic dosimetry. Whole-body scintigraphy was performed at 1 h, 4 h, 24 h, 48 h, and 7 d after injection. Regions of interest covering the whole body, organs, bone marrow, and tumor lesions were drawn for each patient. Absorbed doses for individual patients and pretherapeutic applications were calculated using OLINDA/EXM. To facilitate the comparison of both ligands, we introduced the therapeutic index (TI), defined as the ratio of mean pretherapeutic doses to tumor lesions over relevant organs at risk. **Results:** Mean whole-body pretherapeutic effective doses for ^{177}Lu-rhPSMA-7.3 and ^{177}Lu-PSMA I&T were 0.12 ± 0.07 and 0.05 ± 0.03 Sv/GBq, respectively. Mean absorbed organ doses for ^{177}Lu-rhPSMA-7.3 and ^{177}Lu-PSMA I&T were, for example, 1.65 ± 0.28 and 0.73 ± 0.18 Gy/GBq for the kidneys, 0.19 ± 0.09 and 0.07 ± 0.03 Gy/GBq for the liver, 2.35 ± 0.78 and 0.80 ± 0.41 Gy/GBq for the parotid gland, and 0.67 ± 0.62 and 0.30 ± 0.27 Gy/GBq for the bone marrow, respectively. Tumor lesions received mean absorbed doses of ^{177}Lu-rhPSMA-7.3 and ^{177}Lu-PSMA I&T of 6.44 ± 6.44 and 2.64 ± 2.24 Gy/GBq, respectively. The mean TIs for the kidneys were 3.7 ± 2.2 and 3.6 ± 2.2 for ^{177}Lu-rhPSMA-7.3 and ^{177}Lu-PSMA I&T, respectively, and those for the bone marrow were 15.2 ± 10.2 and 15.1 ± 10.2 for ^{177}Lu-rhPSMA-7.3 and ^{177}Lu-PSMA I&T, respectively. **Conclusion:** Pretherapeutic clinical dosimetry confirmed preclinical results of mean absorbed doses for tumors that were 2–3 times higher for ^{177}Lu-rhPSMA-7.3 than for ^{177}Lu-PSMA I&T. Absorbed doses to normal organs also tended to be higher for ^{177}Lu-rhPSMA-7.3, resulting overall in similar average TIs for both radiopharmaceuticals with considerable interpatient variability. ^{177}Lu-rhPSMA-7.3 has promise for a therapeutic efficacy similar to that of ^{177}Lu-PSMA I&T at smaller amounts of injected activity, simplifying radiation safety measurements (especially for large patient numbers or dose escalation regimens).

Key Words: ^{177}Lu-rhPSMA-7.3; ^{177}Lu-PSMA I&T; dosimetry; mCRPC; prostate cancer; PSMA

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Treatment of metastatic castration-resistant prostate cancer (mCRPC) remains challenging. ^{177}Lu-PSMA radioligand therapy (RLT) is an option with a variety of different prostate-specific membrane antigen (PSMA) ligands developed in recent years (*1*). Several prospective and retrospective studies proved that ^{177}Lu-PSMA (using either PSMA-617 or PSMA I&T) had substantial antitumor effects (*2,3*). Most recently, the VISION trial showed longer median radiographic progression-free survival (8.7 vs. 3.4 mo) and overall survival (15.3 vs. 11.3 mo) for ^{177}LuPSMA-617 versus the standard of care, respectively, in PSMA-positive mCRPC after the use of taxane and next-generation androgen receptor signaling inhibitor agents (*4*).

For the assessment of new radiopharmaceuticals, dosimetry is essential to link the potential range of injected activities with therapeutic responses and possible side effects. For example, PSMA ligands can exhibit intense tracer accumulation in some normal organs, such as the kidneys. Dosimetric results have been published for the theranostic DOTA-conjugated PSMA ligands ^{177}Lu-PSMA-DKFZ-617 and ^{177}Lu-PSMA I&T (*5*), including both pretherapeutic (*6*) and posttherapeutic (*7–10*) evaluations.

Recently, a class of radiohybrid PSMA (rhPSMA) ligands were developed. They are theranostic agents allowing both fluorination and labeling with radiometals (*11–14*). Preclinical data have proposed that the single diastereoisomer ^{18}F-rhPSMA-7.3 is the most promising clinical candidate (*15,16*). ^{18}F-rhPSMA-7.3 is currently in 2 phase 3 trials for PET imaging of primary (NCT04186819) and recurrent (NCT04186845) prostate cancers. Most recently, promising preclinical data on ^{177}Lu-rhPSMA-7.3 in comparison to ^{177}Lu-PSMA I&T were published (*16*).

Here, we present a retrospective analysis exploring the potential of ^{177}Lu-rhPSMA-7.3 in comparison to ^{177}Lu-PSMA I&T for endoradiotherapy in mCRPC. We used pretherapeutic comparative dosimetry data for normal organs and tumor lesions.

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For correspondence or reprints, contact Benedikt Feuerecker (benedikt.feuerecker@tum.de).
*Contributed equally to this work.
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MATERIALS AND METHODS

Patients and Rationale for Comparative Dosimetry

According to current German guidelines, mCRPC patients after chemotherapy and novel antiandrogen therapy can be considered for ^{177}Lu-PSMA RLT after interdisciplinary tumor board discussion (*17*). All patients in the presented analysis had undergone chemotherapy and novel antiandrogen therapy before ^{177}Lu-PSMA.

Patients were informed that there are no approved PSMA-targeted therapies but that preliminary preclinical and clinical data support the antitumor activity of ^{177}Lu-PSMA I&T. Additionally, information about preclinical data showing higher uptake of ^{18}F-rhPSMA-7.3 and higher absorbed doses of ^{177}Lu-rhPSMA-7.3 in tumors (*14,16*), indicating higher radiation doses to tumor tissue of ^{177}Lu-rhPSMA-7.3 than of ^{177}Lu-PSMA I&T for clinical use, was provided.

Patients were offered pretherapeutic administration of both ^{177}Lu-PSMA I&T and ^{177}Lu-rhPSMA-7.3 to determine tumor and normal organ doses. Subsequent treatment was then performed with the agent that showed favorable tumor-to-normal organ dose ratios or with ^{177}Lu-PSMA I&T if the differences in the tumor-to-normal organ dose ratios were similar. ^{177}Lu-PSMA I&T and ^{177}Lu-rhPSMA-7.3 were prepared in compliance with the German Medicinal Products Act, AMG §13 2b, and after informing the responsible regulatory body (Government of Oberbayern, Germany). The institutional review board of the Technical University of Munich approved the retrospective scientific analysis of the dosimetry data (115/18 S-KK).

Between April 2018 and November 2020, 6 patients agreed to undergo these dosimetric investigations. Patient characteristics are presented in Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org). The approach was based on the rationale of individual selection of the optimal ligand for a specific patient to offer the possibility of benefit from higher tumor uptake, as recent preclinical data indicated (*16*).

Definitions of Therapeutic Index (TI) and Relative TI (rTI)

To assess the potential antitumor effect in relation to organs at risk of ^{177}Lu-PSMA I&T versus ^{177}Lu-rhPSMA-7.3, a TI was calculated. It was defined as the mean radiation dose to tumor lesions divided by the radiation dose to relevant organs at risk. As the kidneys and bone marrow are the most relevant organs, we report the TI for the kidneys and the TI for the bone marrow (*4*). The respective rTI was defined as the ratio of the TI of ^{177}Lu-rhPSMA-7.3 to the TI of ^{177}Lu-PSMA I&T, with a value of greater than 1 indicating a distribution favoring ^{177}Lu-rhPSMA-7.3.

Pretherapeutic Dosimetry, Image Analysis, and Dosimetric Calculations

The mean applied pretherapeutic activities were 1,066 ± 83 MBq (range, 1,000–1,243 MBq) for ^{177}Lu-PSMA I&T and 1,012 ± 51 MBq (range, 917–1,083 MBq) for ^{177}Lu-rhPSMA-7.3. Activity was injected over approximately 1 min and was followed by a saline flush. Specific activities were 47.5 GBq/0.59 μmol for ^{177}Lu-PSMA I&T and 47.5 GBq/0.61 μmol for ^{177}Lu-rhPSMA-7.3. The mean time period between application of both agents was 172 h (range, 166–190 h). Whole-body scintigraphy was performed at least 1 h, 4 h, 24 h, 48 h, and 7 d after administration.

Individual patient absorbed doses for the whole body, kidneys, liver, parotid, submandibular, and lacrimal glands, tumor lesions, and red bone marrow were estimated on the basis of the MIRD scheme, as recommended in the European Association of Nuclear Medicine Dosimetry Committee Guidelines. Absorbed organ and tumor doses for each cycle were calculated using OLINDA/EXM (*18–20*). Details on the regions of interest (ROIs) for scintigraphy and the volume calculations for PET are given in the supplemental data (e.g., Supplemental Table 2).

Statistical Analysis

All continuous data reported are expressed as mean ± SD and range. A nonpaired *t* test followed by Welch correction was performed to compare means. Statistical analyses were conducted using GraphPad Prism (version 5.0; GraphPad Software).

RESULTS

Qualitative ^{177}Lu-PSMA I&T and ^{177}Lu-rhPSMA-7.3 Biodistributions on Pretherapeutic Scintigraphy

Physiologic uptake was seen in the lacrimal, parotid, and submandibular glands, kidneys, and small intestine; uptake was less pronounced in the liver and spleen. Uptake in excess of the background was also seen for multiple tumor lesions, with progressive accumulation up to 24–48 h after injection for ^{177}Lu-PSMA I&T and ^{177}Lu-rhPSMA-7.3 (Fig. 1). Delayed whole-body images (up to 7 d after therapy) exhibited long-term retention of ^{177}Lu-PSMA I&T and ^{177}Lu-rhPSMA-7.3 in the metastases, with nearly no residual uptake in normal organs.

Pretherapeutic Dosimetry of Normal Organs

The mean whole-body pretherapeutic effective dose for ^{177}Lu-rhPSMA-7.3 was 0.117 Gy (0.12 ± 0.07 Sv/GBq), and that for ^{177}Lu-PSMA I&T was 0.054 Gy (0.05 ± 0.03 Sv/GBq). The mean absorbed organ doses for ^{177}Lu-rhPSMA-7.3 and ^{177}Lu-PSMA I&T were 1.65 ± 0.28 and 0.73 ± 0.18 Gy/GBq, respectively, for the kidneys; 0.19 ± 0.09 and 0.07 ± 0.03 Gy/GBq, respectively, for the liver; 2.35 ± 0.78 and 0.80 ± 0.41 Gy/GBq for the parotid glands, respectively; 2.10 ± 0.86 and 0.67 ± 0.31 Gy/GBq for the submandibular glands, respectively; and 5.29 ± 2.16 and 1.92 ± 0.80 Gy/GBq for the lacrimal glands, respectively (Supplemental Table 3). Figure 2 and Supplemental

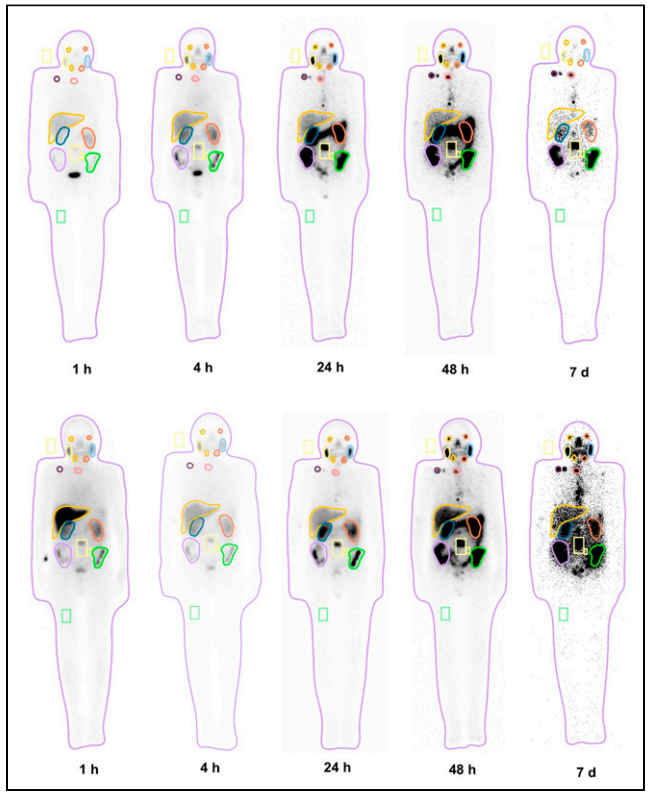

FIGURE 1. Examples of ROIs in 1 patient for ^{177}Lu-PSMA I&T (top) and ^{177}Lu-rhPSMA-7.3 (bottom).

Figs. 1 and 2 display mean organ doses, individual organ doses, and individual percentage injected doses.

Pretherapeutic Dosimetry of Bone Marrow

When ROIs were placed in the thigh regions, red bone marrow absorbed doses were 0.67 ± 0.62 Gy/GBq for ^{177}Lu-rhPSMA-7.3 and 0.30 ± 0.27 Gy/GBq for ^{177}Lu-PSMA I&T. Data for bone marrow dosimetry obtained with ROIs next to the lumbar spine for correction are presented in Supplemental Tables 3 and 4.

Pretherapeutic Dosimetry of Tumor Lesions

A total of 21 representative lesions were analyzed (14 bone and 7 lymph node metastases). Mean and individual sizes of individual tumor lesions are given in the supplemental materials and Supplemental Table 2.

The pretherapeutic mean absorbed doses of tumor lesions were 6.44 ± 6.44 Gy/GBq (range, 0.66–29.25 Gy/GBq) for ^{177}Lu-rhPSMA-7.3 and 2.64 ± 2.24 Gy/GBq (range, 0.38–9.80 Gy/GBq) for ^{177}Lu-PSMA I&T. The pretherapeutic mean absorbed doses for bone and lymph node metastases were 4.09 ± 2.57 and 11.14 ± 8.83 Gy/GBq, respectively, for ^{177}Lu-rhPSMA-7.3 and 1.70 ± 1.13 and 4.51 ± 2.69 Gy/GBq, respectively, for ^{177}Lu-rhPSMA-7.3 (Table 1). Figure 2 and Supplemental Figs. 1–3 display mean tumor doses, individual tumor doses, and individual percentage injected doses.

TI and rTI

The mean TIs for the kidneys were 3.7 ± 2.2 for ^{177}Lu-rhPSMA-7.3 and 3.6 ± 2.2 for ^{177}Lu-PSMA I&T. Intraindividual comparisons of ^{177}Lu-rhPSMA-7.3 and ^{177}Lu-PSMA I&T revealed a higher TIs for the kidneys in 2 patients for ^{177}Lu-rhPSMA-7.3 (patient 2: 5.1 vs. 3.7; patient 4: 1.6 vs. 1.1) and in 1 patient for ^{177}Lu-PSMA I&T (patient 6: 2.9 vs. 4.3). In 3 patients, no clear differences were seen (patient 1: 1.5 vs. 1.6; patient 3: 7.8 vs. 7.9; patient 5: 3.1 vs. 3.1). Consequently, the rTI for the kidneys was greater than 1 in patients 2 and 4 and less than or equal to 1 in all other patients. The individual TIs and the rTIs are shown in Figures 3A and 3B, respectively.

When ROIs in the thigh were used, the mean TIs for the bone marrow were 15.2 ± 10.2 for ^{177}Lu-rhPSMA-7.3 and 15.1 ± 10.2 for ^{177}Lu-PSMA I&T. Intraindividual comparisons of ^{177}Lu-rhPSMA-7.3 and ^{177}Lu-PSMA I&T revealed that ^{177}Lu-rhPSMA-7.3 showed higher TIs for the bone marrow in 4 patients (patient 1: 2.8 vs. 2.7; patient 2: 25.5 vs. 21.3; patient 3: 28.4 vs. 27.5; patient 4: 10.6 vs. 9.8). In 1 patient, no clear difference was measured (patient 5: 3.4 vs. 3.4), and in another patient, ^{177}Lu-PSMA I&T showed a higher TI for the bone marrow (patient 6: 20.3 vs. 25.7).

DISCUSSION

We presented data on pretherapeutic radiation dosimetry for normal organs and tumor lesions for ^{177}Lu-rhPSMA-7.3 and ^{177}Lu-PSMA I&T in 6 mCRPC patients. Quantitative analyses revealed, on average, an absorbed dose to tumor lesions of ^{177}Lu-rhPSMA-7.3 that was 2.4 times higher than that of ^{177}Lu-PSMA I&T. This finding is in line with recent preclinical data demonstrating a 2.6-fold difference (*16*). However, in our clinical investigation, absorbed doses to normal organs were also 2–3 times higher (e.g., 2.3 for the kidneys, 2.9 for the parotid glands, and 2.2 for the bone marrow). Notably, these relationships substantially differed at the patient level.

Because of controversies about the extrapolation of preclinical evaluations, pretherapeutic clinical dosimetry is important (*21*). Currently, dosimetry for PSMA ligands focuses on absorbed doses delivered to normal organs, primarily the kidneys but also the salivary glands as the most relevant organs at risk. Despite numerically high absorbed doses to the salivary and parotid glands, clinically relevant toxicity has only been anecdotally reported and has been mainly transient (*22*). Although red bone marrow dosing is essential, its methodology is prone to errors—for example, as a result of the frequent presence of extensive bone metastases. Nevertheless, bone marrow toxicity even in the presence of extensive osseous metastases is not a frequent side effect (*4,23*).

rhPSMA ligands belong to a new class of fully theranostic agents (*16*). They allow the use of radiochemical twins, such as ^{19}F/^{177}Lu-rhPSMA or ^{18}F/^{nat}Lu-rhPSMA, for potential pretherapeutic PET-based imaging and subsequent PSMA RLT (*24*). Recently published promising preclinical data demonstrated that the radiohybrid ^{19}F/^{177}Lu-rhPSMA-7.3 is a suitable candidate for clinical translation because of similar clearance kinetics and radiation doses but superior tumor uptake and retention compared with ^{177}Lu-PSMA I&T (*16*). Using this approach, our aim was to investigate ^{177}Lu-rhPSMA-7.3 by comparing it to ^{177}Lu-PSMA I&T as the established agent for PSMA RLT, allowing us to maximize the absorbed radiation dose to tumor lesions and to minimize the absorbed radiation dose to relevant organs at risk.

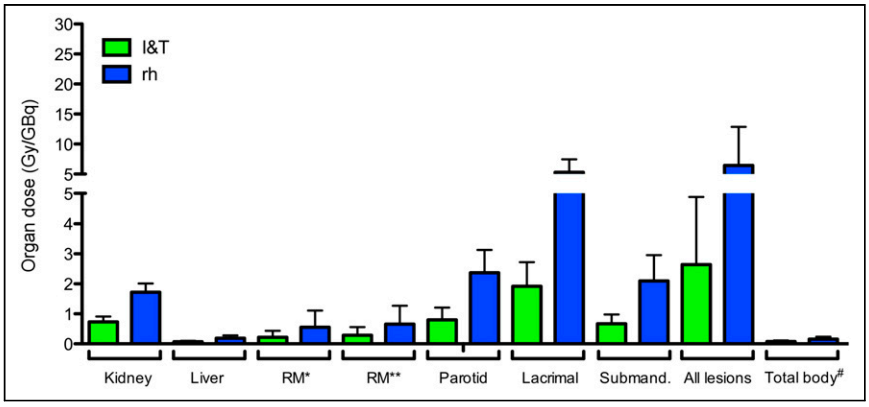

FIGURE 2. Mean organ doses (Gy/GBq) for kidneys, liver, parotid, lacrimal, and submandibular (Submand.) glands, and tumor lesions and total-body doses (Sv/GBq) determined with ^{177}Lu-PSMA I&T (I&T) and ^{177}Lu-rhPSMA-7.3 (rh) for all patients. Individual patient organ doses are shown in Supplemental Figs. 1–3. RM = red bone marrow. RM* = using an ROI for correction next to the lumbar spine (n = 4); RM** = using an ROI in the thigh (n = 6); #Sv/GBq.

When differences in radiation doses to normal organs are investigated, the kidneys are usually regarded as dose-limiting organs at risk. Pretherapeutic kidney doses in our 6 mCRPC patients were 2.3 times higher with ^{177}Lu-PSMA-7.3 than with ^{177}Lu-PSMA I&T. Regarding potential radiation damage, currently either 23 Gy with a 5% probability of late kidney damage within 5 y or 28 Gy with a 50% probability of late kidney damage within 5 y is used (*25*). For ^{177}Lu-PSMA I&T and ^{177}Lu-PSMA-617, severe kidney toxicity has been described as a side effect in only a few patients (*26*). However, care must be taken given the limited overall survival of late-stage mCRPC patients. Kabaskal et al. calculated a maximum activity of 32.9 GBq to achieve a 23-Gy kidney dose report for ^{177}Lu-PSMA-617 using pretherapeutic dosimetry (*10*). For ^{177}Lu-rhPSMA-7.3, our mean data would

TABLE 1
Effective Doses for Tumor and Ratios to Effective Doses for Kidney and Bone Marrow

			^{177}Lu-rhPSMA-7.3 (rh)			^{177}Lu-PSMA I&T (I&T)					
Patient	Tumor no.	Tumor site	Tumor dose (mGy/MBq)	TI for kidneys	TI for bone marrow	Tumor dose (mGy/MBq)	TI for kidneys	TI for bone marrow	Ratio of tumor rh to tumor I&T	rTI for kidneys	rTI for bone marrow*
1	1	B	3.00	1.91	3.63	1.31	2.07	3.45	2.30	0.92	1.05
	2	B	1.58	1.01	1.91	0.73	1.16	1.94	2.16	0.87	0.99
2	1	B	4.05	2.33	11.60	1.38	1.71	9.82	2.95	1.36	1.18
	2	B	6.94	3.99	19.90	2.31	2.88	16.51	3.00	1.39	1.21
	3	LN	29.25	16.81	83.81	9.80	12.20	70.00	2.98	1.38	1.20
	4	B	2.81	1.62	8.05	0.88	1.09	6.27	3.20	1.48	1.28
	5	B	1.53	0.88	4.37	0.52	0.65	3.72	2.94	1.35	1.18
3	1	LN	16.15	11.97	43.42	5.15	10.42	35.99	3.14	1.15	1.21
	2	LN	14.00	10.37	37.63	5.93	12.01	41.49	2.36	0.86	0.91
	3	B	1.56	1.16	4.20	0.73	1.47	5.07	2.15	0.79	0.83
4	1	B	2.21	1.24	8.24	0.92	0.97	8.45	2.40	1.28	0.98
	2	LN	3.46	1.94	12.91	1.22	1.28	11.19	2.84	1.52	1.15
5	1	B	6.88	3.23	3.55	2.79	2.96	3.26	2.47	1.09	1.09
	2	B	6.67	3.13	3.44	3.00	3.18	3.51	2.22	0.99	0.98
	3	B	5.92	2.78	3.05	2.69	2.85	3.14	2.20	0.98	0.97
	4	B	9.49	4.46	4.89	4.37	4.63	5.11	2.17	0.96	0.96
	5	B	3.91	1.84	2.02	1.82	1.93	2.13	2.15	0.95	0.95
6	1	B	0.66	0.50	3.38	0.38	0.66	4.00	1.72	0.75	0.85
	2	LN	8.05	6.05	41.28	4.66	8.06	48.54	1.73	0.75	0.85
	3	LN	3.38	2.54	17.32	1.93	3.33	20.06	1.75	0.76	0.86
	4	LN	3.71	2.79	19.03	2.89	5.00	30.10	1.28	0.56	0.63
Mean ± SD for all			6.44 ± 6.44[†]	3.93 ± 4.07[‡]	16.08 ± 19.79[‡]	2.64 ± 2.24	3.83 ± 3.58	15.89 ± 18.28	2.39	1.05	1.01
Mean ± SD for B			4.09 ± 2.57[§]	2.15 ± 1.17[‡]	5.87 ± 4.68[‡]	1.70 ± 1.13	2.02 ± 1.11	5.46 ± 3.76	2.43	1.08	1.03
Mean ± SD for LN			11.14 ± 8.83[‡]	7.50 ± 5.27[‡]	36.49 ± 22.49[‡]	4.51 ± 2.69	7.47 ± 4.03	36.77 ± 17.90	2.30	1.00	0.97

*Results for red marrow dosimetry using ROI placed in thigh.
[†]$P = 0.02$.
[‡]Not significant.
[§]$P = 0.007$.
B = bone; LN = lymph node.
Data for all patients are presented for individual tumor lesions and grouped by tumor lesion type.

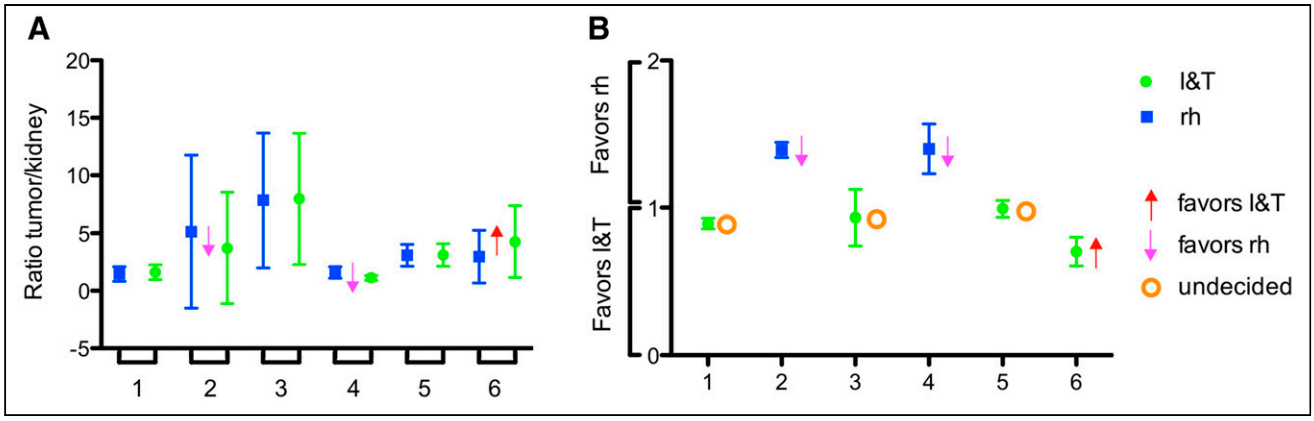

FIGURE 3. TIs (A) and rTIs (B) for tumor-to-kidney ratio for each individual patient. Values of >1 indicate favorable biodistribution for ^{177}Lu-rhPSMA-7.3 (rh) compared with ^{177}Lu-PSMA I&T (I&T) and vice versa. Two patients had favorable distribution of ^{177}Lu-rhPSMA-7.3, 1 patient had favorable distribution of ^{177}Lu-PSMA I&T, and in 3 patients no clear preference was observed.

indicate the option to apply approximately 17 GBq on the basis of a mean of 1.65 Gy/GBq. However, this lower activity would achieve similar absorbed tumor doses. It remains to be decided which activity levels and timing of cycles will be pursued in any potential clinical development of ^{177}Lu-rhPSMA-7.3. Nevertheless, we believe that the presented data might inform potential future study protocols.

Notably, given the results of the VISION trial, bone marrow toxicity is a rare but relevant side effect (*4*). In our retrospective study, the radiation delivery to the bone marrow was 2.2 times higher for ^{177}Lu-rhPSMA-7.3. The relative TI of 1.2, integrating absorbed doses to both tumors and bone marrow, suggests only a slight improvement over ^{177}Lu-PSMA I&T.

However, the calculation of red bone marrow doses is complex when based on scintigraphic images. For example, in 2 of our patients, radiation exposure of the bone marrow was probably overestimated because of the presence of tumor lesions in the ROI. Nevertheless, although important for absolute values, the ratio between ^{177}Lu-rhPSMA-7.3 and ^{177}Lu-PSMA I&T was probably less affected. Our results for bone marrow dosimetry showed mean absorbed doses of 0.67 ± 0.62 mGy/MBq for ^{177}Lu-rhPSMA-7.3 and 0.30 ± 0.27 mGy/MBq for ^{177}Lu-PSMA I&T. These doses resulted in a favorable tumor-to-bone marrow index in 3 patients. The absolute values were substantially higher than those reported in the literature for ^{177}Lu-PSMA-617, but the difference can be mainly explained by the different methods (thigh vs. lumbar spine correction) (*7,8*).

It is important to emphasize that the absorbed dose limits for solid organs are based on conventionally fractionated external-beam therapy and cannot necessarily be directly applied to low-dose-rate radiation (*27*). Patients without risk factors for kidney disease might tolerate a renal biologic equivalent dose up to 40 Gy, on the basis of experience with radiopeptide treatment of neuroendocrine tumors (*28*). However, dosimetry is an important but not the only factor for determining the safety of a radionuclide treatment. As observed in a similar setting comparing somatostatin agonist and antagonist treatments, disproportionately higher hematotoxicity was observed with the somatostatin antagonist, with up to 57% of patients experiencing grade 4 hematotoxicity after 2 cycles (*29*).

High variability of absorbed doses was observed in tumor lesions, similar to data reported for ^{177}Lu-PSMA I&T (*5*) and ^{177}Lu-PSMA-617 (*8,30–32*). The broad range might be partially attributable to the fact that our patients had only a few lesions. Similar to organ dosimetry, the relationship of the absorbed doses of both ligands is a more reliable parameter than the absolute values. Okamoto et al. and Baum et al. reported absorbed doses between 0.22 and 12.0 Gy/GBq and between 0.02 and 78 Gy/GBq, respectively, for ^{177}Lu-PSMA I&T (*5,33*). For ^{177}Lu-PSMA-617, Violet et al. reported mean absorbed doses of 5.28 Gy/GBq for bone metastases and 3.91 Gy/GBq for lymph node metastases (*32*).

Integrating all the previously discussed data for organs and tumor lesions, we calculated the TI for the kidneys in all patients (Fig. 3). Ultimately, 2 patients were treated with ^{177}Lu-rhPSMA-7.3, as pretherapeutic dosimetry indicated a clear advantage. In 1 patient, ^{177}Lu-PSMA I&T was used, given its clearly favorable profile. In the remaining 3 patients, the TI did not favor either of the 2 PSMA ligands. On the basis of the TI for the bone marrow, 3 patients had a favorable profile for ^{177}Lu-rhPSMA-7.3 and 3 patients had a favorable profile for ^{177}Lu-PSMA I&T.

Our analyses warrant some discussion on how the different characteristics of ^{177}Lu-rhPSMA-7.3 can be exploited. Potential options for a drug development program would be the application of similar activities, as recommended for ^{177}Lu-PSMA I&T and ^{177}Lu-PSMA-617, which would lead to higher absorbed tumor doses and potential efficacy (*34*). This approach could be feasible given the so-far low toxicity profile of ^{177}Lu-PSMA in general, with reported injected activities of up to 2 doses of 11 GBq of ^{177}Lu-PSMA-617 (applied within 1 wk) (*35*). However, long-term toxicity for the kidneys of ^{177}Lu-PSMA in general is unclear, and even the potential dose limits are controversial. Alternatively, similar tumor and organ doses with a smaller amount of activity and subsequently with a lower cost could be achieved, especially when non–carrier-added ^{177}Lu is used for treatment (*36*). In the context of an expected large number of patients to be treated with PSMA RLT in the future, smaller amounts of ^{177}Lu would also improve practical aspects (e.g., radioactive material program licensing, improved radiation safety for involved medical personnel).

Our retrospective analysis has limitations. First, only a small number of patients could be analyzed. Second, numerous factors can impair the accuracy of PET and planar dosimetry and can lead to a decreased correlation of the 2 modalities. Overlay in planar scintigraphy can lead to an overestimation of the absorbed dose, and further errors can occur for volumetric assessment (*8,37*). We tried to minimize such errors by adjusting the volume of interest using information from PET for the anatomic configuration of the lesions. However, especially for bone lesions, anatomic delineation can be

difficult. Third, our dosimetry analyses for the bone marrow were prone to substantial challenges, as described earlier. As an alternative, we applied an additional method, using correction from tissue adjacent to the tissue in the thigh. In principle, this method is used in clinical dosimetry. However, as discussed earlier, it usually results in higher absorbed doses (less background to be subtracted in the thigh than adjacent to the lumbar spine), and no data are available in the literature to compare it with other PSMA ligands. Fourth, our pretherapeutic dosimetry using 1 GBq of ^{177}Lu-rhPSMA-7.3 and ^{177}Lu-PSMA I&T might already have achieved some therapeutic effect. Given the higher tumor doses delivered by ^{177}Lu-rhPSMA-7.3, the dosimetry of subsequent ^{177}Lu-PSMA I&T might be more affected than the dosimetry of ^{177}Lu-rhPSMA-7.3 after ^{177}Lu-PSMA I&T. We tried to minimize this bias by alternating the sequence of pretherapeutic applications.

CONCLUSION

Pretherapeutic clinical dosimetry confirmed preclinical results, with mean absorbed doses for tumors of ^{177}Lu-rhPSMA-7.3 that were 2–3 times higher than those of ^{177}Lu-PSMA I&T. Absorbed doses to normal organs increased at different levels, including the bone marrow. The newly introduced TI allowed for individual adjustment of absorbed tumor doses for the kidneys and the bone marrow as organs at risk. For the kidneys, it identified 2 of 6 patients with a clearly favorable biodistribution of ^{177}Lu-rhPSMA-7.3 compared with ^{177}Lu-PSMA I&T and a similar profile in 3 of 6 patients. For the bone marrow, a favorable profile was observed in 3 of 6 patients for ^{177}Lu-rhPSMA-7.3 and in 3 of 6 patients for ^{177}Lu-PSMA I&T. ^{177}Lu-rhPSMA-7.3 holds promise for a therapeutic effect similar to that of ^{177}Lu-PSMA I&T at lower absorbed doses and offers potential economical and radiation safety benefits.

DISCLOSURE

H.-J. Wester, A. Wurzer, and M. Eiber have applied for a patent for rhPSMA. H.-J. Wester is founder, shareholder, and advisory board member of Scintomics GmbH, Fuerstenfeldbruck, Germany. W.A. Weber reports prior consulting activities for Blue Earth Diagnostics Ltd. M. Eiber reports prior consulting activities for Blue Earth Diagnostics Ltd., Novartis, Telix, Progenics, Bayer, Point Biopharma, and Janssen. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Are the biodistribution, dosimetry, and therapeutic efficacy of ^{177}Lu-rhPSMA-7.3 and ^{177}Lu-PSMA I&T comparable?

PERTINENT FINDINGS: In mCRPC, pretherapeutic organ and tumor absorbed doses for ^{177}Lu-rhPSMA-7.3 were higher than those for ^{177}Lu-PSMA I&T, whereas the TI was equal to the mean for the kidney absorbed dose. Using ^{177}Lu-rhPSMA-7.3 could lead to the same therapeutic effect without higher nephrotoxicity and with smaller amounts of radioactivity.

IMPLICATIONS FOR PATIENT CARE: Pretherapeutic data indicate higher tumor absorbed doses for ^{177}Lu-rhPSMA-7.3 in radioligand treatment, a finding that should be explored in prospective clinical studies.

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