Repeated ^{177}Lu-Labeled PSMA-617 Radioligand Therapy Using Treatment Activities of Up to 9.3 GBq

Hendrik Rathke[1], Frederik L. Giesel[1], Paul Flechsig[1], Klaus Kopka[2], Walter Mier[1], Markus Hohenfellner[3], Uwe Haberkorn[1,4], and Clemens Kratochwil[1]

[1]Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany; [2]Division of Radiopharmaceutical Chemistry, German Cancer Research Center (DKFZ), Heidelberg, Germany; [3]Department of Urology, University Hospital Heidelberg, Heidelberg, Germany; and [4]Clinical Cooperation Unit Nuclear Medicine, German Cancer Research Center (DKFZ), Heidelberg, Germany

Current treatment protocols for ^{177}Lu-labeled PSMA-617 therapies were cautiously derived from dosimetry data, but their practical appropriateness has not yet been proven clinically. We retrospectively report our clinical observations using 4 different treatment activities. **Methods:** Forty patients with advanced prostate cancer and positive uptake in prostate-specific membrane antigen (PSMA) imaging were treated with 4 GBq of ^{177}Lu activity/80 nmol of precursor, 6 GBq of ^{177}Lu activity/120 nmol of precursor, 7.4 GBq of ^{177}Lu activity/150 nmol of precursor, or 9.3 GBq of ^{177}Lu activity/150 nmol of precursor (10 patients per group) every 2 mo. Safety was checked every 2 wk by laboratory tests, the prostate-specific antigen response was checked every 4 wk, and other effects were assessed by anamnesis. **Results:** The initial prostate-specific antigen response showed no correlation with treatment activity. However, 2 of 10, 4 of 10, 4 of 10, and 7 of 10 patients receiving doses of 4, 6, 7.4, and 9.3 GBq, respectively, were in partial remission 8 wk after completing all 3 cycles. This finding would be in line with but—because of low patient numbers—would not prove a positive dose–response relationship. Acute hematologic toxicity was also not correlated with treatment activity, and no more than 1 patient per group had grade 3/4 toxicity. Nevertheless, in contrast to the findings for the other groups, the mean platelet count in the 9.3-GBq group decreased chronically over time. **Conclusion:** If patients with diffuse red marrow infiltration and extensive chemotherapeutic pretreatments are excluded, then treatment activities of up to 3 injections of 9.3 GBq of ^{177}Lu-PSMA-617 every 2 mo are tolerated well. Further dose escalation should be conducted with care, as the highest dose seems to be close to the maximum tolerable dose.

Key Words: ^{177}Lu-PSMA-617; metastasized castration-resistant prostate cancer; ^{177}Lu; PSMA-RLT

Approximately 85%–90% of prostate cancer relapses occurring after curative intended primary therapy have a prostate-specific membrane antigen (PSMA)–positive tumor phenotype (1). It has also been reported that invasive growth, metastasis, and hormone independence are associated with an overexpression of PSMA histologically (2–4). Therefore, most patients with metastasized castration-resistant prostate cancer might be suitable for radioligand therapy (RLT) targeting PSMA (PSMA-RLT). The Glu-urea–based ligand PSMA-617 was preclinically optimized for low kidney uptake and improved ligand-induced cellular internalization. Coupling with DOTA enabled labeling with several diagnostic and therapeutic radionuclides (5). Different centers (6–8) reported favorable dosimetry for ^{177}Lu-PSMA-617 which—with regard to the kidney dose ($\sim$0.6 Gy/GBq) and the red marrow dose ($\sim$0.03 Gy/GBq)—outperformed a ^{177}Lu-labeled PSMA antibody (9), an ^{131}I-labeled small-molecule PSMA ligand (10), and the RLT reference compound ^{177}Lu-DOTATATE (11). On the basis of the available dosimetry data, the ^{177}Lu-PSMA-617 activities used for the first PSMA-RLTs were chosen cautiously. However, even these very first reports demonstrated promising antitumor activity (8,12). Nevertheless, tolerance limits for normal organs reported in the literature were based on external-beam radiotherapy and were only extrapolated to RLT using radiobiologic models, which themselves have manifold limitations, as reviewed recently (13). Thus, dosimetry in nuclear medicine can only provide guidance about doses in RLT; the optimal treatment regimen still must be refined clinically.

In this retrospective analysis, we report our clinical experience with doses of 4, 6, 7.4, and 9.3 GBq of ^{177}Lu-PSMA-617 repeated every 2 mo.

MATERIALS AND METHODS

Patients

RLT with ^{177}Lu-PSMA-617 was performed under the conditions of the updated Declaration of Helsinki (item 37 [unproven interventions in clinical practice]) and in accordance with the Pharmaceuticals Act [§13(2b)] as a salvage therapy for patients who had metastasized castration-resistant prostate cancer (which had to be resistant to or ineligible for approved options) and progressive disease. Patient selection is outlined in Figure 1. For patients stratified to receive ^{177}Lu-PSMA-617, each dose level was administered to 10 consecutive patients. If toxicities were comparable to those in the placebo group of the ALSYMPCA trial (14), then individual dose escalations for nonresponders were considered ethically justified; this approach resulted in a short learning phase using heterogeneous dose regimens between respective dose escalation groups. Data from patients in these heterogeneous interim groups were not suitable for this kind of systematic evaluation; however, some are available in other publications (8,15). The chronology of how the dose escalation was embedded into clinical practice is summarized in Figure 2. Patient
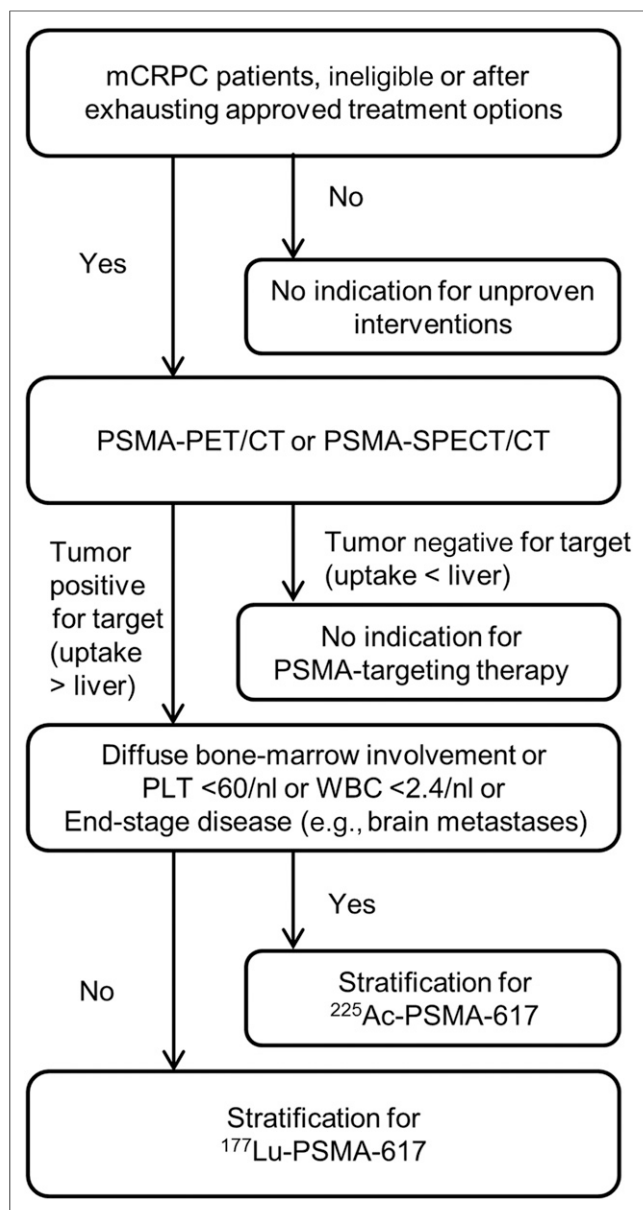
FIGURE 1. Clinical standard operating procedure for selection of patients to receive ^{177}Lu-PSMA-617 therapy. mCRPC = metastasized castration-resistant prostate cancer; PLT = platelets.

characteristics are summarized in Table 1. All patients were informed about the experimental character of the therapy and signed written informed consent forms. The clinical data are reported retrospectively with approval of the Ethics Committee of the Medical Faculty of Heidelberg University (Permit S-321).

Radiopharmaceuticals

The good manufacturing practices–grade precursor for PSMA-617 was obtained from ABX Advanced Biochemical Compounds and labeled with ^{177}Lu, which was obtained from either iTG or Perkin–Elmer, as described previously (8). The molar activity was 1 GBq of ^{177}Lu per 20 nmol of precursor, with a maximum amount of 150 nmol of injected substance. Quality control of the drug was performed by reverse-phase high-performance liquid chromatography and instant thin-layer chromatography pretherapeutically and always revealed labeling yields of greater than 99%.

Treatment Protocol

According to the German Radiation Protection Ordinance, patients were treated as inpatients for 48 h and discharged when the γ-emission from the patients was less than 3.5 μSv/h at a 2-m distance. On the therapy day, laboratory tests and anamnesis were performed. The therapy solution was injected manually over 30–60 s via a low-protein-binding sterile filter (Filtropur S 0.2; Sarstedt). Patients received concomitant intravenous hydration (2,000 mL; started 30 min before application of the therapy solution). The intention-to-treat protocol was a 3-cycle PSMA therapy, with cycles administered every 2 mo. Radiologic restaging was planned for 2 mo after the third cycle but was done earlier in cases of clinical and biochemical progression.

Follow-up

Laboratory tests were performed every 2 wk for 8 wk after each cycle. Blood cell counts were checked every 2 wk; serum creatinine, blood urea nitrogen, alkaline phosphatase, liver enzyme, and prostate-specific antigen (PSA) levels were checked every 4 wk. Hematologic toxicity was translated into a grading scale according to the Common Terminology Criteria for Adverse Events Version 4.0 (16). Clinical side effects at each treatment cycle were assessed by anamnesis.
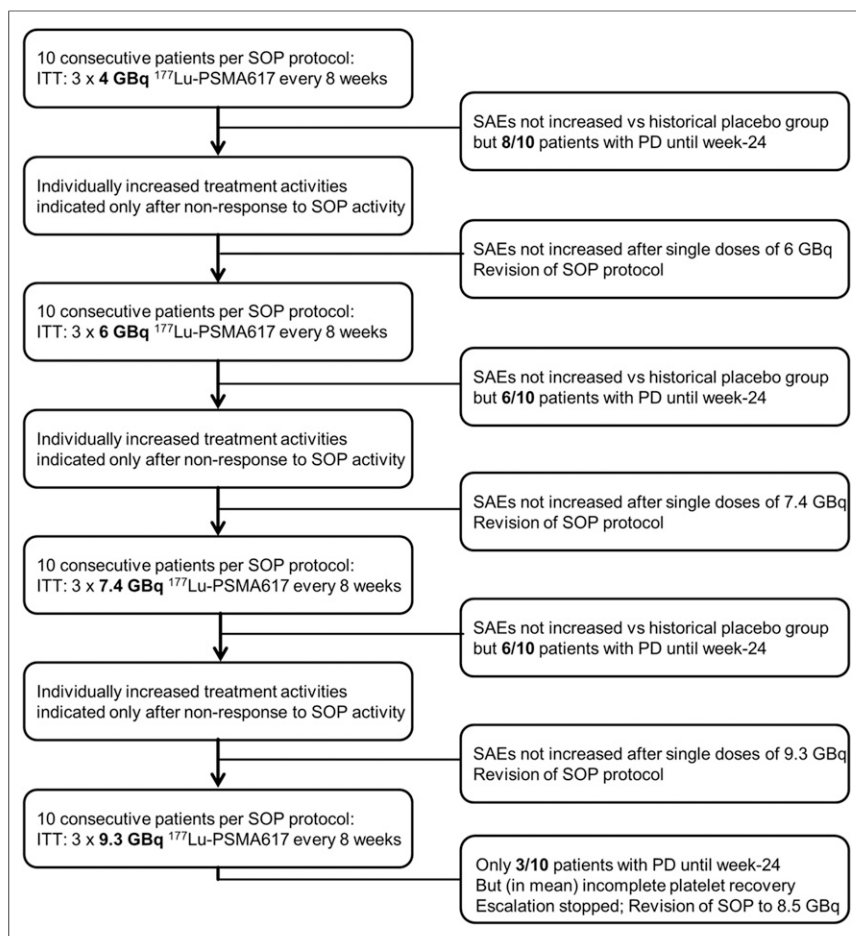
RESULTS

Clinical Findings

The administration of each treatment cycle was tolerated well by all patients. No serious nonhematologic side effects were observed, and grade 4 hematologic toxicity was observed in only 1 patient (in the 9.3-GBq group). Especially after the first cycle and irrespective of dose group, patients with symptomatic bone metastases reported a transient increase in pain (flare-up) in the known metastases in the first 1–4 d after treatment and then a decrease in pain symptoms to below the baseline.

Hematologic Toxicity

Data from 8 wk of follow-up were available for all patients in each group. The mean counts of platelets and white blood cells (WBCs) over time are shown in Figure 3. In the 4-, 7.4-, and 9.3-GBq groups, platelets showed a nadir at week 4, but this trend was very moderate; this pattern was not demonstrated in the 6-GBq group. WBC counts typically dropped during the first 2 wk; later, they were undulant over serial time points. For patients who completed 3 cycles, including the respective follow-up, the courses of platelet and WBC counts over the complete 24-wk period (i.e., 6 mo) are shown in Figure 3. In the 9.3-GBq group, a chronic decrease in platelet counts during follow-up was observed; however, in most patients, the absolute counts were still in the reference range.

After the first cycle, 1 patient in the 4-GBq group had grade 3 thrombocytopenia (38 platelets/nL), and 2 patients in this group had grade 2 leukopenia (WBC counts decreased from 2.46/nL at baseline to 2.3/nL at week 8 in 1 patient and from 3.63/nL at baseline to 2.7/nL at week 8 in the other patient). In the 6-GBq group, only 1 patient had grade 1 thrombocytopenia, and no pathologic leukopenia was observed. In the 7.4-GBq group, 1 patient had grade 2 leukopenia (WBC counts decreased from 3.3/nL at baseline to 2.8/nL at week 8) and 1 patient had grade 3 leukopenia (WBC counts decreased from 4.35/nL at baseline to 1.9/nL at week 6 but recovered to 2.54/nL at week 8) accompanied by grade 1 thrombocytopenia. In the 9.3-GBq group, blood cell counts worsened by only 1 toxicity grade and no grade 3/4 result was observed after the first therapeutic injection.

FIGURE 2. Flowchart demonstrating how dose escalation was embedded in clinical practice, resulting in chronological separation of patients into dose groups. ITT = intention to treat; PD = progression of disease; SAEs = serious adverse events; SOP = standard operating procedure.

During the 24-wk regimen, we additionally observed 1 patient with grade 1 thrombocytopenia (a platelet count of 85/nL at week 8 recovered to 218/nL at week 12) and 1 patient with grade 2 leukopenia (a WBC count of 2.57/μL at week 10 recovered to 4.38/μL at week 24) in the 6-GBq group. In the 7.4-GBq group, only 1 patient had grade 1 leukopenia after the second cycle (a WBC count of 3.0/μL at week 10). In the 9.3-GBq group, 1 patient had grade 4 thrombocytopenia (a platelet count of 21/nL at week 20), 1 patient had grade 1 leukopenia, and 2 patients had grade 2 leukopenia. The patient with grade 4 thrombocytopenia and concurrent grade 2 leukopenia received a dose reduction to 6 GBq for the third cycle to reduce hematologic side effects.

Like the mean cell count data, a small number of patients in all dose regimens developed a worsening of cell blood counts by more than 1 grade. In all affected patients, intratherapeutic ^{177}Lu emission scans indicated red marrow infiltration and progression in comparison with pretherapeutic PSMA imaging; these patients also shared a history of chemotherapy.

Response

The PSA response at 8 wk after the first treatment cycle, as shown graphically in waterfall graphs (Fig. 4), demonstrated no major differences among the 4 dose groups. Any decline in the PSA level was observed in 90%, 70%, 70%, and 80% of patients in the 4 dose

groups. A decline in the PSA level of greater than 50% was observed in 40%, 30%, 50%, and 30% of patients in the 4-, 6-, 7.4-, and 9.3-GBq groups, respectively.

Because of biochemical progression or delayed recovery of blood cell counts, only 21 of 40 patients completed the treatment as planned. From the population receiving the intention-to-treat protocol, 2 of 10 patients (4-GBq group), 5 of 10 patients (6-GBq group), 5 of 10 patients (7.4-GBq group), and 9 of 10 patients (9.3-GBq group) completed the 3 cycles of RLT in accordance with the protocol. An objective radiologic response at week 24 was demonstrated for 2 of 10 patients (4-GBq group), 4 of 10 patients (6-GBq group), 4 of 10 patients (7.4-GBq group), and 7 of 10 patients (9.3-GBq group). Except for 1 patient who experienced 61% PSA progression but had radiologically "stable disease," the imaging-based restaging correlated well with the PSA response. The PSA follow-up data for patients who completed the treatment in accordance with the protocol are summarized in Figure 5.

DISCUSSION

Here, we retrospectively report our clinical experience with various treatment activities of ^{177}Lu-PSMA-617 during salvage therapy of 40 patients with metastasized castration-resistant prostate cancer.

The first clinical application of PSMA-RLT was done in 2011–2012 using a ^{131}I-labeled PSMA ligand. The treatment activity was chosen after [124]I PET-based dosimetry, taking into account a 1-Gy red marrow tolerance dose; hematologic toxicities were mild (10). During repeated treatments, grade 3/4 hematologic toxicities remained rare (16). Any PSA response was demonstrated in 84% (21/25) of the patients (10); a PSA decline of greater than 50% after the first treatment cycle was achieved in 70.6% of 34 patients (17). PSMA-RLT based on ^{177}Lu has practical advantages, and the PSMA-617 ligand even has refined pharmacokinetics and radiation dosimetry (5,8). Thus, theoretically, ^{177}Lu-PSMA-617 should improve the therapeutic range of PSMA-RLT. Nevertheless, until now, the reported PSA response rates commonly have been remarkably lower; the largest multicenter investigation of ^{177}Lu-PSMA-617 reported only a 40% biochemical response rate after the first treatment cycle (17). Therefore, a critical discussion about currently used treatment protocols seems warranted.

Dosimetry studies of ^{177}Lu-PSMA-617 have been performed with variable methodologies at different centers, but all investigators have reported similar results (6–8,18,19). The essential organs red marrow (~0.03 Gy/GBq) and kidneys (~0.6 Gy/GBq) should be considered dose-limiting organs (6–8,18,19). Given a red marrow tolerance dose of 1 Gy, single-cycle activities of up to 30 GBq of ^{177}Lu could be proposed (7). Taking into account the concept of a biologic effective dose during low-dose-rate radionuclide therapy, a kidney tolerance dose of 28–40 Gy was suggested for ^{177}Lu-radiopharmaceuticals

TABLE 1
Baseline Characteristics of Patients

Characteristic	Value in dose group*			
	4 GBq	6 GBq	7.4 GBq	9.3 GBq
Age (y)				
Median	75.5	70.5	70.5	73.5
Range	57–85	66–79	58–85	67–78
Gleason score				
Median	8	8	9	8
7	4	2	0	4
8	2	3	3	1
9	3	3	6	3
Unknown	1	2	1	1
Initial PSA level (ng/mL)				
Median	83	61	107	92
Range	2.4–2,801	1.2–387	12.9–1,176	48.5–626.2
WBCs (/nL)				
Mean	6.4	6.8	5.8	6.5
SD	3.2	3.4	2.3	2.3
Platelets (/nL)				
Mean	235.3	221.8	241.4	204.7
SD	83.2	70.6	81.0	47.6
Alkaline phosphatase level (U/L)				
Mean	138.8	131.7	252.5	202.1
SD	77.1	60.1	217.5	345.4
Hemoglobin level (g/dL)				
Mean	11.8	11.9	11.0	11.4
SD	2.4	1.5	2.1	1.7
Localization of metastases				
Lymph node	5	5	8	9
Bone	9	9	9	7
Liver	0	1	1	1
Lung	2	3	1	2
Brain	1	0	0	0
Other	3	2	3	0
Local recurrence	0	1	1	0
Previous therapy				
RPx	9	8	5	4
LRTx	5	6	6	3
CRPC	10	10	10	10
Abiraterone	4	6	8	8
Enzalutamide	3	2	7	10
Bisphosphonates	2	0	1	3
Denosumab	2	1	2	4
^{223}Ra	1	3	0	3
Taxane	4	4	5	8
Total dose (GBq)†	10.1 ± 4.8	13.3 ± 5.1	18.5 ± 3.9	25.4 ± 4.3

*There were 10 patients in each dose group.
†Reported as mean ± SD.
RPx = radical prostatectomy; LRTx = local radiation therapy; CRPC = castration-resistant prostate cancer.
Data are reported as number of patients unless otherwise indicated.
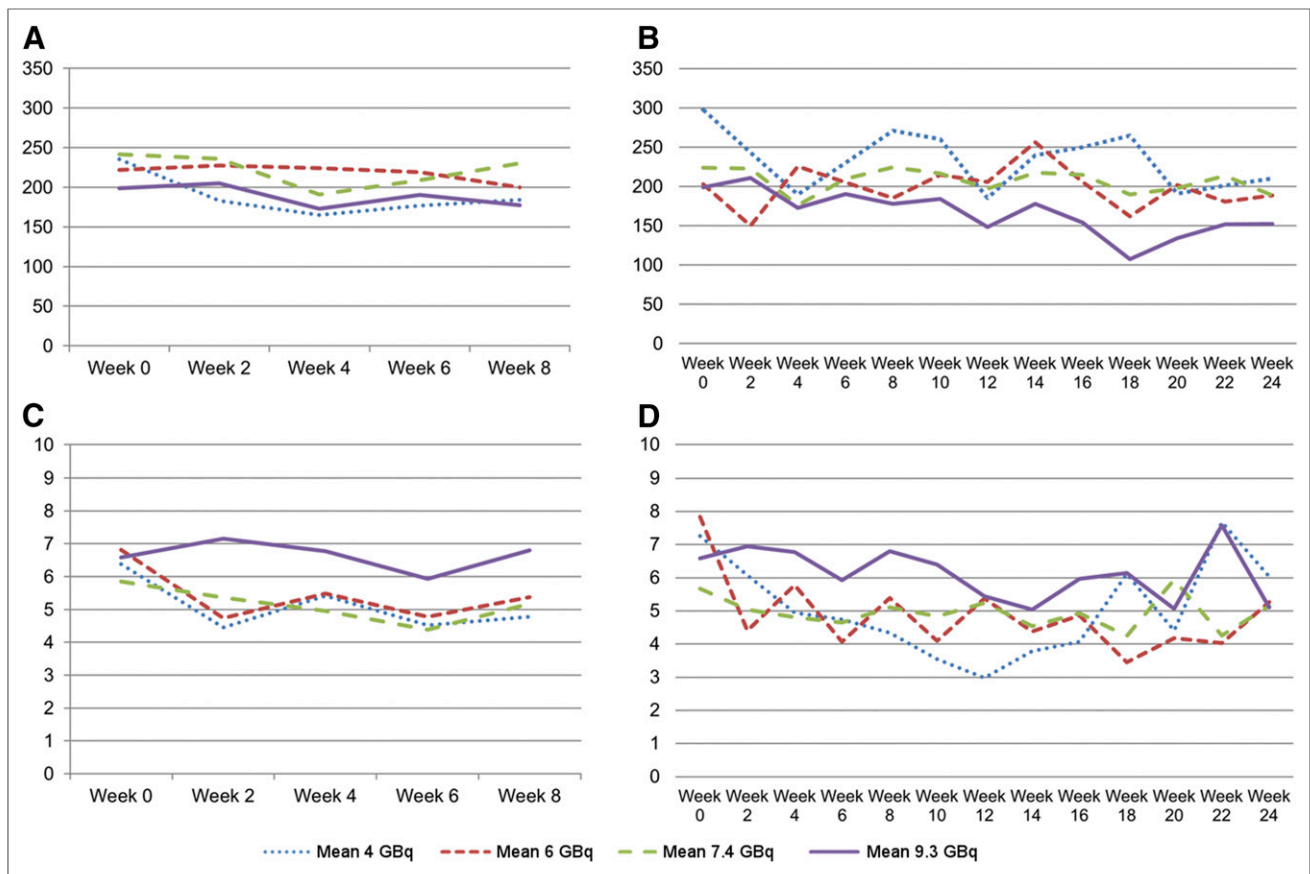
FIGURE 3. Hematologic toxicity over 8 wk (A and C) and 24 wk (B and D) of ^{177}Lu-PSMA-617 RLT. (A and B) Platelet counts (/nL); reference range is 150–440/nL. (C and D) WBC counts (/nL); reference range is 4–10/nL.

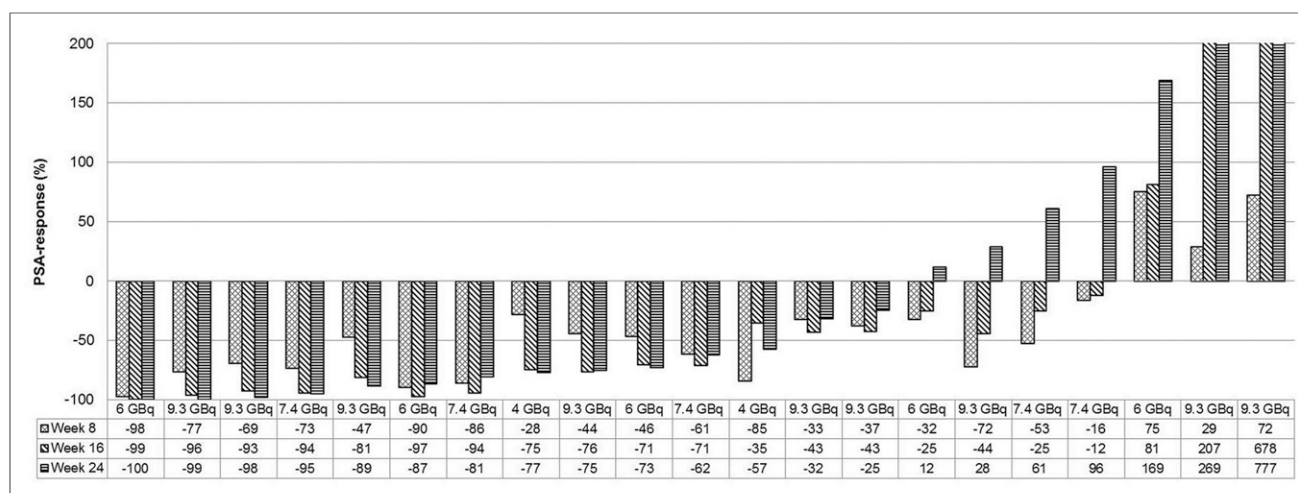*(20)*, theoretically making a cumulative treatment activity of 50 GBq of ^{177}Lu-PSMA-617 reasonable. No grade 3/4 renal toxicity was observed in 55 patients treated with 3 doses of 6 GBq of ^{177}Lu-PSMA-617 *(21)*. However, the high prevalence of bone metastases, the use of approved chemotherapeutic options before salvage therapy, and the

fact that the patients were elderly introduced some doubt about whether the tolerance doses of red marrow and other organs reported in the literature were still valid for the patient cohort. Thus, it was reasonable that ^{177}Lu-PSMA-617 RLT treatment regimens were initially introduced with caution.

Recent publications predominantly focused on a treatment activity of 6 GBq administered every 2 mo *(22–28)*, and the results were in agreement with each other. All authors reported few cases of grade 3/4 toxicity—that is, in the same dimension as the incidence of tumor-related adverse events observed in the placebo arm of the ALSYMPCA trial *(14)*—and, despite moderate xerostomia, there was no evidence of relevant treatment-related toxicity. However, the treatment activities used were remarkably lower than the projected maximum tolerance dose, according to dosimetry estimates: a red marrow dose of only 0.2 Gy (6 GBq × 0.03 Gy/GBq). Simultaneously, the PSA response rates were lower than older ^{131}I-PSMA RLT data obtained with the full 1-Gy red marrow tolerance limit *(10,16)*. Surprisingly, none of the authors *(22–28)* discussed the possibility that the escalation of ^{177}Lu treatment
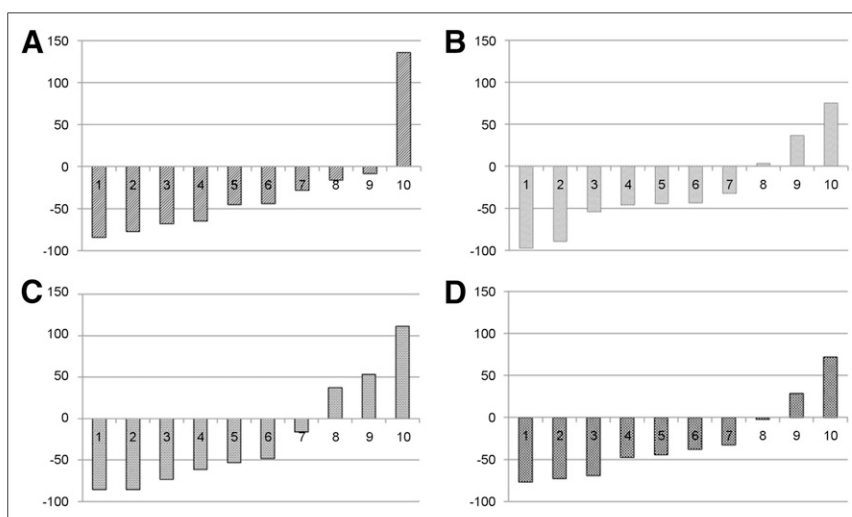
FIGURE 4. Waterfall graphs of initial (week 8) PSA responses for 4-GBq group (A), 6-GBq group (B), 7.4-GBq group (C), and 9.3-GBq group (D).

	6 GBq	9.3 GBq	9.3 GBq	7.4 GBq	9.3 GBq	6 GBq	7.4 GBq	4 GBq	9.3 GBq	6 GBq	7.4 GBq	4 GBq	9.3 GBq	9.3 GBq	6 GBq	9.3 GBq	7.4 GBq	7.4 GBq	6 GBq	9.3 GBq	9.3 GBq
☐ Week 8	-98	-77	-69	-73	-47	-90	-86	-28	-44	-46	-61	-85	-33	-37	-32	-72	-53	-16	75	29	72
☒ Week 16	-99	-96	-93	-94	-81	-97	-94	-75	-76	-71	-71	-35	-43	-43	-25	-44	-25	-12	81	207	678
▤ Week 24	-100	-99	-98	-95	-89	-87	-81	-77	-75	-73	-62	-57	-32	-25	12	28	61	96	169	269	777

FIGURE 5. Longitudinal follow-up of PSA levels during 3 cycles of ^{177}Lu-PSMA-617. Changes in PSA levels are presented as percentages (comparison of PSA level at particular week to PSA level at baseline).

activity to an estimated red marrow absorbed dose of 0.2–1.0 Gy should still be tolerated well and should offer the chance to further improve antitumor activity because a positive dose–response relationship is normally expected in radiotherapy. Therefore, after the clinical introduction of ^{177}Lu-PSMA-617, for us it seemed ethically mandatory to increase treatment activity until either tolerable grade 1/2 toxicity appeared or patients achieved enduring remission.

Because of limited numbers of patients, it is statistically not reasonable and not in the scope of the present report to draw a final conclusion about which dosing regimen provides the optimal therapeutic range. It was already reported that PSA and objective radiologic responses to PSMA-RLT correlated poorly with individual tumor absorbed doses (29). For individual patients, the respective radiosensitivity of the particular tumor and other clinical factors (30) seem to be relevant for determining response probability. It is possible that even high doses of ^{177}Lu-PSMA-617 cannot achieve the same response rates as ^{131}I-MIP1095 because this older ligand was used in the preabiraterone/preenzalutamide era and current patients have more previous therapies than these historical controls. Thus, an efficacy analysis cannot be based on a case series of serially treated patients but requires a group comparison after random assignment. For such a purpose, a prospective phase 2 study would be needed.

Up to the highest treatment activity (9.3 GBq), we did not observe increasing numbers of dose-limiting grade 3/4 toxicities. However, in contrast to a formal clinical trial, salvage therapy must be conservative. Thus, we made the clinical decision to stop dose escalation once we observed an incomplete recovery of blood cell counts to the baseline, even before critical absolute numbers were reached. Because there was no randomization (which would define the study as "medical research" and which is not possible during "unproven interventions in clinical practice"), simply by chance the 9.3-GBq group contained the most patients with previous chemotherapy and the highest alkaline phosphatase and PSA levels—which might be a sufficient explanation for the reduced red marrow reserve. Thus, the dose-limiting effects attributed to the 9.3-GBq activity might have been an accidental observation caused by patient selection, and even higher activities might be possible for

well-selected patients. However, our aim was to establish a reasonable standard operating procedure appropriate for patients currently scheduled to receive PSMA-RLT and without the routine need for sophisticated pretherapeutic dosimetry to identify statistical outliers in advance. The good tolerability observed in our patient series is well in line with the dosimetry-based expectation. The estimated average red marrow dose of 0.3 Gy/cycle (9.3 GBq × 0.03 Gy/GBq) is far below the accepted red marrow tolerance limit of 1 Gy and, with a ratio of 0.3:1 Gy, there are enough safety margins for individual patient variability to warrant the application of standard doses.

It should be noted that for patients with diffuse red marrow infiltration, we use [225]Ac-PSMA-617 targeted α-therapy (Fig. 1) whenever this radionuclide is available. These types of challenging patients might have been underrepresented in our patient cohort. Modeling of red marrow absorbed doses normally neglects the contribution of β-particles that are emitted from bone metastases to the surrounding healthy red marrow. For ^{177}Lu, the 1.5-mm maximum β-range in water corresponds to approximately 30 cell layers; this routinely neglected factor might be relevant in patient with very advanced disease. Thus, individual dose reductions should be considered for patients with diffuse red marrow infiltration.

CONCLUSION

For patients without extensive red marrow involvement, repeated applications of 7.4–9.3 GBq of ^{177}Lu-PSMA-617 per cycle are associated with moderate acute hematologic toxicity and other nonhematologic side effects. The incomplete platelet recovery observed in the 9.3-GBq group might imply that the potential for further dose escalations is limited. However, there is still a high demand for prospective controlled clinical trials to evaluate the fractionation regimen that enables the longest duration of tumor control and survival.

DISCLOSURE

Uwe Haberkorn and Klaus Kopka benefit from a patent for PSMA-617, which is held by their respective affiliations. No other potential conflict of interest relevant to this article was reported.

REFERENCES

1. Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the ^{68}Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging.* 2015;42:197–209.

2. Ross JS, Sheehan CE, Fisher HA, et al. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. *Clin Cancer Res.* 2003;9:6357–6362.

3. Sweat SD, Pacelli A, Murphy GP, Bostwick DG. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. *Urology.* 1998;52:637–640.

4. Wright GL Jr, Grob BM, Haley C, et al. Upregulation of prostate-specific membrane antigen after androgen-deprivation therapy. *Urology.* 1996;48:326–334.

5. Benešová M, Schäfer M, Bauder-Wüst U, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. *J Nucl Med.* 2015;56:914–920.

6. Delker A, Fendler WP, Kratochwil C, et al. Dosimetry for ^{177}Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2016;43:42–51.

7. Kabasakal L, AbuQbeitah M, Aygün A, et al. Pre-therapeutic dosimetry of normal organs and tissues of ^{177}Lu-PSMA-617 prostate-specific membrane antigen (PSMA) inhibitor in patients with castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging.* 2015;42:1976–1983.

8. Kratochwil C, Giesel FL, Stefanova M, et al. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with ^{177}Lu-labeled PSMA-617. *J Nucl Med.* 2016;57:1170–1176.

9. Bander NH, Milowsky MI, Nanus DM, Kostakoglu L, Vallabhajosula S, Goldsmith SJ. Phase I trial of [177]lutetium-labeled J591, a monoclonal antibody to prostate-specific membrane antigen, in patients with androgen-independent prostate cancer. *J Clin Oncol.* 2005;23:4591–4601.

10. Zechmann CM, Afshar-Oromieh A, Armor T, et al. Radiation dosimetry and first therapy results with a [124]I/^{131}I-labeled small molecule (MIP-1095) targeting PSMA for prostate cancer therapy. *Eur J Nucl Med Mol Imaging.* 2014;41:1280–1292.

11. Wild D, Fani M, Fischer R, et al. Comparison of somatostatin receptor agonist and antagonist for peptide receptor radionuclide therapy: a pilot study. *J Nucl Med.* 2014;55:1248–1252.

12. Ahmadzadehfar H, Eppard E, Kürpig S, et al. Therapeutic response and side effects of repeated radioligand therapy with ^{177}Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. *Oncotarget.* 2016;7:12477–12488.

13. Kumar C, Shetake N, Desai S, Kumar A, Samuel G, Pandey BN. Relevance of radiobiological concepts in radionuclide therapy of cancer. *Int J Radiat Biol.* 2016;92:173–186.

14. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369:213–223.

15. Rahbar K, Ahmadzadehfar H, Kratochwil C, et al. German multicenter study investigating ^{177}Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. *J Nucl Med.* 2017;58:85–90.

16. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Published May 28, 2009 (v4.03: June 14, 2010). Accessed November 10, 2017.

17. Afshar-Oromieh A, Haberkorn U, Zechmann C, et al. Repeated PSMA-targeting radioligand therapy of metastatic prostate cancer with ^{131}I-MIP-1095. *Eur J Nucl Med Mol Imaging.* 2017;44:950–959.

18. Yadav MP, Ballal S, Tripathi M, et al. Post-therapeutic dosimetry of ^{177}Lu-DKFZ-PSMA-617 in the treatment of patients with metastatic castration-resistant prostate cancer. *Nucl Med Commun.* 2017;38:91–98.

19. Kabasakal L, Toklu T, Yeyin N, et al. Lu-177-PSMA-617 prostate-specific membrane antigen inhibitor therapy in patients with castration-resistant prostate cancer: stability, bio-distribution and dosimetry. *Mol Imaging Radionucl Ther.* 2017; 26:62–68.

20. Bodei L, Cremonesi M, Ferrari M, et al. Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE: the role of associated risk factors. *Eur J Nucl Med Mol Imaging.* 2008;35:1847–1856.

21. Yordanova A, Becker A, Eppard E, et al. The impact of repeated cycles of radioligand therapy using [^{177}Lu]Lu-PSMA-617 on renal function in patients with hormone refractory metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2017;44:1473–1479.

22. Yadav MP, Ballal S, Tripathi M, et al. ^{177}Lu-DKFZ-PSMA-617 therapy in metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. *Eur J Nucl Med Mol Imaging.* 2017;44:81–91.

23. Fendler WP, Reinhardt S, Ilhan H, et al. Preliminary experience with dosimetry, response and patient reported outcome after ^{177}Lu-PSMA-617 therapy for metastatic castration-resistant prostate cancer. *Oncotarget.* 2017;8:3581–3590.

24. Ahmadzadehfar H, Rahbar K, Kürpig S, et al. Early side effects and first results of radioligand therapy with ^{177}Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Res.* 2015;5:36.

25. Rahbar K, Schmidt M, Heinzel A, et al. Response and tolerability of a single dose of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer: a multicenter retrospective analysis. *J Nucl Med.* 2016;57:1334–1338.

26. Rahbar K, Bode A, Weckesser M, et al. Radioligand therapy with ^{177}Lu-PSMA-617 as a novel therapeutic option in patients with metastatic castration resistant prostate cancer. *Clin Nucl Med.* 2016;41:522–528.

27. Bräuer A, Grubert LS, Roll W, et al. ^{177}Lu-PSMA-617 radioligand therapy and outcome in patients with metastasized castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging.* 2017;44:1663–1670.

28. Ahmadzadehfar H, Zimbelmann S, Yordanova A, et al. Radioligand therapy of metastatic prostate cancer using ^{177}Lu-PSMA-617 after radiation exposure to [223]Ra-dichloride. *Oncotarget.* 2017;8:55567–55574.

29. Okamoto S, Thieme A, Allmann J, et al. Radiation dosimetry for ^{177}Lu-PSMA I&T in metastatic castration-resistant prostate cancer: absorbed dose in normal organs and tumor lesions. *J Nucl Med.* 2017;58:445–450.

30. Ferdinandus J, Eppard E, Gaertner FC, et al. Predictors of response to radioligand therapy of metastatic castrate-resistant prostate cancer with ^{177}Lu-PSMA-617. *J Nucl Med.* 2017;58:312–319.