Pharmacokinetics and Biodistribution of ^{111}In- and ^{177}Lu-Labeled J591 Antibody Specific for Prostate-Specific Membrane Antigen: Prediction of ^{90}Y-J591 Radiation Dosimetry Based on ^{111}In or ^{177}Lu?

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^{111}In-Labeled antibodies and peptides have been routinely used as chemical and biologic surrogates for ^{90}Y-labeled therapeutic agents. However, recent studies have shown that there are significant differences in biodistribution between ^{111}In- and ^{90}Y-labeled agents. Yttrium and lutetium metals favor the +3 oxidation state, similar to indium, but there are minor differences in the solution and coordination chemistries among these metals. These 3 metals, however, form strong complexes with the macrocyclic chelator, 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid (DOTA). We, therefore, compared the pharmacokinetics and biodistribution of ^{111}In- and ^{177}Lu-labeled J591 antibody. The radiation dosimetry of ^{90}Y-J591 was estimated based on both ^{111}In and ^{177}Lu data to validate the usage of ^{111}In as a chemical and biologic surrogate for ^{90}Y. **Methods:** J591 is a deimmunized monoclonal antibody with specificity for the extracellular domain of prostate-specific membrane antigen. In patients with prostate cancer, phase I dose-escalation studies were conducted with ^{90}Y-J591 ($n = 29$) and ^{177}Lu-J591 ($n = 25$). Each patient had pharmacokinetics and imaging studies with ^{111}In-J591 (185 MBq/20 mg) over a period of 1 wk and before treatment with ^{90}Y-J591 antibody. In the ^{177}Lu trial, the pharmacokinetics and imaging studies were performed after treatment with the ^{177}Lu-J591 dose (370–2,590 MBq/m^2/10 mg/m^2) over a 2-wk period after treatment. **Results:** Blood and urinary pharmacokinetics were similar for both tracers. Based on biexponential decay, the terminal half-life was 44 ± 15 h for both tracers. In addition, the total-body retention of radioactivity over a 7-d period was also similar between the 2 isotopes. The percentage uptake in liver was about 20% greater with ^{111}In than with ^{177}Lu. Radiation dosimetry estimates for ^{90}Y-J591 calculated on the basis of ^{111}In or ^{177}Lu data were mostly similar and showed that liver is the critical organ, followed by spleen and kidney. Based on blood radioactivity, the radiation dose (mGy/MBq) to the bone marrow was 3 times higher with ^{90}Y (0.91 ± 0.43) compared with that with ^{177}Lu (0.32 ± 0.10). **Conclusion:** ^{111}In- and ^{177}Lu-labeled J591 antibodies have similar plasma and whole-body clearance kinetics. The net retention of ^{111}In activity by lung, liver, and spleen is slightly higher compared with that with ^{177}Lu. These results justify using ^{111}In as a chemical and biologic surrogate for ^{90}Y. However, the radiation dose to the liver may be overestimated by about 25% based on ^{111}In data. In addition, the data also suggest that ^{177}Lu may be a potential alternative for estimating the pharmacokinetics and biodistribution of ^{90}Y-labeled radiopharmaceuticals.

Key Words: antiprostate-specific membrane antigen antibody; ^{90}Y dosimetry; ^{177}Lu-labeled J591 monoclonal antibody

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In recent years targeted radioimmunotherapy (RIT) using monoclonal antibodies (mAbs) directed to cancer-related, cell-surface antigens has been clinically validated. ^{90}Y- and ^{131}I-labeled anti-B1 mAbs have shown 40%–70% antitumor response in patients with lymphoma and are approved by the Food and Drug Administration (*1,2*) for the treatment of patients with low-grade, non-Hodgkin's follicular lymphoma. ^{131}I and ^{90}Y have emerged as the primary choices for RIT; however, these 2 nuclides have potential advantages and disadvantages. ^{131}I has lower energy β^--particles and a longer physical half-life (maximum β^-, 0.61 MeV; $t_{1/2} = 8.04$ d) compared with that with ^{90}Y (maximum β^-, 2.28 MeV; $t_{1/2} = 2.67$ d). The radioiodinated mAb is dehalogenated in vivo, and the free radioiodide and the iodinated

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peptide fragments are washed out of tissues and excreted in the urine. In contrast, when ^{90}Y is bound to mAbs via a bifunctional chelate, the radiolabeled antibody complex is stable in vivo and ^{90}Y is trapped within the cell, leading to higher accretion by the tumor. ^{131}I has γ-photons (0.364 MeV) useful for biodistribution and dosimetry studies. Since ^{90}Y does not emit γ-photons, ^{111}In-labeled antibodies are generally used as chemical and biologic surrogates (*3,4*) to study biodistribution and estimate radiation dosimetry of ^{90}Y-labeled antibodies. Some recent studies, however, have shown that there are significant differences in biodistribution between ^{111}In- and ^{90}Y-labeled agents (*5*).

In addition to ^{90}Y, other β^--emitters—such as the lanthanide radiometals ^{177}Lu (maximum β^-, 0.497 MeV; $t_{1/2}$ = 6.74 d) and ^{166}Ho (maximum β^-, 1.84 MeV; $t_{1/2}$ = 1.12 d)—are also potentially useful for RIT. Unlike ^{90}Y, both ^{177}Lu (γ = 0.21 MeV) and ^{166}H (γ = 0.21 MeV) have useful γ-photons for biodistribution and dosimetry studies. Chemically, yttrium and lutetium metals favor the +3 oxidation state, similar to indium, but there are minor differences in the solution and coordination chemistries among these metals (*6–8*). Preclinical studies have shown that the in vivo behavior of ^{90}Y-labeled mAb is much more similar to that of ^{177}Lu-labeled antibody compared with that with ^{111}In-labeled antibody (*9*). Therefore, comparison of the pharmacokinetics and biodistribution of ^{111}In- and ^{177}Lu-labeled antibodies in human subjects would provide a better understanding of the in vivo behavior of mAbs labeled with these radiometals.

The process of developing successful radiolabeled antibodies for cancer RIT requires identification of a cancer-restricted, cell-surface antigen and development of an antibody specific for that target molecule. The most well-established, prostate cancer–restricted cell-surface antigen identified to date is prostate-specific membrane antigen (PSMA) (*10*). It is an ideal target for RIT, since it is a highly prostate-restricted, type II integral membrane cell-surface glycoprotein expressed by all prostate cancers (*11,12*), and expression levels progressively increase in more poorly differentiated, metastatic, and hormone-refractory cancers (*13,14*). J591 is an anti-PSMA mAb that binds with high affinity to the extracellular domain of PSMA and is rapidly internalized (*15–17*). We have recently reported excellent tumor targeting of radiolabeled J591 mAb in patients with prostate cancer (*18*).

We report here the pharmacokinetics and biodistribution data of 2 independent phase I dose-escalation clinical studies with J591 mAb labeled with ^{90}Y or ^{177}Lu. We compared the pharmacokinetics and biodistribution of ^{111}In-DOTA-J591 (DOTA = 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid) (^{111}In-J591) mAb with that of ^{177}Lu-DOTA-J591 (^{177}Lu-J591) mAb (*19*). In addition, we have also compared the radiation dosimetry estimates of ^{90}Y-DOTA-J591 (^{90}Y-J591) based on either ^{111}In or ^{177}Lu studies.

MATERIALS AND METHODS

Patient Population

Eligible patients had a prior histologic diagnosis of prostate cancer with evidence of recurrent or metastatic disease as defined by an increasing PSA level or abnormal radiologic studies, including bone scan, axial CT, or MRI. Patients were required to have a PSA level of ≥1.0 at the time of entry with 3 consecutive increasing PSA values over a period of ≥2 wk. Additional requirements included a platelet count of ≥150,000/mm^3 and a neutrophil count of ≥2,000/mm^3 and a bone marrow biopsy demonstrating ≤10% replacement by tumor on a unilateral sample or a mean of ≤25% replacement by tumor on bilateral samples.

Antibody

Murine J591 mAb was deimmunized by Biovation, Ltd. The deimmunization involves removal of mouse amino acid sequences and replacement with homologous human, nonimmunogenic sequences (*20*). Clinical grade deimmunized J591 mAb was produced under Good Manufacturing Practice (GMP) conditions at Lonza Biologics, Plc., and supplied in 5 mL of phosphate buffer (pH 7.0) containing 5 mg/mL of antibody. Subsequently, J591 antibody was covalently linked with the chelating agent, DOTA (Goodwin Biotech), as previously reported (*17*). The sterile pyrogen-free clinical material, DOTA-J591 mAb in 0.3 mol/L ammonium acetate buffer (pH 7.0) (8 mg/mL), was provided by BZL Biologics, Inc.

Radiolabeled Antibodies

^{111}In chloride and ^{90}Y chloride were purchased from Nordion. ^{177}Lu chloride was purchased from the University of Missouri-Columbia Research Reactor Center. The DOTA-J591 mAb was labeled by incubating radiometals in an ammonium acetate buffer with antibody as previously described (*17*). Radiolabeled J591 mAb was purified by gel filtration and sterilized by membrane (0.2 μm) filtration before administration to patients. The labeling efficiency and radiochemical purity of radiolabeled antibody were determined using Gelman ITLC-SG and 5 mmol/L diethylenetriaminepentaacetic acid (DTPA) solution as the solvent. The immunoreactivity of radiolabeled J591 mAb preparations was determined based on the method of Lindmo et al. (*21*) using PSMA-positive LNCaP tumor cells.

Dose Escalation and Administration

In a dose-escalation trial with ^{90}Y-J591 (Table 1), patients received 185 MBq of ^{111}In-J591 for pharmacokinetics and biodistribution studies 1 wk before ^{90}Y-J591 administration. After com-

TABLE 1
Phase I Dose-Escalation Trial with ^{90}Y-J591

Dose level	Patients (*n*)	^{111}In-J591		^{90}Y-J591	
		MBq	J591 (mg)*	MBq/m^2	J591 (mg)*
1	4	185	20	185	20
2	7	185	20	370	20
3	6	185	20	555	20
4	6	185	20	647.5	20
5	4	185	20	740	20

*^{111}In- or ^{90}Y-labeled DOTA-J591 (1–10 mg) was mixed with unlabeled J591 mAb to administer a total of 20-mg antibody mass.

pletion of the ^{111}In studies, each patient received the ^{90}Y dose, which was escalated in cohorts of 3–6 patients at the following planned dose levels: 185, 370, 555, 647.5, and 740 MBq/m^2 (5–20 mCi/m^2). In the dose-escalation trial with ^{177}Lu-J591 (Table 2), patients received ^{177}Lu activity ranging from 370 to 2,775 MBq/m^2 (10–75 mCi/m^2). Additional unconjugated (unlabeled) J591 antibody was added to give a constant protein dose of 20 mg with the ^{111}In- or ^{90}Y-J591 dose or 10 mg/m^2 with the ^{177}Lu dose. The final radiolabeled J591 mAb was diluted to 20 mL with physiologic saline solution and was infused intravenously over a period of 5 min.

Pharmacokinetics

After infusion of the diagnostic dose of ^{111}In-J591 or the treatment dose of ^{177}Lu-J591, venous blood samples were obtained at 10 min, 1, 2, 4, and 24 h, and 2, 3, 4, and 7 d. In the ^{177}Lu protocol, 2 additional samples were obtained during 10–14 d. The radioactivity in 1-mL plasma samples was measured in an automatic γ-counter (MINAXI γ-5550; Packard Instrument Co.) along with a known ^{111}In or ^{177}Lu standard, and the activity in plasma was expressed as the percentage injected dose per milliliter (%ID/mL) The time–activity data were plotted using GraphPad Prism software, and the curves were fitted to mono- and biexponential functions to generate plasma clearance rate constants. Based on the initial (α) and terminal (β) $t_{1/2}$ and the *y*-intercepts, several parameters—including the area under the curve (AUC), maximum concentration in plasma (C_{max}), volume of distribution (V_d), and clearance rate—were calculated.

Imaging Studies

To assess the biodistribution of J591 mAb, total-body images were obtained within 1 h after infusion (day 0) and again at 4 additional time points in the subsequent week (e.g., 1, 2, 3, and 6–7 d) for ^{111}In and over the next 2 wk (e.g., 1, 3, 6–9, and 13–14 d) for ^{177}Lu. The γ-camera images were obtained using a dual-head ADAC Laboratories or General Electric γ-camera fitted with an appropriate collimator. All 5 scans for each patient were obtained with the same γ-camera. Scan consistency and camera reliability were verified with an ^{111}In (1.85 MBq/20 mL) or a ^{177}Lu (11.1 MBq/20 mL) standard placed between the patient's legs. The imaging dataset at each time point was corrected for the presence of the standard, background counts, scan speed, and physical decay and then the data were normalized to the day 0 counts. SPECT studies of the abdomen, pelvis, or areas of suspected metastatic lesions were performed on day 2–3 or day 6–7 in selected patients.

TABLE 2
Phase I Dose-Escalation Trial with ^{177}Lu-DOTA-J591

Dose level	Patients (*n*)	^{177}Lu-DOTA-J591	
		MBq/m^2	J591 (mg*/m^2)
1	3	370	10
2	3	555	10
3	5	1,110	10
4	5	1,665	10
5	3	2,220	10
6	6	2,590	10
7	3	2,775	10

*^{177}Lu-DOTA-J591 (1–15 mg) was mixed with unlabeled J591 mAb to administer a total of 10 mg/m^2 antibody mass.

Radiation Dosimetry

To determine the biodistribution of radiolabeled antibody, regions of interest (ROIs) were drawn around the major organs (heart, liver, spleen, kidneys, bone marrow, gastrointestinal tract, and bladder) and the whole body. The remainder was defined as whole-body counts minus the sum of counts in the specific ROIs. The data points representing the percentage injected dose (%ID/organ) were created and fitted to a monoexponential, a biexponential, or an uptake-and-clearance curve. After curve fitting and integration, the cumulative activity in each organ and the residence time (τ) for each organ were calculated. The percentage injected dose in blood (plasma) was used to estimate the cumulative activity in bone marrow assuming a ratio of 0.36 for bone marrow to blood (*22*). The ^{111}In data were used to estimate the residence times for ^{90}Y. The radiation-absorbed doses of ^{111}In-J591 and ^{90}Y-J591 were calculated by entering the corresponding residence times into the MIRDOSE software program (*23*), which computes the radiation-absorbed dose values as mGy/MBq (or rad/mCi) for each of the target organs. Since the MIRDOSE software did not provide S factors for ^{177}Lu, S factors were initially calculated based on the emission spectrum of ^{177}Lu. Subsequently, the radiation dosimetries of ^{111}In-, ^{90}Y-, and ^{177}Lu-labeled J591 mAb were all calculated based on a new code called OLINDA (Organ Level INternal Dose Assessment), developed at Vanderbilt University. This program performs internal dose calculations, principally for radiopharmaceuticals, using the RADAR (Radiation Dose Assessment Resource) method of dose calculations and RADAR dose factors (*24*). RADAR is a working group that maintains resources for internal and external dose calculations.

RESULTS

Patients

Sixty-four patients were enrolled in 2 independent phase I dose-escalation trials with ^{111}In/^{90}Y-J591 (n = 29) or ^{177}Lu-J591 (n = 35) between October 2000 and August 2003. We report here the dosimetry data in 27 patients from the ^{90}Y trial and 28 patients from the ^{177}Lu trial. Patients in both groups were 47–85 y old and had prior hormonal therapy, except for 1 patient. In the ^{90}Y study, some patients had prior radiotherapy (62%) or chemotherapy (41%). Similarly, in the ^{177}Lu study, some patients had radiotherapy (46%) or chemotherapy (29%). Most patients (60%) in both groups had bone metastasis based on bone scans, whereas some of them had soft-tissue metastasis identified by CT or MRI.

Radiolabeled Antibodies

With DOTA-J591 mAb, the radiolabeling efficiency of ^{111}In is higher (91% ± 8%) than that with either ^{177}Lu (78% ± 8%) or ^{90}Y (71% ± 8%). However, the radiochemical purity of radiolabeled J591 mAb is similar with ^{111}In (98% ± 2.1%), ^{177}Lu (99% ± 1%), or ^{90}Y (98% ± 1.5%). The specific activity with both ^{111}In-J591 and ^{90}Y-J591 is 111–222 MBq/mg compared with 185–481 MBq/mg with ^{177}Lu-J591. The immunoreactivity with all the 3 preparations is >80% (90 ± 8).

TABLE 3
Plasma Clearance Kinetics: ^{111}In-J591 vs. ^{177}Lu-J591

Pharmcokinetic parameter	Biexponential		Monoexponential	
	^{111}In-J591*	^{177}Lu-J591*	^{111}In-J591	^{177}Lu-J591
$t_{1/2}$ (h)			32.3 ± 8.1	39.1 ± 13.3
α	2.37 ± 1.94	2.04 ± 1.96		
β	44.20 ± 13.9	43.60 ± 16.1		
AUC	1.19 ± 0.44	1.49 ± 0.63	1.08 ± 0.4	1.42 ± 0.60
C_{max} (%ID/mL)	0.026 ± 0.001	0.027 ± 0.005	0.023 ± 0.005	0.025 ± 0.005
V_d (mL) at t_0	4,042 ± 863	3,952 ± 1,072	4,467 ± 811	4,156 ± 858
Clearance (mL/h)	94 ± 34	84 ± 46	98 ± 43	88 ± 47

*Last time point with ^{111}In was 146 ± 13 h and with ^{177}Lu was 320 ± 15 h.
t_0 = time zero.
The difference between ^{111}In and ^{177}Lu data was statistically insignificant ($P > 0.05$).

Pharmacokinetics

Pharmacokinetic analysis of plasma samples obtained after the administration of ^{111}In-J591 or ^{177}Lu-J591 mAbs is summarized in Table 3. After intravenous administration, the maximum concentration (C_{max}) in plasma (%ID/L) was about 25% for both agents. There is biexponential plasma clearance; <20% of the activity had a fast component with a $t_{1/2}$ of <3 h. The remaining 80% of both ^{111}In-J591 and ^{177}Lu-J591 activity cleared from plasma slowly, with an average $t_{1/2}$ of 44 ± 15 h. Based on monoexponential clearance, the $t_{1/2}$ was a little longer with ^{177}Lu-J591 (39 ± 13) than that with ^{111}In-J591 (32 ± 8), but the difference was not significant ($P > 0.05$). The other pharmacokinetic parameters, such as AUC, V_d, and clearance, were also similar between these 2 agents.

The kinetics of urinary excretion of ^{111}In and ^{177}Lu activity until 72 h after injection is shown in Figure 1. After administration of radiolabeled J591, the percentage of injected radioactivity in the total urine collected over a period of 3 d is similar for both ^{111}In (6.2% ± 2.4%) and ^{177}Lu (7.3% ± 2.8%).

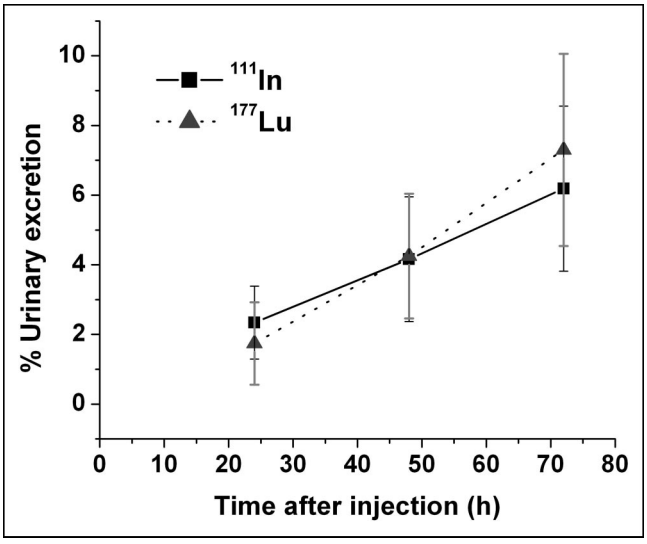

FIGURE 1. Urinary excretion of ^{111}In- and ^{177}Lu-labeled J591 mAb over 72-h period from time of administration to patients.

Imaging Studies and Biodistribution

Whole-body γ-camera images comparing the biodistribution of ^{111}In-J591 and ^{177}Lu-J591 are shown in Figures 2A and 2B. With both radionuclides, at 1 and 24 h after injection, radioactivity was predominantly in the blood pool, as

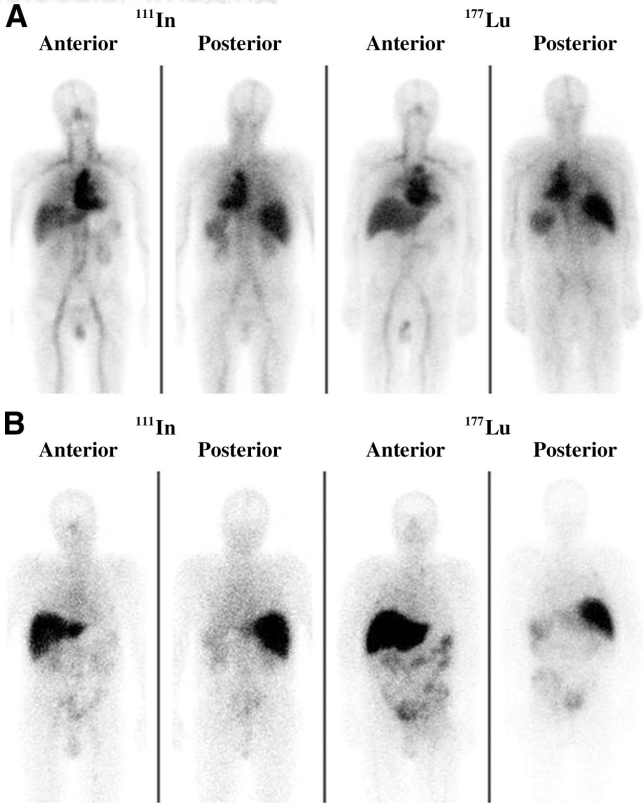

FIGURE 2. Whole-body images of ^{111}In-J591 and ^{177}Lu-J591 mAb on day 0 (A) and day 6 (B) after administration to 2 different patients.

TABLE 4
Biodistribution of Radiolabeled J591 mAb in Patients with Prostate Cancer: ^{111}In vs. ^{177}Lu

Organ	%ID of ^{111}In-DOTA-J591 (n = 26)			%ID of ^{177}Lu-DOTA-J591* (n = 23)			
	Day 0	Day 3	Day 6	Day 0	Day 2	Day 7	Day 13
Whole body	100	81.0 ± 5.5	66.1 ± 18	100	91.6 ± 10	69.8 ± 9.5†	41.6 ± 9.0
Remainder	52.3 ± 5.7	39.4 ± 7.1	24.9 ± 16.8	57.5 ± 6.4‡	51.5 ± 7.2	34.7 ± 6.9‡	18.4 ± 5.2
Heart contents	8.9 ± 2.3	4.5 ± 1.0	3.4 ± 1.2	8.8 ± 2.2†	5.7 ± 1.3	3.1 ± 0.9†	1.9 ± 0.4
Lungs	9.0 ± 2.0	5.5 ± 1.5	4.4 ± 1.7	6.9 ± 1.9‡	4.9 ± 1.4	3.1 ± 0.7‡	2.2 ± 0.6
Liver	14.7 ± 3.2	24.1 ± 5.9	28.0 ± 7.8	15.0 ± 3.8†	20.3 ± 6.2	23.7 ± 7.0§	16.5 ± 4.8
Spleen	10.9 ± 5.0	3.0 ± 2.2	1.2 ± 1.1	7.4 ± 2.4‡	3.6 ± 1.5	0.6 ± 0.4§	0.1 ± 0.1
Kidneys	2.4 ± 0.8	3.0 ± 0.8	2.5 ± 0.7	2.2 ± 0.5†	3.3 ± 0.9	2.5 ± 0.5†	1.3 ± 0.4

*Statistical significance of the difference between ^{177}Lu and ^{111}In was calculated for values on day 0 and day 6–7.
†$P > 0.1$.
‡$P < 0.01$.
§$P < 0.05$.

seen by the increased activity in the heart and major blood vessels compared with uptake of the radioactivity by the organs. Subsequently, there was a decrease in blood-pool activity with a gradual accumulation of activity in liver, spleen, kidneys, and bone or bone marrow. Starting from day 2, both tracers showed some gastrointestinal activity. Images on day 6–7 clearly showed that ^{111}In and ^{177}Lu were equally effective in identifying the metastatic lesions with a very high target-to-background contrast. For ^{111}In-J591 and ^{177}Lu-J591, the percentage injected dose in several organs at different times after injection are compared in Table 4. For both tracers, the liver accumulated the highest amount of radioactivity and there were minor differences between the 2 radiotracers. Time–activity data in Figure 3 demonstrate that, although the initial liver uptake kinetics were similar for both tracers, the mean liver uptake with ^{177}Lu was about 20% less than that with ^{111}In on day 6 and shows washout of activity on day 13. The whole-body retention of activity, however, was similar for both tracers.

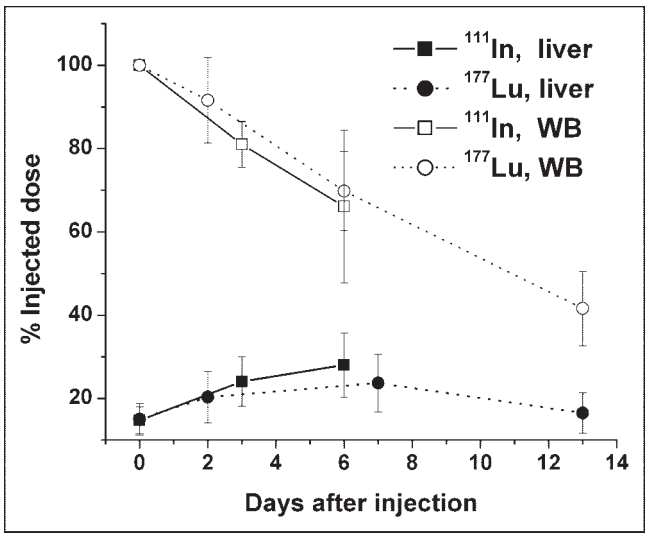

FIGURE 3. Whole-body (WB) clearance and liver uptake and washout kinetics of ^{111}In-J591 and ^{177}Lu-J591 mAb from time of administration to patients.

Radiation Dosimetry

Radiation-absorbed dose estimates (mGy/MBq) for several target organs from ^{111}In-J591 and ^{177}Lu-J591 are summarized in Table 5. For both tracers, the liver received the highest dose, followed by spleen and kidney. Hence, liver is the critical organ, with a radiation-absorbed dose of 1.14 ± 0.89 mGy with ^{111}In and 2.10 ± 0.60 mGy with ^{177}Lu for each megabecquerel of administered dose. For most organs, the dose from ^{177}Lu is about 2–3 times that with ^{111}In.

TABLE 5
Radiation Absorbed-Dose Estimates:
^{111}In-J591 vs. ^{177}Lu-J591 mAb

Organ	Radiation dosimetry (mGy/MBq)	
	^{111}In-J591	^{177}Lu-J591
Liver	1.14 ± 0.89	2.10 ± 0.60
Spleen	0.71 ± 0.88	1.97 ± 0.92
Kidneys	0.68 ± 0.76	1.41 ± 0.35
Heart wall	0.57 ± 0.66	0.95 ± 0.19
Lungs	0.46 ± 0.66	0.75 ± 0.22
Gallbladder	0.35 ± 0.10	0.15 ± 0.02
Pancreas	0.25 ± 0.06	0.14 ± 0.02
Bone surfaces	0.20 ± 0.15	0.19 ± 0.04
Bone marrow*	0.19 ± 0.22	0.32 ± 0.10
ULI wall	0.15 ± 0.05	0.12 ± 0.02
Urin. bladder wall	0.14 ± 0.06	0.26 ± 0.06
Small intestine	0.13 ± 0.05	0.12 ± 0.02
Muscle	0.11 ± 0.06	0.11 ± 0.02
Testes	0.07 ± 0.06	0.10 ± 0.04
Total body	0.15 ± 0.10	0.19 ± 0.03
Effective dose equiv.	0.33 ± 0.32	0.58 ± 0.09
Effective dose	0.24 ± 0.21	0.36 ± 0.05

*Bone marrow dose was estimated based on blood activity, assuming bone marrow-to-blood ratio of 0.36.
ULI = upper large intestine; Urin. = urinary; equiv. = equivalent.

The radiation dosimetry of ^{90}Y-J591 was estimated based on the pharmacokinetics and biodistribution of ^{111}In-J591 and ^{177}Lu-J591 studies and the results are compared in Table 6. The radiation dose (mGy/MBq) to liver was about 26% higher based on the ^{111}In data (6.57 ± 2.27) compared with the value based on the ^{177}Lu data (4.9 ± 1.45). For other major organs, such as spleen, kidneys, and bone marrow, the radiation dosimetry estimates were very close with minimal difference.

DISCUSSION

PSMA is the most well-established, prostate-restricted, cell-surface antigen identified to date. Hence, it is an excellent target to develop radiolabeled mAbs for the treatment of prostate cancer. To our knowledge, deimmunized J591 mAb is the first radiolabeled antibody specific for the extracellular domain of PSMA to be tested as a radiotherapeutic in patients with prostate cancer. We have previously documented that radiolabeled J591 binds with high affinity (1 nmol/L) to PSMA and that the PSMA-antibody complex is internalized, thereby delivering the radionuclide only to the interior of the targeted cancer cells (*16,17*). We have also reported previously that radiolabeled J591 specifically and sensitively targets bone and soft-tissue metastatic sites (Fig. 4) in patients with prostate cancer (*18*). This article reports the biodistribution, pharmacokinetics, and radiation dosimetry of radiolabeled J591 mAb from data obtained in phase I dose-escalation trials.

The development of radiolabeled mAbs as therapeutic agents involves the estimation of radiation-absorbed dose as part of the safety assessment in phase I dose-escalation clinical trials. Typically, radiation dosimetry is not part of treatment planning. However, knowledge of the radiation-absorbed doses to various critical organs—especially bone marrow, liver, kidney, and spleen—is crucial for understanding the dose–response relationships of myelotoxicity and second organ toxicities. Quantitative dosimetric imaging and pharmacokinetic studies of the radiolabeled therapeutic agent are essential to accurately measure the time course of radioactivity in organs to calculate residence times, which are used in MIRD schema for estimating the radiation dosimetry. Among the most popular β^--emitters used for radiotherapy, ^{90}Y is the only radionuclide that has no γ-photons for external scintigraphy. The positron emitter ^{86}Y ($t_{1/2}$ = 14.74 h) may be an appropriate isotope to study the in vivo distribution of ^{90}Y-labeled peptide (*4*) but is not suitable for dosimetric studies of radiolabeled mAbs because of the relatively shorter physical $t_{1/2}$ compared with the biologic $t_{1/2}$ of antibody clearance from circulation. In a small group of patients, the plasma clearance kinetics of ^{90}Y-J591 were similar to those of ^{111}In- and ^{177}Lu-labeled J591 (data not reported). ^{111}In-Labeled agent is generally used as a chemical and biologic surrogate to trace the biodistribution of ^{90}Y-labeled therapeutic agent. However, preclinical and clinical studies have reported the similarities and differences in the biodistribution of ^{111}In- and ^{90}Y-labeled antibodies and challenged the assumption that ^{111}In is a biologic surrogate for ^{90}Y (*4,5*). Since it has been well documented that the chemistry of yttrium is more similar to that of lutetium (*6,7*), we hypothesized that ^{177}Lu may be a more appropriate radionuclide to trace the biodistribution of ^{90}Y. This article reports a direct comparison of ^{90}Y dosimetry based on ^{111}In and ^{177}Lu studies in the same patient population.

TABLE 6
Radiation Dosimetry of ^{90}Y-J591

Organ	^{90}Y-J591 dosimetry (mGy/MBq)		Difference (%)	*P* value
	^{111}In-J591	^{177}Lu-J591		
Liver	6.59 ± 2.27	4.90 ± 1.45	26	<0.03
Spleen	4.92 ± 1.66	5.29 ± 2.24	−7	0.61
Kidneys	4.47 ± 1.08	4.10 ± 1.06	8	0.37
Heart wall	2.99 ± 0.61	3.43 ± 0.69	−15	0.08
Lungs	2.87 ± 0.71	2.32 ± 0.70	19	<0.05
Red marrow	0.91 ± 0.43	1.02 ± 0.22	−12	0.38
Urin. bladder wall	0.71 ± 0.29	0.88 ± 0.22	−24	0.08
Muscle	0.29 ± 0.08	0.64 ± 0.11	−118	<0.001
LLI wall	0.29 ± 0.08	0.64 ± 0.11	−118	<0.001
ULI wall	0.29 ± 0.08	0.64 ± 0.11	−118	<0.001
Effective dose	1.13 ± 0.16	1.21 ± 0.14	−7	0.15
Effective dose equiv.	1.78 ± 0.25	1.81 ± 0.26	−1	0.79

Urin. = urinary; LLI = lower large intestine; ULI = upper large intestine; equiv. = equivalent.

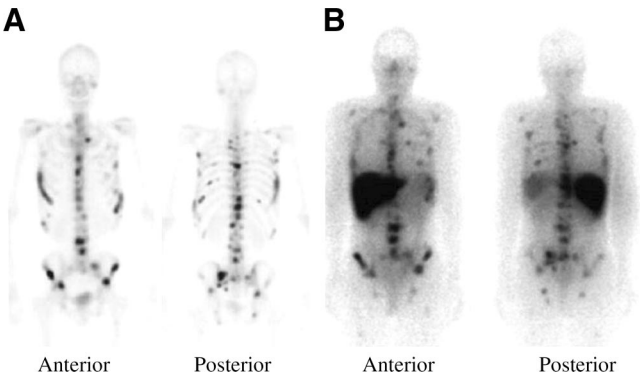

FIGURE 4. Whole-body images of ^{99m}Tc-methylene diphosphonate (A) and ^{177}Lu-J591 mAb (B) in patient with metastatic prostate cancer. ^{177}Lu images obtained on day 7 show significant localization of radiolabeled J591 mAb in most lesions identified on bone scan (A).

Pharmacokinetics and Biodistribution: ^{111}In-J591 Versus ^{177}Lu-J591

After intravenous administration, the plasma clearance kinetics of ^{111}In-J591 and ^{177}Lu-J591 from circulation are similar. Between these 2 tracers, no statistically significant differences were observed in the biologic $t_{1/2}$, AUC, C_{max}, V_d, and clearance (Table 3). More than 80% of radiolabeled

J591 cleared from blood with a terminal $t_{1/2}$ (β) of 44 ± 15 h. In the same patient population within a small group ($n = 6$), ^{90}Y-J591 also had a similar $t_{1/2}$ of 41 ± 11 h. In the published literature, there is only one other mAb that was labeled with these 3 nuclides. The murine mAb CC49 binds to an epitope of mucin antigen, TAG-72 (*25*). In patients with adenocarcinomas, the terminal $t_{1/2}$ for ^{111}In-CC49 was 59.8 h (range, 33–90 h) and for ^{177}Lu-CC49 was 67 ± 15 h (*26,27*). The ^{90}Y-CC49 had a lower $t_{1/2}$ of 47.4 h (range, 28–66 h), but the difference was not significant. Both J591 and CC49 antibodies were first conjugated with the chelating agent, DOTA, before labeling with radiometals. Therefore, these 2 studies clearly document that plasma clearance of mAbs is similar when labeled with ^{111}In, ^{177}Lu, or ^{90}Y.

Similarly, the whole-body retention of radiolabeled J591 at 6 d after injection determined on the basis of imaging studies was also similar between ^{111}In (66.1% ± 18%) and ^{177}Lu (69.8% ± 9.5%). In addition, no significant difference was observed between these 2 tracers in the amount of activity excreted in the urine during this time.

The imaging studies, however, showed that there were minor differences (Table 4) in the biodistribution of ^{111}In- and ^{177}Lu-labeled J591. During the first week, both tracers showed a gradual accumulation in the liver and, by day 6, the amount of ^{111}In activity was 25% higher compared with that with ^{177}Lu ($P < 0.05$). Since ^{177}Lu imaging studies were continued for an additional week, we were able to document that the liver time–activity curve is biphasic. There was significant washout of ^{177}Lu activity from the liver: 24% ± 7% on day 7 compared with 16% ± 5% on day 13 ($P < 0.03$). Similarly, there were minor, but significant, differences in the spleen, lung, and remainder activities between these 2 nuclides. The biodistribution data with ^{111}In- and ^{177}Lu-labeled CC49 mAb were not available for direct comparison (*26,27*).

Radiation Dosimetry

For both ^{111}In- and ^{177}Lu-labeled J591 mAb, liver is the critical organ, followed by spleen and kidney (Table 5). The dose (mGy/MBq) to liver with ^{177}Lu (2.10 ± 0.60) was about 80% higher compared with that with ^{111}In (1.14 ± 0.89). Similarly, for all other source organs (spleen, kidneys, lung, heart contents), the dose with ^{177}Lu was 60%–80% higher compared with that with ^{111}In. But for all target organs, the dose with ^{177}Lu was either similar or less than that with ^{111}In. The higher radiation dose to source organs with ^{177}Lu is understandable since the equilibrium dose constant (rad·g/h) for β^--particles is 0.284 with ^{177}Lu compared with 0.117 with ^{111}In. In contrast, the equilibrium dose constant for γ-photons with ^{111}In (0.822) is about 11 times greater compared with that with ^{177}Lu (0.075).

A comparison of radiation dosimetry estimates for Y-J591 based on ^{111}In and ^{177}Lu studies is summarized in Table 6. For most of the source organs, the difference between these 2 estimates was <25%. The dose estimates for liver and lung were significantly higher (20%–25%) with ^{111}In compared with those with ^{177}Lu. This difference can be explained based on the observation that the net retention of ^{111}In activity in the liver and lungs was significantly higher compared with that with ^{177}Lu (Table 4). With ^{90}Y-J591, the estimates for radiation dose to bone marrow were similar based on ^{111}In or ^{177}Lu blood activity. This is in agreement with the observation that there were no significant differences in the plasma clearance rates for these 2 radiolabeled J591 mAb preparations (Table 3). For some target organs (muscle and intestines), the dose estimates for ^{90}Y were significantly higher with ^{177}Lu since the remainder activity was higher with ^{177}Lu compared with that with ^{111}In (Table 4).

Based on clinical studies, Carrasquillo et al. (*5*) demonstrated the similarities and differences in ^{111}In- and ^{90}Y-labeled mAb distribution. Using DTPA-mAbs, they observed that the differences in the biodistribution between these 2 preparations were between 10% and 15%. The differences in the intravascular kinetics were small, and the major differences were in bone accumulation and urinary excretion of these 2 nuclides.

Since ^{86}Y is a chemically equivalent surrogate for ^{90}Y, Lovqvist et al. (*4*) recently compared the biodistribution of ^{86}Y- and ^{111}In-labeled mAbs in a nude mouse model. The uptake of these 2 agents at 2 d after injection was generally similar in most tissues. However, after 4 d, ^{86}Y activity was 20%–30% higher in several tissues (liver, spleen, kidney, tumor, bone) compared with that with ^{111}In. In contrast, using DOTA conjugated mAbs, Stein et al. (*28*) previously reported that ^{88}Y- and ^{177}Lu-labeled DOTA-RS7 mAbs have almost identical biodistribution results in a human lung cancer xenograft model. In a prostate cancer xenograft model, we have recently compared the biodistribution of ^{111}In-, ^{90}Y-, and ^{177}Lu-labeled DOTA-J591 mAbs. We have reported that the biodistribution of ^{177}Lu- and ^{90}Y-J591 were also similar. However, the uptake and retention of ^{111}In activity in the liver and spleen were significantly higher compared with those with either ^{90}Y or ^{177}Lu (*29,30*). All clinical and preclinical data strongly suggest that the chelating agent used for labeling radiometals to mAbs determines the in vivo stability of radiolabeled mAbs.

CONCLUSION

The trivalent metals, ^{111}In, ^{90}Y, and ^{177}Lu, favor the +3 oxidation state and form strong complexes with the macrocyclic chelator, DOTA. However, there are minor differences in the solution and coordination chemistries among these metals. In patients with prostate cancer, we compared the pharmacokinetics and biodistribution of ^{111}In- and ^{177}Lu-labeled DOTA-J591 mAb. ^{111}In-J591 and ^{177}Lu-J591 have similar plasma and whole-body clearance kinetics. The net retention of ^{111}In activity by lung, liver, and spleen is slightly higher compared with that with ^{177}Lu. Radiation dosimetry estimates for ^{90}Y-J591 calculated based on ^{111}In or ^{177}Lu data were mostly similar and show that the liver is

the critical organ, followed by spleen and kidney. These results justify using ^{111}In as a chemical and biologic surrogate for ^{90}Y. In addition, the data also suggest that ^{177}Lu may be a potential alternative for estimating the pharmacokinetics and biodistribution of ^{90}Y-labeled radiopharmaceuticals.

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