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Phase I Trial of ^{177}Lutetium-Labeled J591, a Monoclonal Antibody to Prostate-Specific Membrane Antigen, in Patients With Androgen-Independent Prostate Cancer

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ABSTRACT

Purpose

To determine the maximum tolerated dose (MTD), toxicity, human anti-J591 response, pharmacokinetics (PK), organ dosimetry, targeting, and biologic activity of ^{177}Lutetium-labeled anti–prostate-specific membrane antigen (PSMA) monoclonal antibody J591 (^{177}Lu-J591) in patients with androgen-independent prostate cancer (PC).

Patients and Methods

Thirty-five patients with progressing androgen-independent PC received ^{177}Lu-J591. All patients underwent ^{177}Lu-J591 imaging, PK, and biodistribution determinations. Patients were eligible for up to three retreatments.

Results

Thirty-five patients received ^{177}Lu-J591, of whom 16 received up to three doses. Myelosuppression was dose limiting at 75 mCi/m^2, and the 70-mCi/m^2 dose level was determined to be the single-dose MTD. Repeat dosing at 45 to 60 mCi/m^2 was associated with dose-limiting myelosuppression; however, up to three doses of 30 mCi/m^2 could be safely administered. Nonhematologic toxicity was not dose limiting. Targeting of all known sites of bone and soft tissue metastases was seen in all 30 patients with positive bone, computed tomography, or magnetic resonance images. No patient developed a human anti-J591 antibody response to deimmunized J591 regardless of number of doses. Biologic activity was seen with four patients experiencing ≥ 50% declines in prostate-specific antigen (PSA) levels lasting from 3+ to 8 months. An additional 16 patients (46%) experienced PSA stabilization for a median of 60 days (range, 1 to 21+ months).

Conclusion

The MTD of ^{177}Lu-J591 is 70 mCi/m^2. Multiple doses of 30 mCi/m^2 are well tolerated. Acceptable toxicity, excellent targeting of known sites of PC metastases, and biologic activity in patients with androgen-independent PC warrant further investigation.

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INTRODUCTION

Prostate-specific membrane antigen (PSMA) is the most well established, prostate cancer (PC) –restricted, cell-surface antigen identified to date.[1] PSMA is a 100-kD type II transmembrane glycoprotein that is expressed by all prostate cancers.[2] The density of PSMA expression progressively increases in higher-grade cancers, metastatic disease, and hormone-refractory PC.[3-6] The 19–amino acid cytoplasmic domain of this nonsecreted protein contains a novel MXXXL internalization motif,[7,8] resulting in its internalization and endosomal recycling. These characteristics make PSMA an ideal target for monoclonal antibody (mAb) therapy.

J591 is an anti-PSMA mAb that binds with 1-nM affinity to the extracellular domain of PSMA.[9,10] Murine J591 antibody

was deimmunized using a novel method involving specific deletion of human B- and T-cell recognized epitopes.[11]

In vitro and animal studies of radiolabeled J591 demonstrated the superiority of radiometals Yttrium-90 (^{90}Y) and Lutetium-177 (^{177}Lu), presumably due to their longer intracellular half-life ($t_{1/2}$), as compared with the rapid dehalogenation and washout of ^{131}I-J591.[10,12-13] ^{90}Y and ^{177}Lu have very different physical properties. As compared with ^{177}Lu, ^{90}Y has a shorter $t_{1/2}$ (2.7 *v* 6.7 days), a higher energy (max, 2.3 *v* 0.5 MeV), and a longer range (max, 12.0 *v* 2.2 mm). Modeling of radioimmunotherapy (RIT) reveals that the optimal tumor size for treatment using the higher energy beta of ^{90}Y is 28 to 42 mm, while that for the lower energy beta of ^{177}Lu is 1.2 to 3.0 mm.[14] In the case of tumors smaller than the optimum, energy is deposited beyond the boundaries of the tumor; in larger tumors, the periphery is not adequately dosed. As a pure beta emitter, ^{90}Y cannot be used for imaging and requires the use of ^{111}Indium as a surrogate label for scintigraphy and dosimetry calculations. In contrast, ^{177}Lu emits 15% of its energy as a gamma emission in addition to the beta emissions, and can be imaged directly using a gamma camera. These properties of ^{177}Lu confer several theoretical benefits over ^{90}Y for RIT: (1) the longer $t_{1/2}$ of ^{177}Lu may provide for emission of radiation over a longer time period while the radiometal is sequestered in the tumor cell; (2) the shorter range of ^{177}Lu may result in less bystander toxicity, particularly in the bone marrow, the most common site of PC metastases, as well as the most radiosensitive normal tissue compartment; and (3) the shorter range may be beneficial by delivering a greater proportion of its energy within micrometastatic sites rather than around the tumor.[14] Despite the potential benefits, there is very little clinical experience with ^{177}Lu.[15-17] We elected to evaluate both ^{90}Y- and ^{177}Lu-J591 in two independent phase I clinical trials. We recently reported the results of a phase I trial of ^{90}Y-J591.[11] We now report the results of the phase I dose-escalation trial of ^{177}Lu-J591 in patients with progressing androgen-independent PC.

PATIENTS AND METHODS

Patient Eligibility and Screening

Eligible patients had a prior histologic diagnosis of PC with a rising prostate-specific antigen (PSA) level and/or tumor progression on radiologic studies including bone scan, computed tomography (CT), and/or magnetic resonance imaging (MRI), despite androgen deprivation therapy and castrate testosterone levels. Patients were required to have three sequential rising PSA values over a period of $\geq$ 2 weeks and a PSA $\geq$ 1.0 ng/mL at study entry. Eligible patients had a Karnofsky performance status $\geq$ 60% and life expectancy more than 6 months at the time of entry. Luteinizing hormone-releasing hormone agonist was either maintained for the duration of treatment and follow-up, or terminated $\geq$ 10 weeks (for 28-day depot) or $\geq$ 24 weeks (for 3-month depot) before entry. Nonsteroidal antiandrogen therapy was either maintained for the duration of treatment and follow-up, or terminated $\geq$ 6 weeks before entry. Patients were not permitted to receive aspirin or nonsteroidal anti-inflammatory agents within 2 weeks of entry; corticosteroids, adrenal hormone inhibitors or the herbal supplement PC-SPES within 4 weeks of entry; and systemic chemotherapy or radiation therapy within 6 weeks of entry. Patients with a history of prior radiation therapy encompassing more than 25% of the skeleton or prior treatment with ^{89}Strontium or ^{153}Samarium were ineligible for the trial. Patients were required to have adequate bone marrow function with an absolute neutrophil count (ANC) $\geq 2.0 \times 10^9$/L and a platelet count $\geq 150 \times 10^9$/L. Patients were required to have a unilateral or bilateral posterior iliac crest bone marrow biopsy demonstrating $\leq$ 10% or $\leq$ 25%, respectively, of the intratrabecular marrow space involved by PC. Additional exclusion criteria included serum creatinine greater than 2.0 mg/dL, serum AST $\geq$ 2.0$\times$ the upper limit of normal (ULN), serum total bilirubin $\geq$ 1.5$\times$ the ULN, serum calcium $\geq$ 12.5 mg/dL, and an abnormal coagulation profile (prothrombin time and partial thromboplastin time) unless on anticoagulant therapy. Anticoagulant therapy was to be stopped if the platelet count fell to less than 50×10^9/L.

Patients were excluded from the study for CNS metastases, history of seizure and/or stroke, HIV infection, active serious infection, active ischemic heart disease or heart failure (New York Heart Association Classification III-IV), and other serious illnesses involving the cardiac, respiratory, CNS, renal, hepatic, or hematologic organ systems that might preclude completion of the study or interfere with determination of causality of any adverse effects experienced. All patients provided written institutional review board (IRB) –approved informed consent.

Pretreatment evaluation included a history, physical examination, routine laboratory studies including PSA, prostatic acid phosphatase, testosterone, and an ECG. Radiologic studies included a chest x-ray; CT or MRI of the abdomen, pelvis, and brain; as well as a bone scan. Patients were required to have a bone marrow biopsy within 6 weeks of study entry.

Treatment Plan and Toxicity Evaluation

Dose preparation. The deimmunized J591 antibody was first conjugated with the macrocyclic chelating agent, 1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid (DOTA). J591-DOTA was supplied by BZL Biologics Inc (Framingham, MA) under IND 9638. J591-DOTA was labeled with ^{177}Lu (Missouri University Research Reactor, Columbia, MO) in an ammonium acetate buffer. The specific activity of ^{177}Lu-J591 was 9.4 $\pm$ 3.6 mCi/mg (350 $\pm$ 133 MBq/mg) to reach the specified dose of ^{177}Lu. Immunoreactivity was more than 80% in all cases. Radiolabeled J591 was purified by gel filtration and sterilized by membrane filtration before administration into patients. The radiolabeled J591-DOTA was combined with cold J591 such that all patients received a total mass of 10 mg/m^2 of mAb J591. J591 mAb was infused intravenously at $\leq$ 5 mg/min. Patients were treated as outpatients in the New York-Presbyterian Hospital General Clinical Research Center.

Pharmacokinetics and biodistribution studies. Venous blood samples (4 mL) were obtained at 10 minutes; 1, 2, 4, and 24 hours; and days 2, 3, 4, and 7. The percent injected dose was determined by measuring an aliquot of blood along with a known ^{177}Lu standard.

To assess the biodistribution of mAb J591, total body images were obtained within 1 hour postinfusion (day 0) and again at four additional time points in the subsequent 2 weeks (days 2, 4 to 5, 6 to 7, and 12 to 14). The gamma camera images were obtained

using a dual-head gamma camera with a medium energy collimator (ADAC, Milpitas, CA; General Electric Medical Systems Inc, Milwaukee, WI). The percent injected dose in major organs (heart, liver, spleen, kidneys, bone marrow, GI tract, and bladder) was estimated by drawing regions of interest and determining the relative counts in each organ and compared with a standard. SPECT studies of the abdomen, pelvis, and/or areas of suspected metastatic lesions were performed on day 2 or 3 in selected patients. Using the values obtained from sequential biodistribution studies and plasma PK, radiation dosimetry of ^{177}Lu-J591 was estimated by substituting the physical characteristics of ^{177}Lu.[18]

Evaluation of targeting. With rare exception, lesions outside the prostate were not assessed by biopsy. To evaluate/compare targeting on antibody scan, bone lesions were defined as metastatic versus benign on the basis of clinical interpretation by a nuclear medicine physician with occasional corroboration by CT and/or MRI. Soft tissue masses $\geq$ 2 cm were defined as metastatic cancer.

^{177}Lu-J591 dose-escalation design. Based on limited prior clinical experience with ^{177}Lu-labeled antibodies consisting of a single trial[15] where the MTD of intravenously administered CC49-DOTA-^{177}Lu was 15 mCi/m^2, the US Food and Drug Administration initially approved only two dose levels of 10 and 15 mCi/m^2 to be followed by a data safety review before further dose escalation. Following the data review, the US Food and Drug Administration and IRB approved an amendment to (1) increase the dose increment between dose levels from 5 mCi/m^2 to 15 mCi/m^2 with dose increment reductions at the onset of grade 3 and/or 4 toxicity, and (2) to allow for repeat dosing if the patient had recovered from any earlier hematologic toxicity and continued to meet study entry criteria. The following dose levels were ultimately evaluated: 10, 15, 30, 45, 60, 70, and 75 mCi/m^2. The ^{177}Lu dose was escalated in cohorts of three to six patients. Dose escalation was held until at least three patients at each dose level had been followed for $\geq$ 6 weeks until the onset of blood count recovery was demonstrated. If one patient experienced dose-limiting toxicity (DLT), at least six patients were entered at that dose level and followed until onset of blood count recovery before dose escalation. If, at any time, two instances of DLT were observed at a given dose level, further entry at that dose level was terminated. The MTD was defined as the dose level at which 0 of six or one of six patients experiences a DLT with the next higher dose level having two or more patients experiencing DLT. Once the MTD was reached, at least six patients were to be evaluated at that dose level.

DLT was defined as the following: *hematologic toxicity* consisting of grade 4 thrombocytopenia (platelet $< 10 \times 10^9$/L) and/or grade 4 neutropenia (ANC $< 0.5 \times 10^9$) lasting more than 5 days; and *other toxicity* consisting of any grade $\geq$ 3 nonhematologic toxicity attributable to ^{177}Lu-J591. Any patient experiencing a $\geq$ grade 2 allergic reaction while receiving ^{177}Lu-J591 would not receive further treatment with mAb J591. The National Cancer Institute Cancer Therapy Evaluation Program Common Toxicity Criteria (version 2.0) was utilized.

Patients were followed for a minimum of 12 weeks after ^{177}Lu-J591 administration. Routine clinical and laboratory assessments (including biochemical profile, PSA, prostatic acid phosphatase, and testosterone) were performed at defined intervals. CBC and platelet counts were initially monitored one to two times per week, and then every 4 weeks until blood count stabilization. If the ANC was less than 1.0×10^9/L, and/or platelets less than 50×10^9/L, blood counts were monitored every other day. Chest x-ray, CT or MRI of the abdomen and pelvis, and a bone scan were performed 12 weeks post-treatment. Human anti-J591 antibody response was monitored at weeks 1, 2, 4, 8, and 12.

Grading bone scans. As part of the data analysis, we compared bone marrow involvement and myelotoxicity. Bone scans were graded 0 (no involvement), 1 (one to five lesions), two (six to 10 lesions), three (11 to 20 lesions), four ($>$ 20 lesions), and five (superscan).

Re-Treatment

After US Food and Drug Administration and IRB review of the data on the first six patients, the trial was amended to allow patients to be re-treated. Patients were considered eligible for up to three re-treatments with ^{177}Lu -J591 at $\geq$ 6 to 12 week intervals if they continued to meet initial eligibility requirements and their platelet and ANC recovery was satisfactory. Initially, satisfactory recovery was defined as a platelet count $\geq$ 70% of the baseline platelet count of the prior or initial treatment with a minimum recovery to at least 75×10^9/L; and ANC recovery to $\geq$ 80% of the baseline ANC of the prior treatment cycle with a minimum recovery to 1.3×10^9/L. This was later revised, for the purposes of clarity and simplicity, to: platelet count recovery to $\geq 125 \times 10^9$/L and ANC to $\geq 2 \times 10^9$/L. Any $\geq$ grade 3 nonhematologic toxicity in a prior treatment cycle precluded re-treatment. Patients were not required to undergo a repeat bone marrow biopsy.

Re-treatment consisted of patients receiving the same ^{177}Lu-J591 dose as their initial cycle unless dose modification was required based on the hematological toxicity of the preceding treatment cycle. Dose modification was as follows: 25% dose reduction for platelet count nadir 50 to 75×10^9/L (grade 2); no re-treatment for a platelet count nadir less than 50×10^9/L (grade 3 or 4); 25% dose reduction for ANC count nadir 1,000 to 1,499/L (grade 2) and 50% dose reduction for ANC 500 to 999/L (grade 3). Patient 4, who was initially treated at 15 mCi/m^2 with grade 0 platelet and ANC toxicity, was permitted to receive re-treatment at 30 mCi/m^2. After completing the 75 mCi/m^2 dose level and defining the single dose MTD, additional patients were entered to define the tolerability and toxicity of repeated dose therapy. Patients were followed for a minimum of 12 weeks after their last dose of ^{177}Lu-J591, and those patients with stable or responding disease were followed until progression.

Human Anti-J591 Antibody Response

Human anti-J591 antibodies in the serum of patients was assayed using surface-enhanced laser desorption/ionization mass spectrometry technology as previously described.[11] Human anti-J591 antibody response was measured on day 0, before ^{177}Lu-J591 treatment and post-treatment weeks 1, 2, 4, 8, 12, and every 12 weeks until disease progression.

Response Criteria

Response was assessed either biochemically (PSA change) and/or by change in size of measurable lesions (using Response Evaluation Criteria in Solid Tumors criteria). Biochemical response was determined by comparing the nadir PSA level after treatment to the PSA determined immediately before initiating therapy. PSA response was defined as a more than 50% decrease from baseline maintained for at least 4 weeks. The duration was based on the time from treatment initiation to return of PSA to baseline pretreatment value. Biochemical (PSA) progression was defined as a $\geq$ 25% rise in PSA above the baseline pretreatment value.

RESULTS

Thirty-five patients with androgen-independent PC whose pertinent demographic characteristics are presented in Table 1 were enrolled on the study between March 2001 and August 2003. The ^{177}Lu-J591 dose levels, number of patients treated at each dose level and number of re-treated patients are listed in Table 2.

Table 1. Baseline Patient Characteristics

Characteristics	Patients No.	Patients %
Age, years		
Median	69	
Range	47-85	
PSA, μg/L		
Median	29.6	
Range	2.3-2,746.0	
Alkaline phosphatase, U/L		
Median	120	
Range	55-858	
Hemoglobin, g/liter		
Median	12.8	
Range	8.2-16.0	
WBC × 10^9/L		
Median	6.0	
Range	3.5-13.3	
ANC × 10^9/L		
Median	3.5	
Range	1.6-9.5	
Platelet count × 10^9/L		
Median	242	
Range	127*-411	
Primary local treatment		
RP	6	17
XRT	4	11
RP + XRT	12	34
Cryosurgery	1	3
None	12	34
Sites of metastases		
Bone only	21	60
Soft tissue only	6	17
Bone and soft tissue	3	9
None	5	14
Prior therapy		
Hormonal	34	97
LHRH	34	
Orchiectomy	4	
Nonsteroidal antiandrogen	25	
Ketoconazole	11	
Steroid	14	
PC-SPES	5	
DES	3	
Cytotoxic chemotherapy	13	37
Radiation therapy (to bone)	10	29

Abbreviations: PSA, prostate-specific antigen; ANC, absolute neutrophil count; RP, radical prostatectomy; XRT, radiation therapy; LHRH, luteinizing hormone-releasing hormone; DES, diethylstilbesterol.
*Two patients who met screening criteria had platelet counts below 150 × 10^9/L on the day of treatment.

Table 2. Summary of Dose-Escalation Design

Dose Level	mAb ^{177}Lu-J591 (mCi/m^2)	No. of Patients	No. of Re-Treated Patients
1	10	3	0
2	15	3	1*
3	30	12	10
4	45	5	3
5	60	3	2
6	70	6	0
7	75	3	0
Total	—	35	16

Abbreviations: mAb, monoclonal antibody; ^{177}Lu-J591, ^{177}Lutetium-labeled J591.
*One patient initially treated at 15 mCi/m^2 was re-treated at 30 mCi/m^2.

Pharmacokinetics, Biodistribution, and Dosimetry

Based on plasma-time activity data and fit to a mono-exponential curve, the plasma $t_{1/2}$ for ^{177}Lu-J591 was 39 ± 13 hours. The volume of distribution was estimated to be 4,156 ± 858 mL with a clearance rate of 88 ± 47 mL/h. The biexponential curve fit of plasma-time activity data showed that more than 80% of labeled antibody clears from circulation with a $t_{1/2}$ (β component) of 44 ± 16 hours. Early images document most of the activity in the circulation with the liver as the only organ sequestering a significant amount of ^{177}Lu activity. By day 7, the whole body activity was almost 70% of the injected dose; the liver activity was 24% ± 7% of the injected dose. The radiation dosimetry of ^{177}Lu -J591 is summarized in Table 3. The critical organ with highest radiation dose is liver (7.8 ± 2.2 cGy/mCi), followed by spleen and kidneys. The radiation dose to bone marrow based on blood radioactivity is 1.2 ± 0.4 cGy/mCi of ^{177}Lu administered.

J591 Targeting

Among the 35 patients receiving ^{177}Lu-J591, 30 (86%) had metastatic disease detected on screening imaging studies. Specifically, 21 (60%) patients had bone-only metastases, six (17%) had soft tissue–only metastases, and three (9%) had both bone and soft tissue disease. In all of these 30 patients, all known sites of metastatic disease were successfully imaged by ^{177}Lu-J591 scintigraphy. One patient with bone metastases had many more lesions visible on antibody scan than on bone scan (Fig 1). Another patient with a negative bone scan had a positive antibody scan that was confirmed positive by MRI.[17] The bone scan of both patients later converted to positive in sites presaged by their antibody scans.

In addition to the series of imaging sessions after the first J591 dose for PK and dosimetry studies, patients receiving multiple doses were imaged 1 week after dose 2 and, where applicable, dose 3. In all of these cases, consistent

Table 3. Radiation Dosimetry (rads/mCi) of ^{177}Lu-J591 in Patients With Prostate Cancer

Organ	Value	
	Mean	Standard Deviation
Adrenals	0.52	0.08
Brain	0.40	0.07
Gall bladder	0.55	0.08
Colon	0.42	0.07
Small intestine	0.43	0.07
Stomach	0.45	0.07
Heart	3.50	0.70
Kidneys	5.20	1.29
Liver	7.77	2.23
Lungs	2.79	0.80
Muscle	0.42	0.07
Pancreas	0.52	0.08
Red marrow	1.17	0.37
Bone surfaces	0.70	0.14
Skin	0.42	0.07
Spleen	7.28	3.41
Testes	0.36	0.13
Thymus	0.44	0.07
Thyroid	0.41	0.07
Urinary bladder	0.97	0.22
Total body	0.71	0.10
Effective dose equivalent	2.14	0.35
Effective dose	1.33	0.19

Abbreviation: ^{177}Lu-J591, ^{177}Lutetium-labeled J591.

tumor targeting was seen on serial images (Fig 2). No change in ^{177}Lu-J591 clearance rate nor increased reticuloendothelial system uptake was noted after any dose.

Hematologic Toxicity

Hematologic toxicity was dose related and is summarized in Table 4. Of the three patients at the 75-mCi/m^2 dose level, one experienced dose-limiting (grade 4) thrombocytopenia, while the remaining two patients experienced grade 3 thrombocytopenia. All three of these patients experienced grade 4 neutropenia, one of which was dose-limiting neutropenia of 6 days' duration. As two of three patients at this dose level experienced DLT, no additional patients were entered at this dose. At the prior dose level of 70mCi/m^2, six patients were entered. Two patients had transient grade 4 neutropenia not meeting the definition of DLT; one of these patients had grade 4 thrombocytopenia. As there was only one DLT in these six patients, the 70-mCi/m^2 dose level was determined to be the MTD.

Post-treatment platelet counts followed a consistent pattern regardless of how many doses the patient received. Platelet declines generally begin at 2.5 to 3 weeks post-treatment, with platelet nadirs occurring at 4 to 5 weeks post-treatment thereafter, followed by a recovery phase. A composite graph of the mean normalized platelet counts at each dose level (Fig 3) reveals that each successively higher dose level was associated with a lower platelet nadir and longer time to recovery. Interestingly, when comparing dose levels, the decline phase of the platelet curves follows a more consistent, less variable time course whereas the recovery phase is more variable. As seen in Figure 3, the mean platelet counts returned to 80% to 95% of their pretreatment values.

Neutrophil (ANC) toxicity (Table 4) was significantly more variable and demonstrated less consistent post-treatment patterns than platelet counts. As the dose level increased, the ANC nadir was reached earlier. For example, at doses less than 60 mCi/m^2, the ANC nadir occurred at approximately day 49; at 60 mCi/m^2: day 42 to 49; at 70 mCi/m^2: day 42; and at 75 mCi/m^2, the ANC nadir occurred at day 39.

Of 19 patients receiving a single dose, 16 (84%) recovered platelet counts to $\geq 150 \times 10^9$/L. Of the three who did not recover to $\geq 150 \times 10^9$/L, two patients with acceptable counts at screening were subsequently determined to have platelet counts below 150×10^9/L on samples drawn just before treatment on the day of drug administration (146×10^9/L and 126×10^9/L, respectively). These patients recovered to 129×10^9/L and 85×10^9/L, respectively. The remaining patient recovered to a platelet count of 130×10^9/L. Of 11 patients receiving two treatment doses, only two recovered to normal platelet counts. The remaining nine patients recovered to a range of 53 to 149×10^9/L (median, 97×10^9/L). Of five patients receiving three treatment doses, two recovered to $\geq 150 \times 10^9$/L, one was not assessable, as he started chemotherapy 34 days after his third dose, before completing his recovery period, when his platelet count was 105×10^9/L, and two had repeat bone marrow biopsies indicating marrow replacement due to tumor progression when their platelet counts were 78×10^9/L and 121×10^9/L, respectively.

All 35 patients in the trial had ANC recovery to $\geq 2 \times 10^9$/L. Beyond the relationship between dose level and the degree of hematological toxicity, no other pretreatment parameter had a predictable impact on the degree of toxicity. While these observations are limited by the small number of patients at any given dose level, no association was evident between hematologic toxicity and extent of bone marrow involvement determined by pretreatment bone marrow biopsy. As marrow involvement in PC is more focal than in the case of some hematological malignancies such as non-Hodgkin's Lymphoma (NHL), the biopsy might be less reliable due to sampling error. Therefore, we also compared myelotoxicity to the extent of osseous metastases represented on bone scan using a scale related to the extent of bone marrow involvement (see Patients and Methods). We could discern no correlation between bone scan involvement and myelotoxicity. Furthermore, prior radiotherapy or chemotherapy did not correlate with myelotoxicity (data not shown).

Nonhematologic Toxicity

Nonhematologic toxicity was only mild or moderate and was not dose-limiting (Table 5). The majority of

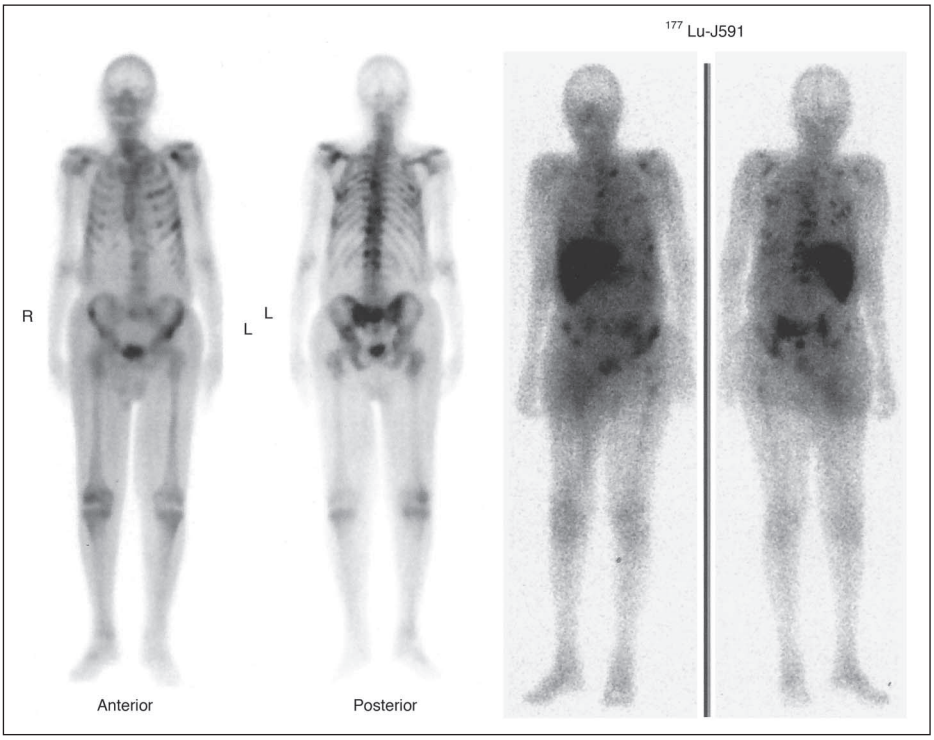

Fig 1. Anterior and posterior images of bone scan and ^{177}Lutetium-labeled J591 (^{177}Lu-J591) scan done 10 days apart. The latter reveals significantly more areas of increased uptake than the former. Area of prior radiation to lumbar spine shows no increase in isotope uptake with either technique. Prostate-specific antigen at the time was 51.0 ng/mL.

episodes were grade 1 and were limited to fatigue. Mild transaminitis (grade 1 to 2) occurred in 10 patients. One patient at the 75-mCi/m^2 dose had a dose-limiting grade 3 AST elevation lasting 1 week. Four of the 10 patients with grade 1 to 2 AST/ALT elevations had elevated transaminase levels (grade 1) at baseline. Two patients developed elevated serum creatinine related to ureteral obstruction from cancer progression. In both cases, renal function responded promptly to ureteral stenting. Three patients had thromboembolic events. One deep venous thrombosis (DVT) was associated with dehydration, hyperkalemia, and disease progression 2 months post-treatment. A second case of DVT was associated with progressing left pelvic adenopathy compressing the left iliac vein. A third patient was found to have two incidental, asymptomatic pulmonary emboli on a follow-up chest CT 3 months after treatment without evidence of DVT. One patient had a grade 3 ileus related to narcotic analgesic use. One patient had grade 3 hematuria, in the absence of significant thrombocytopenia, due to direct extension of tumor into his bladder.

Re-Treatment

Re-treatment was prescribed at the same dose as initially administered unless prior hematologic toxicity mandated a dose reduction (see Patients and Methods). A US Food and Drug Administration and IRB-approved exception was permitted for the first patient to be re-treated (patient 4). This patient was among the first six treated, and he had received a dose of 15 mCi/m^2. This patient had grade 0 platelet and ANC toxicity after his first dose, accompanied by a 50% PSA decline lasting 5 months. Due to the time for data collection, submission, review, and trial amendment, his second dose was administered 238 days after his first dose. At that time, a dose of 30 mCi/m^2 had been shown to be safe, and he was granted a protocol exception to receive re-treatment at a dose of 30 mCi/m^2.

At the time the single-dose MTD was defined as 70 mCi/m^2, 10 patients had received more than one dose: five patients had received two or three doses at 30 mCi/m^2, three patients had received two doses at 45 mCi/m^2, and two patients had received two doses at 60 mCi/m^2. At 45 mCi/m^2, two of the three patients developed prolonged grade 3 thrombocytopenia, each requiring three platelet transfusions between days 35 to 48 and 38 to 56, respectively, after the second dose (Table 6). The one remaining patient receiving two doses at 45 mCi/m^2 had grade 0 hematologic toxicity. At 60 mCi/m^2, two patients received two doses: one experienced grade 4 platelet toxicity and required 13 platelet transfusions between days 40 to 105 after the second dose. This patient also experienced grade 4 neutropenia lasting 22 days, including a 16-day course of granulocyte-colony-stimulating factor. Before entry in this trial, he had failed radiation therapy, primary and secondary hormonal therapy, chemotherapy with carboplatin, paclitaxel and estramustine, an experimental telomerase vaccine plus granulocyte macrophage colony-stimulating factor (GM-CSF), and a protocol of interleukin-2 plus GM-CSF. Thirteen months after receiving his first dose of ^{177}Lu-J591, he received

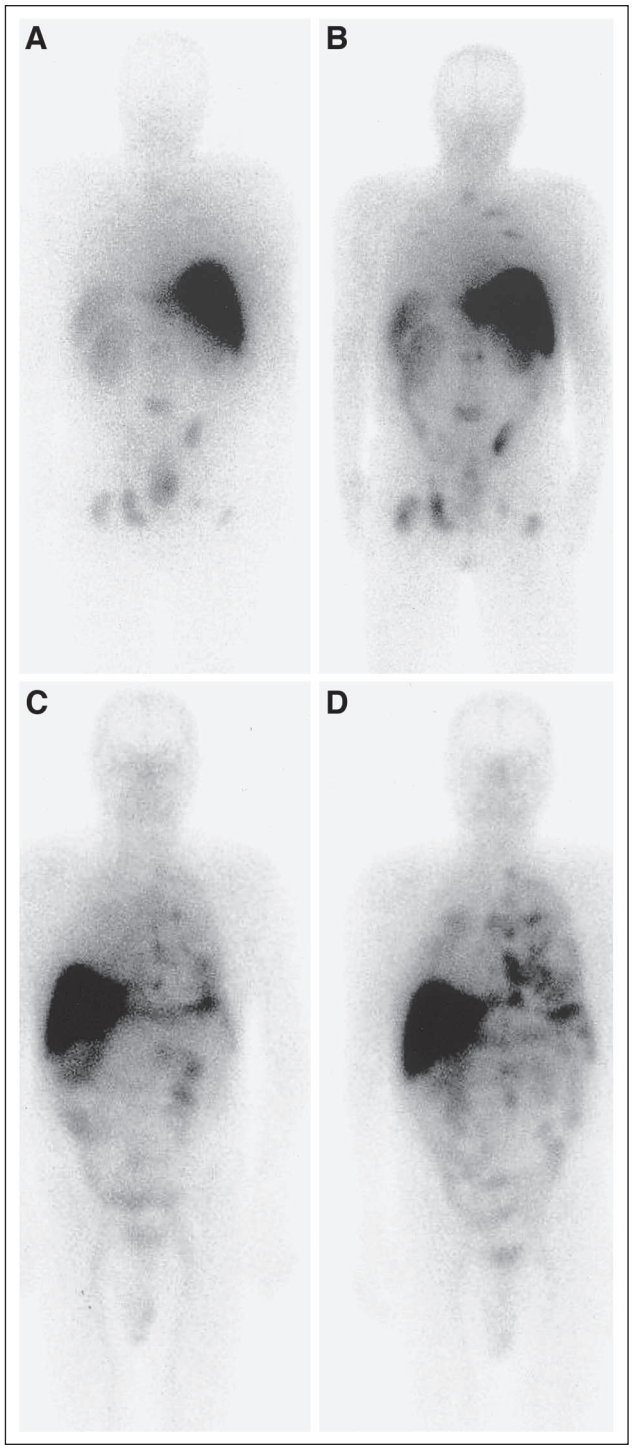

Fig 2. Antibody scans of two patients who each received two doses of ^{177}Lutetium-labeled J591 (30 mCi/m^2). Patient 34 (panels A and B) received doses 8 weeks apart. (A) Posterior view 8 days after first dose (prostate-specific antigen [PSA] = 50.7 ng/mL). (B) Seven days after second dose (PSA = 90.9 ng/mL). Anterior views of patient 33 (panels C and D) who received doses 13 weeks apart. (C) Seven days after first dose (PSA = 415 ng/mL). (D) Seven days after second dose (PSA = 570 ng/mL).

Table 4. Platelet and Neutrophil Toxicities at Single Doses of ^{177}Lu-J591

Dose (mCi/m^2)	Thrombocytopenia CTC Grade					Neutropenia CTC Grade				
	0	1	2	3	4	0	1	2	3	4
10 (n = 3)	3	0	0	0	0	3	0	0	0	0
15 (n = 3)	2	1	0	0	0	3	0	0	0	0
30 (n = 12)	4	7	1*	0	0	7	0	4†	1‡	0
45 (n = 5)	0	1	3	1	0	2	1	2	0	0
60 (n = 3)	0	1	1	1	0	0	1	0	2	0
70 (n = 6)	0	0	1	4	1	0	1	2	1	2
75 (n = 3)	0	0	0	2	1	0	0	0	0	3

NOTE. Toxicity after first dose at indicated dose level.
Abbreviations: ^{177}Lu-J591, ^{177}Lutetium-labeled J591; CTC, Common Toxicity Criteria; ANC, absolute neutrophil count.
*Baseline platelet count: 146 $\times$ 10^9/L (grade 1).
†One grade 2 ANC at 30 mCi/m^2 had grade 1 at baseline.
‡Grade 3 ANC at 30 mCi/m^2 was in a patient whose marrow was replaced by tumor who entered on protocol exemption.

XRT to the brain and spine for progression of disease. Subsequent to this last course of radiation, he became platelet transfusion-dependent and a bone marrow biopsy indicated a hypocellular marrow mostly replaced by cancer cells. This patient expired 20 months after his first dose of ^{177}Lu-J591 as a result of widespread PC. A week before his death, he was noted to have an elevated blast count, and flow cytometric analysis was consistent with a diagnosis of acute myelogenous leukemia. The only other patient treated with two doses of 60 mCi/m^2 experienced grade 0 to 1 platelet and ANC toxicity.

In contrast to the significant hematologic toxicity seen with more then one dose of $\geq$ 45 mCi/m^2, multiple doses of 30 mCi/m^2 were well tolerated. With IRB permission, seven more patients were added to further evaluate the safety of up to four doses of 30 mCi/m^2. A total of 11 patients received two or more doses of 30 mCi/m^2: one patient received three doses consisting of 15 mCi/m^2 followed by two doses at 30 mCi/m^2; six patients received two doses; and four patients received three doses. The median time between doses 1 and 2 was 64 days (range, 42 to 238 days) and between doses 2 and 3 was 53 days (range, 50 to 55 days). The four patients who received three doses totaling 90 mCi/m^2 did so over a period of 98 to 126 days.

Hematologic toxicity of all re-treated patients is presented in Table 6. Among the 10 patients receiving two doses of 30 mCi/m^2 (excluding patient 4), seven were eligible for a third dose. The three ineligible patients were disqualified by platelet nadirs less than 50 $\times$ 10^9/L (two cases) and ANC recovery to less than 2 $\times$ 10^9/L (in a patient carrying a pretreatment diagnosis of benign neutropenia). Of the seven eligible patients, four received the third dose, while three were not further treated due to disease progression. Of four patients receiving three doses at 30 mCi/m^2, three were eligible to receive a fourth dose, while one began a different therapy due to disease progression, before being

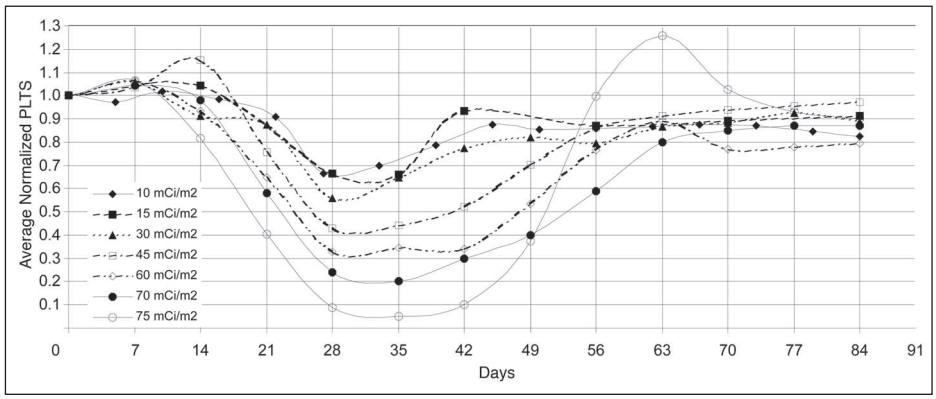

Fig 3. Mean normalized platelet counts at different doses of ^{177}Lutetium-labeled J591. Patients' platelet counts before and after therapy (day 0) were normalized to 1.0 on the day of treatment. For each cohort, the normalized counts were averaged and plotted.

able to fully assess toxicity from the third dose. Although three patients were eligible for a fourth dose, none received further treatment due to tumor progression. Platelet count recovery of these 11 patients (including patient four) was as follows: two patients recovered to $\geq 150 \times 10^9$/L; five patients recovered to $\geq 120 \times 10^9$/L; three patients recovered to platelet counts of 58×10^9/L to 104×10^9/L. One patient could not be evaluated, as he started chemotherapy 34 days after his third dose, before an adequate recovery period; at the time his platelet count was 105×10^9/L.

No dose-limiting nonhematologic toxicity was seen in the re-treated patients. Three of the 10 patients experiencing grade 1 AST and/or ALT elevations were among those patients receiving multiple doses. However, in none of these cases was there evidence of a cumulative or dose-related association. One patient receiving three doses of 30 mCi/m^2 had a single episode of grade 1 AST 9 weeks after dose 1 and 6 weeks after dose 3 but no toxicity after dose 2. The second patient, at 45 mCi/m^2, had grade 1 AST elevation at 8 and 12 weeks after dose 1, and at 5 weeks after dose 2. The third patient, at 60 mCi/m^2, had grade 1 AST and ALT elevations after each of two doses.

Imaging was performed in all patients after each dose, and in every case, tumor targeting remained consistent. No evidence of more rapid clearance was seen, nor were there any allergic reactions, consistent with the lack of human anti-J591 antibody response detected in any of the patients.

Formation of Human Anti-J591 Antibodies

Human anti-J591 antibody assays were negative throughout the trial, including those patients that received

Table 5. Nonhematologic Toxic Effects

Adverse event	No. of Patients With Given Toxicity Grade			
	1	2	3	4
Fatigue	13	3	0	0
Anorexia	3	0	0	0
Fever	1	0	0	0
Rigors	1	0	0	0
Nausea	5	0	0	0
Vomiting	1	0	0	0
Diarrhea	3	1	0	0
Constipation	4	0	0	0
Rash	2	1	0	0
Elevated ALT*	3	1	1	0
Elevated AST*	9	1	0	0
Elevated creatinine	1	0	0	1

*Five of the 15 episodes of AST/ALT elevations had elevated levels at baseline.

Table 6. Hematologic Toxicity Grade in Patients Receiving More Than One Dose

Dose Level/ Patient No.	Platelet Toxicity Grade			ANC Toxicity Grade		
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
60 mCi/m^2						
17	1	1	—	1	0	—
18	3	4	—	3	4	—
45 mCi/m^2						
11	1	1	—	1	0	—
12	2	3	—	0	2	—
14	2	3	—	0	3	—
30 mCi/m^2						
4	0*	0	1	0*	0	0
8	1	1	1	2	0	1
9	0	0	1	0	0	0
10	2	3	—	2	3	—
16	1	3	—	3	0	—
30	0	0	1	0	0	1
31	0	0	4†	0	0	1†
32	1	2	—	0	1	—
33	1	2	—	2‡	3‡	—
34	1	2	—	1	2	—
35	1	3	—	0	1	—

Abbreviation: ANC, absolute neutrophil count.
*Dose, 15 mCi/m^2.
†Bone marrow biopsy, replaced by cancer.
‡Grade 1 ANC at baseline.

multiple doses. In the patients who received multiple doses, there was no change in the rate of drug clearance or tumor targeting on scans with sequential doses, though in some cases, it appeared that increased uptake and/or additional lesions were seen on the later antibody scan(s) consistent with disease progression (data not shown).

Antitumor Activity

All 35 patients in this trial had abnormal, rising PSAs, and seven patients had measurable disease. None of the seven patients with measurable disease had an objective tumor response or a $\geq$ 50% PSA decline. Based on PSA, 14 demonstrated progressive disease (PSA increase of $\geq$ 25%) after treatment, while 21 of the 35 patients had evidence of biologic activity. Four patients had $\geq$ 50% PSA declines lasting 3+ to 8 months before return to baseline, and 16 patients had PSA stabilization ($<$ 25% increase from baseline) of $\geq$ 28 days. The median duration of PSA stabilization was 60 days, with a range of 28 to 601+ days.

DISCUSSION

RIT has proven very successful in the treatment of NHL, with both ^{131}I- and ^{90}Y-labeled antibodies inducing high and durable response rates. The reasons for the success relate to the high radiosensitivity of lymphoid cells and their ready accessibility in bone marrow and lymph nodes to circulating antibody. Yet it remains an unanswered question whether RIT can be effectively applied to treat solid tumors. Current efforts in several types of solid tumors will help answer this question. In this regard, PC represents a particularly favorable setting in which to test the relevance of this approach in solid tumors. PC is a relatively radiosensitive malignancy with a propensity to form small foci in the bone marrow and lymph nodes. These small foci allow ready accessibility of circulating mAb to its target antigen, in contrast to many other solid tumors that may be more radioresistant and where tumor masses are often bulky and poorly perfused. Furthermore, PSMA is an ideal cell-surface antigen given its expression by all PC, its high degree of specificity, its high level of expression ($\pm$ 10^6 sites per cell),[10] its internalization leading to the irreversible sequestration of radiometals within the targeted tumor cells,[10] and the absence of a competing reservoir of antigen in the plasma. Given the favorable setting, PC and the PSMA antigenic system offer a model for the investigation and development of RIT as well as a litmus test of RIT in solid tumors. If RIT cannot succeed in PC, it will likely be very difficult to succeed in other solid tumors.

We have previously published our experience with ^{111}In/^{90}Y-labeled J591, which demonstrated excellent tumor targeting in PC patients without prior selection for PSMA expression.[11,19] In that trial, ^{90}Y-J591 was well-tolerated, with observed biologic activity consisting of concordant biochemical (PSA) and measurable tumor responses. The concordance of PSA and measurable responses implies that PSA may provide a reasonable assessment of biologic activity in early-phase RIT trials. In this trial, using the same preparation of J591-DOTA and a similar patient population, we set out to study a second radiometal, ^{177}Lu, with physical characteristics different from ^{90}Y. ^{177}Lu has the advantage over ^{90}Y of allowing direct imaging. In addition, the longer $t_{1/2}$, lower energy, and shorter range of the beta emission of ^{177}Lu provide theoretical advantages in PC, in which the metastases tend more often to be small volume sites measured in μm to mm in bone marrow rather than bulky multicentimeter sites in lymph nodes or viscera.

As in our previous trials, patients in this trial were not prescreened or selected for PSMA expression. Nevertheless, as previously observed with the J591 antibody, targeting in this trial was excellent, further confirming immunopathological studies indicating that all prostate cancers are PSMA-positive[2] and are therefore, potential candidates for the J591-targeted monoclonal antibody. In this trial, all known lesions clinically defined on bone scan and CT or MRI were detectable on planar J591 images. In at least three cases, bone lesions were apparent on the J591 scan before becoming evident on conventional bone scan. Sequential imaging in patients who received multiple doses continued to consistently localize to tumor sites with no change in pharmacokinetics or biodistribution, consistent with laboratory assays that demonstrated a lack of J591 immunogenicity and human anti-J591 antibody development.

DLT in this trial, as in RIT trials in general, was limited to myelotoxicity. The MTD of a single dose of ^{177}Lu-J591 was 70 mCi/m^2. This MTD is significantly higher than the MTD of 17.5 mCi/m^2 we observed with ^{90}Y using the same J591-DOTA preparation in a similar patient population. This finding likely relates to the lower energy and range of ^{177}Lu, resulting in less bystander radiation to the bone marrow. Ultimately of course, a higher MTD is irrelevant unless it results in an improved therapeutic ratio.

Prior published experience with ^{177}Lu-labeled antibody is very limited. Only three previous trials have been reported, all of which used murine mAb CC49, targeting the TAG72 antigen, and the PA-DOTA chelate.[15-17] Only one of these trials used intravenous administration,[14] while the other two trials used an intraperitoneal approach.[16,17] In the trial using the intravenous route, patients with breast, colon or lung cancer received ^{177}Lu-PA-DOTA-CC49 (^{177}Lu-CC49) with the finding of a MTD of 15 mCi/m^2, as compared with our MTD of 70 mCi/m^2. The significantly lower MTD in this ^{177}Lu-CC49 trial was likely due to the labeling of CC49 up to a week before administration. The resulting radiolytic damage to the CC49 led to high reticuloendothelial uptake, including the bone marrow, of the radiopharmaceutical. In the two intraperitoneal trials, ovarian cancer patients given ^{177}Lu-CC49

monotherapy[16] exhibited an MTD of 45 mCi/m^2, while those given ^{177}Lu-CC49 in combination with paclitaxel and IFN[17] had an MTD of 40 mCi/m^2.

There is limited prior experience with RIT in PC, and no previous RIT trials have studied ^{177}Lu-labeled antibodies in PC. The MTD of 70 mCi/m^2, however, compares well with that of ^{131}I-labeled mAbs in other RIT trials in PC[20,21] and other cancers. ^{131}I is another beta/gamma emitter with similar physical characteristics to ^{177}Lu ($t_{1/2}$: 8 ν 6.7 days; average energy: 0.2 ν 0.15 MeV; average range: 0.4 ν 0.25 mm, respectively). While ^{177}Lu and ^{131}I have similar decay characteristics, use of the latter is compromised in this antigenic system, as after internalization, ^{131}I-labeled antibody is rapidly dehalogenated and diffuses out of tumor cells, while radiometals such as ^{177}Lu or ^{90}Y remain sequestered within the targeted tumor cells.

In this study, as in our ^{90}Y-J591 trial, we found no clear relationship between a history of prior chemotherapy treatment and the degree of toxicity. Similarly, we found no correlation between prior radiotherapy and toxicity. In addition, we found that there was no relationship between the extent of bone marrow involvement by cancer and toxicity. While this observation is somewhat different from that seen in NHL, a similar observation in PC was made by Knox et al[22] and O'Donnell et al.[23] This difference may be due to the fact that NHL involves the marrow much more diffusely than PC where the disease tends to be more focal. As a result, radiolabeled-antibody localization in NHL may radiate the marrow more diffusely than in PC.

The nonhematologic toxicity in RIT trials, in general, and in this ^{177}Lu-J591 trial, was minimal and not dose limiting. Radiation dosimetry calculations indicate a radiation dose to liver of 7.7 cGy/mCi or approximately 1,088 cGy at the MTD of 70 mCi/m^2. This is well below the acceptable radiation limits to the liver. In this trial, 11 patients had transaminase elevations, 10 of which were $\leq$ grade 2 and 1 was grade 3, with four of these patients having pretreatment elevations. These elevations were transient, and the patients experienced no related symptoms. The transaminase elevations in this trial were very similar to that seen with ^{90}Y-J591. In addition, in this ^{177}Lu-J591 trial, no significant hepatotoxicity was seen in patients who received multiple doses, including eight patients who received cumulative doses between 90 and 120 mCi/m^2. Radiation doses to kidney and spleen were also well within acceptable limits, and no related organ toxicity was noted.

Sixteen of 35 patients in the trial received multiple doses. To our knowledge, this represents the largest experience with multiple dosing of RIT yet reported. Two doses of 45 or 60 mCi/m^2, totaling 90 to 120 mCi/m^2, proved to be quite toxic, with three of five patients experiencing prolonged and incomplete platelet recovery. Two or more doses of 30 mCi/m^2, however, were well tolerated, and four patients received cumulative doses of 90 mCi/m^2, almost 30% higher than the single-dose MTD. In this study, each dose was administered after allowing for hematologic recovery from the prior dose. It therefore took 3 to 4 months to administer the three doses, resulting in a higher cumulative dose, but lower dose-rate. While there may be advantages to the higher cumulative dose, the time required to deliver this dose using this regimen may be offset by unrelenting tumor progression. Given the kinetics of platelet decline and recovery, a dose interval of 14 to 17 days may allow a two-dose regimen that might result in a higher cumulative dose (than a single-dose regimen) to be given over a shorter period than attempted in this trial. Such a schedule would result in the onset of platelet recovery from the first dose to coincide with platelet decline from the second dose, thereby resulting in a longer but shallower nadir than with a single MTD dose. Such a dose schedule remains to be explored.

Although no patients in this trial had an objective measurable disease response (PR or CR), in our ^{90}Y trial, there was a correlation of PSA response with measurable disease response,[11] indicating that PSA was a reasonable measure of antitumor activity in patients with PC treated with RIT. In the current trial, four patients had PSA declines of $\geq$ 50%, and 16 patients had PSA stabilization, suggesting that ^{177}Lu-J591 may have biologic activity. This merits exploration in a phase II trial.

There are limited comparisons that can be drawn between our trials of ^{177}Lu-J591 and ^{90}Y-J591. Both radiopharmaceuticals were dose limited by myelosuppression with little nonhematologic toxicity. Both demonstrated biologic activity. In the case of ^{90}Y-J591, the two PSA declines seen could be corroborated by measurable regressions.[11] With ^{177}Lu-J591, the four PSA declines occurred in patients without measurable disease. This may be explained by the responses to ^{177}Lu-J591, with the optimum tumor size for ^{177}Lu treatment of 1.2 to 3.0 mm being more likely to occur in small-volume unmeasurable disease sites, whereas responses to ^{90}Y-J591 would be more likely to occur in bulkier disease sites,[14] or it may simply be an artifact of the small sample size in these phase I trials. There appeared to be more uniformity of myelotoxicity grades among patients at any given dose of ^{177}Lu-J591 than with ^{90}Y-J591. This may reflect the higher energy and range of ^{90}Y and the greater difficulty in calibrating the dose of ^{90}Y combined with its narrower tolerable dose range. Approval of administering repeat doses came relatively late in the course of the ^{90}Y-J591 trial, and, as a result, only four patients received multiple doses of ^{90}Y-J591 compared with 16 patients in the ^{177}Lu-J591 trial. Interestingly, in the ^{90}Y-J591 study in which the MTD was 17.5 mCi/m^2, three patients tolerated two to three doses at 17.5 mCi/m^2, and the fourth patient tolerated two doses of 20 mCi/m^2. That is, the repeat dosing in the ^{90}Y-J591 trial resulted in patients receiving, and tolerating, multiples of the MTD. Conversely, in the ^{177}Lu-J591 trial, there seemed to be more cumulative myelotoxicity, such that repeated dosing was poorly tolerated at doses $\geq$ 65% of the MTD. The reason for this difference is not clear to us.

In conclusion, ^{177}Lu-J591 is well-tolerated, nonimmunogenic, can be administered in multiple doses, and targets PC metastases with sensitivity and specificity. Having determined the single-dose MTD of 70 mCi/m^2 and the tolerability of multiple doses of ^{177}Lu-J591, phase II trials are have begun to assess antitumor activity in both the single- and multiple-dose formats. Additional studies can evaluate the combination of radiolabeled J591 plus chemotherapy such as docetaxel, an agent active in PC also known to have radiosensitizing properties. Preclinical data in human PC xenografts applying RIT in combination with taxanes have demonstrated therapeutic synergy without excess toxicity.[24]

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