

Radioimmunotherapy of Prostate Cancer Using ^{90}Y - and ^{177}Lu -Labeled J591 Monoclonal Antibodies: Effect of Multiple Treatments on Myelotoxicity

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Abstract Purpose: Bone marrow is the dose-limiting organ in radioimmunotherapy. Fractionated dose regimens may decrease myelotoxicity and increase greater total administered dose. We have studied the effect of two or three treatments of ^{177}Lu -J591 and ^{90}Y -J591 monoclonal antibodies (mAb) on myelotoxicity.

Experimental Design: J591 is a deimmunized anti-PSMA mAb. Seven groups of patients with prostate cancer ($n = 35$) received 10 to 75 mCi/m² of ^{177}Lu -J591 and five additional groups ($n = 28$) received 5 to 20 mCi/m² of ^{90}Y -J591. Fifteen patients received two to three treatments of ^{177}Lu -J591 (30, 45, or 60 mCi/m²) and four patients received two or three doses of ^{90}Y -J591 (17.5 or 20 mCi/m²). Re-treatment consisted of patients receiving the same ^{177}Lu or ^{90}Y dose as their initial cycle. Time between treatments was 2 to 4 months.

Results: The single dose maximum tolerated dose was 70 mCi/m² with ^{177}Lu -J591 and 17.5 mCi/m² with ^{90}Y -J591. With a single dose of ^{177}Lu , no severe toxicity was observed below 60 mCi/m². With ^{177}Lu , two doses of 45 or 60 mCi/m², totaling 90 to 120 mCi/m², proved to be quite toxic. Three doses of 30 mCi/m² (total 90 mCi/m²), however, were well tolerated. With ^{90}Y , four patients tolerated two to three doses of 17.5 or 20 mCi/m². Thrombocytopenia increased at higher doses and after repeat treatments. At higher doses, the nadir was lower and the time to reach nadir was longer. Time for recovery of platelets seems related to the total dose.

Conclusions: Multiple (two or three) administrations of ^{177}Lu -J591 (30-60 mCi/m²) or ^{90}Y -J591 (17.5 mCi/m²) over a 4- to 6-month period were tolerated by the patients with manageable thrombocytopenia. Although a single large dose may deliver optimal radiation dose to kill a larger fraction of tumor cells, fractionated therapy offers the advantage of lower myelotoxicity and prolonged tumor response. With ^{177}Lu -J591, dose fractionation in combination with taxanes should be considered as an alternative approach to achieve optimal therapeutic efficacy in patients with prostate cancer.

Metastatic prostate cancer is a reasonable candidate for radioimmunotherapy, because prostate cancer is radioresponsive and typically develops as small-volume micrometastatic sites of disease in marrow and lymph nodes that receive high levels of antibody. In prostate cancer, the most well established,

prostate-restricted, cell surface antigen yet identified is prostate-specific membrane antigen (PSMA; refs. 1–3). PSMA is an ideal target as it is expressed by all prostate cancers (1, 2) and the expression levels progressively increase in more poorly differentiated, metastatic, and hormone-refractory cancers (4). J591 is a deimmunized monoclonal antibody (mAb), which specifically binds with high affinity to the extracellular domain of PSMA (5, 6). In addition, the PSMA-J591 antibody complex is internalized thereby delivering any radiolabeled antibody to the interior of the targeted cancer cells (7).

We have recently completed two phase I dose escalation studies with ^{90}Y -J591 and ^{177}Lu -J591 mAbs in patients with hormone-refractory metastatic prostate cancer. Based on imaging studies, we have shown that J591 was able to sensitively and specifically targets sites of metastatic prostate cancer in both bone and soft tissue (8). Radiolabeled J591 was well tolerated and serious toxicity was confined to reversible myelosuppression (9–12). The preliminary efficacy data showed significant objective antitumor responses including reduction or stabilization of serum PSA and decrease in tumor volume (9, 10).

The antitumor response of low dose rate radiotherapy is primarily due to induction of apoptosis by radiation (13, 14).

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However, the degree of antitumor response following the administration of radiolabeled mAbs depends on several variables, especially total (cumulative) radiation dose to the tumor, dose rate, and tumor radiosensitivity. Bone marrow is the dose-limiting organ in radioimmunotherapy in the absence of marrow reconstitution. Dose fractionation or multiple dosing is a practical strategy to decrease the dose to bone marrow while increasing the cumulative radiation dose to the tumor at an optimal dose rate (15–17). Preclinical data have shown that dose fractionation or multiple low dose treatments can decrease toxicity while increasing the efficacy (18–20).

As part of phase 1 clinical studies, we have studied the safety and myelotoxicity of multiple treatments or doses of ^{177}Lu -J591 or ^{90}Y -J591 mAbs. We report here our preliminary data of myelotoxicity (thrombocytopenia) following multiple treatments.

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 a rising PSA and/or abnormal radiologic studies including bone scan, computed axial tomography and/or magnetic resonance imaging. Patients were required to have a PSA ≥ 1.0 at the time of entry with three consecutive rising PSA values over a period of ≥ 2 weeks. Additional requirements included platelet count of $\geq 150,000/\text{mm}^3$, neutrophil count of $\geq 2,000/\text{mm}^3$, and a bone marrow biopsy showing $\leq 10\%$ replacement by tumor on a unilateral sample or a mean of $\leq 25\%$ replacement by tumor on bilateral samples (9, 10).

Radiolabeled antibodies. Clinical-grade J591 mAb was covalently linked with the chelating agent, 1,4,7,10-tetraazacyclododecane- N,N',N'',N''' -tetraacetic acid (DOTA), as previously reported (6). 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. (Framingham, MA). ^{90}Y chloride was purchased from Nordion (Kanata, Ontario, Canada) and ^{177}Lu chloride was purchased from the University of Missouri-Columbia Research Reactor Center (Columbia, MO). The DOTA-J591 mAb was then labeled by incubating radiometals in an ammonium acetate buffer with antibody. Radiolabeled J591 mAb was then purified and sterilized before administration into patients as previously described (9, 10).

Dose escalation and administration. In the dose escalation trial with ^{177}Lu -J591, patients received ^{177}Lu activity ranging from 10 to 75 mCi/ m^2 . In the dose escalation trial with ^{90}Y -J591, patients received a ^{90}Y dose of 5 to 20 mCi/ m^2 . Additional unconjugated (“cold”) J591 antibody was added to give a constant protein dose of 10 mg/ m^2 with the ^{177}Lu dose and a total of 20 mg with ^{90}Y -J591 dose. The final radiolabeled J591 mAb in 20 mL was given i.v. at an infusion rate of ≤ 5 mg/min.

Re-treatment. Patients were considered eligible for up to two or three re-treatments with ^{177}Lu -J591 or ^{90}Y -J591 at 6-week intervals if their platelet and neutrophil count recovery was satisfactory (platelet count of $>70\%$ of the baseline platelet count of the prior treatment cycle with a minimum recovery to at least $75 \times 10^9/\text{L}$ and ANC $>80\%$ of the baseline ANC of the prior treatment cycle with a minimum recovery to $1.3 \times 10^9/\text{L}$). Patients who experienced any grade >3 nonhematologic toxicity in a prior treatment cycle were ineligible for re-treatment. Patients were also required to fulfill all initial eligibility criteria except for a repeat bone marrow biopsy. Re-treatment consisted of patients receiving the same ^{177}Lu or ^{90}Y dose as their initial cycle.

Follow-up. Patients were observed for a minimum of 12 weeks after their last dose of radiolabeled J591 and those patients with stable or responding disease were observed until disease progression. Routine

clinical and laboratory assessments (including biochemical profile, PSA, PAP, and testosterone) were done at defined intervals. Complete blood count and platelet counts were initially monitored once to twice per week and then every 4 weeks until blood count stabilization. If the ANC was $<1.0 \times 10^9/\text{L}$ and/or platelets $<50 \times 10^9/\text{L}$, blood counts were monitored every other day.

Toxicity evaluation. Dose-limiting toxicity (DLT) was defined as the following: hematologic toxicity consisting of grade 4 thrombocytopenia (platelet $<10 \times 10^9/\text{L}$) and/or grade 4 neutropenia (ANC $<0.5 \times 10^9$) lasting >5 days and other toxicity consisting of any grade ≥ 3 nonhematologic toxicity attributable to ^{177}Lu - or ^{90}Y -labeled J591. The National Cancer Institute Cancer Therapy Evaluation Program Common Toxicity Criteria, version 2.0 was used. The maximum tolerated dose (MTD) was defined as the dose level at which none of six or one of six patients experience 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. The stopping point for single doses and the subsequent doses were the same. DLT and MTD were determined with multiple doses using the same criteria that were used for single doses.

Myelotoxicity and especially thrombocytopenia is often the dose-limiting factor for radionuclide therapy. Fractional decrease in platelets (FDP) was calculated based on baseline level (platelets on the day of treatment) and the nadir following radioimmunotherapy using the following formula:

$$\text{FDP} = 100 \times [(\text{Baseline} - \text{Nadir})/\text{Baseline}]$$

The FDP at different dose levels and following repeat dosing was plotted as a function of time (days posttreatment) using the Origin 6.1 software (OriginLab Corporation, Northampton, MA).

Results

A total of 63 patients with androgen-independent prostate cancer were enrolled in ^{177}Lu and ^{90}Y phase I clinical trials (Table 1). Twenty-four patients (38%) received at least one prior chemotherapy regimen before radioimmunotherapy. Most often, these were taxane-based regimens with mitoxantrone + prednisone being next most common. All patients were maintained at castrate levels of testosterone. In the ^{177}Lu trial ($n = 35$), 19 patients received a single dose, whereas 16 patients received two to three doses. Re-treatment was prescribed at the same dose as initially administered. However, one patient who received 15 mCi/ m^2 was given a second dose of 30 mCi/ m^2 after 7 months following the first dose. The remaining 15 patients had received re-treatment as shown in Table 1. In the ^{90}Y trial ($n = 28$), 24 patients received a single dose and only four patients received re-treatment as shown in the Table 1.

Hematologic toxicity

^{177}Lu protocol. Among patients receiving a single dose of ^{177}Lu -J591, thrombocytopenia was dose related and is summarized in Table 1. Of the three patients at the 75 mCi/ m^2 dose level, one experienced dose-limiting (grade 4) platelet toxicity, whereas the remaining two patients experienced grade 3 platelet toxicity. At the prior dose level of 70 mCi/ m^2 , six patients were entered. One of these patients had grade 4 platelet toxicity. As there was only one DLT in these six patients, the 70 mCi/ m^2 dose level was determined to be the MTD.

Posttreatment platelet counts decline generally at 2.5 to 3 weeks with platelet nadirs occurring at 4 to 5 weeks thereafter followed by a recovery phase. In all the three subjects at 75 mCi/ m^2 , the fractional decrease in platelets as a function of

Table 1. Thrombocytopenia following radioimmunotherapy treatment with a single dose: ^{177}Lu -J591 versus ^{90}Y -J591 mAb

^{177}Lu -J591						^{90}Y -J591									
Dose (mCi/m ²)	Patients		TCP grade				Dose (mCi/m ²)	Patients		TCP grade					
	Total	Re-treatment	0	1	2	3		4	Total	Re-treatment	0	1	2	3	4
10	3	—	3				5	4	—	3	1				
15	3	1	2	1			10	7	—	2	2	3			
30	12	10	4	7	1		15	7	—	3	2	2			
45	5	3		1	3	1	17.5	6	3	1	1	4			
60	3	2		1	1	1	20	4	1	1		1	2		
70	6	—			1	4	1								
75	3	—				2	1								

Abbreviation: TCP, thrombocytopenia.

time (days) is shown in Fig. 1. The mean platelet counts returned to 80% to 90% of their pretreatment values. However, two of three patients required platelet transfusion twice before returning to normal levels.

In contrast to the significant hematologic toxicity seen at 75 mCi/m², multiple doses of 30 mCi/m² were well tolerated. Six patients received two doses, and four patients received three doses. The median time between doses 1 and 2 was 64 days (range, 42-238 days) and between doses 2 and 3 was 53 days (range, 50-55 days). The four patients who received three doses totaling 90 mCi/m² did so over a period of 98 to 126 days. The fractional decrease in platelets following the three doses at 30 mCi/m² is shown in Fig 2. The platelet recovery was very good in three patients whereas the fourth patient had grade 4 platelet toxicity (Table 2) and began a different therapy due to disease progression, before being able to fully assess toxicity.

At 45 mCi/m², two of the three patients developed prolonged grade 3 platelet toxicity (Table 2; Fig. 3) each requiring three platelet transfusions between days 35 to 48 and 38 to 56, respectively, after the second dose. The third patient had grade 0 hematologic toxicity and showed good recovery of platelets after the third dose (Fig. 3).

At 60 mCi/m², two patients received two doses: one experienced grade 4 platelet toxicity (Table 2; Fig. 4) 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. The only other patient treated with two doses of 60 mCi/m² experienced grade 1 platelet and ANC toxicity similar to a patient who received only one dose of 60 mCi/m² and showed good platelet recovery (Fig. 4).

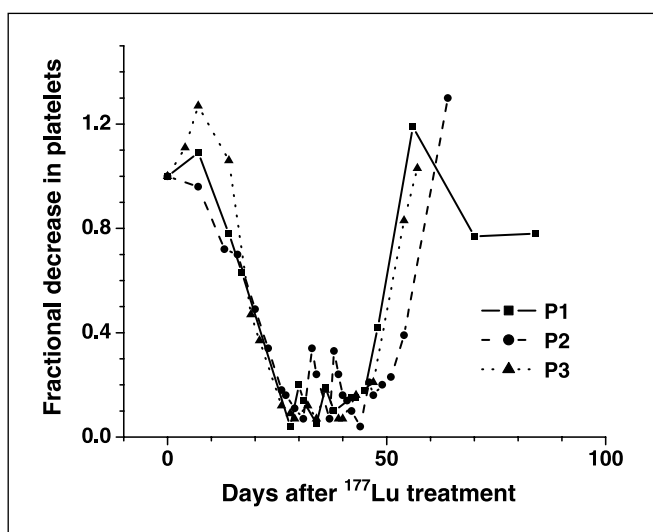


Fig. 1. Thrombocytopenia following treatment with ^{177}Lu -J591 mAb. Each patient received a single dose of 75 mCi/m². The pretreatment platelets (baseline) for patients P1, P2, and P3 were 260, 174, and 270 $\times 10^9$ /L, respectively. Dose-limiting platelet toxicity (grade 4) was experienced by P2, whereas P1 and P3 experienced grade 3 toxicity. Platelet transfusions were given twice to P1 (days 30 and 34) and P2 (days 31 and 44).

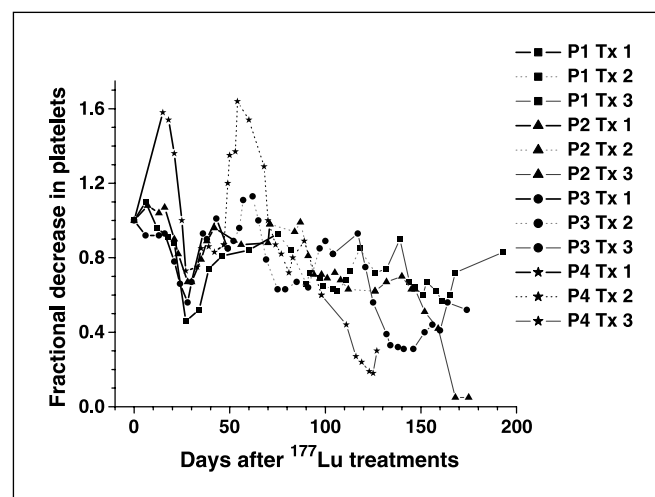


Fig. 2. Thrombocytopenia following treatment with ^{177}Lu -J591 mAb. Each patient received three treatments (Tx) or doses of 30 mCi/m². The pretreatment platelets (baseline) for patients P1, P2, P3, and P4 were 183, 249, and 273 and 273 $\times 10^9$ /L, respectively. The re-treatments (Tx 2 and Tx 3) for P1 was on days 75 and 126, P2 on days 71 and 126, P3 on 49 and 104, and P4 on days 47 and 98. After the three doses, P1, P3, and P4 showed good platelet recovery, whereas P2 after 168 days began a different therapy due to disease progression before being able to fully assess toxicity from the third dose.

Table 2. Thrombocytopenia following radioimmunotherapy treatment with multiple doses of ¹⁷⁷Lu-J591 mAb

Dose (mCi/m ²)	Patient	TCP grade (0-4)		
		Dose 1	Dose 2	Dose 3
30	1	1	1	1
	2	0	0	1
	3	0	0	1
	4	0	0	4
45	1	1	1	
	2	2	3	
	3	2	3	
60	1	1	1	
	2	3	4	

Abbreviation: TCP, thrombocytopenia.

Following treatment (single or multiple doses) of ¹⁷⁷Lu-J591, the percent decrease in platelets and the time to reach nadir was dependent on the amount of dose (Table 3) and the number of doses. The fractional decrease in platelets increased with increasing dose and after repeat treatments. At higher doses, the time to reach nadir was longer and the time for recovery seems related to the total dose. The slope of the platelet declines, however, are remarkably similar, independent of dose, and probably relates to failure of new platelet production and half-life of the existing platelets. The reason it takes longer to reach nadir is simply the fact that the decline lasts longer in those getting higher doses as the production of new platelets is interrupted for a longer time.

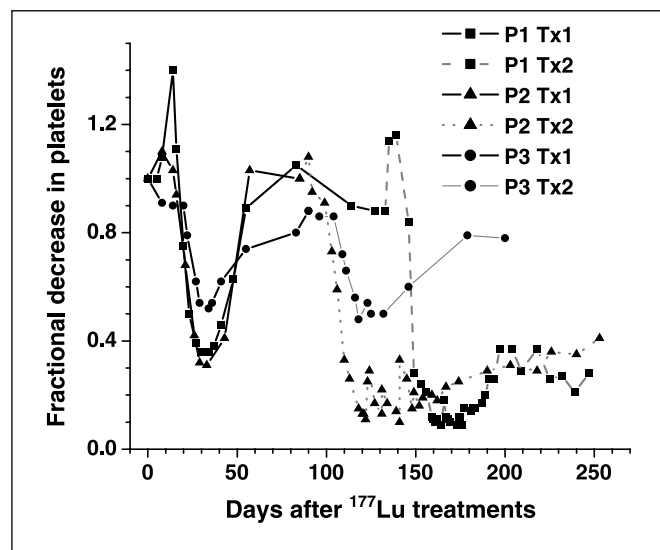


Fig. 3. Thrombocytopenia following treatment with ¹⁷⁷Lu-J591 mAb. Each patient received two treatments (Tx) or doses of 45 mCi/m². The pretreatment platelets (baseline) for patients P1, P2, and P3 were 205, 189, and 242 × 10⁹/L, respectively. The re-treatment (Tx 2) for P1 was on day 127, P2 on day 85, and P3 on day 90. After the two doses, P3 showed good platelet recovery, whereas P1 and P2 required three platelet transfusions between days 35 and 48 and between 38 and 56, respectively, following the second dose.

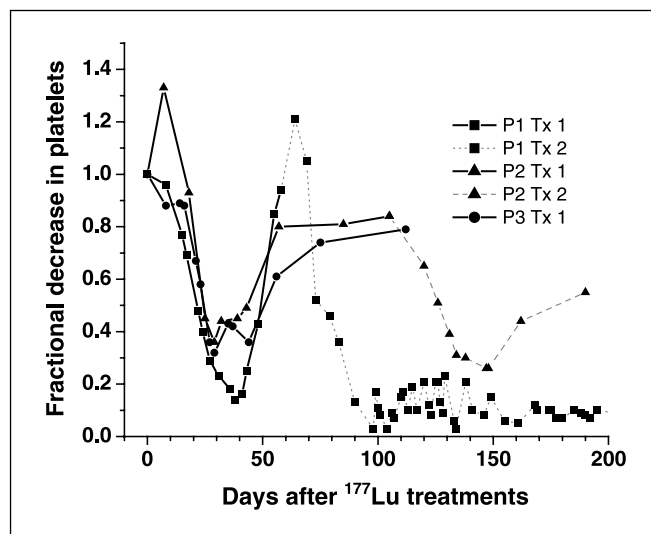


Fig. 4. Thrombocytopenia following treatment with ¹⁷⁷Lu-J591 mAb. Patients (P1 and P2) received two treatments (Tx) or doses of 60 mCi/m². The pretreatment platelets (baseline) for patients P1, P2, and P3 were 239, 325, and 206 × 10⁹/L, respectively. The re-treatment (Tx 2) for P1 was on day 58 and P2 on day 105. After the two doses, P2 showed good platelet recovery, whereas P1 experienced grade 4 platelet toxicity and required 13 platelet transfusions between days 40 and 105 after the second dose. P3 had only one treatment.

⁹⁰Y protocol. In the ⁹⁰Y-J591 dose escalation scheme, the numbers of patients treated at each dose level, and the number of re-treated patients are listed in Table 1. At the 20 mCi/m² dose level, two of four patients developed grade 3 platelet toxicity (Table 1) with grade 3 non-life-threatening bleeding episodes (one patient had an upper gastrointestinal bleed and the other merely had persistent hematuria) requiring transfusions. Although this was not the predefined DLT, these events were considered to be dose limiting. All four patients showed good platelet recovery (Fig. 5). One of the patients received a second dose of 20 mCi/m² and showed good platelet recovery.

At the 17.5 mCi/m² dose level, a total of six patients were treated with no DLTs (Table 1), and this dose level represents the MTD. At this dose, three patients received a second dose of ⁹⁰Y-J591. Two of these three patients experienced grade 3 thrombocytopenia and neutropenia and both patients recovered a platelet count to >120 × 10⁹/L. One of these patients at the 17.5 mCi/m² dose level also received a third dose and experienced grade 3 thrombocytopenia (platelet recovery was 61 × 10⁹/L) after the third dose (Fig. 5). No DLTs were seen in the re-treated patients.

Discussion

Among solid tumors, prostate cancer is a reasonable target for radioimmunotherapy, because it is relatively radiosensitive and its predilection for forming small foci in the marrow and lymph nodes makes its target antigens readily accessible to circulating antibodies. Furthermore, PSMA is an attractive cell surface antigen given its expression by all prostate cancers (1–3), its high degree of specificity, its high level of expression (6), and its internalization (7) leading to the irreversible sequestration of radiometals within the targeted tumor cells and the absence of a competing reservoir of antigen in the plasma. Given the favorable setting, prostate cancer and the

Table 3. Thrombocytopenia following ^{177}Lu -J591 mAb treatment: effect of dose and number of treatments

Dose (mCi/m ²)	Patients, <i>n</i>	% Decrease in platelets			Time (d) to reach nadir		
		Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
30	4	40 ± 12	24 ± 7	67 ± 34	27 ± 1	29 ± 5	40 ± 5
45	3	60 ± 11	75 ± 26		34 ± 1	34 ± 5	
60	3	73 ± 12	83		32 ± 5	41	
70	6	87 ± 6			33 ± 6		
75	3	95 ± 2			38 ± 6		

PSMA antigenic system offers a model for the investigation and development of radioimmunotherapy in solid tumors. J591 is a humanized anti-PSMA mAb that binds with high affinity (1 nm) to the extracellular domain of PSMA (6, 8). We have previously reported on the pharmacokinetics and biodistribution of radiolabeled J591 mAbs in patients with prostate cancer (11) labeled with either ^{111}In or ^{177}Lu radionuclides (18). We have also reported on the safety, toxicity, and preliminary efficacy of both ^{90}Y - and ^{177}Lu -labeled J591 (9, 10). In this article, we are reporting our data on the effect of multiple doses of ^{177}Lu -J591 and ^{90}Y -J591 on the myelotoxicity, especially thrombocytopenia.

DLT in this trial, as in radioimmunotherapy trials in general, was limited to myelotoxicity. The MTD of a single dose of ^{177}Lu -J591 was 70 mCi/m². This MTD is significantly higher than the MTD of 17.5 mCi/m² we found with ^{90}Y using the same J591-DOTA preparation in a similar patient population. Based on our phase I dose escalation studies, we also showed (12) that with ^{177}Lu , the FDP correlates well with both the radioactive dose administered ($R = 0.88$) and the bone marrow radiation dose ($R = 0.86$). In contrast, with ^{90}Y , there was poor correlation between the FDP and radioactive dose administered ($R = 0.20$) or the BMrad ($R = 0.26$). But in our clinical studies, we found no clear relationship between a history of prior

chemotherapy treatment and degree of toxicity with these two agents (9, 10). Similarly, we found no correlation between prior radiotherapy and toxicity.

Sixteen of 35 patients in the ^{177}Lu trial and 4 of 28 patients in ^{90}Y trial received multiple doses. To our knowledge, this represents the largest experience with multiple dosing of radioimmunotherapy yet reported for prostate cancer. With ^{177}Lu , two doses of 45 or 60 mCi/m², totaling 90 to 120 mCi/m², proved to be quite toxic, with three of five patients experiencing prolonged and incomplete platelet recovery. Two or more doses of 30 mCi/m², however, were well tolerated and four patients received cumulative doses of 90 mCi/m², almost 30% higher than the single-dose MTD.

Interestingly, in the ^{90}Y -J591 study where the MTD was 17.5 mCi/m², three patients tolerated two to three doses at 17.5 mCi/m² and the fourth patient tolerated two doses of 20 mCi/m². That is, the repeat dosing in the ^{90}Y -J591 trial resulted in patients receiving, and tolerating, multiples of the MTD. In the ^{90}Y trial, none of the patients received multiple doses at <17.5 mCi/m². In the ^{177}Lu -J591 trial, there seemed to be more cumulative myelotoxicity such that repeated dosing was poorly tolerated at doses of $\geq 65\%$ of the MTD.

In the ^{177}Lu dose fractionation protocol, 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. Whereas there may be advantages to the higher cumulative dose, the time required to deliver this dose using this regimen may be offset by tumor progression. Given the kinetics of platelet decline and recovery with three doses at 30 mCi/m² (Fig. 2), a dose interval of 14 to 17 days may allow a two dose regimen (40-45 mCi/m² per dose) that might 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 nadir than with a single MTD dose.

The preliminary data with the ^{177}Lu dose fractionation strategy is not robust enough to provide any statistically meaningful results. Although this strategy results in *only* a 30% increase in cumulative dose, the data shows that fractionation of doses allows for incremental cumulative dosing. In addition, the data did show that reduction in dose rate due to dose fractionation did help reduce the myelotoxicity.

Dose rate effects are important in conventional radiotherapy. Sealed radionuclide source implant radiotherapy involves continuous, high-dose rate radiation rather than the multiple, short bursts of radiation characteristic of external beam radiotherapy. The benefit from fractionation of the total dose of radiation for external beam radiotherapy is well established;

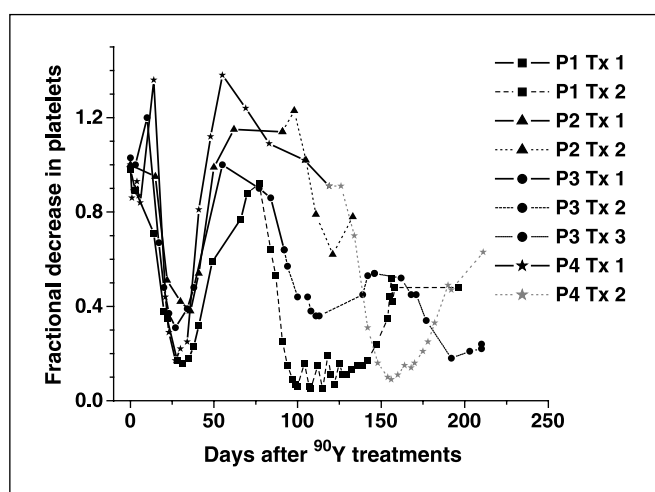


Fig. 5. Thrombocytopenia following treatment with ^{90}Y -J591 mAb. Patients, P1, P2, and P3 received two or three treatments (Tx) or doses of 17.5 mCi/m² and P4 received two treatments of 20 mCi/m². The pretreatment platelets (baseline) for patients P1, P2, P3, and P4 were 261, 175, 258, and 197 $\times 10^9/\text{L}$, respectively. The re-treatment (Tx 2) for P1 was on day 70, P2 on day 91, and P3 received Tx 2 on day 92 and Tx 3 on day 146. All four patients showed good recovery after re-treatments.

multiple doses, usually given daily, extend the total radiation dose that can be given to the malignancy by decreasing normal tissue toxicity (15).

In contrast, the average dose rates involved in radioimmunotherapy are much lower than those encountered in external beam radiotherapy or in continuous low-dose rate brachytherapy. Most radioimmunotherapy treatments will achieve average dose rates that are substantially lower than 0.5 Gy h^{-1} (21). Radioimmunotherapy involves continuous and continuously decreasing low-dose rate radiation that seems to destroy cells primarily through apoptosis, rather than through the necrosis characteristic of the cellular effects of external beam radiotherapy and chemotherapy (13–15). Because of the complexity of the spatial and temporal variations in dose rate associated with radioimmunotherapy treatment, it is difficult to assess the real effect of dose rate on antitumor response (21).

The theoretical advantages of dose fractionation have been shown in animal models (18–20) but not in clinical studies (10, 22). Although a single large dose may deliver optimal radiation dose to kill a larger fraction of tumor cells, fractionated therapy offers the advantage of lower myelotoxicity and prolonged tumor response.

Combination of radioimmunotherapy with chemotherapeutic agents that affect the cell cycle, such that tumors are sensitized to the effects of radiation are of particular interest in developing strategies to improve the efficacy of radioimmunotherapy. Preclinical data in human prostate cancer xenografts applying radioimmunotherapy in combination with taxanes have shown therapeutic synergy without excess toxicity (23). With ^{177}Lu -J591, dose fractionation in combination with taxanes, should be considered as an alternative approach to achieve optimal therapeutic efficacy in patients with prostate cancer.

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