Prediction of Myelotoxicity Based on Bone Marrow Radiation-Absorbed Dose: Radioimmunotherapy Studies Using ⁹⁰Y- and ¹⁷⁷Lu-Labeled J591 Antibodies Specific for Prostate-Specific Membrane Antigen

Shankar Vallabhajosula, PhD¹; Stanley J. Goldsmith, MD¹; Klaus A. Hamacher, PhD¹; Lale Kostakoglu, MD¹; Shota Konishi, MD¹; Mathew I. Milowski, MD²;³; David M. Nanus, MD²;³; and Neil H. Bander, MD³

¹Division of Nuclear Medicine, Department of Radiology, New York Presbyterian Hospital–Weill Medical College of Cornell University, New York, New York; ²Division of Hematology and Medical Oncology, New York Presbyterian Hospital–Weill Medical College of Cornell University, New York, New York; and ³Laboratory of Urological Oncology, Department of Urology, New York Presbyterian Hospital–Weill Medical College of Cornell University, New York, New York

In radioimmunotherapy, myelotoxicity due to bone marrow radiation-absorbed dose is the predominant factor and frequently is the dose-limiting factor that determines the maximum tolerated dose (MTD). With ⁹⁰Y- and ¹³¹I-labeled monoclonal antibodies, it has been reported that myelotoxicity cannot be predicted on the basis of the amount of radioactive dose administered or the bone marrow radiation-absorbed dose (BMrad), estimated using blood radioactivity concentration. As part of a phase I dose-escalation study in patients with prostate cancer with ⁹⁰Y-DOTA-J591 (DOTA = 1,4,7,10-tetraazacyclododecane-ΝΝ′,Ν″,Ν‴-tetraacetic acid) (⁹⁰Y-J591) and ¹⁷⁷Lu-DOTA-J591 (¹⁷⁷Lu-J591), we evaluated the potential value of several factors in predicting myelotoxicity. Methods: Seven groups of patients (n = 28) received 370–2,775 MBq/m² (10–75 mCi/m²) of ¹⁷⁷Lu-J591 and 5 groups of patients (n = 27) received 185–740 MBq (5–20 mCi/m²) of ⁹⁰Y-J591. Pharmacokinetics and imaging studies were performed for 1–2 wk after ¹⁷⁷Lu treatment, whereas patients receiving ⁹⁰Y had these studies performed with ¹¹¹In-DOTA-J591 (¹¹¹In-J591) as a surrogate. The BMrad was estimated based on blood radioactivity concentration. Myelotoxicity consisting of thrombocytopenia or neutropenia was graded 1–4 based on criteria of the National Cancer Institute. Results: Blood pharmacokinetics are similar for both tracers. The radiation dose (mGy/Mbq) to the bone marrow was 3 times higher with ⁹⁰Y (0.91 ± 0.43) compared with that with ¹⁷⁷Lu (0.32 ± 0.10). The MTD was 647.5 MBq/m² with ⁹⁰Y-J591 and 2,590 MBq/m² with ¹⁷⁷Lu-J591. The percentage of patients with myelotoxicity (grade 3–4) increased with increasing doses of ⁹⁰Y (r = 0.91) or ¹⁷⁷Lu (r = 0.92). There was a better correlation between the radioactive dose administered and the BMrad with ¹⁷⁷Lu (r = 0.91) compared with that with ⁹⁰Y (r = 0.75). In addition, with ¹⁷⁷Lu, the fractional decrease in platelets (FDP) correlates well with both the radioactive dose administered (r = 0.88) and the BMrad (r = 0.86). In contrast, with ⁹⁰Y, there was poor correlation between the FDP and the radioactive dose administered (r = 0.20) or the BMrad (r = 0.26). Similar results were also observed with white blood cell toxicity. Conclusion: In patients with prostate cancer, myelotoxicity after treatment with ¹⁷⁷Lu-J591 can be predicted on the basis of the amount of radioactive dose administered or the BMrad. The lack of correlation between myelotoxicity and ⁹⁰Y-J591 BMrad may be due to several factors. ⁹⁰Y-J591 may be less stable in vivo and, as a result, higher amounts of free ⁹⁰Y may be localized in the bone. In addition, the cross-fire effect of high-energy β⁺-particles within the bone and the marrow may deliver radiation dose nonuniformly within the marrow.

Key Words: radioimmunotherapy; myelotoxicity; ¹⁷⁷Lu-labeled J591 monoclonal antibody


The goal of targeted radioimmunotherapy (RIT) is to administer the maximum treatment dose that would deliver optimal radiation-absorbed dose to tumor tissue with minimal or acceptable toxicity to critical organs such as bone marrow, liver, spleen, and kidney. Several RIT studies have demonstrated that, in the absence of bone marrow or hematopoietic stem cell support, radiation-induced myelotoxicity is the dose-limiting toxicity (DLT) (1,2). The manifestations of myelotoxicity are somewhat related to the pretreatment peripheral blood cell counts and assumed to be due to variability of the bone marrow reserve, which may have been compromised by prior therapies (1,3). Several investigators have developed quantitative methods to determine the bone marrow radiation-absorbed dose (BMrad) based on...
blood radioactivity to assess the predictive dose–response relationship for myelotoxicity (4–9). The potential dose–response relationships between myelotoxicity and total radionuclide administered dose and whole-body radiation dose have been studied also to identify predictors of myelotoxicity. For several monoclonal antibodies (mAbs) labeled with 131I or 90Y, the correlation between myelotoxicity and BMrad has been poor and, as a result, bone marrow dosimetry in general has not proven to be useful to predict myelotoxicity (8,10–12). However, some recent studies with 111In/90Y have shown improvement in the correlation between myelotoxicity and bone marrow dose, when the bone marrow dose was estimated on the basis of the radioactivity localization in the lumbar vertebrae of 111In images (13,14).

We have recently completed phase I dose-escalation RIT clinical studies in patients with prostate cancer using 90Y- and 177Lu-labeled J591 deimmunized mAb specific for the extracellular domain of prostate-specific membrane antigen (PSMA) (15–18). With both radionuclides, myelotoxicity was the dose-limiting factor and we have also observed that the correlation between myelotoxicity and BMrad was very poor with 90Y. However, with 177Lu, the BMrad is a good predictor of myelotoxicity (19). We report here the myelotoxicity for these 2 radiolabeled antibodies and compare the correlation data between myelotoxicity and BMrad.

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 (patient-specific antigen) level or abnormal radiologic studies, including bone scan, 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/mm³ and an absolute neutrophil count (ANC) of ≥2,000/mm³ 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.

Radiolabeled Antibodies

Clinical grade deimmunized J591 mAb was covalently linked with the chelating agent, 1,4,7,10-tetraazacyclododecane-N,N',N''N'''-tetraacetic acid (DOTA) as previously reported (20). The DOTA-J591 mAb was then labeled with 111In, 90Y, or 177Lu chloride in an ammonium acetate buffer as previously described (18,20). Radiolabeled J591 mAb was then purified by gel filtration and sterilized by membrane (0.2 µm) filtration before administration to patients.

Dose Escalation and Administration

In the dose-escalation trial with 90Y-J591, patients received 185 MBq of 111In-J591 for pharmacokinetics and biodistribution studies 1 wk before 90Y-J591 administration. After completion of the 111In studies, each patient received the 90Y dose, which was escalated in cohorts of 3–6 patients at the planned dose levels between 185 and 740 MBq/m². In the dose-escalation trial with 177Lu-J591, patients received 177Lu activity ranging from 370 to 2,775 MBq/m². Additional unconjugated (unlabeled) J591 antibody was added to give a constant protein dose of 20 mg with the 111In- or 90Y-J591 dose or 10 mg/m² with the 177Lu dose. The final radiolabeled J591 mAb in 20 mL was given intravenously at an infusion rate of ≤5 mg/min.

Pharmacokinetics and Imaging Studies

After infusion of the diagnostic dose of 111In-J591 or the treatment dose of 90Y-J591, venous blood samples were obtained at 10 min, 1, 2, 4, and 24 h, and days 2, 3, 4, and 7 d. In the 177Lu 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 111In or 177Lu standard, and the activity in plasma was expressed as the percentage injected dose per milliliter (%ID/mL). The time–activity data was plotted using GraphPad Prism software (GraphPad Software, Inc.), and the curves were fitted to mono- and biexponential functions to generate plasma clearance rate constants.

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 (1, 2, 3, and 6–7 d) for 111In and over the next 2 wk (1, 3, 6–9, and 13–14 d) for 177Lu. The γ-camera images were obtained using a dual-head ADAC Laboratories or General Electric γ-camera (General Electric Medical Systems).

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 per organ (%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 (6,18). The 111In data were corrected to estimate the residence times for 90Y. The radiation dosimetry of 111In-J591 and 90Y-J591 was calculated by entering the corresponding residence times into the MIRDOS and OLINDA (Organ Level INternal Dosage Assessment) software programs (21–23), which compute the radiation-absorbed dose (mGy/MBq or rad/ mCi) for each of the target organs.

Toxicity Evaluation

DLT was defined as hematologic toxicity consisting of grade 4 thrombocytopenia (platelet count < 10 × 10⁹/L) or grade 4 neutropenia (ANC < 0.5 × 10⁹/L) lasting >5 d; other toxicity was defined as consisting of any grade ≥3 nonhematologic toxicity attributable to 177Lu-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 0 of 6 or 1 or 6 patients experience a DLT, with the next higher dose level having ≥2 patients experiencing a DLT. Once the MTD was reached, at least 6 patients were to be evaluated at that dose level.
Patients were monitored for a minimum of 12 wk after 177Lu-J591 administration. Routine clinical and laboratory assessments (including biochemical profile, PSA, prostatic acid phosphatase, and testosterone) were performed at defined intervals. The complete blood count and platelet counts were initially monitored 1 or 2 times per week and then every 4 wk until blood count stabilization. If the ANC was \( \leq 1.0 \times 10^9/L \) or the platelet count was \( \leq 50 \times 10^9/L \), blood counts were monitored every other day.

**Correlation Studies**

Myelotoxicity, and especially thrombocytopenia, is often the dose-limiting factor for radionuclide therapy. The fractional decrease in platelets (FDP) and the ANC were calculated on the basis of the baseline level and the nadir after RIT using the following formula:

\[
\text{FDP or ANC} = 100 \times \left( \frac{\text{baseline} - \text{nadir}}{\text{baseline}} \right)
\]

To understand the dose–response relationship of myelotoxicity, simple linear regression (univariate regression analysis) was used to assess the correlation between platelet and ANC toxicity grades and FDP and ANC with total radioactive dose administered and the estimated BMrad. The data were plotted and the correlation coefficient \( (r) \) was calculated using Origin 6.1 software (OriginLab Corp.).

**RESULTS**

Sixty-four patients with advanced prostate cancer were enrolled in 2 independent phase I dose-escalation trials with \(^{111}\text{In}/^{90}\text{Y}-\text{J591} (n = 29)\) or \(^{177}\text{Lu}-\text{J591} (n = 35)\) between October 2000 and August 2003. We report here the dosimetry data in 28 patients from the \(^{90}\text{Y}\) trial and 28 patients from the \(^{177}\text{Lu}\) trial. The pertinent demographic characteristics of patients are given in Table 1.

**Pharmacokinetics, Biodistribution, and Dosimetry**

Pharmacokinetic analysis of plasma samples obtained after the administration of \(^{111}\text{In}-\text{J591}\) or \(^{177}\text{Lu}-\text{J591}\) mAb is...
1. SUMMARY

The biodistribution of both tracers based on γ-camera imaging studies is also similar. Liver is the only organ accumulating the maximum amount of radioactivity and there was no significant difference between the 2 radiotracers. The initial liver uptake kinetics were similar for both tracers; however, the mean liver uptake with 177Lu was about 25% less than that with 111In on day 6 (P < 0.05). Subsequently, 177Lu activity showed gradual washout from liver. The whole-body retention of activity, however, was similar for both tracers.

The radiation dosimetry of 177Lu-J591 and 90Y-J591 (estimated based on 111In-J591 data) are compared in Table 3. The critical organ receiving the highest radiation dose is the liver, followed by spleen and kidneys. The BM rad (cGy/37 MBq or rad/mCi) based on blood radioactivity is 3.4 ± 1.6 with 90Y and 1.2 ± 0.4 with 177Lu. For a person with a body surface area of 2.0 m², 177Lu-J591 (2,590 MBq/m²) would deliver approximately 164 cGy to the bone marrow. In comparison, 90Y-J591 (647.5 MBq/m²) would deliver 118 cGy to the bone marrow.

2. TOXICITY

The DLT for both 90Y- and 177Lu-labeled J591 mAbs was myelotoxicity. The MTD was 647.5 MBq/m² with 90Y-J591 and 2,590 MBq/m² with 177Lu-J591. The hematologic toxicity (thrombocytopenia and neutropenia) in patients at different dose levels is summarized in Tables 4 and 5. With both radiolabeled antibodies, nonhematologic toxicity was only mild or moderate and not dose limiting. With 90Y-J591, 2 of 4 patients at 740 MBq/m² had grade 4 thrombocytopenia and 1 patient had neutropenia, whereas none of the 6 patients at 647.5 MBq/m² had grade 4 hematologic toxicity (Table 4). The percentage decrease in platelets and ANCs as a function of administered dose level (MBq/m²) is summarized in Figure 1A. Although there was a significant decrease in platelets and ANCs at the highest dose (740 MBq/m²) compared with the decrease at 185 MBq/m², there was no well-defined dose–response relationship. The median time to platelet nadir was day 28 and the median time to ANC nadir was day 35. The median time to full platelet recovery (>150 × 10⁹/L) was day 49 and the median time to full ANC recovery (>2.0 × 10⁹/L) was day 63. With a single dose of 90Y-J591, full platelet recovery (>150 × 10⁹/L) and full ANC recovery (>2.0 × 10⁹/L) was observed in 20 and 23 of 25 patients, respectively.

With 177Lu-J591, hematologic toxicity increased directly with the dose of 177Lu (Table 5; Fig. 1B). The FDP gradually increased as the 177Lu dose increased, but with the ANC no dose–response relationship was found between 370 and 1,665 MBq/m². Of the 3 patients at the 2,775 MBq/m² dose level, 1 experienced dose-limiting (grade 4) thrombocytopenia and the remaining 2 patients experienced grade 3 thrombocytopenia. One of these patients experienced dose-limiting neutropenia with the remaining 2 patients experiencing grade 4, but not dose-limiting neutropenia. Because 2 of the 3 patients at this dose level experienced DLT, no additional patients were studied at this dose. At the dose level of 2,590 MBq/m², 6 patients were studied. Two pa-

### Table 3

<table>
<thead>
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<th>Organ</th>
<th>177Lu-DOTA-J591</th>
<th>90Y-DOTA-J591</th>
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<td>Liver</td>
<td>24.39 ± 8.39</td>
<td>18.22 ± 6.14</td>
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<td>Spleen</td>
<td>16.55 ± 4.00</td>
<td>12.85 ± 3.41</td>
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<td>Kidneys</td>
<td>11.07 ± 2.24</td>
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<td>Heart wall</td>
<td>2.53 ± 0.97</td>
<td>2.63 ± 1.09</td>
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<tr>
<td>Lungs</td>
<td>3.37 ± 1.59</td>
<td>3.08 ± 1.08</td>
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<tr>
<td>Red marrow</td>
<td>1.08 ± 0.28</td>
<td>1.08 ± 0.28</td>
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<tr>
<td>Bone surfaces</td>
<td>2.05 ± 0.31</td>
<td>2.63 ± 1.09</td>
</tr>
<tr>
<td>Urinary bladder wall</td>
<td>1.08 ± 0.28</td>
<td>1.08 ± 0.28</td>
</tr>
<tr>
<td>Muscle</td>
<td>6.60 ± 0.94</td>
<td>6.60 ± 0.94</td>
</tr>
<tr>
<td>Testes</td>
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<tr>
<td>Total body</td>
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<td>0.94</td>
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<td>Effective dose equiv.</td>
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<td>0.31</td>
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<td>Effective dose</td>
<td>0.22</td>
<td>0.14</td>
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### Table 4

<table>
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<th>Dose (MBq/m²)</th>
<th>Patients (n)</th>
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<th>Neutropenia</th>
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<td>0</td>
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<td>3</td>
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<td>185</td>
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<td>555</td>
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<td>647.5</td>
<td>6</td>
<td>1</td>
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<tr>
<td>740</td>
<td>4</td>
<td>1</td>
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</table>

## References

The critical organ receiving the highest radiation dose is the liver, followed by spleen and kidneys. The BM rad (cGy/37 MBq or rad/mCi) based on blood radioactivity is 3.4 ± 1.6 with 90Y and 1.2 ± 0.4 with 177Lu. For a person with a body surface area of 2.0 m², 177Lu-J591 (2,590 MBq/m²) would deliver approximately 164 cGy to the bone marrow. In comparison, 90Y-J591 (647.5 MBq/m²) would deliver 118 cGy to the bone marrow.
tients had transient grade 4 neutropenia not meeting the definition of DLT; however, 1 of these patients had a grade 4 dose-limiting thrombocytopenia. As there was only 1 DLT in these 6 patients, this dose (2,590 MBq/m²) was denoted the MTD. Platelet nadirs generally are reached at 4–5 wk and followed by a recovery phase. ANCs were significantly more variable and demonstrated less consistent patterns after treatment than platelet counts and, at higher doses, the ANC nadir was reached earlier.

Correlation Studies

With both ⁹⁰Y- and ¹⁷⁷Lu-labeled J591 mAbs, the percentage of patients at each dose level showing grade 3–4 toxicity correlated very well ($r = 0.9$) with the treatment dose (Figs. 2A and 2B). The BMrad based on blood radioactivity (Figs. 3A and 3B) correlated much better with the ¹⁷⁷Lu treatment dose ($r = 0.91$) than with the ⁹⁰Y treatment dose ($r = 0.75$).

The FDP after administration of ⁹⁰Y-J591 showed very poor correlation (Figs. 4A and 4C) with both the total treatment dose of ⁹⁰Y ($r = 0.20$) and the BMrad ($r = 0.26$). The fractional decrease in ANCs also showed poor correlation with the treatment dose ($r = 0.20$) and the BMrad ($r = 0.08$) (Figs. 5A and 5C). In contrast, with ¹⁷⁷Lu-J591, the FDP showed very good correlation (Figs. 4B and 4D) with the treatment dose ($r = 0.88$) and the BMrad ($r = 0.86$). Similarly, the fractional decrease in ANCs also correlated well with the treatment dose ($r = 0.82$) and BMrad ($r = 0.72$) (Figs. 5B and 5D).

DISCUSSION

In this article, we report a very strong correlation between myelotoxicity and BMrad in patients with prostate cancer who were treated with ¹⁷⁷Lu-J591, a radiolabeled antibody that binds specifically to PSMA. The most important finding is that, in a similar patient population and with the same antibody, myelotoxicity can be predicted using BMrad estimates on the basis of blood activity of ¹⁷⁷Lu-J591 but not of ⁹⁰Y-J591. We believe that this finding may help us understand the importance of the energy of radiation and the relative in vivo stability of the radionuclide-antibody complex in the overall assessment of radiation dose and myelotoxicity.

We have previously reported on the pharmacokinetics and biodistribution of J591 mAb labeled with either ¹¹¹In or ¹⁷⁷Lu (18). The plasma clearance of ¹¹¹In-J591 and ¹⁷⁷Lu-J591 is quite similar. Based on biexponential decay, the terminal half-life is 44 ± 15 h for both tracers. In addition, the total-body retention of radioactivity over a 7-d period is also similar between the 2 isotopes. The percentage uptake in liver is about 25% greater with ¹¹¹In than that with ¹⁷⁷Lu. Radiation dosimetry estimates for ⁹⁰Y-J591 calculated on the basis of ¹¹¹In or ¹⁷⁷Lu data were mostly similar and show

![FIGURE 1](https://example.com/fig1.png)

**FIGURE 1.** Percentage decrease in platelets and granulocytes after treatment with radiolabeled J591 mAb. (A) ⁹⁰Y-J591. (B) ¹⁷⁷Lu-J591.
that liver is the critical organ, followed by spleen and kidneys (18). Based on blood radioactivity, the radiation dose (mGy/MBq) to the bone marrow was 3 times higher with $^{90}$Y ($0.91 \pm 0.43$) compared with that with $^{177}$Lu ($0.32 \pm 0.10$). For both tracers, liver is the only organ accumulating the maximum amount of radioactivity. As expected, the radiation dosimetry estimates to source organs with $^{177}$Lu is significantly less compared with that with $^{90}$Y since the equilibrium dose constant (cGy·g/h) for $^{177}$Lu (0.284) is almost one-sixth that of $^{90}$Y (1.99), which has much higher energy $^{177}$Lu-parti-

Because the plasma clearance kinetics of J591 mAb la-
beled with $^{111}$In/$^{90}$Y or $^{177}$Lu are quite similar, there is a good correlation between the estimates of BMrad based on blood and the administered total dose (MBq) for both $^{177}$Lu ($r = 0.91$) and $^{90}$Y ($r = 0.75$). Surprisingly, the FDP shows a strong correlation with $^{177}$Lu BMrad ($r = 0.86$) but not $^{90}$Y BMrad ($r = 0.26$). Recently, Shen et al. (14) concluded that marrow radiation-absorbed doses estimated from the blood radioactivity method are not a good predictor of myelotoxicity for nonmarrow targeting $^{90}$Y-antibody therapy. Thrombocytopenia in their group of patients with non–small cell lung cancer correlated much better with BMrad estimated from lumbar vertebrae based on imaging studies ($r = 0.85$) than with BMrad based on blood and patient-specific mar-
row mass ($r = 0.29$). It is quite interesting that with $^{90}$Y-J591 mAb the correlation ($r = 0.26$) between thrombocy-
topenia and the BMrad based on blood is almost identical to the value reported by Shen et al. A similar weak association between myelotoxicity and BMrad based on blood has also been previously reported for both $^{131}$I- and $^{90}$Y-labeled mAbs (8,10–12).

An accurate estimation of BMrad is essential for reliable predictions of myelotoxicity. In a homogeneous population, myelotoxicity is a classic nonstochastic (deterministic) ef-

FIGURE 2. Percentage of patients with thrombocytopenia (grade 3 and 4 toxicity) after treatment with radiolabeled J591 mAb. (A) $^{90}$Y-J591. (B) $^{177}$Lu-J591.

FIGURE 3. Correlation of bone marrow (BM) radiation-absorbed dose (cGy) with total treatment dose (MBq) of radiolabeled J591 mAb. (A) $^{90}$Y-J591. (B) $^{177}$Lu-J591.

The Dosimetry Task Group of the American Association of Physicists in Medicine has recommended a standardized method for calculating marrow radiation dose, using blood radionuclide as the contributing source (24). Sgouros (5) subsequently recommended modification of this method to adjust for the patient’s own hematocrit. DeNardo et al. (25) have described a method for radiation dose that accounts for both blood and body contributions. Several groups have described imaging methods to measure bone marrow dose from radiolabeled molecules that bind specifically to bone

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FIGURE 4. Correlation of FDP with total treatment dose (MBq) of radiolabeled J591 mAb and bone marrow radiation-absorbed dose (cGy). (A and C) $^{90}$Y-J591. (B and D) $^{177}$Lu-J591.

FIGURE 5. Correlation of fractional decrease in ANCs with total treatment dose (MBq) of radiolabeled J591 mAb and bone marrow radiation-absorbed dose (cGy). (A and C) $^{90}$Y-J591. (B and D) $^{177}$Lu-J591.
and bone marrow (4,6,13,14,25–28). However, the correlation between myelotoxicity and marrow radiation dose estimates for $^{131}$I- and $^{90}$Y-labeled antibodies has generally been weak. As a result, radiation dosimetry has not been useful for planning the treatment dose of radiolabeled antibodies. In a recent review, DeNardo et al. conclude that bone marrow dosimetry continues to be a “work in progress” (1).

Several factors may account for the poor prediction of myelotoxicity using BMrad estimated from $^{90}$Y activity in the blood. (a) An unpredictable fraction of administered $^{111}$In/$^{90}$Y can be recycled into marrow or trabecular bone space after the radiolabeled antibodies have been metabolized, mainly in the liver (13). (b) The specific uptake of radiolabeled antibodies by the metastatic bone lesions further complicates the determination of cumulative activities in the bone marrow, particularly micrometastases. (c) In the dosimetry calculations using the MIRDose3 program, a standard marrow mass (1,120 g) may introduce substantial errors due to a large variation of the actual marrow mass of a specific patient (7,13). (d) Dose rate or dose per unit time may have a crucial role in determining the resulting myelotoxicity (2,29). (e) Also other important factors, such as the linear energy transfer or the cross-organ irradiation or cross-fire effect from adjacent tissues, may play an important role in the radiation-induced myelotoxicity (30).

Myelotoxicity may be due to factors not entirely explained by pharmacokinetic and dosimetric variables. The patient’s biologic response to radiation may vary because of inherent interpatient differences, such as decreased bone marrow reserve or increased radiosensitivity due to prior chemotherapy or external-beam radiation (3). Despite the fact that all of these factors may contribute to myelotoxicity, the finding that the BMrad dose based on $^{177}$Lu-J591 blood activity is indeed a good predictor of myelotoxicity may provide an opportunity to refine and modify the dosimetry calculations to improve the accuracy of dose estimates in the determination of patient-specific radiation dosimetry.

CONCLUSION

In RIT, myelotoxicity due to BMrad is the predominant factor and frequently is the dose-limiting factor that determines the MTD. Phase I dose-escalation studies were performed in patients with prostate cancer using $^{90}$Y- and $^{177}$Lu-labeled J591 mAb specific for PSMA. The MTD was 647.5 MBq/m² with $^{90}$Y-J591 and 2,590 MBq/m² with $^{177}$Lu-J591. Only with $^{177}$Lu was there a very good correlation between BMrad and thrombocytopenia or neutropenia. These results demonstrate that in patients with prostate cancer, myelotoxicity after treatment with $^{177}$Lu-J591 can be predicted on the basis of the amount of radioactive dose administered or BMrad.

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