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Predicting Hematologic Toxicity in Patients Undergoing Radioimmunotherapy with ^{90}Y-Ibritumomab Tiuxetan or ^{131}I-Tositumomab

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Abstract

This study aimed at identifying clinical factors for predicting hematologic toxicity after radioimmunotherapy with ^{90}Y-ibritumomab tiuxetan or ^{131}I-tositumomab in clinical practice.

Methods—Hematologic data were available from 14 non-Hodgkin lymphoma patients treated with ^{90}Y-ibritumomab tiuxetan and 18 who received ^{131}I-tositumomab. The percentage baseline at nadir and 4 wk post nadir and the time to nadir were selected as the toxicity indicators for both platelets and neutrophils. Multiple linear regression analysis was performed to identify significant predictors ($P < 0.05$) of each indicator.

Results—For both platelets and neutrophils, pooled and separate analyses of ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab data yielded the time elapsed since the last chemotherapy as the only significant predictor of the percentage baseline at nadir. The extent of bone marrow involvement was not a significant factor in this study, possibly because of the short time elapsed since the last chemotherapy of the 7 patients with bone marrow involvement. Because both treatments were designed to deliver a comparable bone marrow dose, this factor also was not significant. None of the 14 factors considered was predictive of the time to nadir. The R^2 value for the model predicting percentage baseline at nadir was 0.60 for platelets and 0.40 for neutrophils. This model predicted the platelet and neutrophil toxicity grade to within ±1 for 28 and 30 of the 32 patients, respectively. For the 7 patients predicted with grade I thrombocytopenia, 6 of whom had actual grade I–II, dosing might be increased to improve treatment efficacy.

Conclusion—The elapsed time since the last chemotherapy can be used to predict hematologic toxicity and customize the current dosing method in radioimmunotherapy.

Keywords

radioimmunotherapy; ^{90}Y-ibritumomab tiuxetan; ^{131}I-tositumomab; hematologic toxicity

The radioimmunoconjugates ^{90}Y-ibritumomab tiuxetan (Zevalin; Spectrum Pharmaceuticals, Inc.) and ^{131}I-tositumomab (Bexxar; GlaxoSmithKline) are currently approved by the U.S. Food and Drug Administration for non-Hodgkin lymphoma treatment. Both conjugates have comparable efficacy and toxicity profiles (1–7). The major toxicities

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have been transient thrombocytopenia and neutropenia. These toxicities are mainly caused by radiation that damages the bone marrow. In radioimmunotherapy, the absorbed dose delivered to the bone marrow is relatively high because of the long clearance time of the radiolabeled antibodies in the blood. The activity that can be safely administered to patients is therefore limited by the bone marrow dose (BMD).

In addition to the BMD, hematologic toxicity after radioimmunotherapy also has been associated with the treatment history of patients and variable marrow reserve. Radioimmunotherapy patients have frequently undergone other therapies that may have damaged a large fraction of their bone marrow reserve (8). For patients treated with ^{90}Y-ibritumomab tiuxetan, baseline platelet counts, extent of bone marrow involvement, and number of prior chemotherapy regimens were identified as significant predictors of hematologic toxicity, whereas BMD was not (9). These results indicate that individual response to radiation may vary largely because of inherent interpatient differences. Predicting hematologic toxicity on a patient-specific basis is therefore crucial in optimizing treatment and avoiding complications in radioimmunotherapy. Presently, baseline platelet count is the only factor considered when deciding between a standard and an attenuated dose regimen, for both ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab (1). Indeed, baseline platelet count is considered as a surrogate for bone marrow damage from prior therapies and bone marrow involvement.

In this study, multiple linear regression analyses were performed to identify clinical factors that could be used to predict hematologic toxicity after radioimmunotherapy with ^{90}Y-ibritumomab tiuxetan or ^{131}I-tositumomab administered in clinical practice. Furthermore, if knowledge of certain clinical factors enables identification of patients at low risk for toxicity, the prescribed dosing could be increased, potentially leading to a greater treatment benefit.

MATERIALS AND METHODS

Study Design and Patient Population

Thirty-eight chemotherapy-refractory non-Hodgkin lymphoma patients treated with ^{90}Y-ibritumomab tiuxetan (n = 20) or ^{131}I-tositumomab (n = 18) were described in a previous study that compared the response rate and hematologic toxicities of both agents (10). A subset of 32 patients was considered for the present analysis because 6 patients treated with ^{90}Y-ibritumomab tiuxetan had only partial hematologic toxicity data available. Both radioimmunotherapy agents are used routinely at our institution, and the choice of agent was based on patient and disease characteristics, referring physician preference and familiarity, and radiation safety issues. The 14 patient characteristics recorded at the time of radioimmunotherapy and considered as potential predictors of hematologic toxicity are given in Table 1.

Absorbed Dose to Bone Marrow

The dosing guidelines for ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab require an adjustment based on platelet counts. The standard activity level is recommended only for patients with a platelet count of at least 150,000/mm^3; patients with a platelet count of 100,000–149,000/mm^3 receive less administered activity (4,5). In addition to the baseline platelet count, dosing for ^{90}Y-ibritumomab tiuxetan is based on the patient's body weight. Nine patients received the standard activity level (14.8 MBq/kg [0.4 mCi/kg]), and 5 patients received the reduced level (11.1 MBq/kg [0.3 mCi/kg]). The BMD was approximated by multiplying the actual activity administered to the patient by the median absorbed dose per unit activity of 1.3 mGy/MBq reported in the ^{90}Y-ibritumomab tiuxetan

package insert (11). In a recent MIRD report (12), a higher median BMD of 2.4 mGy/MBq was reported. Both values were obtained using imaging-based marrow dosimetry. Estimates of BMD with the blood-based model were not considered, because this approach does not account for direct targeting of non-Hodgkin lymphoma within the bone marrow (13).

The therapeutic administered activity for ^{131}I-tositumomab is determined by a pretherapeutic dosimetry used to verify clearance kinetics in each patient and thereby the activity required to deliver a total-body absorbed dose of 0.75 (platelet count ≥ 150,000/mm^3) or 0.65 Gy (platelet count within 100,000–149,000/mm^3) (14,15). Twelve patients received a full total-body dose of 0.75 Gy. Six patients received attenuated doses of 0.65 Gy (n = 3), 0.60 Gy (n = 1), 0.55 Gy (n = 1), and 0.45 Gy (n = 1). Estimates of BMD were derived from the total-body dose using a conversion factor of 2.7 given by the ratio of the median BMD (0.65 mGy/MBq) to the median total-body dose (0.24 mGy/MBq) obtained from the ^{131}I-tositumomab package insert (16). A factor of 2.0 may be derived from the study of O'Donoghue et al. (17) using various ^{131}I-labeled antibodies; similarly, a factor of 2.1 may be deduced from a dosimetry study with ^{131}I-rituximab (18).

Hematologic Toxicity Assessment

Platelet counts and absolute neutrophil counts (ANCs) were measured before therapy as a baseline and then weekly for about 12 wk after radioimmunotherapy for all patients (n = 32). Both the percentage of the baseline cell counts at nadir (PBN) and the time to nadir (TTN) were used as indicators of toxicity. Additionally, the percentage of the baseline cell counts at 4 wk postnadir (PBP) was used to parameterize the recovery phase. Figures 1A and 1B plot these parameters in relation to platelet counts and ANCs, respectively, normalized to baseline for patient 25.

Statistical Analysis

Multiple linear regression analysis was performed for both outcome variables describing hematologic toxicity (i.e., PBN and TTN) to assess the predictive value of the 14 potential toxicity-related factors listed in Table 1. Platelets and neutrophils were treated separately. The basic model equation takes the following form: $Y = B_0 + B_1X_1 + \ldots + B_nX_n$, where Y corresponds to the outcome (dependent) variable, and X_is are the predictor (independent) variables. B_0 is the constant intercept, and $B_1 \ldots B_n$ are the regression coefficients. A stepwise variable-selection procedure with entry and removal criteria of 0.05 and 0.10, respectively, was used to include in the model only statistically significant predictors. The measure used for statistical assessment of the model was a P value less than 0.05. The R^2 value was examined to measure the goodness of fit. The test for multicolinearity was based on the variance inflation factor. Statistical analyses were performed using the SPSS statistical program (version 15.0; SPSS Inc.).

Practical Model for Clinical Application

The best resulting regression model was then used to predict absolute cell counts at nadir (nadir count) of platelets and neutrophils by simply multiplying the predicted PBN by the baseline cell counts at the time of radioimmunotherapy. The nadir counts of platelets and neutrophils are the clinically important parameters with respect to the degree of hematologic toxicity. However, considering PBN instead of nadir count for the statistical analysis circumvents the evident dependence of baseline cell counts in the linear regression model. A validation using the leave-1-out analysis was performed to assess our final regression model. In other words, 1 patient was removed from the original set of 32. The predictors selected for the final model and the data from the remaining 31 patients were used to fit a regression equation. The resulting equation was then used to predict PBN and nadir count of the patient who had been removed. This process was repeated for every patient so that the final model

was tested 32 times. For further analysis, observed and predicted nadir counts were clustered into toxicity grade representation. Grade I–IV thrombocytopenia and neutropenia were determined using the Common Terminology Criteria for Adverse Events (version 3.0; National Cancer Institute). Observed and predicted toxicity grades were compared with each other using percentages of correct predictions and percentages of predictions within 1 grade of deviation.

Modeling of Recovery Phase

Comparing PBN with PBP provides information about the degree of reversibility of thrombocytopenia and neutropenia. Scatter plots were used to qualitatively determine whether there was a correlation between both variables. Furthermore, PBP was quantitatively related to PBN based on simple theoretic considerations. Cell population recovery often exhibits nonexponential kinetics that can be described satisfactorily using a logistic function. This model was used to characterize the recovery phase of white blood cells after chemotherapy (19). Taking S(t) as the percentage of the baseline cell counts at time t after the nadir, the specific growth rate of S(t), [dS(t)/dt]/S(t), decreases linearly with an increase of S(t). Accordingly, the logistic recovery function may be expressed as:

$$S(t)=\frac{S_{max}}{1+(S_{max}/S_0-1)\times e^{-\lambda\times t}}. \quad \text{Eq. 1}$$

S_0 denotes the initial value of S(t) in the recovery phase and S_{max} the asymptotic limit to repopulation. The parameter λ is the maximal specific growth rate. In our study, S_0 is equivalent to PBN, and S_{max} is set to 100%, assuming that the baseline is the maximum-achievable recovery value. According to Equation 1, the value of S(t) at 4 wk postnadir—that is, PBP—may be expressed as:

$$PBP=\frac{100}{1+a\times(100/PBN-1)}, \quad \text{Eq. 2}$$

where a is set to $e^{-\lambda\times(28\ d)}$. Regression analysis was used to test if the model in Equation 2 was appropriate to describe the relationship between PBP and PBN.

RESULTS

In Table 1, continuous data are expressed as mean ± SD, and categoric data are presented as counts and percentages. As reported previously by Jacene et al. (10), excepting for BMD, those characteristics did not significantly differ between both patient groups treated either with ^{90}Y-ibritumomab tiuxetan or with ^{131}I-tositumomab ($P < 0.05$, 2-tailed *t* test and 2-tailed Fisher exact test). The mean BMD for patients treated with ^{90}Y-ibritumomab tiuxetan was 1.3 ± 0.2 Gy according to the information provided by Spectrum Pharmaceuticals, Inc. (11), and 2.5 ± 0.4 Gy according to the study by Fisher et al. (12). Both values were significantly different from the mean BMD of 1.9 ± 0.2 Gy obtained for ^{131}I-tositumomab patients ($P < 0.001$ for both estimates); however, the average of both values, 1.9 ± 0.3 Gy, was perfectly compatible. For platelets, mean values of PBN, TTN, and PBP were 30% ± 25%, 37 ± 14 d, and 70% ± 34%, respectively, and for neutrophils, mean values were 33% ± 24%, 42 ± 14 d, and 89% ± 44%, respectively.

The multiple linear regression analysis of PBN showed that the elapsed time since the last chemotherapy (TLC) was the only significant variable ($P < 0.05$) affecting PBN for both platelets and neutrophils. The regression coefficients were $B_0 = 2.8 \pm 4.9$ and $B_1 = 3.02 \pm$

0.45 for platelets and $B_0 = 11.9 \pm 5.7$ and $B_1 = 2.37 \pm 0.43$ for neutrophils. In both cases, the *P* value associated with B_1 was less than 0.001. The resulting 1-variable linear equation is plotted in Figures 2A and 2B for platelets and neutrophils, respectively. The R^2 value of the model predicting PBN was 0.60 for platelets and 0.40 for neutrophils. Both models were statistically significant ($P < 0.001$). No multicolinearity problem was detected using the variance inflation factor test, meaning that none of the 14 factors examined was strongly correlated with any of the other factors. Regarding TTN, none of the 14 factors considered was predictive, and thus no regression model was available.

The linear regression of PBN on TLC was also performed separately for the ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab groups. Results are shown in Figures 2C and 2D. The slopes between ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab were not statistically different at the 0.05 significance level (Chow test).

Predicted counts at nadir resulting from the leave-1-out analysis are shown in Supplemental Table 1 (supplemental materials are available online only at http://jnm.snmjournals.org) for platelets and in Supplemental Table 2 for neutrophils. The model was able to predict platelet counts at nadir within ±25,000/mm^3 for 21 of 32 patients (66%) and ANC at nadir within ±500/mm^3 for 19 of 32 patients (59%). The ability to predict toxicity grade at nadir is also reported in Supplemental Tables 1 and 2. For platelets, an exact classification—that is, grade I, II, III, or IV—was obtained for 16 of 32 patients (50%), and predicted toxicity grades ranged within ±1 grade for 28 of 32 patients (88%). Regarding neutrophils, 13 of 32 patients (41%) were predicted with the correct toxicity grade, and 30 of 32 patients (94%) were predicted within ±1 toxicity grade.

Figure 3 shows the relationship between PBP and PBN. The function given in Equation 2 fits well with the platelet data using a nonlinear regression method ($R^2 = 0.51$). However, this model was not appropriate for neutrophils ($R^2 = 0.21$).

DISCUSSION

Multiple linear regression analysis revealed TLC as the only significant variable affecting PBN for both platelets and neutrophils. The increased toxicity for short TLC supports the hypothesis that hematopoietic stem or progenitor cells are hyperproliferative and more radiosensitive immediately after chemotherapy. Siegel et al. (20) showed that elevated levels of the plasma FLT3-L, a stimulatory cytokine of hematopoiesis, may indicate increased radiosensitivity of the bone marrow in patients receiving radioimmunotherapy. Moreover, we found that short TLC was not correlated with a decrease of baseline blood cell counts at the time of radioimmunotherapy; on the contrary, the correlation is somewhat negative ($R = -0.37$, $P < 0.05$ for platelets; $R = -0.11$, $P = 0.54$ for neutrophils). In other words, baseline platelet count and ANC were not lower for patients who underwent recent chemotherapy, suggesting that they have recovered to their prior chemotherapy values. The increased hematologic toxicity observed for low values of TLC may be related to an incomplete bone marrow recovery after chemotherapy. As suggested by Juweid et al. (8), there is a time delay between hematologic recovery and actual bone marrow recovery. In our toxicity-prediction model, the TLC can be seen as a surrogate for the degree of bone marrow recovery from prior chemotherapy.

Factors such as BMD, number of prior chemotherapy regimens, and, surprisingly, bone marrow involvement were not statistically significant factors affecting hematologic toxicity after radioimmunotherapy. The latter finding may reflect the dominant effect of the short TLC on the 7 patients with bone marrow involvement. For comparison, Juweid et al. (8) showed that BMD was the most important factor. However, their multivariate analysis was

based on patients receiving a wide range of BMDs—that is, between 0.34 and 3.11 Gy. BMDs delivered to patients in the present study ranged in a narrower interval (Table 1). Treatments with ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab in the clinical setting were designed to deliver a fixed BMD to each patient, to avoid high-grade toxicity. This may explain why BMD was not a significant predictor of hematologic toxicity in our case. Moreover, we were possibly able to identify TLC as a significant predictor because BMD only weakly differed among patients. Nevertheless, as shown by Fisher et al. (12) for ^{90}Y-ibritumomab tiuxetan, estimates of BMD largely differ among studies, and accurate dosimetry of bone marrow is challenging, even if individualized image-based approaches are used (13).

Among patients treated with ^{90}Y-ibritumomab tiuxetan, Wiseman et al. (9) found that baseline platelet count, degree of bone marrow involvement, and number of prior therapies, but not BMD, were accurate predictors of hematologic toxicity. Gregory et al. (21) reported similar predictors of grade III–IV hematologic toxicity among patients treated with ^{131}I-tositumomab. In our study, 6 of 7 patients with bone marrow involvement showed a severe hematologic toxicity, with a PBN below 30%. However, all 7 patients with bone marrow involvement also had a relatively short TLC, ranging between 3 and 10 mo, which has been shown with statistic significance ($P < 0.001$) to deplete platelets and neutrophils more severely. Supplemental Figure 1 shows PBN for platelets and neutrophils and TLC for each patient with respect to the presence of bone marrow involvement. On the basis of a Mann–Whitney test, neither PBN for platelets and neutrophils nor TLC was significantly different between groups both with and without bone marrow involvement ($P = 0.05$). A larger study of patients with bone marrow involvement would be required to draw a conclusion about these predictors. Similar to the finding of Juweid et al. (8), we found that the number of prior chemotherapy regimens was not a significant predictor of hematologic toxicity, in contrast to TLC.

One might expect that beyond a certain TLC this parameter would no longer predict PBN because recovery would be complete. Figure 2 suggests no apparent threshold of TLC within the 25-mo range of TLC values shown. According to Figure 3 and the logistic-based model, patients with PBN of platelets above 20% reach more than 70% of baseline counts at 4 wk postnadir. This relationship between the PBN and PBP is of major importance for defining the optimal time interval between cycles when designing trials of radioimmunotherapy with multiple cycles (22). Such a relationship did not apply to ANC recovery. The maximum specific growth rate λ was probably more patient-specific for ANC than it was for platelets, particularly because 7 patients received granulocyte colony-stimulating factor therapy. On the other hand, 6 patients treated with granulocyte colony-stimulating factor had PBN below 20%, and the large variability of PBP above a PBN of 20% is not compatible with our simple model.

The toxicity-prediction model may be used to modify the current dosing method of radioimmunotherapy by taking into account the TLC and baseline platelet counts. For this purpose, we considered patients predicted with grade IV thrombocytopenia to be at high risk of toxicity and those predicted with grade I thrombocytopenia to be at low risk of toxicity. Six of the 7 patients predicted with grade IV had actual severe grade III–IV thrombocytopenia, and 1 had grade II thrombocytopenia (patient 15). In the same way, 6 of the 7 patients predicted with grade I had actual moderate grade I–II thrombocytopenia, and 1 had grade III thrombocytopenia (patient 18). Table 2 shows the patients predicted with grade I or IV thrombocytopenia for whom we proposed reconsidering the dosing regimen. On the basis of our predictions, the current low-dose regimen (L) would be proposed instead of the current high-dose regimen (H) for 2 patients. In addition, a reduced low-dose regimen (L^{-}) would be suggested for 5 patients, to avoid severe toxicity (grade III or IV). Postponing the

treatment (i.e., increasing TLC) could be an interesting alternative to avoid severe toxicity without reducing the dosing. Conversely, the current high-dose regimen (H) would be proposed instead of the current low-dose regimen (L) for 2 patients, and an increased high-dose regimen (H^+) would be suggested for 5 other patients, to potentially improve treatment efficacy. In case of patient 18, applying an increased high-dose regimen (H^+) would aggravate the actual grade III thrombocytopenia. Nevertheless, with actual platelet count of 44,000/mm^3 at nadir, it is highly improbable that this change produces life-threatening toxicity. Ongoing data accumulation and analysis, as presented in this work, will be important in assessing the clinical impact of the proposed L^- and H^+ dosing approach regimens.

This study is limited by the small number of patients and needs to be expanded to a larger population to determine the reproducibility of the coefficients used to predict hematologic toxicity. Furthermore, the BMD estimates used have a high level of uncertainty. However, the interpatient variability of BMD is probably sufficiently small for both radiopharmaceuticals when used in the clinical setting and thus not likely to be a factor of variability in hematologic toxicity. Finally, the model used to modify the current dosing method does not consider tumor burden at the time of radioimmunotherapy. Clinically, for patients with high tumor burden, it might not be appropriate to reduce the administered activity to avoid reversible hematologic toxicity if this proposed dosing regimin jeopardizes the treatment efficacy.

CONCLUSION

Hematologic toxicity was best predicted by TLC in this limited population of radioimmunotherapy patients. This finding supports the hypothesis that hematopoietic stem or progenitor cells are hyperproliferative and potentially more radiosensitive during the recovery period after chemotherapy. Considering TLC in the adjustment of the radioimmunotherapy dosing regimen may prevent overdosing, which could produce severe hematologic toxicity and, conversely, avoid unnecessary underdosing, which could reduce treatment efficacy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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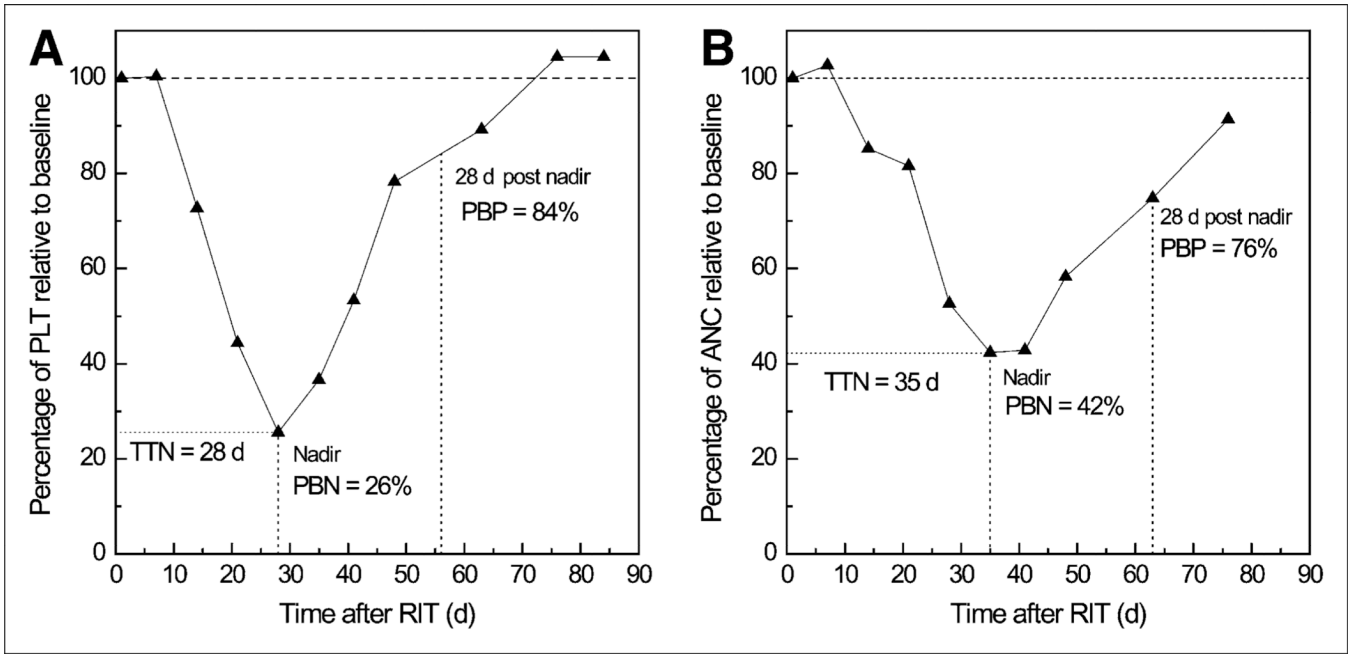

FIGURE 1.

Measured platelet counts (A) and ANCs (B) for patient 25 treated with ^{90}Y-ibritumomab tiuxetan. All counts were normalized to baseline counts at beginning of radioimmunotherapy. PLT = platelet; RIT = radioimmunotherapy.

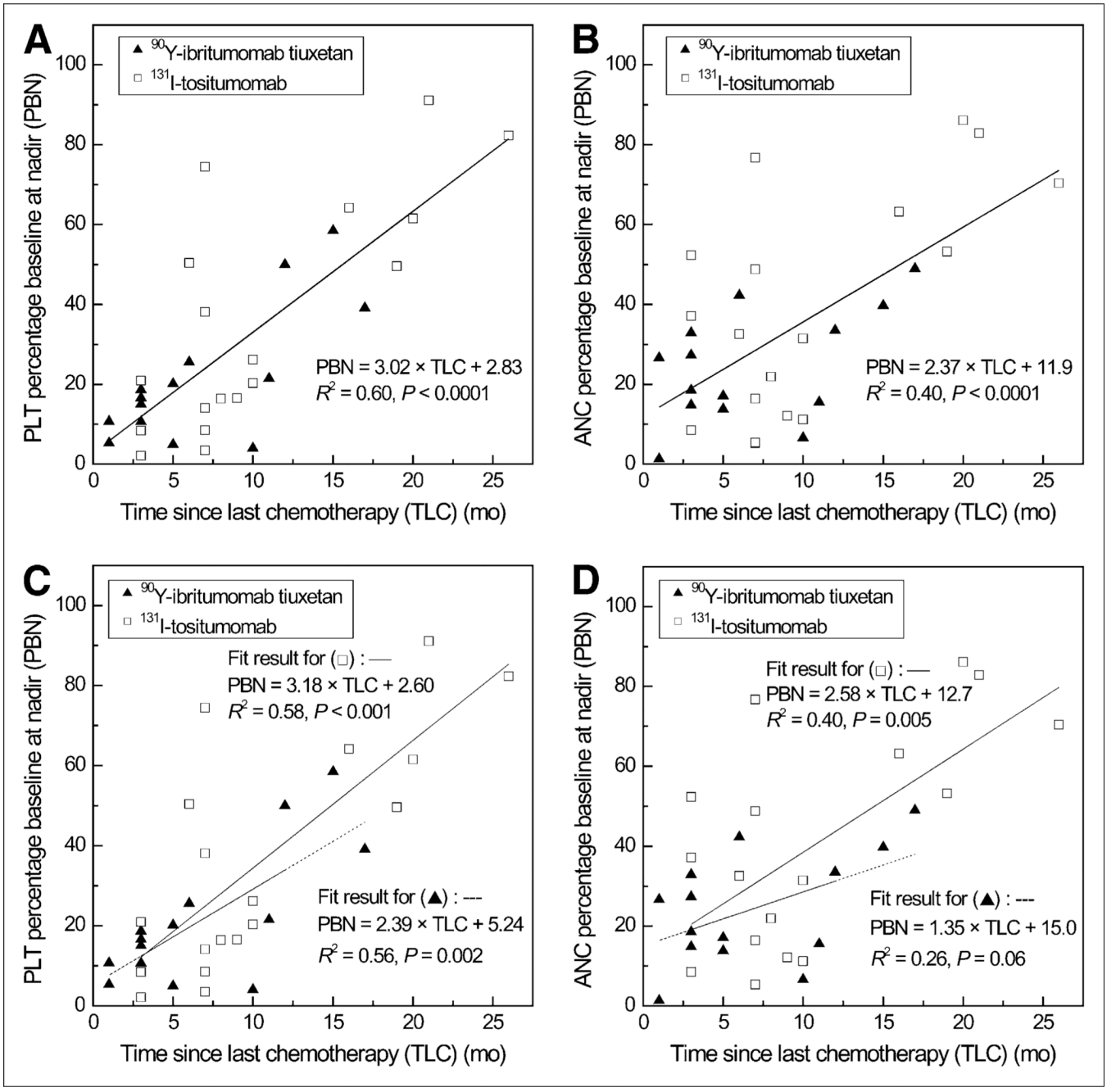

FIGURE 2.

Linear regression of PBN on TLC for platelets (A) and neutrophils (B). (C and D) Results of linear regression of PBN on TLC performed separately for ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab groups. PLT = platelet.

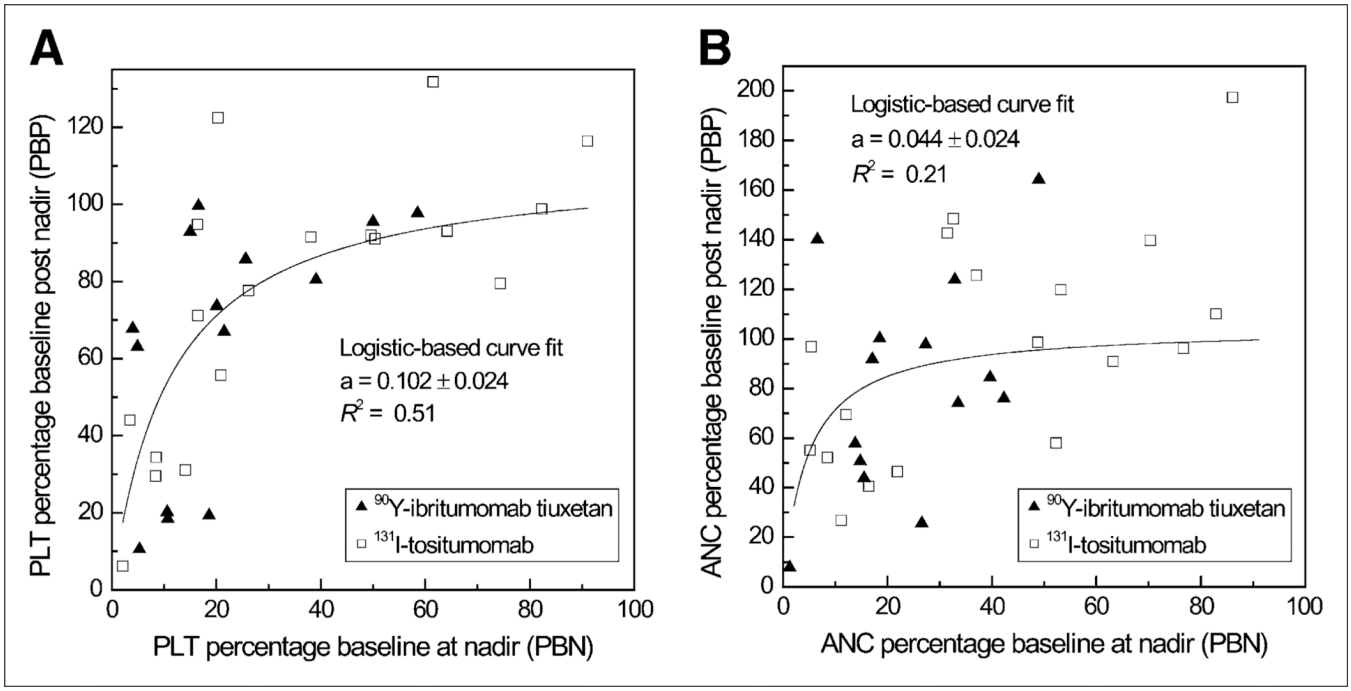

FIGURE 3.
Relationship between PBP and PBN for platelets (A) and neutrophils (B) in whole radioimmunotherapy patient population.

TABLE 1

Fourteen Patient Characteristics (Variables) Considered as Potential Predictors of Hematologic Toxicity (32 Patients)

Variable	Mean ± SD	Range	*n*
Age at radioimmunotherapy (y)	63 ± 10	40–80	
Number of prior chemotherapy regimens at radioimmunotherapy (including rituximab)	3.1 ± 1.7	1–8	
Time since last chemotherapy (mo)	8.9 ± 6.4	1–26	
Bone marrow dose (Gy)	1.6 ± 0.4*	1.0–2.0*	
	2.1 ± 0.4†	1.2–2.8†	
Baseline at time of radioimmunotherapy			
Platelets (10^3/mm^3)	206 ± 100	67–535	
Absolute neutrophil count (1/mm^3)	3,860 ± 1,880	1,530–11,080	
Male sex			23 (72%)
Type of radioimmunotherapy agent			
^{90}Y-ibritumomab tiuxetan			14 (44%)
^{131}I-tositumomab			18 (56%)
Disease stage at radioimmunotherapy			
I–II			5 (16%)
III–IV			27 (84%)
Prior treatment with rituximab			
Alone			8 (25%)
With chemotherapy			23 (72%)
Refractory to rituximab			14 (44%)
Bone marrow involvement at radioimmunotherapy			7 (22%)
History of prior bone marrow transplant			4 (13%)
History of prior radiation therapy			7 (22%)
History of prior treatment with fludarabine			9 (28%)

*For patients treated with ^{90}Y-ibritumomab tiuxetan, BMDs were obtained from BMD per unit activity reported in package insert provided by the manufacturer (11).

†For patients treated with ^{90}Y-ibritumomab tiuxetan, BMDs were obtained from BMD per unit activity reported by Fisher et al. (12).

TABLE 2

Patients Predicted with Thrombocytopenia Grade I or IV for Whom Dosing Regimens Were Reevaluated According to Toxicity-Prediction Model

	Dosing regimen	
Patient no.	**Actual**	**Proposed**
2	H	H^+
3*	H	L
6	H	H^+
10	L	L^-
11	L	L^-
12	H	H^+
15	L	L^-
18	H	H^+
20	H	L
21	H	H^+
23	L	L^-
25*	L	H
28	L	L^-
29	L	H

*Patient with presence of bone marrow involvement.

H = high-dosing regimen (15 MBq/kg for ^{90}Y-ibritumomab tiuxetan and whole-body dose of 75 cGy with ^{131}I-tositumomab); H^+ = increased high-dosing regimen (above 15 MBq/kg for ^{90}Y-ibritumomab tiuxetan and whole-body dose of 75 cGy with ^{131}I-tositumomab); L = low-dosing regimen (11 MBq/kg for ^{90}Y-ibritumomab tiuxetan and whole-body dose of 65 cGy with ^{131}I-tositumomab); L^- = reduced low-dosing regimen (below 11 MBq/kg for ^{90}Y-ibritumomab tiuxetan and whole-body dose of 65 cGy with ^{131}I-tositumomab).