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Spleen Volume Reduction Is a Reliable and Independent Biomarker for Long-Term Risk of Leukopenia Development in Peptide Receptor Radionuclide Therapy

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^{177}Lu-DOTATATE therapy is an effective treatment for advanced neuroendocrine tumors, despite its dose-limiting hematotoxicity. Herein, the significance of off-target splenic irradiation is unknown. Our study aims to identify predictive markers of peptide receptor radionuclide therapy–induced leukopenia. **Methods:** We retrospectively analyzed blood counts and imaging data of 88 patients with histologically confirmed, unresectable metastatic neuroendocrine tumors who received ^{177}Lu-DOTATATE treatment at our institution from February 2009 to July 2021. Inclusion criterium was a tumor uptake equivalent to or greater than that in the liver on baseline receptor imaging. We excluded patients with less than 24 mo of follow-up and those patients who received fewer than 4 treatment cycles, additional therapies, or blood transfusions during follow-up. **Results:** Our study revealed absolute and relative white blood cell counts and relative spleen volume reduction as independent predictors of radiation-induced leukopenia at 24 mo. However, a 30% decline in spleen volume 12 mo after treatment most accurately predicted patients proceeding to leukopenia at 24 mo (receiver operating characteristic area under the curve of 0.91, sensitivity of 0.93, and specificity of 0.90), outperforming all other parameters by far. **Conclusion:** Automated splenic volume assessments demonstrated superior predictive capabilities for the development of leukopenia in patients undergoing ^{177}Lu-DOTATATE treatment compared with conventional laboratory parameters. The reduction in spleen size proves to be a valuable, routinely available, and quantitative imaging-based biomarker for predicting radiation-induced leukopenia. This suggests potential clinical applications for risk assessment and management.

Key Words: PRRT; spleen volumetry; imaging-based biomarker; ^{177}Lu-DOTATATE; leukopenia

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Peptide receptor radionuclide therapy (PRRT) using ^{177}Lu-labeled somatostatin analogs has emerged as an effective treatment approach for patients with somatostatin receptor–positive advanced neuroendocrine tumors. This therapy has demonstrated clinically significant effects, including symptom relief, improved quality of life, and radiologic response (*1–3*). Notably, the NETTER-1 study showed that ^{177}Lu-DOTATATE treatment led to longer progression-free survival and higher response rates than did high-dose octreotide long-acting release in patients with midgut neuroendocrine tumors (*4*).

Although PRRT is generally well tolerated, it is known that the kidneys and bone marrow receive off-target radiation doses, potentially leading to hematologic toxicity (*2,5–9*). Another factor that may contribute to hematologic toxicity is radiation exposure of the spleen. The spleen, as a major immune system organ, also plays a role in blood cell production and storage (*10*). Histophysiologic examinations have confirmed significant expression of somatostatin receptor subtype 2A in the spleen with a strong affinity for somatostatin analogs, including octreotide and octreotate, which are frequently used in the treatment of neuroendocrine tumors, including ^{177}Lu-DOTATATE treatment (*11–14*). Consequently, this distinctive receptor affinity contributes to high splenic uptake, resulting in elevated absorbed doses during PRRT (*9*).

Previous studies on external radiotherapy targeting the spleen have shown a decline in hemoglobin, white blood cell (WBC), and platelet counts (*15–17*). Herein, a correlation of spleen radiation dose and leukopenia has been revealed, as well as a decrease in spleen volume associated with an increased incidence of infectious events and poorer survival outcomes (*18,19*).

In this retrospective study, we aimed to evaluate the correlation between splenic volume and the emergence of leukopenia in a large cohort of patients with metastatic neuroendocrine tumors treated with ^{177}Lu-DOTATATE. Our investigation focused on assessing the prognostic significance of alterations in spleen volume in relation to the potential development of leukopenia. Notably, the integration of automated splenic volume assessments through deep learning has streamlined the process, rendering it more practical for daily clinical applications, particularly when considering the time-consuming and potentially variable manual assessments on CT or MR images.

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MATERIALS AND METHODS

Patients

In a retrospective analysis, all patients who underwent ^{177}Lu-DOTATATE treatment at our institution between February 2009 and July 2021 were extracted from the institution's database. Inclusion criteria were histologically confirmed, unresectable, metastatic neuroendocrine tumors; sufficient tumor uptake, equivalent to or greater than liver uptake on baseline receptor imaging; a baseline glomerular filtration rate above 50 mL/min/1.73 m^2; adequate bone marrow function with a WBC count of 4,000/μL or higher; a hemoglobin level of 8 g/dL or higher; a platelet level of 70,000/μL or higher; and adequate liver function with a total bilirubin level no more than 2 times the upper limit of normal, a transaminase level no more than 5 times the upper limit of normal, and a serum albumin level of more than 3 g/dL with normal prothrombin time (>70%). Each fraction was administered as a 30-min intravenous infusion, coinfused with kidney-protecting amino acids (2.5% lysine and 2.5% arginine in 1 L of 0.9% NaCl; infusion rate, 250 mL/h), and was preceded by an antiemetic regime consisting of a 5-HT3 antagonist (e.g., granisetron or ondansetron). Long-acting somatostatin analogs were discontinued approximately 4 wk before the treatment start date. We excluded patients with a follow-up duration of less than 24 mo and those who had fewer than 4 cycles of ^{177}Lu-DOTATATE treatment, who received additional treatments, or who required blood product transfusions during the follow-up period. Ethical approval for this retrospective analysis was obtained from the local institutional review boards (reference 87/18S). Patients who underwent PRRT in our study received the treatment under compassionate use (§13.2b Arzneimittelgesetz). Therefore, the number of cycles was not limited to the approval status of Lutathera (Novartis). Supplemental Figure 1 illustrates the recruitment flowchart (supplemental materials are available at http://jnm.snmjournals.org).

CT and MRI Scans

Diagnostic CT or MRI scans were used to assess spleen volumes before treatment and at the 12-mo follow-up (12 ± 1 mo) after the start of treatment. To estimate the spleen volume from CT scans, a pretrained and publicly available deep-learning segmentation model (TotalSegmentator; University Hospital Basel) was used (*20*). The algorithm was applied to contrast-enhanced and native CT scans with a slice thickness of 3 or 5 mm (Fig. 1). Each segmentation was manually reviewed, and adjustments were made to the automatically measured contour if necessary ($n = 2$). In cases where only MRI scans were available ($n = 3$), spleen volume measurements were manually performed by segmenting the spleen parenchyma on all slices using the Philips IntelliSpace Radiology image platform.

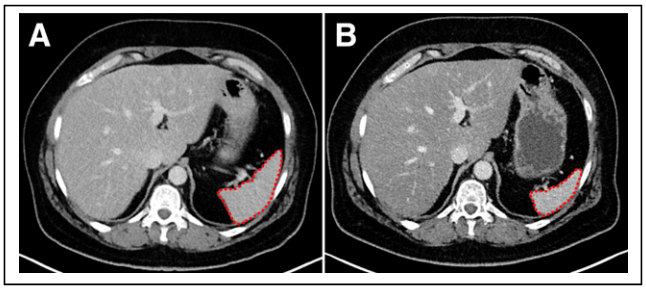

FIGURE 1. CT images from patient with ileal neuroendocrine tumor presenting with hepatic and bone metastases. Patient underwent total of 8 cycles of ^{177}Lu-DOTATATE treatment. (A) Baseline splenic volume was measured at 161 cm^3. (B) At 1-y follow-up after initiation of treatment, splenic volume was reduced to 79 cm^3, representing volume reduction of 51%.

Assessment of Hematologic Response

Hemoglobin, WBC, and platelet counts were systematically monitored throughout the treatment duration, with blood samples collected at 3- to 4-wk intervals according to standard hospital protocols. The decline in hemoglobin, WBC, and platelet counts was evaluated at 12 and 24 mo after the start of treatment. The relative decline ($\Delta_{\%}$) was defined as the percent change from baseline and then correlated with the splenic volume. Additionally, the severity of leukopenia, lymphopenia, and neutropenia was subsequently defined according to the Common Terminology Criteria for Adverse Events at the 12- and 24-mo follow-up.

Statistical Methods

Statistical analyses were performed using Python 3.10.5 (Python) and R (R Project for Statistical Computing) (*21*) with a 2-sided level of significance of less than 0.05. Descriptive statistics were used to illustrate patient characteristics. Mean values with SD or median and interquartile ranges were reported, unless indicated otherwise. Overall correlation between the decline of spleen volume and blood count data was assessed using the Spearman correlation coefficient. To determine potential confounders, further clinical data of all patients, including age, weight, comorbidities, tumor characteristics, and therapy details, were analyzed. Continuous variables were tested for normality using the Shapiro–Wilk test. Differences among patients developing leukopenia after 24 mo were analyzed using the 2-sided *t* test for normally distributed features and the Mann–Whitney *U* test for nonnormally distributed or ordinal features. Binary data between the groups were analyzed using the Fisher exact test. The level of significance was adjusted using Bonferroni adjustment. Furthermore, uni- and multivariate logistic regression tests of features significantly associated with the development of leukopenia were performed to assess both the predictive value of spleen decline compared with the other significant features and the relative risk of developing leukopenia with respect to those features. To assess the overlap of significant features between patients developing leukopenia and those who did not, the Bhattacharyya coefficient was used. Furthermore, analysis of receiver operating characteristics (ROC) was applied to determine specific cutoff values to distinguish between the 2 groups. Thresholds were selected using the Youden index.

RESULTS

Patients

In total, 88 patients with metastatic neuroendocrine tumors and a follow-up time of at least 24 mo were selected for the analysis. All patients exhibited tumor progression before receiving ^{177}Lu-DOTATATE treatment and underwent a total number of 547 cycles.

The median administered activity per cycle and median total administered activity of ^{177}Lu-DOTATATE were 7.4 GBq (interquartile range, 6.5–7.9 GBq) and 44 GBq (interquartile range, 29.6–57.7 GBq), respectively. The median number of cycles was 6 (interquartile range, 4–8), and the median time interval between 2 cycles was approximately 8 wk. Before initiation of PRRT, 62 patients were receiving long-acting octreotide every 4 wk. The median time interval between their last octreotide dose and PRRT initiation was 28 d (range, 27–31.5 d). Patient characteristics are presented in Table 1.

Correlation of Changes in Spleen Volume and Blood Count

A strong and statistically significant correlation emerged between the early-onset decrease in spleen volume after 12 mo and the late-onset decrease in WBC counts after 24 mo (correlation coefficient, 0.603; $P < 0.001$). Based on these insights, further investigation was

TABLE 1
Patient Characteristics

Parameter	Data
Age (y)	62 (13)
Sex	
Male	$n = 51$ (65%)
Female	$n = 37$ (35%)
Baseline leukocytes (μL)	6.57 (1.69)
Baseline spleen volume (mL)	239 (133)
Prior treatment	
Primary surgery	$n = 42$ (48%)
Somatostatin analog	$n = 62$ (77%)
Primary tumor	
Pancreas	34 (38)
Small intestine	31 (35)
Colon	6 (7)
Lung	6 (7)
Rectum	3 (3)
Stomach	3 (3)
Other	8 (9)

Continuous data are mean with SD in parentheses.

conducted to identify additional parameters predictive of the development of leukopenia during the follow-up period.

Development of Leukopenia After 24 Months

Of 88 patients, 29 developed leukopenia after 24 mo, which was defined as a WBC count below 4,000/μL, with at least grade 1 severity. Mild leukopenia (grades 1 and 2) occurred in 24% of patients, with grade 3 leukopenia noted in 8% of patients and grade 4 in 1% of patients. Lymphocytopenia, grades 1 and 2, was observed in 22% of patients, with the most severe toxicity at grade 3 in 3% of patients. Notably, neutrophil toxicity, primarily at grades 3 and 4, affected 7% of patients (Table 2). Importantly, none developed myelodysplastic syndrome. Clinical parameters were also examined for potential confounding factors. The *t* test was significant on 3 parameters: baseline WBC count, $\Delta_{\%}$ of WBC count, and $\Delta_{\%}$ of spleen volume after 12 mo; therefore, they were significantly associated with leukopenia development (Table 3). The results for all tested variables are presented in Supplemental Tables 1–3.

Patients developing leukopenia after 24 mo had an average spleen volume reduction of 36% ± 14%, whereas those with normal WBC levels after 24-mo follow-up had a spleen volume reduction of 19% ± 10%. When categorizing patients on the basis of their leukocyte decline after 24 mo, we found that those with a greater $\Delta_{\%}$ in leukocytes also exhibited a larger $\Delta_{\%}$ in spleen volume after 12 mo (Supplemental Fig. 2). Patients with higher baseline WBC levels were less likely to develop leukopenia (leukopenia group: 5,750 ± 1,150/μL; normal WBC level group: 6,980 ± 1,790/μL). Patients with leukopenia at 24 mo exhibited a smaller $\Delta_{\%}$ in WBC counts after 12 mo than did those without leukopenia, indicating that the early dynamics of hematologic parameters may not consistently result in long-term leukopenia.

However, in the multivariate logistic regression, only the $\Delta_{\%}$ in spleen volume remained significantly associated with the development of leukopenia (OR, 1.16; 95% CI, 1.09–1.26; $P < 0.001$), the results of which are shown in Supplemental Table 4. No other confounding features were identified (Supplemental Table 3).

Based on these results, ROC analyses provided specific threshold values to distinguish among patients developing leukopenia after 24 mo and those who would not. The best cutoff values regarding the univariate significant features are shown in Table 4.

A 30% decline in spleen volume most effectively differentiated between the 2 groups, achieving an excellent ROC area under the curve of 0.91 with a sensitivity of 0.93 and a specificity of 0.90. The $\Delta_{\%}$ in spleen volume in relation to the presence of leukopenia after 24 mo is presented in Figure 2.

TABLE 2
Distribution of Patients in Subgroups Based on Severity of Leukopenia, Lymphopenia, and Neutropenia at 12 and 24 Months After Initiation of PRRT ($n = 88$)

	Toxicity grade				
Parameter	0	I	II	III	IV
Total WBC count (per μL)	≥4,000	3,000–3,999	2,000–2,999	1,000–1,999	<1,000
12 mo	87 (99)	1 (1)	0 (0)	0 (0)	0 (0)
24 mo	59 (67)	8 (9)	13 (15)	7 (8)	1 (1)
ALC (per μL)	≥1,000	800–999	500–799	200–499	<200
12 mo	83 (94)	4 (5)	1 (1)	0 (0)	0 (0)
24 mo	65 (73)	16 (18)	4 (4)	3 (3)	0 (0)
ANC (per μL)	≥2,000	1,500–1,999	1000–1499	500–999	<500
12 mo	85 (97)	2 (2)	1 (1)	0 (0)	0 (0)
24 mo	63 (72)	9 (10)	10 (11)	5 (6)	1 (1)

ALC = absolute lymphocyte count; ANC = absolute neutrophil count.
Values for 12 and 24 mo are number with percentage in parentheses.

TABLE 3
Significant Clinical and Imaging Characteristics Differentiating Patients Developing Leukopenia After 24 Months from Those with Normal WBC Counts

Feature	Patients with leukopenia at 24 mo	Patients with normal WBC counts at 24 mo	*P*
$\Delta_{\%}$ of spleen volume after 12 mo	0.36 ± 0.14	0.19 ± 0.10	<0.001
$\Delta_{\%}$ of WBC after 12 mo	0.07 ± 0.10	0.19 ± 0.17	0.002
Baseline WBC count (×1,000/μL)	5.75 ± 1.15	6.98 ± 1.79	<0.001

Data are presented as mean ± SD, with feature decline relative to baseline values. Full analysis results are available in supplemental materials.

TABLE 4
Decline in Spleen Volume from Baseline After 12 Months Enables Discrimination Between Patients with Low and Normal WBC Levels After 24 Months*

Feature	Cutoff value	Sensitivity	Specificity	ROC-AUC	95% CI	*P*
Baseline WBC count (×1,000/μL)	6.0	0.68	0.69	0.68	0.60–0.83	<0.001
$\Delta_{\%}$ of spleen volume after 12 mo	0.3	0.93	0.90	0.91	0.80–0.98	<0.001
$\Delta_{\%}$ of WBC count after 12 mo	0.2	0.54	0.90	0.72	0.62–0.83	<0.001

*High sensitivity and specificity outperforming differences in baseline WBC levels and $\Delta_{\%}$ of WBC levels after 12 mo.
AUC = area under curve.

A baseline WBC level cutoff of 6,000/μL showed an ROC area under the curve of 0.68 for distinguishing among patients with reduced and normal WBC levels after 24 mo. Sensitivity was 0.68, and specificity was 0.69. The discrimination capability of this parameter was lower than that for the spleen volume.

Decline in Spleen Volume as an Independent, Imaging-Based Predictor of Leukopenia

The $\Delta_{\%}$ in spleen volume after 12 mo emerged as a robust indicator for the future development of leukopenia in patients undergoing PRRT, surpassing all other identified predictive parameters.

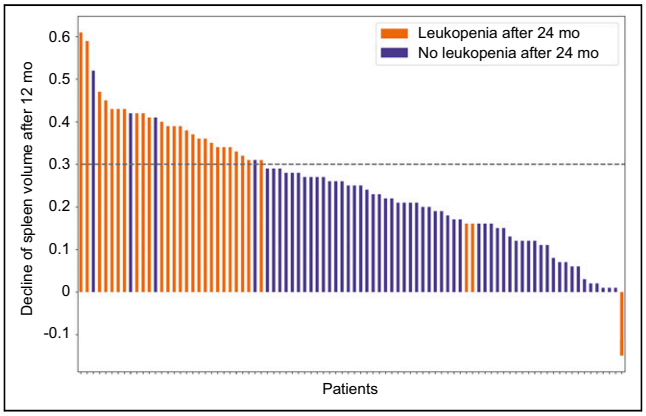

FIGURE 2. Waterfall plot showing distinct decline in spleen volume for all patients, including identified cutoff value for optimal differentiation between 2 patient groups. Decline of 30% in spleen volume after 12 mo demonstrates accuracy in distinguishing between patients who will develop leukopenia and those with normal WBC counts after 24 mo.

This is shown by the decreased degree of overlap in the distribution of spleen volume decline between the 2 patient groups compared with other parameters. By setting a threshold of 30% decline, a highly accurate discrimination was achieved between patients developing leukopenia after 24 mo and those with normal WBC levels, as evident from the high ROC area under the curve of 0.91. Figure 3 emphasizes this aspect by illustrating the correlation between the decrease in spleen volume after 12 mo and the reduction in WBC levels after 24 mo. Furthermore, the mean and 2 SDs are displayed. As can be seen, the 2 patient groups can be distinctly separated on the basis of the $\Delta_{\%}$ in spleen volume after 12 mo.

DISCUSSION

This retrospective analysis investigates the prognostic significance of changes in splenic volume and their relationship to leukopenia development in patients undergoing ^{177}Lu-DOTATATE treatment. For the fully automated extraction of spleen volume from routine CT imaging data, we used an open-source tool. In our retrospective analysis, a 30% reduction in spleen volume at 12 mo proved to be a highly accurate predictor for identifying patients at risk of developing leukopenia at 24 mo, with an excellent ROC area under the curve of 0.91, demonstrating excellent sensitivity of 0.93 and specificity of 0.90, outperforming all other tested parameters.

Regarding the irradiation effect on the spleen and subsequent hematologic changes, our findings demonstrate results comparable to those observed with radiation exposure in palliative splenic irradiation or off-target splenic irradiation during external radiotherapy. Lavrenkov et al. reported that palliative splenic irradiation reduced spleen size in over 75% of cases (*17,22*). Trip et al. in

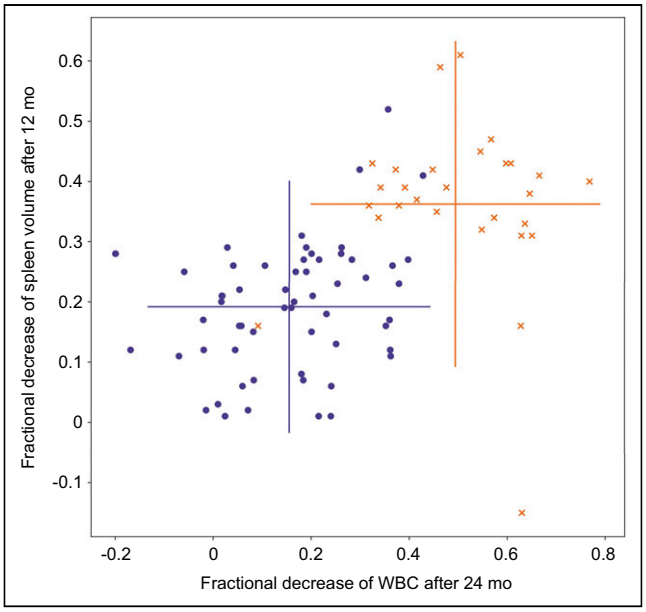

FIGURE 3. Correlation between $\Delta_{\%}$ in spleen volume after 12 mo and late reduction in WBC levels at 24-mo follow-up. Representation of mean (intersection) and 2 SDs (lines) for change in feature values for both groups is provided. Good discrimination between patients developing leukopenia (orange) and those with normal WBC counts (blue) is achieved on basis of early changes in spleen volume.

2015 first classified the spleen as an organ at risk, studying radiation-induced dose-dependent changes in spleen volume and hematologic toxicity after chemoradiation therapy (*23*). This finding has been confirmed in several studies related to external radiotherapy of neighboring organs. For example, Chadha et al. established a relationship between splenic radiation exposure in palliatively treated pancreatic cancer patients and lymphocyte count, showing a significant correlation between severe lymphopenia and the medium spleen dose and fraction exposed to low radiation doses (*24*).

Similarly, Liu et al. found a significant correlation between spleen irradiation dose and peripheral blood lymphocytes in their study of 59 patients with hepatocellular carcinoma (*18*). Saito et al.'s retrospective study with 61 esophageal cancer patients demonstrated that each 1-Gy increase in mean splenic dose resulted in a 2.9% decline in absolute lymphocyte count, with the mean splenic dose predicting grade 4 lymphopenia (*25*). In addition, histopathologic changes in the parenchyma of irradiated spleens from lymphoma patients revealed parenchymal collapse, diffuse fibrosis, and lymphocyte depletion, suggesting structural alterations responsible for the observed changes in spleen volume and resultant leukopenia (*25*). However, the pathophysiology of irradiation-induced damage to the spleen and its effects on the hematopoietic system are complex and suggest a dose dependency, since acute high radiation exposure resulted in complete ablation of the spleen and limited hematotoxicity (*26,27*). Furthermore, a study conducted on blood cell migration in mice indicated a notable change in the distribution of WBC counts from spleen tissue cavities to the bloodstream after surgical spleen removal (*28*). Therefore, surgical and radiotherapeutic splenectomy might impact the peripheral WBC count through a comparable mechanism.

The correlation observed between a higher $\Delta_{\%}$ in leukocytes after 24 mo and a larger decline in spleen volume after 12 mo suggests that spleen volume could serve as a predictive marker for hematologic toxicity in patients undergoing PRRT. In alignment with our findings, Svensson et al. identified a substantial association between hematologic toxicity and the cumulative radiation dose absorbed by the spleen during PRRT (*29*). Notably, baseline risk factors such as diabetes, hypertension, and the number of therapy cycles were not significantly associated with a more pronounced reduction in splenic volume at the 24-mo follow-up. Furthermore, there was no correlation observed with prior therapies or patient age. In summary, our findings indicate a significant physiologic impact of PRRT on hematopoietic functions, suggesting that radiation-induced alterations in the spleen involve intricate interactions with leukopenia, extending beyond the established effects on bone marrow and WBC dynamics. Although our study did not directly investigate the correlation between infections and leukocyte reduction, existing literature underscores the association between hematotoxicity and susceptibility to infections, particularly in cancer patients (*30–32*). Using spleen volume as a biomarker holds promise in identifying patients at risk and in facilitating proactive management of hematologic issues.

The retrospective design of this study introduces the potential for bias from unidentified confounding factors, emphasizing the need for further investigations using different datasets to validate these findings. To avoid investigator bias, blood count and splenic volumetry were done independently. Further research is needed to validate the results of our study, given the lack of standard reference values for splenic size reduction and the increased risk of leukopenia in patients undergoing ^{177}Lu-DOTATATE treatment.

CONCLUSION

Despite these limitations, our findings highlight the feasibility of applying automated splenic volumetry from routine imaging data in patients receiving ^{177}Lu-DOTATATE treatment. The automated approach offers several advantages, including a reduction in the time required for image analysis and the potential to effectively mitigate investigator bias.

A 30% reduction in spleen volume at 12 mo emerged as a highly accurate predictor for identifying patients at risk of developing leukopenia at 24 mo. Stratifying patients on the basis of this biomarker could prompt the implementation of a more rigorous follow-up protocol, enabling the early detection and proactive management of hematologic issues in patients receiving ^{177}Lu-DOTATATE treatment. This might involve adjusting treatment cycles, considering reinduction of PRRT, or using more sensitive patient monitoring for further treatments that can cause leukopenia. Additionally, administering granulocyte colony-stimulating factor preventively could be an option.

Further research including prospective multicenter testing of spleen volume reduction as an independent biomarker is warranted to identify and validate a universal cutoff value, validate its utility, and further explore its broader applicability in risk stratification and treatment optimization for this patient population.

DISCLOSURE

Matthias Eiber reports fees from Blue Earth Diagnostics Ltd. (consultant, research funding), Novartis/AAA (consultant, speaker), Telix (consultant), Bayer (consultant, research funding), RayzeBio (consultant), Point Biopharma (consultant), Eckert & Ziegler (speaker), Janssen Pharmaceuticals (consultant, speakers bureau), Parexel (image review), and Bioclinica (image review) outside the submitted work and a patent application for rhPSMA.

KEY POINTS

QUESTION: Can predictive biomarkers be used to identify PRRT-induced leukopenia?

PERTINENT FINDINGS: In this retrospective study, early spleen volume reduction was identified as a predictive imaging-based biomarker for radiation-induced WBC count changes in 88 patients undergoing ^{177}Lu-DOTATATE treatment. A 30% decline in spleen volume 12 mo after treatment accurately identifies patients at risk of developing leukopenia at 24 mo, with excellent sensitivity and specificity.

IMPLICATIONS FOR PATIENT CARE: Changes in spleen volume serve as a highly accurate and independent quantitative biomarker, automatically extracted from routine clinical imaging data, to predict radiation-induced leukopenia.

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