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ORIGINAL ARTICLE

Myelosuppression in patients treated with ^{177}Lutetium-lilotomab satetraxetan can be predicted with absorbed dose to the red marrow as the only variable

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ABSTRACT

Background: The aim of this study was to investigate dosimetry data and clinical variables to predict hematological toxicity in non-Hodgkin lymphoma (NHL) patients treated with [^{177}Lutetium]Lu-lilotomab satetraxetan.

Material and methods: A total of 17 patients treated with [^{177}Lu]Lu-lilotomab satetraxetan in a first-in-human phase 1/2a study were included. Absorbed dose to the red marrow was explored using SPECT/CT-imaging of the lumbar vertebrae L2–L4 over multiple time points. Percentage reduction of thrombocytes and neutrophils at nadir compared to baseline (PBN) and time to nadir (TTN) were chosen as indicators of myelosuppression and included as dependent variables. Two models were applied in the analysis, a multivariate linear model and a sigmoidal description of toxicity as a function of absorbed dose. A total of 10 independent patient variables were investigated in the multivariate analysis.

Results: Absorbed dose to the red marrow ranged from 1 to 4 Gy. Absorbed dose to the red marrow was found to be the only significant variable for PBN for both thrombocytes and neutrophils. The sigmoid function gave similar results in terms of accuracy when compared to the linear model.

Conclusion: Myelosuppression in the form of thrombocytopenia and neutropenia in patients treated with [^{177}Lu]Lu-lilotomab satetraxetan can be predicted from the SPECT/CT-derived absorbed dose estimate to the red marrow.

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Introduction

Radioimmunotherapy (RIT) is a treatment modality where an antibody guides a radioactive nuclide to the tumor cells, delivering a tumoricidal amount of localized radiation [1,2]. The treatment has proven itself a promising part of the cancer therapy armamentarium in the treatment of the radiosensitive NHL [3,4].

Two RIT agents have been granted approval by the U.S. Food and Drug Administration for treatment of refractory or relapsed low-grade, follicular, or transformed B-cell NHL: [^{131}Iodine]I-tositumomab (Bexxar®) and [^{90}Yttrium]Y-ibritumomab tiuxitan (Zevalin®) [5]. Both RITs target B-cell NHL by binding to epitopes on the CD20 antigen. The RIT agents carry two different radionuclides, ^{131}I and ^{90}Y. ^{90}Y is a pure β-emitter that deposits 90% of its energy in a sphere with a radius of 5.2 mm while ^{131}I is a β emitter with shorter penetration (a sphere of 1.0 mm radius) and also emits γ-radiation suitable for medical imaging [6]. Both treatments can also induce cytotoxic events by binding the antibody itself, besides the treatment mechanism provided by the localized radiation from the beta-emitting nuclides [5].

[^{177}Lutetium]Lu-lilotomab satetraxetan (Betalutin®) is a RIT targeting the CD37-antigen [7]. CD37 is expressed on mature B-cells and the majority of B-cell NHL, and previous studies of CD37-targeting treatments have shown promising results in both clinical and preclinical studies [8–13]. Targeting CD37 may be an especially promising alternative for relapsed indolent NHL patients, as previous treatment with anti-CD20 drugs can lead to resistance against further anti-CD20 treatment [14]. This RIT is currently being investigated in three trials, including the multi-center, non-randomized, open-label, first in human phase 1/2a-study LYMRIT-37-01 (NCT01796171). The radionuclide carried by [^{177}Lu]Lu-lilotomab satetraxetan is ^{177}Lu. This radionuclide is, similarly to ^{131}I and ^{90}Y, also a β-emitter that deposits 90% of its radiation energy in a sphere with a radius of 0.6 mm. It also has γ-emission suitable for medical imaging. These imaging

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Supplemental data for this article can be accessed here.

capabilities of ^{177}Lu allow in-depth studies of biodistribution and consequently the absorbed dose to different tissues in each patient post-treatment.

Myelosuppression has been established as the primary dose-limiting toxicity in other RIT treatments [15–17]. Early studies indicated that this toxicity was not dependent on the amount of administered radioactivity, precluding prediction based on administered radioactivity alone [18]. This variation could possibly be explained by two factors. One is patient-specific biodistribution of the RIT, resulting in different absorbed doses to the bone marrow between patients. Red marrow absorbed dose or indirect markers has been shown to correlate with hematological toxicity in various targeted therapies with radionuclides [19–23]. The second factor is interpatient differences in bone marrow reserve. This reserve will vary between patients and can be dependent on previous treatment, for example, external beam radiation therapy or myelotoxic chemotherapy [24]. As RIT is primarily used in relapsed patients, many will have undergone substantial previous treatments.

Myelosuppression has also been identified as the dose-limiting toxicity in [^{177}Lu]Lu-lilotomab satetraxetan, resulting in transient thrombocytopenia and neutropenia [25]. Previously, we have shown for a smaller group of eight patients that the absorbed dose to red marrow, derived by quantitative imaging, is related to this toxicity [26]. Therefore, the aim of the current work was to devise a model to predict myelosuppression in patients treated with [^{177}Lu]Lu-lilotomab satetraxetan considering both patient pretreatment characteristics and individual absorbed dose to red marrow.

Methods

Patient population

A total of 17 CD37-positive patients with relapsed indolent NHL treated with [^{177}Lu]Lu-lilotomab satetraxetan at Oslo University Hospital between 2012 and 2017 in the open-label, non-randomized LYMRIT 37-01-study were included. Key inclusion criteria in the LYMRIT-37-01-study were follicular lymphoma grade I-IIIA, marginal zone lymphoma, small lymphocytic lymphoma, and mantle cell lymphoma $\geq$18 years with $<$25% tumor infiltration in the bone marrow determined by bone marrow biopsy. Key exclusion criteria were central nervous system involvement of lymphoma, history of human anti-mouse antibodies, previous irradiation of more than 25% of the bone marrow, absolute neutrophil counts below 1.5 $\times$ 10^9/l, platelet count below 150 $\times$ 10^9/l, total bilirubin above 30 mmol/l, liver values ALP and ALAT above four times of normal values, and elevated creatinine. The study was approved by the regional ethical committee and all patients participated upon informed consent form.

The majority of the included patients had follicular subtype Grade 1–2 ($n = 14$), two had mantle cell lymphoma and one had marginal zone lymphoma. Patients from four treatment arms with different pretreatment and pre-dosing regimens were included. All patients received a single injection of [^{177}Lu]Lu-lilotomab satetraxetan. This was a phase 1/2a activity escalation trial, where the amount of activity was based on patient body mass; either 10, 15, or 20 MBq per kilogram. Patients in Arm 1 received pretreatment with 375 mg per m^2 body surface area of rituximab 28 and 21 days before pre-dosing with 40 mg non-radioactive lilotomab followed by an administration of [^{177}Lu]Lu-lilotomab satetraxetan. Patients in arm 2 received the same pretreatment as those in arm 1, but no pre-dosing. Patients in arm 3 had a single administration of rituximab (375 mg/m^2) pretreatment 14 days before the day of administration of [^{177}Lu]Lu-lilotomab satetraxetan, and a pre-dosing with rituximab (375 mg/m^2). In arm 4, patients were pretreated with rituximab (375 mg/m^2) 14 days before treatment with [^{177}Lu]Lu-lilotomab satetraxetan and received a pre-dosing of 100 mg/m^2 body surface area non-radioactive lilotomab.

Analysis of hematological toxicity and blood pharmacokinetic parameters

Blood samples to monitor thrombocytes and neutrophil counts were collected before treatment, and posttreatment on days 1, 2, 3, 4, and 7, and then weekly from weeks 4 to 12. Additional blood samples were taken if deemed necessary. Hematologic adverse events (thrombocytopenia and neutropenia) were graded by the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 [27]. The PBN and TTN were used as measures of toxicity.

Pharmacokinetic parameters were calculated as previously described [25]. In brief, total radioactivity in the blood was sampled at several time points and AUC and half-life in blood were calculated by noncompartmental modeling using the 'linear up log down'-method implemented in Phoenix WinLonLin 64 version 8.1 build 8.1.0.3530 (Certera). These parameters were available for 15 of the included patients.

Bone marrow dosimetry

Image-based quantification of the radioactivity in lumbar vertebrae L2–L4 at multiple time points post-injection was carried out as previously described [26]. In brief, patients were imaged on a dual-headed Symbia T16 SPECT/CT-scanner. Attenuation and scatter-corrected images were acquired nominally (mean, range) 96 (100, 94–122) and 168 (173, 145–193) hours p.i. Images were reconstructed using the vendor's software (Siemens Medical Esoft). A nuclear medicine specialist delineated the volumes of interest in a slice-by-slice manner. Care was taken to not include the activity of adjacent physiological or tumor tissue. The total numbers of disintegrations (time-integrated activity) were found from the resulting mono-exponentially fitted time-activity curves. Factors to convert the total number of disintegrations to absorbed dose were calculated with the cellularity factor proposed by the International Commission on Radiological Protection (ICRP) [28]. In Supplementary Appendix A, a detailed description of the methodology is shown.

Statistical analysis

The following ten patient characteristics and variables were considered potential predictors of toxicity and included as independent variables:

1. Age at treatment (years).
2. Baseline cell-counts.
   i. Baseline cell-count of thrombocytes (10^9/l).
   ii. Baseline cell-count of neutrophils (10^9/l).
3. History of prior external beam radiation treatment (yes/no).
4. Total number of previous chemotherapy treatments (including rituximab).
5. Elapsed time since last chemotherapy (months).
6. Absorbed dose to the red marrow (Gy).
7. Activity dosage level (either 10, 15 or 20 MBq/kg body mass).
8. Total administered radioactivity (MBq).
9. Area under the curve for [^{177}Lu]Lu-lilotomab satetraxetan in blood (AUC) (h kBq/ml).
10. Half-life of [^{177}Lu]Lu-lilotomab satetraxetan in blood ($t_{1/2}$) (h).

Multiple linear regression analyses were performed with PBN and TTN as the dependent variables. The model is formed as a linear sum:

$$Y = \sum_i \alpha_i \times X_i + \beta \quad (1)$$

with fitting variables α_i and β and independent variables X_i. Thrombocytes and neutrophils were treated separately.

Variable selection was done by choosing the models that had all variables with a significance level (p) less than 0.05. Multiple significant models for the same dependent variable were evaluated based on the Akaike Information Criteria (AIC). The variance of inflation factor in model candidates was evaluated to ensure that predictors with multicollinearity were not included. The best model was tested with a leave-1-out analysis where one patient was left out and coefficients were calculated and used to predict the PBN of the patient that had been removed. This was repeated for all patients and the predicted and observed CTCAE grade of myelosuppression was compared.

As the initial multivariate analysis found absorbed dose to the red marrow to be the only significant parameter for PBN, a sigmoid relationship between absorbed dose to red marrow and PBN was also explored. This was performed with a simple sigmoid function [29]:

$$\mathrm{PBN} = 100 - \frac{100 \cdot D^N}{D^N + D_{50}^N} \quad (2)$$

with D being the absorbed dose to red marrow and D_{50} and N being fitting parameters. D_{50} is the absorbed dose resulting in a 50% reduction.

To compare the two models, the sums of mean square errors were used. Intra-patient variability for multiple sites was investigated by examining the absolute difference between the maximum and the minimum dose calculated in the same patient.

Results

A summary of the patient characteristics and variables for the 17 patients included in the prediction analysis are shown in Table 1. Red marrow absorbed dose was calculated for all patients and ranged from 1.0 to 3.7 Gy. As an illustration, the thrombocyte counts relative to baseline and activity distribution 4 days after treatment for two patients are shown in Figure 1.

Myelosuppression

PBN ranged from 4% to 56% and 1% to 53% for thrombocytes and neutrophils respectively. Median PBN values were 21% (thrombocytes) and 26% (neutrophils). The Median and range of TTN were 37 (28–251) and 44 (34–62) days for thrombocytes and neutrophils respectively. All patients experienced thrombocytopenia, grade 4 ($n = 5$), 3 ($n = 2$), 2 ($n = 4$) or 1 ($n = 6$). Fourteen patients experienced neutropenia, grade 4 ($n = 2$), 3 ($n = 8$) or 2 ($n = 4$) whereas three patients did not experience any neutropenia (grade 0).

Percentage reduction at nadir

Figure 2 shows the predicted and observed values for the individual predictor candidates. The multivariate linear analysis showed that absorbed dose to red marrow was the only significant predictive parameter of PBN for both thrombocytes (F-test, $p = 0.0415$, AIC = 138.1, $r^2 = 0.249$) and neutrophils (F-test, $p = 0.0178$, AIC = 134.3, $r^2 = 0.321$). Figure 3(a,b) shows the PBN as a function of absorbed dose to the red marrow. The root-mean-square error was 12.5 and 11.2

Table 1. Patient characteristics and variables of the 17 patients included in the prediction analysis.

Patient charecteristics included as potential predictors	Mean	STD	Range min	Range max	*n*
Age at treatment (years).	68.7	9.7	48.3	87.5	
Baseline cell-count of thrombocytes (10^9/l)	232	52.3	127	369	
Baseline cell-count of neutrophils (10^9/l)	4	1.7	1.7	8.1	
History of prior external beam radiation treatment. (yes/no)					5
Total number of previous chemotherapy treatments (including rituximab)	2.1	1.1	1	5	
Elapsed time since last chemotherapy (days)	635.4	508.7	89	1830	
Absorbed dose to the red marrow (Gy)	2.2	0.8	1.0	3.7	
Activity dosage level (either 10, 15 or 20 MBq/kg body mass)	15.3	3.6	10	20	
Total administered activity (MBq)	1238.2	291.2	746	1769	
Area under the curve for [^{177}Lu]Lu-lilotomab satetraxetan in blood (AUC) (h kBq/ml)	9737.3	4972.7	3860	20,200	
Half-life of [^{177}Lu]Lu-lilotomab satetraxetan in blood ($t_{1/2}$) (h)	53.9	12.3	26.3	75.8	

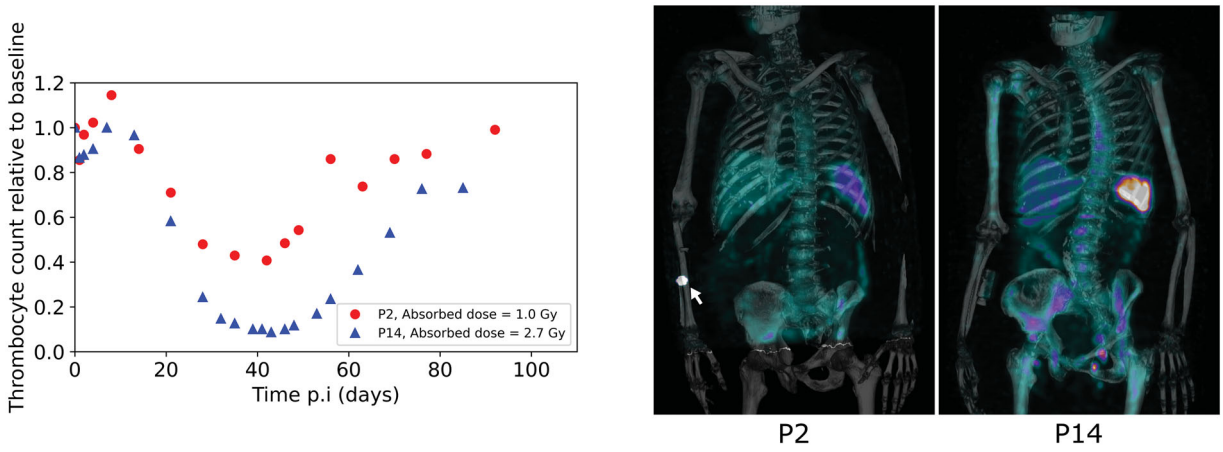

Figure 1. Left: The thrombocyte and neutrophil counts in blood, relative to baseline, were used to indicate myelosuppression. The relative thrombocyte count after treatment with [^{177}Lu]Lu-lilotomab satetraxetan is shown for two patients, patient 2 and 14. The absorbed dose of the two patients is indicated in the figure. Right: Volume renderings of the activity distributions of the two patients. The white arrow on patient 2 points to a vial filled with a known amount of 177-Lu activity, included for technical quality assurance. Note that the SPECT-image does not cover the whole CT in patient 2. The image intensities in both images have been scaled to the same range.

for thrombocytes and neutrophils respectively. In the leave-1-out analysis, the exact thrombocytopenia and neutropenia grade was predicted in 3/17 and 6/17 for thrombocytopenia and neutropenia respectively. Haematological toxicity grade ± 1 was predicted in 12/17 (thrombocytopenia) and 15/17 (neutropenia).

Time to nadir

Multivariate analysis of the ten parameters yielded one significant model of TTN of neutrophils: Absorbed dose to red marrow as the single parameter (*F*-test, $p = 0.00753$, AIC = 111.0, $r^2 = 0.388$). Figure 3(c,d) shows the TTN plotted against the absorbed dose to red marrow. For thrombocytes, no significant model between the ten parameters and TTN was found (the lowest p for the linear model was 0.096).

Sigmoid fit

The sigmoid function was fitted with coefficients $D_{50} = 0.59$ and $N = 0.95$ and $D_{50} = 0.66$ and $N = 0.96$ for thrombocytes and neutrophils respectively (Figure 4). The root means squared errors of the sigmoid function were 12.6 and 11.4 for thrombocytes and neutrophils. A similar leave-1-out analysis as for the linear model was performed, resulting in an agreement of 12/17 and 15/17 for thrombocytopenia and neutropenia grade ± 1, and 3/17 and 8/17 for exact agreement between predicted and observed toxicity grade.

Discussion

Absorbed dose to red marrow was the only variable that predicted hematological toxicity for both thrombocytes and neutrophils in patients treated with [^{177}Lu]Lu-lilotomab satetraxetan. The absorbed dose was also found to be predictive of the TTN of neutrophils.

Correlations between myelosuppression and potential risk factors including absorbed dose to the red marrow have been investigated previously, both for RIT- and other radionuclide treatments. In a phase III study with [^{90}Y]Y-ibritumomab tiuxitan no correlation was found between absorbed dose and myelosuppression; possibly due to limitations with the absorbed dose calculation [30,31]. In another study with ^{131}I-labelled anti carcinoembryonic antigen RIT absorbed dose to the red marrow, baseline blood cell counts, multiple bone metastasis, and chemotherapy within the last 3–6 months of treatment were found to be predictors of myelosuppression [32]. In a study with [^{131}I]I-tositumomab ($n = 14$) and [^{90}Y]Y-ibritumomab tiuxitan ($n = 18$), the elapsed time from the last chemotherapy was identified as the only predictive parameter [33]. However, the authors argued, the range of absorbed dose to the red marrow was narrow (mean 1.6 ± 0.4 Gy and 2.1 ± 0.4 Gy for [^{131}I]I-tositumomab and [^{90}Y]Y-ibritumomab tiuxitan, respectively), and therefore not a factor of variability. Using whole-body absorbed dose as a surrogate for absorbed dose to the bone marrow, a relationship between this parameter and myelosuppression was found for patients treated with [^{131}I]I-metaiodobenzylguanidine, whereas no relationship was found for administered radioactivity [20]. In a study with [^{90}Y]Y-DOTATOC, a peptide receptor radionuclide therapy, a correlation was observed between the level of platelets at nadir and absorbed dose to red marrow [19]. Unlike previous studies, we found absorbed dose to red marrow to be the only variable to significantly predict PBN also after having adjusted for other candidate factors. Further, neither activity dosage level (MBq/kg) nor amount of total administered radioactivity were predictive of myelosuppression. Hence other means, that is, image-based dosimetry taking the individual biodistribution into account as we have done in this study, is most likely the best method to predict hematological toxicity for patients receiving [^{177}Lu]Lu-lilotomab satetraxetan. We have previously shown that specific pre-dosing with unlabeled lilotomab resulted in reduced absorbed dose to the red marrow and thus pre-dosing was not included as an independent variable [34]. When we included several parameters in the multivariate analyses, this did not strengthen the prediction models. For the neutrophils there was a model that was borderline

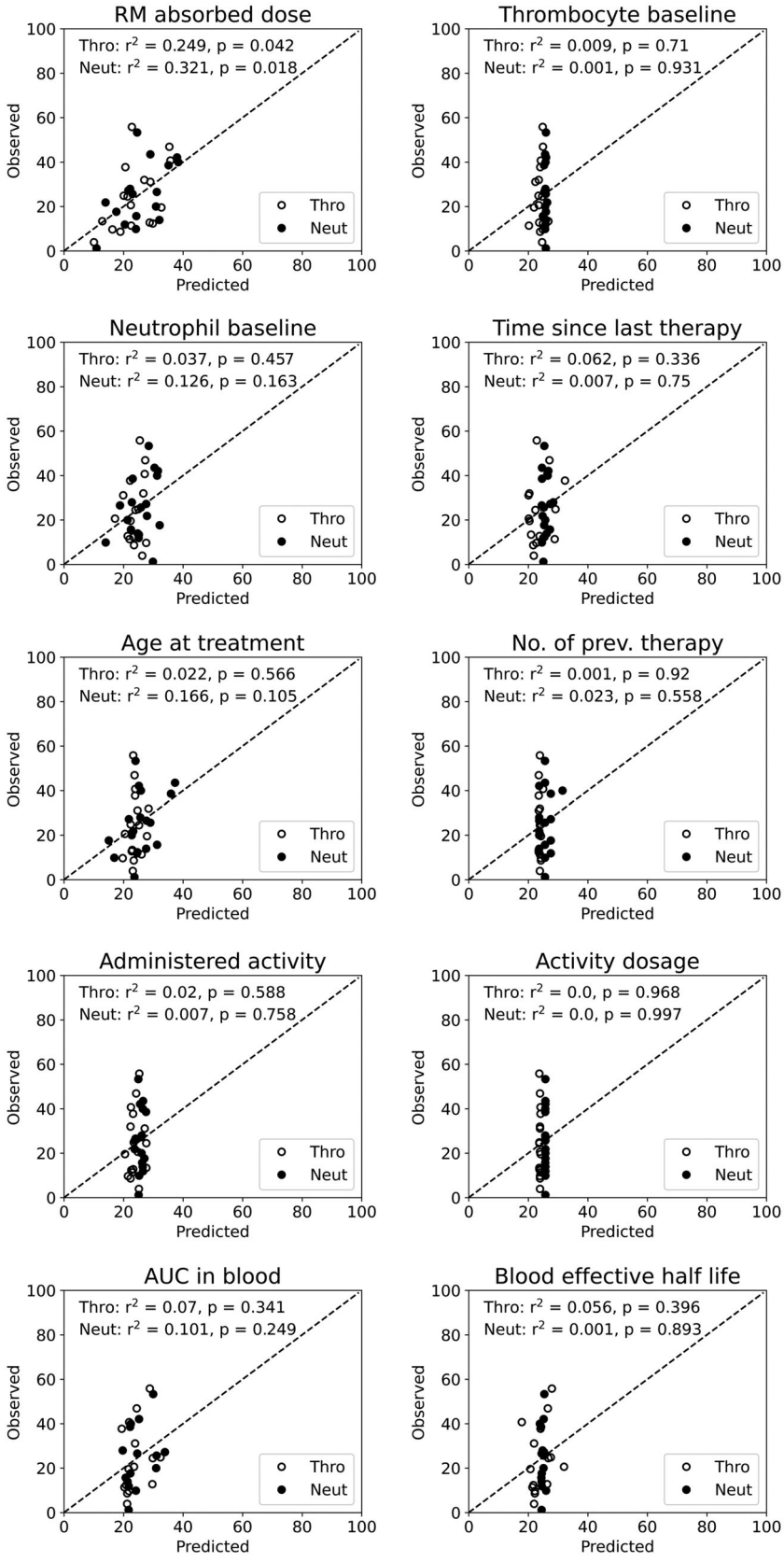

Figure 2. Absorbed dose to red marrow (upper left panel) was found as the only significant predictive parameter of PBN. None of the other parameters, shown here with predicted and observed PBN-values, were predictive of PBN. The r^2- and p-values are indicated for each parameter. Thrombocytes and neutrophils are shown as unfilled and filled dots respectively.

significant including neutrophils at baseline (F-test p-value = 0.01, absorbed dose p-value = 0.008, baseline neutrophils p-value = 0.058) while as for the thrombocytes the second most promising model included absorbed dose, history of previous EBRT-therapy and baseline neutrophil counts (F-test p-value = 0.08, absorbed dose p-value = 0.036, the other p-

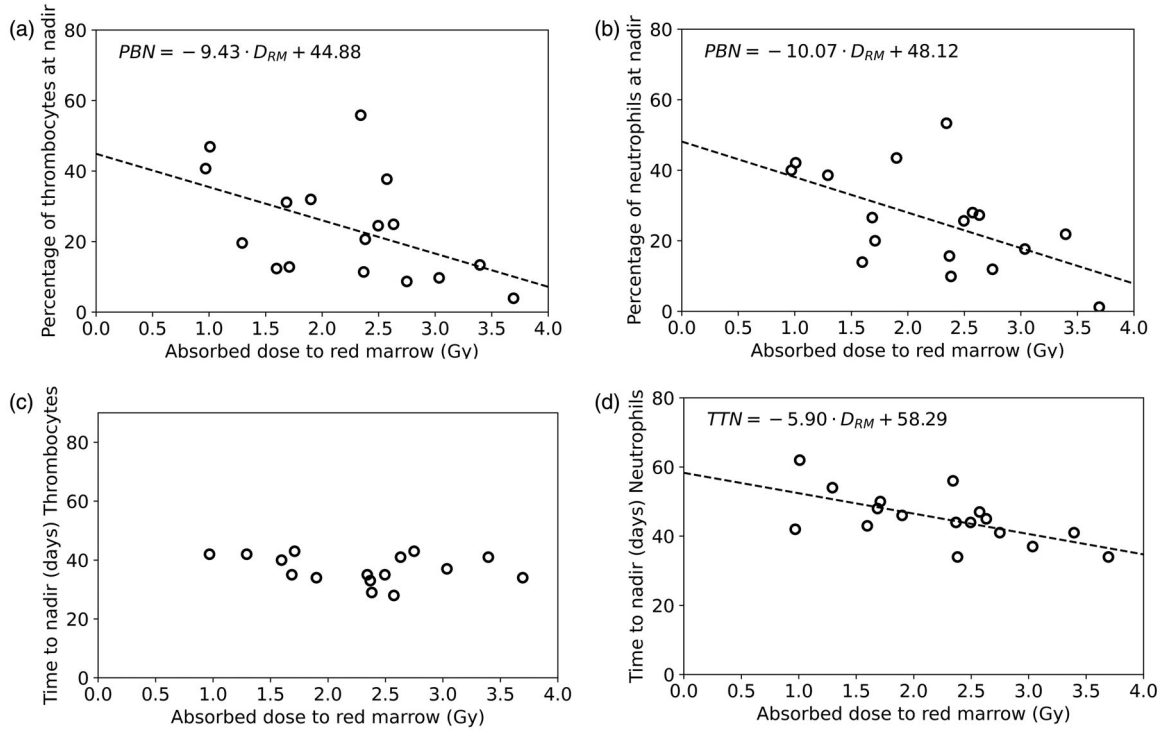

Figure 3. The dominating predictor was absorbed dose to the red marrow. The four toxicity indicators are here shown plotted against this predictor: PBN of thrombocytes (a) and neutrophils (b) and TTN for thrombocytes (c) and neutrophils (d). PBN for thrombocytes and neutrophils and TTN for neutrophils were all found to be significantly correlated to red marrow absorbed dose. One patient (P19) had a thrombocyte TTN value of 251 days and is excluded from panel C.

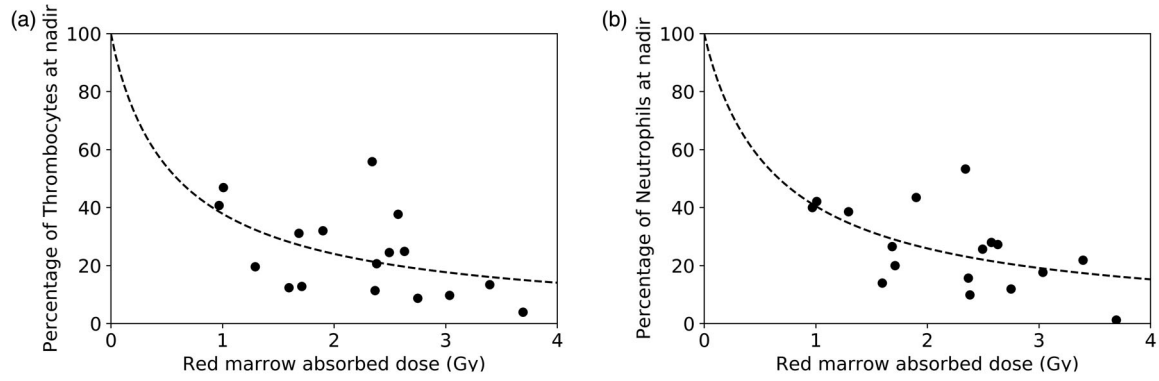

Figure 4. A sigmoid relationship between red marrow absorbed dose and PBN was explored. The s-shaped response curve is shown plotted against PBN of thrombocytes (a) and neutrophils (b). The root mean squared errors of the s-curves were almost identical to the linear response curves.

values > 0.18). Pharmacokinetic parameters did not yield significant predictors in the linear toxicity model. This could potentially be due to that pharmacokinetics alone is an incomplete description of the distribution of [^{177}Lu]Lu-lilotomab satetraxetan in the red marrow for individual patients.

Absorbed doses to red marrow ranged from approximately 1 to 4 Gy in our study. This is higher than previously reported for a subgroup of patients from the same trial [26], as a correction factor for reference cellularity was here included in the dose calculation. While this has shifted the absolute values, the relative interpatient differences remain unchanged with some differences due to whole-body contribution and patient sex. The upper absorbed doses are somewhat higher than the toxicity limit of 2 Gy used in dosimetry-guided radioiodine treatment of differentiated thyroid cancer protocols [35]. Our absorbed doses are however in the same order of magnitude as those reported for patients treated with high dose [^{131}I]I-metaiodobenzylguanidine therapy for neuroblastoma (range 2.06–5.02 Gy) [22]. With a hybrid, SPECT/CT-imaging technique of patients treated with the RIT [^{131}I]I-rituximab, absorbed doses were found to be comparable to ours (range 1.09–1.90 Gy) [23]. Direct comparison of absorbed doses from previous studies of other therapies is however to be done with caution. This is mainly due to differences in biological vectors and radionuclides, which leads to differences in absorbed dose rate and energy deposition, which in turn can result in variations in radiobiological effects. Moreover, while the recent improvements in radioactivity quantification technology have enabled more direct and accurate measurements of radioactivity, there are still methodological differences to be considered [36]. Overall, our findings indicate an upper limit in the same order of magnitude as previous relevant publications, approximately 3 Gy when our methodology is used.

After having established that absorbed dose dominated in the multivariate analyses, we proceeded to further investigate the best model for this predictor. Relationships between absorbed dose and normal tissue complications are usually expected to follow sigmoid functions, of which parameters are found for specific clinical situations [37]. The sigmoid function used in our work has previously been reported to describe the relationship between absorbed dose to red marrow and decrease in thrombocytes in metastatic prostate cancer patients treated with [^{186}Rhenium]Re-HEDP [29]. The value for D_{50}, the absorbed dose resulting in a 50% reduction of platelets, was there reported to be 2.09 Gy in a group of previously untreated patients, four times the value found in the current work. This difference could be explained by the fact that the patients included in the current study have been heavily pretreated, and thus more radiosensitive. An alternative explanation may be differences between the radiobiological effects of the different radionuclides and carrier molecules. The sigmoid model had a similar root mean square error as the linear model, however, the sigmoid model showed slightly superior predictive abilities in the cross-validation compared to the linear model. The two models seem to overlap in the range of the recorded absorbed doses. Due to the comparable predictive power and the simplicity of the linear description, we recommend that the linear description should be considered the preferred working model except at very high or very low absorbed doses.

Absorbed dose to red marrow enabled identification of high-risk patients for myelotoxicity after therapy with [^{177}Lu]Lu-lilotomab satetraxetan as it could be calculated as early as 7 days post-treatment, before the onset of neutropenia and thrombocytopenia. Severe myelosuppression was uncommon for our patient group [25] who received a single dose of radioimmunotherapy. However, the prediction of hematologic toxicity might become particularly interesting for repeated administrations. Dosimetry after the first treatment cycle can then, in a multi-cycle treatment protocol, be used to predict the toxicity of future cycles, and thus be used to tailor the number and size of the cycles. Such an approach has been explored in peptide receptor radionuclide therapy [38]. Results in a murine model have suggested that fractionated therapy is a possible treatment strategy for [^{177}Lu]Lu-lilotomab satetraxetan [39]. In such a treatment setting, patients could benefit from being stratified into groups that can allow for more intensive treatment for those that have a more favorable therapeutic index.

Conclusion

It is possible to predict levels of thrombocytopenia and neutropenia by applying absorbed dose to red marrow as the only predictor. No other investigated patient characteristics or variables strengthened this correlation in this study.

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Disclosure statement

Arne Kolstad is a member of the Scientific Advisory Board of Nordic Nanovector ASA. Jostein Dahle is an employee and shareholder of Nordic Nanovector ASA. The authors have no further conflicts of interest to disclose.

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References

[1] Larson SM, Carrasquillo JA, Cheung NKV, et al. Radioimmunotherapy of human tumours. Nat Rev Cancer. 2015; 15(6):347–360.
[2] Steiner M, Neri D. Antibody-radionuclide conjugates for cancer therapy: Historical considerations and new trends. Clin Cancer Res. 2011;17(20):6406–6416.
[3] Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol. 2021;81(10):1229–2463.
[4] Kaminski MS, Tuck M, Estes J, et al. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med. 2005; 352(5):441–449.
[5] Jacene HA, Filice R, Kasecamp W, et al. Comparison of 90Y-ibritumomab tiuxetan and 131I-tositumomab in clinical practice. J Nucl Med. 2007;48(11):1767–1776.
[6] Papadimitroulas P, Loudos G, Nikiforidis GC, et al. A dose point kernel database using GATE Monte Carlo simulation toolkit for nuclear medicine applications: comparison with other Monte Carlo codes. Med Phys. 2012;39(8):5238–5247.
[7] Dahle J, Repetto-Llamazares AHV, Mollatt CS, et al. Evaluating antigen targeting and anti-tumor activity of a new anti-cd37 radioimmunoconjugate against non-hodgkin's lymphoma. Anticancer Res. 2013;33(1):85–96.
[8] Zhao X, Tridandapani S, Lehman A, et al. Targeting CD37-positive lymphoid malignancies with a novel engineered small modular immunopharmaceutical. Blood. 2007;110(7):2569–2577.
[9] Schwartz-Albiez R, Dörken B, Hofmann W, et al. The B cell-associated CD37 antigen (gp40-52). Structure and subcellular expression of an extensively glycosylated glycoprotein. J Immunol. 1988;140:905–914.
[10] Heider K-h, Kiefer K, Zenz T, et al. LYMPHOID NEOPLASIA A novel Fc-engineered monoclonal antibody to CD37 with enhanced ADCC and high proapoptotic activity for treatment of B-cell malignancies. Blood. 2011;118(15):4159–4169.
[11] Deckert J, Park PU, Chicklas S, et al. A novel anti-CD37 antibody-drug conjugate with multiple anti-tumor mechanisms for the treatment of B-cell malignancies. Blood. 2013;122(20):3500–3510.
[12] Bertoni F, Stathis A. Staining the target: CD37 expression in lymphomas. Blood. 2016;128(26):3022–3023.
[13] Kaminski MS, Zasadny KR, Francis IR, et al. Iodine-131-anti-B1 radioimmunotherapy for B-cell lymphoma. J Clin Oncol. 1996; 14(7):1974–1981.
[14] Hiraga J, Tomita A, Sugimoto T, et al. Down-regulation of CD20 expression in B-cell lymphoma cells after treatment with

rituximab-containing combination chemotherapies: its prevalence and clinical significance. Blood. 2009;113(20):4885–4893.
[15] Kaminski MS, Fig LM, Zasadny KR, et al. Imaging, dosimetry, and radioimmunotherapy with iodine 131-labeled anti-CD37 antibody in B-cell lymphoma. J Clin Oncol. 1992;10(11):1696–1711.
[16] Hindorf C, Glatting G, Chiesa C, et al. EANM dosimetry committee guidelines for bone marrow and whole-body dosimetry. Eur J Nucl Med Mol Imaging. 2010;37(6):1238–1250.
[17] Puvvada SD, Guillén-Rodríguez JM, Yan J, et al. Yttrium-90-ibritumomab tiuxetan (Zevalin®) radioimmunotherapy after cytoreduction with ESHAP chemotherapy in patients with relapsed follicular non-Hodgkin lymphoma: final results of a phase II study. Oncology. 2018;94(5):274–280.
[18] Wahl RL. The clinical importance of dosimetry in radioimmunotherapy with tositumomab and iodine I 131 tositumomab. Semin Oncol. 2003;30(2 Suppl 4):31–38.
[19] Walrand S, Barone R, Pauwels S, et al. Experimental facts supporting a red marrow uptake due to radiometal transchelation in 90Y-DOTATOC therapy and relationship to the decrease of platelet counts. Eur J Nucl Med Mol Imaging. 2011;38(7):1270–1280.
[20] Buckley SE, Chittenden SJ, Saran FH, et al. Whole-body dosimetry for individualized treatment planning of 131I-MIBG radionuclide therapy for neuroblastoma. J Nucl Med. 2009;50(9):1518–1524.
[21] Matthay KK, Panina C, Huberty J, et al. Correlation of tumor and whole-body dosimetry with tumor response and toxicity in refractory neuroblastoma treated with (131)I-MIBG. J Nucl Med. 2001; 42:1713–1721.
[22] DuBois SG, Messina J, Maris JM, et al. Hematologic toxicity of high-dose iodine-131–metaiodobenzylguanidine therapy for advanced neuroblastoma. J Clin Oncol. 2004;22(12):2452–2460.
[23] Boucek JA, Turner JH. Validation of prospective whole-body bone marrow dosimetry by SPECT/CT multimodality imaging in131I-anti-CD20 rituximab radioimmunotherapy of non-Hodgkin's lymphoma. Eur J Nucl Med Mol Imaging. 2005;32(4):458–469.
[24] Aksentijevich I, Flinn I. Chemotherapy and bone marrow reserve: lessons learned from autologous stem cell transplantation. Cancer Biother Radiopharm. 2002;17(4):399–403.
[25] Kolstad A, Illidge T, Bolstad N, et al. Phase 1/2a study of 177Lu-lilotomab satetraxetan in relapsed/refractory indolent non-Hodgkin lymphoma. Blood Adv. 2020;4(17):4091–4101.
[26] Blakkisrud J, Løndalen A, Dahle J, et al. Red marrow-absorbed dose for non-Hodgkin lymphoma patients treated with 177Lu-lilotomab satetraxetan, a novel anti-CD37 antibody-radionuclide conjugate. J Nucl Med. 2017;58(1):55–61.
[27] CTCAE4. Common terminology criteria for adverse events. 4th ed. Bethesda (MD): US National Cancer Institute; 2009.
[28] ICRP. Basic anatomical and physiological data for use in radiological protection – the skeleton. ICRP Publication 70. Ann ICRP. 1995;25(2):1–80.
[29] de Klerk JM, van Dieren EB, van Het Schip AD, et al. Bone marrow absorbed dose of rhenium-186-HEDP and the relationship with decreased platelet counts. J Nucl Med. 1996;37(1):38–41.
[30] Wiseman GA, White CA, Sparks RB, et al. Biodistribution and dosimetry results from a phase III prospectively randomized controlled trial of Zevalin™ radioimmunotherapy for low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. Crit Rev Oncol Hematol. 2001;39(1-2):181–194.
[31] Wiseman G, Kornmehl E, Leigh B, et al. Radiation dosimetry results and safety correlations from 90Y-ibritumomab tiuxetan radioimmunotherapy for relapsed or refractory non-Hodgkin's lymphoma: Combined data from 4 clinical trials. J Nucl Med. 2003;44:465–474.
[32] Juweid ME, Zhang CH, Blumenthal RD, et al. Prediction of hematologic toxicity after radioimmunotherapy with 131-I-labeled anti-carcinoembryonic antigen monoclonal antibodies. J Nucl Med. 1999;40(10):1609–1616.
[33] Baechler S, Hobbs RF, Jacene HA, et al. Predicting hematologic toxicity in patients undergoing radioimmunotherapy with 90Y-ibritumomab tiuxetan or 131I-tositumomab. J Nucl Med. 2010; 51(12):1878–1884.
[34] Stokke C, Blakkisrud J, Løndalen A, et al. Pre-dosing with lilotomab prior to therapy with 177Lu-lilotomab satetraxetan significantly increases the ratio of tumor to red marrow absorbed dose in non-Hodgkin lymphoma patients. Eur J Nucl Med Mol Imaging. 2018;45(7):1233–1241.
[35] Lassmann M, Flux G, Hindorf C, et al. EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy. Eur J Nucl Med Mol Imaging. 2008;35(7):1405–1412.
[36] Lassmann M, Eberlein U. The relevance of dosimetry in precision medicine. J Nucl Med. 2018;59(10):1494–1499.
[37] Yorke ED. Modeling the effects of inhomogeneous dose distributions in normal tissues. Semin Radiat Oncol. 2001;11(3):197–209.
[38] Sundlöv A, Sjögreen-Gleisner K, Svensson J, et al. Individualised 177Lu-DOTATATE treatment of neuroendocrine tumours based on kidney dosimetry. Eur J Nucl Med Mol Imaging. 2017;44(9): 1480–1489.
[39] Heyerdahl H, Repetto-Llamazares AHV, Dahle J. Administration of beta-emitting anti-CD37 radioimmunoconjugate lutetium (177Lu) lilotomab satetraxetan as weekly multiple injections increases maximum tolerated activity in nude mice with non-Hodgkin lymphoma xenografts. GJCT. 2018;4(1):181–190.