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Title: Red Marrow Absorbed Dose for non-Hodgkin's Lymphoma Patients treated with the novel anti-CD37 antibody radionuclide conjugate ^{177}Lu-lilotomab satetraxetan

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ABSTRACT

Red bone marrow (RM) is often the primary organ at risk in radioimmunotherapy; irradiation of marrow may induce short and long term hematological toxicity. ^{177}Lu-lilotomab satetraxetan is a novel anti-CD37 antibody-radionuclide-conjugate (ARC) currently in phase 1/2a. Two pre-dosing regimens have been investigated, one with 40 mg unlabeled lilotomab antibody (arm 1) and one without (arm 2). The aim of this work was to compare RM absorbed doses for the two arms and to correlate absorbed doses with hematological toxicity. ***Methods:*** Eight patients with relapsed CD37+ indolent B-cell non-Hodgkin's lymphoma were included for RM dosimetry. Hybrid Single Photon Emission Computed Tomography (SPECT) and Computed Tomography (CT) images were used to estimate activity concentration in the RM of lumbar L2-L4. Pharmacokinetic parameters were calculated after measurement of ^{177}Lu-lilotomab satetraxetan concentration in blood samples. Adverse events were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. ***Results:*** The mean absorbed doses to RM were 0.94 mGy/MBq for arm 1 (lilotomab+) and 1.53 mGy/MBq for arm 2 (lilotomab-). There was a statistically significant difference between arm 1 and 2 (student t-test, $p = 0.02$). Total RM absorbed doses ranged from 67 to 127 cGy in arm 1 and from 158 to 207 cGy in arm 2. For blood, the area under the curve (AUC_{blood}) was higher with lilotomab pre-dosing compared to without pre-dosing ($p = 0.001$), while the volume of distribution and the clearance of ^{177}Lu-lilotomab satetraxetan was significantly lower ($p = 0.01$ and $p = 0.03$, respectively). Patients with Grade 3/4 thrombocytopenia had received significantly higher radiation doses to RM than patients with Grade 1/2 thrombocytopenia ($p = 0.02$). A surrogate, non-imaging based, method underestimated the RM dose and did not show any correlation with toxicity. ***Conclusion:*** Pre-dosing with lilotomab reduces the RM absorbed dose for ^{177}Lu-lilotomab satetraxetan patients.

The decrease in RM dose could be explained by the lower volume of distribution. Hematological toxicity was more severe for patients receiving higher absorbed radiation doses, indicating that adverse events possibly can be predicted by the calculation of absorbed dose to RM from SPECT/CT images.

Key words: Red marrow absorbed dose, antibody-radionuclide-conjugate, non-Hodgkin's lymphoma, ^{177}Lu-lilotomab satetraxetan

INTRODUCTION

Radioimmunotherapy, or ARC-therapy, utilizes targeting antibodies linked to a radionuclide, and ARC therapy based on CD20 specific antibodies has been routinely used for treatment of non-Hodgkin's lymphoma. ^{177}Lu-lilotomab satetraxetan (previously referred to as ^{177}Lu-DOTA-HH1, trade name Betalutin®) is a novel ARC which targets the CD37 antigen expressed on malignant B-cells (*1*). Myelosuppression is the main adverse effect for the CD20 based ARC-therapies ^{131}Iodine-tositumomab (Bexxar) and ^{90}Yttrium-ibritumomab-tiuxetan (Zevalin), and is widely regarded to be a consequence of marrow irradiation (*2,3*). ARCs composed of a CD37 antibody labeled with Iodine-131 and a CD20 antibody labeled with Lutetium-177 also demonstrated hematological toxicity (*4,5*). Estimating the absorbed dose to the RM is therefore an imperative when a new ARC is studied. Preclinical studies and preliminary phase 1/2a clinical results indicate that myelosuppression is dosage limiting also for ^{177}Lu-lilotomab satetraxetan (*6,7*).

The distributed nature of the marrow, intricate micro-structure and dependence on sex and age result in dosimetric challenges. Extensive work has resulted in S-values of the skeleton, making dosimetry in accordance with the Medical Internal Radiation Dose scheme possible (*8*). A requirement is then to estimate the activity concentration both in the RM itself and in the surrounding tissues contributing to cross fire dose (*9*). An indirect measuring procedure for RM itself has traditionally been the method of choice, with blood doses being used as a surrogate. There is a growing consensus that this surrogate is sub-optimal for ARC therapy dose estimation, mainly given the often observed lack of correlation with toxicity and deviations found when compared to direct imaging methods (*10-12*). By imaging the uptake in marrow itself, correlations between absorbed dose and toxic effects have been found (*13*). Correlations have

been found to improve with the use of three-dimensional modalities, i.e. SPECT or Positron Emission Tomography, compared to planar imaging (*14*).

Pre-dosing with unlabeled antibody the same day as the radioactive antibody has been demonstrated effective as a way of blocking accessible non-cancerous B-cells for treatment with ^{131}I-tositumomab (*15*,*16*). In the present phase 1/2a trial only patients in arm 1 received pre-dosing with lilotomab. In addition, all patients were pre-treated with a larger amount of the anti-CD20 antibody rituximab before ^{177}Lu-lilotomab satetraxetan injection.

The aim of this work was to calculate RM doses using SPECT/CT images of patients receiving treatment with ^{177}Lu-lilotomab satetraxetan and investigate whether pre-dosing with unlabeled lilotomab affects the RM dose. We have also investigated the correlation between absorbed doses to RM and hematological toxicity measured by reduction in thrombocytes and neutrophils.

MATERIALS AND METHODS

Patient Population

8 patients with relapsed indolent non-Hodgkin's lymphoma treated in the phase 1 LYMRIT-37-01 trial were included for RM dosimetry. All patents had received prior chemotherapy treatments (Table 1). Patients with prior external beam radiation therapy to L2-L4 were excluded. The study was approved by the regional ethical committee and all patients had signed informed consent. The participants received a single injection of ^{177}Lu-lilotomab satetraxetan. Patients were pre-treated with 375 mg/m^2 of the anti-CD20 antibody rituximab 4 weeks and 3 weeks before injection. In arm 1 the patients received pre-dosing with 40 mg lilotomab before administration of ^{177}Lu-lilotomab satetraxetan, and in arm 2 they did not.

Hematological Analyses

Blood samples were collected prior to administration of ^{177}Lu-lilotomab satetraxetan and several times day 0 as well as day 1, 2, 3, 4, 7, and then every week until week 4 and later every 6 months. The blood samples from the first month were decay corrected to yield blood activity concentration curves. AUC_{blood}, clearance and volume of distribution were found analytically after mono-exponential curve fitting.

The decrease in thrombocytes and neutrophils at nadir relative to baseline were calculated. Hematological adverse events, thrombocytopenia and neutropenia, were graded by the CTCAE version 4.0 (*17*).

Image Acquisition and Probe Measurements

The SPECT/CT imaging protocol has been described in part 1 (*1*). In brief, attenuation and scatter corrected SPECT/CT images were acquired approximately 96 and 168 hours post injection (p.i.) of ^{177}Lu-lilotomab satetraxetan. Patients 13, 14 and 15 had an additional scan 24

hours p.i. Whole body activity half-lives were determined by anterior and posterior probe measurements at a fixed distance of the patients, at the height of the sternum. The first measurement was performed pre-void, within 5 minutes p.i. Additional measurements were performed 10 minutes p.i., and 4, 24, 96 and 196 hours p.i.

Quantification and Dosimetry

Absorbed dose to RM was found both by a surrogate method, using blood and whole body (WB) measurements, and a method based on SPECT/CT images. The surrogate method was primarily performed for comparison purposes. Both methods include both a contribution from the marrow itself (self-dose) and cross-dose from the "remainder of body" (RB). The time-integrated activity coefficient for RB is:

$$\tau_{RB(patient)} = \tau_{WB(patient)} - \tau_{RM(patient)} \quad (1)$$

To find $\tau_{WB(patient)}$, time-activity curves were calculated by the geometrical mean of the probe measurements, fitted to mono-exponential curves and integrated analytically. When not available, a mean $\tau_{WB(patient)}$ was used.

SPECT/CT Method

The lumbar vertebrae L2-L4 were used for activity quantification performed using SPECT/CT images as previously described for tumors in part 1(*1*). The mass of the marrow in L2-L4 was estimated for each patient by drawing a volume of interest defining the interior space of the vertebrae corpus. This volume, $V_{L2-L4(patient)}$, mainly consists of RM, yellow marrow and trabecular bone. Activity in trabecular bone was assumed zero, and a multiplicative correction factor (1 - f_{TB}) was applied to the interior volume. The factor f_{TB} was assumed 0.135 for male and

0.148 for female patients (*18*). The rest of $V_{L2-L4(patient)}$ was assumed RM. The RM activity concentration in L2-L4 is then

$$[A_{L2-L4(patient)}] = \frac{A_{L2-L4(patient)}}{V_{L2-L4(patient)}\ (1 - f_{TB})} \quad (2)$$

with $A_{L2-L4(patient)}$ being the activity in L2-L4.

Activity concentration points were fitted by mono-exponential curves and integrated analytically, resulting in RM cumulative activity in L2-L4, $\tilde{A}_{L2-L4(patient)}$. RM time-integrated activity coefficient L2-L4 and L2-L4 RM mass, $\tau_{L2-L4(patient)}$ and $m_{L2-L4(patient)}$, can then be written as

$$\tau_{L2-L4(patient)} = \frac{\tilde{A}_{L2-L4(patient)}}{A_{0(patient)}} \quad (3)$$

and

$$m_{L2-L4(patient)} = V_{L2-L4(patient)} * (1 - f_{TB}) \quad (4)$$

with $A_{0(patient)}$ being administered activity.

It was assumed equal cumulative concentrations throughout the marrow, and that L2-L4 account for 6.7 % of total RM, therefore $m_{L2-L4(patient)}$ and $\tau_{L2-L4(patient)}$ were both scaled by (1/0.067) (*19*). These parameters, together with $\tau_{RB(patient)}$, were used as input to OLINDA/EXM, resulting in the image derived RM dose $D_{RM(SPECT)}$ (*20*).

Surrogate Method

The surrogate RM dosimetry is based on the assumption that cumulative concentration in RM is proportional to that of blood (*21*). Cumulative concentration in blood is derived from AUC_{blood}. Assuming a proportionality constant of unity and expressing the whole RM mass with reference RM, reference WB mass and patient WB mass as

$$m_{RM(patient)} = \frac{m_{RM(ref)}}{m_{WB(ref)}} m_{WB(patient)}, \quad (5)$$

, the time-integrated activity coefficient of RM can be expressed as

$$\tau_{RM(patient)} = \frac{[\tilde{A}_{blood}]}{A_{0(patient)}} m_{RM(patient)} \quad (6)$$

Reference values for WB and RM were taken from OLINDA/EXM for male and female phantoms. $\tau_{RM(patient)}$, $\tau_{RB(patient)}$ and $m_{RM(patient)}$ were used as input in OLINDA/EXM, resulting in dose to RM; $D_{RM(surrogate)}$

Statistics

Mean RM dose for arm 1 and 2 was compared using a two-sided student-t-test. AUC_{blood}, volume of distribution and clearance from the blood measurements were also compared for arm 1 and 2 using the same test. The difference in RM dose for the two groups CTCAE grade 1/2 versus 3/4 was investigated by a two-sided student-t-test. RM doses were individually tested by a Pearson-test for correlation with thrombocyte and neutrophil values at nadir. $D_{RM(SPECT)}$ and $D_{RM(surrogate)}$ were compared with a paired student-t-test. For all statistical tests, a significance level of 0.05 was used.

RESULTS

Dosimetry was primarily performed using SPECT/CT images; Figure 1 shows fused SPECT/CT images of the L1-L5 lumbar vertebrae of two of the patients. The RM absorbed dose ranged from 0.7 to 2.1 Gy, and even though the patients had been treated with different dosage levels (10 or 15 MBq/kg) every patient with pre-dosing received lower absorbed dose than every patient without pre-dosing (Table 2). The contribution from cross-dose to the total RM dose was maximum 17 % for the SPECT/CT based method. Therefore, introducing the scaling factor 0.067 shifted the final RM absorbed doses with less than 2 %. Figure 2 illustrates the RM doses separated with regard to pre-dosing with lilotomab (corresponding to arm 1 and 2). The mean dose of the pre-dosed group of 0.9 mGy/MBq was significantly lower than the mean dose for the group without pre-dosing of 1.6 mGy/MBq ($p = 0.02$).

Patients with grade 3/4 thrombocytopenia received a significantly higher RM absorbed dose than patients with grade 1/2 thrombocytopenia ($p = 0.02$) (Fig. 3A). Two of the patients, both in arm 2, experienced thrombocytopenia of grade 4 3-6 weeks p.i. Difference between RM doses for grade 1/2 and 3/4 neutropenia was not statistically significant ($p = 0.39$) (Fig. 3B). There was a moderate, but non-significant, linear correlation between the relative reduction in the thrombocyte and neutrophil counts at nadir and the RM dose ($p = 0.10$ and $p = 0.11$, respectively) (Fig. 3C and 3D). The CTCAE grading reflects the absolute cell count at nadir. When calculating the correlation between the absolute thrombocyte count and RM dose, a strong and significant linear relationship is found ($r = -0.74$, $p = 0.04$). A moderate to strong but non-significant relationship is found for the neutrophils ($r = -0.63$, $p = 0.09$).

An increased AUC_{blood} was observed with lilotomab pre-dosing compared to without pre-dosing ($p = 0.001$) (Table 3). The volume of distribution and the clearance of ^{177}Lu- lilotomab

satetraxetan was significantly lower for patients given lilotomab compared to those not given lilotomab ($p = 0.01$ and $p = 0.03$, respectively).

The surrogate method resulted in a significant underestimation of RM dose compared to SPECT/CT-derived dose ($p = 0.002$). The relative difference ranged from 80 to 638 %. RM dose calculated by the surrogate method did not show any correlation with hematological toxicity (Fig. 4).

DISCUSSION

RM is one of the most radiation sensitive organs in the body. In this work we have calculated the RM doses and correlated them to hematological adverse events for 8 patients treated with ^{177}Lu-lilotomab satetraxetan.

The RM doses were significantly higher for arm 2 (lilotomab-) than for arm 1 (lilotomab+). This difference indicates that pre-dosing with lilotomab will have a protective effect for RM, most likely because the unlabeled antibody blocks binding to CD37 in the RM. The activity in blood, AUC_{blood}, was higher, and the volume of distribution and the clearance were lower for arm 1 than for arm 2. This is likely due to binding of unlabeled lilotomab to CD37 expressed on cells in the highly perfused compartment including peripheral blood and RM. This binding by lilotomab to the readily accessible CD37 target antigens then prevents ^{177}Lu-lilotomab satetraxetan binding to the cells in this compartment, increasing the concentration in the blood, reducing the available volume of distribution and eventually resulting in reduced amounts of radioactivity in RM. There is a risk that pre-dosing with cold antibody could block the CD37 antigen on tumor tissues as well, but there was no difference in the tumor absorbed dose for arm 1 and 2 (*1*). The reduced distribution volume and clearance in arm1 might explain this finding because it implies that the concentration of ^{177}Lu-lilotomab satetraxetan was higher for arm 1 patients than for arm 2 patients and the increased concentration will counteract an eventual blocking of CD37 on tumor tissue. The combined findings of these works recommend to use pre-dosing with lilotomab before treatment with ^{177}Lu-lilotomab satetraxetan. The optimal amount of unlabeled antibody has yet to be investigated.

Although the numbers of patients are limited, a clear tendency of increasing RM dose with patient dosage (10 MBq/kg vs 15 MBq/kg, Table 2) can be seen for each arm. This is in

accordance with the findings for tumors in part 1, where the absorbed dose significantly increased with patient dosage level (*1*).

The overall RM dose range was 0.64 to 1.82 mGy/MBq. These doses are of the same order of magnitude as the RM doses listed in the package inserts of ^{90}Y-ibritumomab-tiuxetan and ^{131}I-tositumomab (*22,23*). Somewhat varying ^{90}Y-ibritumomab-tiuxetan RM doses have been reported, possibly since substitute radioligands have been used for planar imaging and dosimetry (*24,25*). For ^{131}I-tositumomab, the dosage is adjusted to produce a 0.75 Gy whole body dose, shown to correspond with SPECT/CT-derived RM doses no higher than 1.9 Gy and a median of 1.56 Gy with typical dosage (*26*). Here, RM absorbed doses for ^{177}Lu-lilotomab satetraxetan are demonstrated in accordance with typical dose ranges reported for other ARC treatments.

Clear relationships between RM doses and hematological toxicity for ARC-therapies have traditionally been difficult to establish, and possible explanations include heterogeneous patient groups and dosimetric methodology. In our study, patients developing thrombocytopenia grade 3/4 had received significant higher RM doses than the grade 1/2 group. For the group level neutropenia analysis, the difference was not significant, and a larger patient material should be investigated. This is also demonstrated by the absolute neutrophil count and RM dose statistical analyses ($p = 0.09$). Prior chemotherapy, limiting the RM reserve, can also alter the relationship between RM dose and hematological toxicity (*27*). All patients in our study had undergone prior chemotherapy, with the number of previous treatments ranging considerably (Table 1). While the limited number of patients prevents quantitative analyses regarding the influence of prior treatments, our findings suggest that the dose-toxicity relationship also depends on the extent of prior chemotherapy. E.g. patient 2 had received the most extensive prior treatment, possibly leading to a reduced marrow reserve and explaining the unexpected neutropenia grade 3 after an RM dose of only 67 cGy. On the contrary patient 15, whom received an RM dose of 159 cGy,

suffered only minor hematological toxicity. This well tolerated RM radiation could potentially be explained by the relatively limited prior treatment of only one chemotherapy regime.

Our RM dose calculation relies on L2-L4 being representative for the whole marrow. This part of the skeleton has frequently been used, and the resulting doses have shown correlation with hematological toxicity (*11,12,19*). Ideally; analyses of all skeletal sites containing RM would strengthen the dosimetry, visual inspection of the SPECT/CT-images did however suggest similar uptake in other skeletal sites, e.g. costae, the sacrum, the sternum and ilium. A two-point dosimetry model was used to avoid introducing systematic errors. An additional time point was available for 2 patients (patient 13 and 14) and calculations for these three-point curves demonstrated a low relative difference in RM dose (0 and 8 %, data not shown). For other radionuclide treatments it has been suggested to calculate RM doses based on the radioactivity concentration in blood, and this method is sometimes also erroneous used to estimate doses for ARCs with specific RM binding. Assuming a conservative estimate of equal activity concentration in blood and RM we found doses between 80 and 638 % lower than the SPECT/CT derived RM doses and no correlation with toxicity (Fig. 4). This clearly shows that this surrogate method should not be used to calculate RM doses for patients treated with ^{177}Lu-lilotomab satetraxetan. However; a seemingly inverse proportionality between AUC_{blood} itself and RM dose suggests that alternative models for linking AUC_{blood} and RM dose can possibly be developed.

The reduction in cell count relative to baseline is commonly used to evaluate RM dose against toxicity (*11,13,28,29*). When extrapolating the regression curve in Figure 3B, a 100 % reduction of both thrombocytes and neutrophils are found at 2 – 3 Gy. While our data suggest linear regression, sigmoidal fits have been demonstrated in other works, and this value should be considered an estimate (*29*). This is further supported by the range in prior chemotherapies for the patient population; this variation can preclude trends for different patient groups. The two

patients in our study (patient 13 and 14) that experienced grade 4 thrombocytopenia had received the highest RM doses and were also the only patients receiving an RM dose above 1.8 Gy. The widely used 2 Gy dose limit for RM was initially determined for treatment of differentiated thyroid cancer using ^{131}I in the early 60s (*30*). Later, the potential differences in biological and physical factors (e.g. dose rate and electron energy) have been suggested to demonstrate a need for empiric determination of dose limits for other/novel therapies. Our results support an RM absorbed dose limit of approximately 2 Gy for patients treated with ^{177}Lu-lilotomab satetraxetan.

CONCLUSION

While pre-dosing with 40 mg unlabeled lilotomab significantly reduces the RM absorbed dose for patients treated with ^{177}Lu-lilotomab satetraxetan, the tumor absorbed dose is not affected by this amount of unlabeled antibody. These findings support to use pre-dosing with lilotomab for patients to be treated with ^{177}Lu-lilotomab satetraxetan, and encourage investigations regarding the optimal amount of pre-dosing, which currently is ongoing. Hematological toxicity was more severe for patients receiving higher absorbed radiation doses, and our results indicate an RM absorbed dose limit of about 2 Gy for ^{177}Lu-lilotomab satetraxetan therapy. Given the extent of prior chemotherapy for the population, a somewhat higher dose limit can be expected for patients without such treatment. A surrogate method based on blood sampling instead of imaging demonstrated severe shortcomings for ^{177}Lu-lilotomab satetraxetan patients. The calculation of RM absorbed dose, based on SPECT/CT imaging approximately day 4 and 7, can possibly predict adverse events weeks before occurring. In our experience, such calculations can be performed by trained and prepared personnel within 2 days of the imaging.

DISCLOSURE

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FIGURE LEGENDS

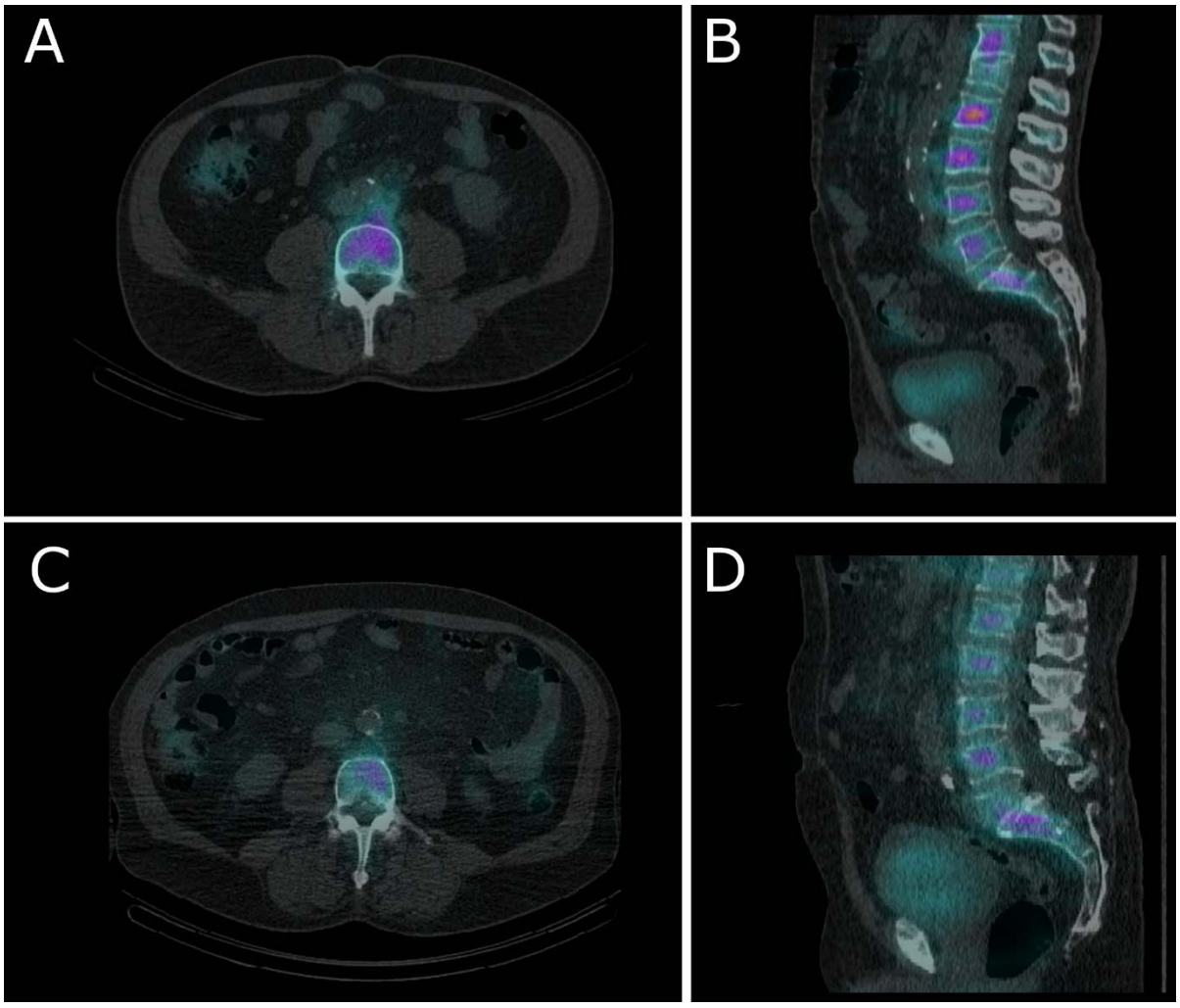

FIGURE 1. (A and B) Axial and sagittal fused SPECT/CT-images of patient 13 at 96 hours after ^{177}Lu-lilotomab satetraxetan injection. This patient did not receive pre-dosing with lilotomab. The L4 lumbar vertebra can be seen in the axial slice. Uptake of activity is observed in the vertebrae and the sacrum; the uptake in L2-L4 was quantified and used for RM dosimetry. (C and D) SPECT/CT images of patient 9. This patient received pre-dosing with lilotomab.

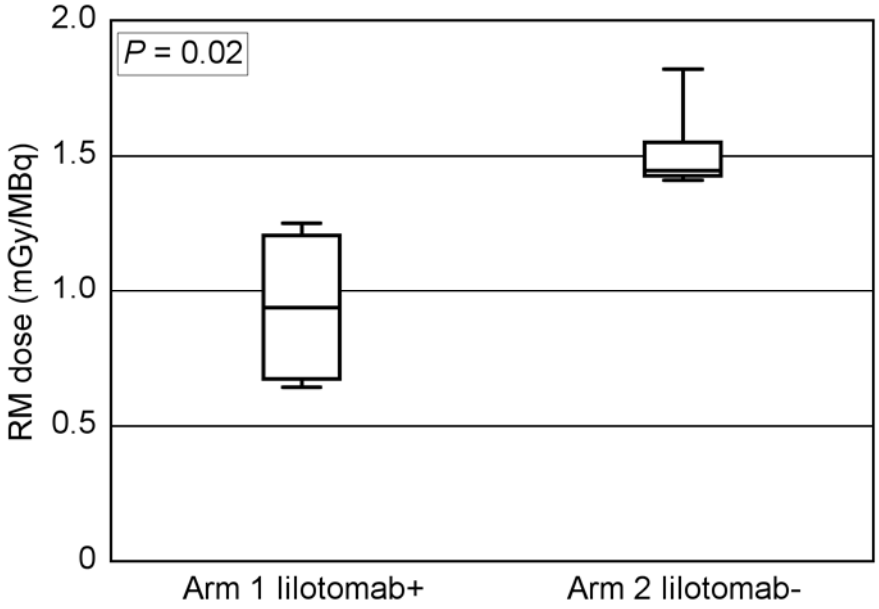

FIGURE 2. RM dose was significantly lower for ^{177}Lu-lilotomab satetraxetan patients in arm 1 than arm 2. Patients in arm 1 received pre-dosing with unlabeled antibody (lilotomab), and patients in arm 2 did not. The absorbed dose is normalized for administered activity.

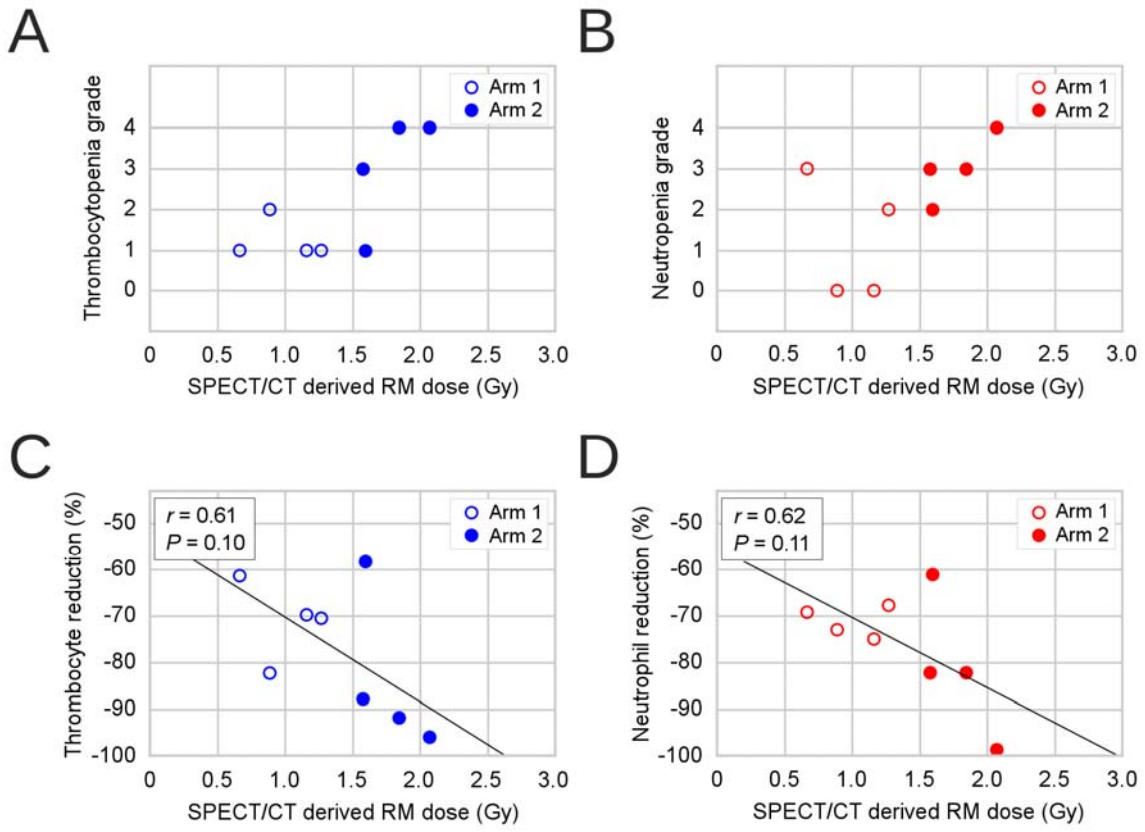

FIGURE 3. Hematological toxicity versus RM absorbed dose for patients receiving ^{177}Lu-lilotomab satetraxetan treatment. (A) CTCAE grading of thrombocytopenia plotted against dose. The dose was significantly higher for patients with grade 3/4 thrombocytopenia than grade 1/2 thrombocytopenia ($p = 0.02$). (B) CTCAE grading of neutropenia plotted against dose. Higher doses were found for patients with grade 3/4 than grade 1/2 neutropenia but the difference was not statistically significant ($p = 0.39$). (C and D) The relative reduction in blood-cells at nadir with respect to RM dose. Thrombocytes are shown in C and neutrophils in D. Filled symbols represent patients without pre-dosing (arm 2) and open symbols patients with pre-dosing (arm 1).

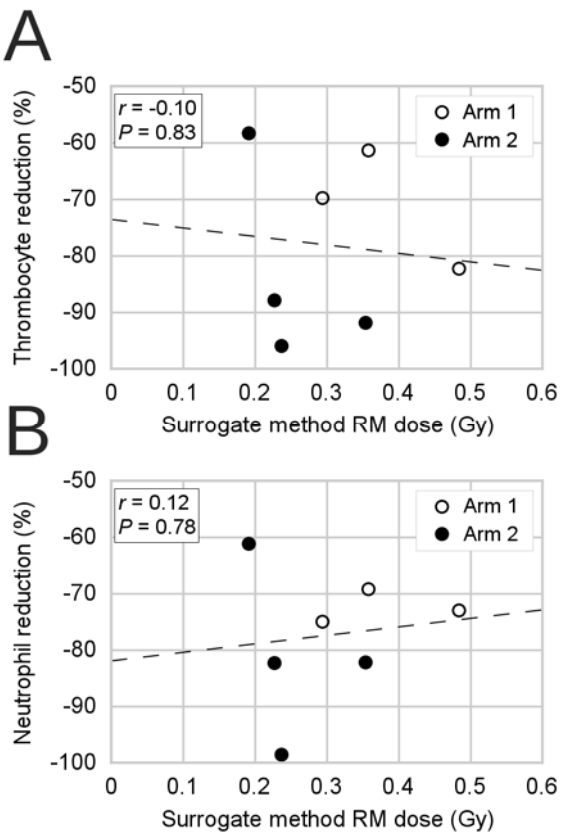

FIGURE 4. The lack of correlation between RM dose derived by surrogate method and the reduction in thrombocyte and neutrophil counts demonstrates that this non-imaging based method is unfit to predict marrow toxicity for ^{177}Lu-lilotomab satetraxetan therapy. Thrombocytes are shown in A and neutrophils in B. Filled symbols represent patients without pre-dosing (arm 2) and open symbols patients with pre-dosing (arm 1).

TABLES

TABLE 1. Patients included for RM dosimetry. Pre-treatment and pre-dosing are indicated with R (rituximab, pre-treatment) and lilotomab (unlabeled antibody, pre-dosing).

Patient	**Sex**	**Age**	**Dosage level**	**Injected Activity**	**Pre-treatment**	**Baseline Thrombocytes**	**Baseline Neutrophils**	**Prior treatments**
		(Years)	**(MBq/kg)**	**(MBq)**		**(10^9/L)**	**(10^9/L)**	
1	Female	58	10	1102	R	345	4.5	Rituximab x 4 R-CHOP x 2 + CHOP x 4
13	Male	72	15	1416	R	198	2.1	R-CVP x 6 R-Bendamustin x 6
14	Female	70	15	1013	R	243	2.8	Radiotherapy 30 Gy Rituximab x 4 R-Bendamustin x 6 R-CHOP x 6
15	Male	68	10	1130	R	206	3.6	R-CHOP x 6
2	Male	58	10	1036	R + lilotomab	233	2.6	Rituximab x 8 Rituximab x 4 Chlorambucil x 6 R-CHOP x 6 Radiotherapy 30 Gy R-Bendamustin x 6 Rituximab x 2
3	Male	50	10	746	R + lilotomab	339	7	Chlorambucil x 3 Radiotherapy 30 Gy R-Galaximab x 6 R-CHOP x 6 R Maintenance
9	Male	65	15	1696	R + lilotomab	298	6.8	Rituximab x 4
12	Female	49	15	1015	R + lilotomab	268	3.1	Intratumorally Rituximab with dendritic cells x 3 + radiotherapy 8 Gy Intratumorally Rituximab with dendritic cells x 2 + radiotherapy 8 Gy Rituximab x 4 R-Bendamustin x 1

TABLE 2. RM doses, absolute and normalized. Activity in L2-L4 96 h p.i. and biological half-life computed with 2 or 3 time points are also included. Pre-treatment and pre-dosing are indicated with R (rituximab, pre-treatment) and lilotomab (unlabeled antibody, pre-dosing).

Patient	**Pre-treatment**	**Activity L2-L4**	**Half-life 2 time points (3 when available)**	**Absorbed Dose**	**Dose/injected activity**
		(MBq)	(Days)	(cGy)	(mGy/MBq)
1	R	4.8	3.1	158	1.4
13	R	9.2	1.9 (2.3)	207	1.5
14	R	5.3	3.3 (4.3)	184	1.8
15	R	10.1	3.0	159	1.4
2	R + lilotomab	2.3	6.4	67	0.6
3	R + lilotomab	2.5	4.8	89	1.2
9	R + lilotomab	4.4	4.4	116	0.7
12	R + lilotomab	3.4	2.5	127	1.2

TABLE 3. Blood pharmacokinetics

Parameter	**Arm 1 Median (SD) N=3**	**Arm 2 Median (SD) N=4**	**p-value**
Dosage-adjusted AUC_{blood} (h*kBq/mL/(MBq/kg))	661 (31.4)	421 (53.8)	0.001
Volume of distribution (L)	11.7 (1.6)	17.6 (2.8)	0.010
Clearance (mL/h)	148 (28.6)	227 (47.1)	0.029