Biokinetics of Radiolabeled Monoclonal Antibody BC8: Differences in Biodistribution and Dosimetry among Hematologic Malignancies

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ABSTRACT

We reviewed ^{111}In-DOTA-anti-CD45 antibody (BC8) imaging and bone marrow biopsy measurements to ascertain biodistribution and biokinetics of the radiolabeled antibody and to investigate differences based on type of hematologic malignancy. **Methods:** Serial whole-body scintigraphic images (4 time-points) were obtained after infusion of the ^{111}In-DOTA-BC8 (176-406 MBq) in 52 adult patients with hematologic malignancies (lymphoma, multiple myeloma, acute myeloid leukemia and myelodysplastic syndrome). Counts were obtained for the regions of interest for spleen, liver, kidneys, testicles (in males), and two marrow sites (acetabulum and sacrum) and correction for attenuation and background was made. Bone marrow biopsies were obtained 14-24 hours post-infusion and percent of administered activity was determined. Radiation absorbed doses were calculated. **Results:** Initial uptake in liver averaged 32% ± 8.4% (S.D.) of administered activity (52 patients), which cleared monoexponentially with biological half-time of 293 ± 157 hours (33 patients) or did not clear (19 patients). Initial uptake in spleen averaged 22% ± 12% and cleared with a biological half-time 271 ± 185 hours (36 patients) or longer (6 patients). Initial uptake in kidney averaged 2.4% ± 2.0% and cleared with a biological half-time of 243 ± 144 hours (27 patients) or longer (9 patients). Initial uptake in red marrow averaged 23% ± 11% and cleared with half-times of 215 ± 107 hours (43 patients) or longer (5 patients). Whole-body retention half-times averaged 198 ± 75 hours. Splenic uptake was higher in the AML/MDS group when compared to the lymphoma group ($p \leq 0.05$) and to the multiple myeloma group ($p \leq 0.10$). Liver represented the dose-limiting organ. For liver uptake, no significant differences were observed between the three malignancy groups. Average calculated radiation absorbed doses per unit administered activity for a therapy infusions of ^{90}Y-DOTA-BC8 were for red marrow: 470 ± 260 cGy/MBq, liver 1100 ± 330 cGy/MBq, spleen 4120 ± 1950 cGy/MBq, total body 7520 ± 20 cGy/MBq, osteogenic cells 290 ± 200 cGy/MBq, and kidneys 240 ± 200 cGy/MBqR. **Conclusions:** ^{111}In-DOTA-BC8 had long retention time in liver, spleen, kidneys, and red marrow, and the highest absorbed doses were calculated for spleen and liver. Few differences were observed by malignancy type. The exception was greater splenic uptake among leukemia/MDS group when compared to lymphoma and multiple myeloma groups.

INTRODUCTION

Radiolabeled monoclonal antibodies approved for treating patients with B-cell non-Hodgkins lymphomas have shown both safety and efficacy. These radiopharmaceuticals include Ibritumomab Tiuxetan (trade name Zevalin), an ^{90}Y-labeled-anti-CD20 monoclonal antibody (1), and Tositumomab (trade name Bexxar), an ^{131}I-labeled-anti-CD monoclonal antibody (2, 3). Since some lymphomas do not express CD20 antigens, the possibility of targeting other antigens has been investigated. Also, some lymphomas that express CD20 may have been modulated by prior extensive exposure to rituximab, therefore exhibiting decreased response to radioimmunotherapy using anti-CD20 antibodies (4). One such potential monoclonal antibody currently assessed in clinical trials is BC8 a murine anti-CD45 IgG1antibody (that binds to all CD45 isoforms), which is conjugated with the DOTA chelate (also known as tetraxetan), for binding the radiotracers ^{90}Y and [111]In. The CD45 antigen can be found on all hematopoietic cells except mature erythrocytes and platelets.

Both [90]Y -DOTA-BC8 and directly labeled iodine [131]I -BC8 were used in several clinical trials as part of the conditioning regimen before hematopoetic stem cell transplant (HSCT). (5-10) [111]In -DOTA-BC8 was used as a low-activity tracer surrogate for ^{90}Y-DOTA-BC8 to facilitate quantitative imaging for projecting follow-on therapeutic doses.

We report here the biodistribution and dosimetry data obtained from four clinical trials using low tracer levels of ^{111}In-DOTA-BC8 prior to high-dose ^{90}Y-DOTA-BC8 for radioimmunotherapy. We assumed that both indium-labeled and yttrium-labeled conjugates behaved similarly in the same patients. We then looked for differences in radiolabeled antibody biodistribution among patients with different types of hematologic malignancies: lymphoma versus multiple myeloma and acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS). We also looked at two potential differences in biodistribution using two different antibody BC8 concentrations (0.5 mg/kg versus 0.75 mg/kg).

METHODS AND MATERIALS

Patient population

The clinical studies were approved by the Fred Hutchinson Cancer Research Center Institutional Review Board for protocols 2728, 2450, 2468, and 2361 and written informed consent to participate was obtained from each patient.
Fifty-two patients with hematologic malignancies (lymphoma, multiple myeloma, acute myeloid leukemia or myelodysplastic syndrome) from among four separate clinical trials were included in our analysis for biodistribution assessment and dosimetry. From 21 patients with lymphoma included in our analysis there were 18 patients with aggressive forms of lymphoma (8 with diffuse large B-cell lymphoma, 1 with intermediate features between DLBCL and Burkitt

lymphoma, 4 with mantle cell lymphoma, 4 with Hodgkin lymphoma, 1 with peripheral T-cell lymphoma) and **3** patents with indolent type of lymphoma (follicular lymphoma). Radioimmunotherapy was added as part of the conditioning regimen before HSCT to reduce the side effects encountered with classic high dose conditioning therapy. Table 1 shows patient population by clinical protocol. Patient demographics are summarized in Table 2.

Study design

The anti-CD45 MAb BC8 was produced in the Biologics Production Facility (FHCRC, Seattle) in high purity under cGMP conditions, as previously described (11). Patient serum was tested for the presence of human anti-mouse antibody (HAMA) using an enzyme-linked immunosorbent assay (ELISA) prior to infusion of ^{111}In-DOTA-BC8 and ^{90}Y-BC8-DOTA. Patients in two of the clinical trials (2450 multiple myeloma and 2468 AML, MDS) received an antibody concentration (radiolabeled DOTA-BC8) of 0.5 mg/kg. A protein concentration of 0.75 mg/kg was used for lymphoma patients (trials 2728 and 2361) which was based on antibody dose-escalation results from a previous trial of ^{131}I-BC8 in lymphoma which used a protein-escalation schema and sought to optimize the protein dose of BC8 (12).

^{111}In-DOTA-BC8 (5-10 mCi) was administered at the rate of 7.5 mg/hour after premedication with acetaminophen, diphenhydramine, and hydrocortisone. To determine radiolabeled antibody biodistribution kinetics, 4 time-points whole body planar anterior/posterior gamma-camera images were obtained at the end of infusion (hour 0) and on the subsequent 3 days (usually 24, 48, and 72 or 120 hours) using a Philips Brightview XCT camera with medium-energy collimators (Fig 1). Acquired count data were corrected for attenuation and radioactive decay against a known counting standard. Organ volumes (liver, lungs, spleen, and kidney) were calculated from computed tomographic images for correcting the standard organ volumes (13, 14).

To determine the uptake and retention of radiolabeled antibody, regions of interest were drawn over the major imageable source organs, including: two marrow sites (right or left acetabulum and sacrum), spleen, liver, and kidneys using the 180-degree opposing-view quantitative planar technique as described by Eary et al.(15) and shown in fig. 2. Initial uptakes and biological retention half-times were determined from fitting mathematical functions (usually a single exponential) to the time-activity data. The best-fit functions were integrated to determine the time-integrated activity coefficients.

A bone marrow biopsy was obtained at approximately 24 hours after the end of infusion, weighed, and counted against a weighed reference aliquot (counting standard) of the administered ^{111}In activity to calculate the percent administered activity per gram in marrow at the time of biopsy. The bone marrow biopsy results were then used as calibration points to quantitate the radioactivity observed in red marrow.

Images and bone marrow biopsy results obtained after ^{111}In-DOTA-BC8 administration were used to calculate radiation absorbed doses to normal organs and tissues, including marrow. For calculation, methods recommended by the special committee on Medical Internal Radiation Dose (MIRD) of the Society of Nuclear Medicine and Medical Imaging were applied to obtain radiation dose per ^{90}Y nuclear transformation for each organ, including self-organ and cross-organ energy contributions, and ultimately, the absorbed dose to target organs of the body per unit administered activity (cGy/mCi). Reported dosimetry for the marrow, spleen, liver, other

nontarget organs, and the whole body delivered per millicurie of ^{90}Y-DOTA-BC8 (cGy/mCi) is presented in Table 3. Differences in biodistribution based on the type of disease were also assessed. Calculated therapy activity for ^{90}Y-DOTA-BC8 was based on maximizing radiation dose to the critical limiting normal non-target organ (usually liver) starting at 10 Gy for all patients to a level that would not exceed normal organ toxicity escalating the maximum normal organ dose by 2 Gy per group. For example, for a multiple myeloma patient, the estimated dose for the liver (the dose- limiting non-target organ), was 36.1 cGy/mCi. For a desired therapy dose of 26 Gy to the dose-limiting organ the calculated Y-90 activity was 72 mCi.

We then looked at clinical outcomes for patients with high-risk lymphoma (8), AML and MDS (9), and multiple myeloma (10).

RESULTS

Initial uptake of ^{111}In-labeled-BC8
Initial uptake of ^{111}In-DOTA-BC8 in the liver averaged 32% ± 8.4% of administered activity (52 patients). The radioimmunoconjugate cleared from the liver monoexponentially with a biological half-time of 293 ± 157 hours (33 patients) or longer to infinity (19 patients). Initial uptake in the spleen averaged 22% ± 12% and cleared with a biological half-time of 271 ± 185 hours (36 patients) or longer (6 patients). Initial uptake in the kidney was 2.4% ± 2.0% and cleared with a biological half-time of 243 ± 144 hours (27 patients) or longer (9 patients). Initial uptake in the red marrow initial uptake was 23% ± 11% and cleared with a biological half-time of 215 ± 107 hours (43 patients) or longer (5 patients) (Fig. 3). Whole-body biological retention half-times averaged 198 ± 75 hours. The radiolabeled DOTA-BC8 was tenaciously retained in major source organs and the whole body. In some patients, no biological clearance was observed.

Radiation absorbed doses
We calculated radiation absorbed doses per unit administered activity from analysis of the ^{111}In-DOTA-BC8 serial planar imaging data and bone marrow radioactivity measurements: marrow 12.8 ± 7 cGy/mCi, liver 29.7 ± 8.95 cGy/mCi, spleen 111. 3 ± 52.8 cGy/mCi, total body 2.02 ± 0.53 cGy/mCi, osteogenic cells 7.77 ± 5.4 cGy/mCi, and kidneys 6.4 ± 5.5 cGy/mCi (Table 3 and Fig. 4).

Differences among different groups of hematologic diseases - initial uptake
Further analysis of differences in biodistribution based on the patient's disease (lymphoma versus multiple myeloma versus AML/MDS) showed a statistical significantly higher initial splenic uptake in the AML/MDS group when compared to lymphoma group ($p \leq 0.05$) and multiple myeloma group ($p \leq 0.1$). At the $p \leq 0.10$ level of significance, we observed no significant differences between the three groups for initial liver initial uptake and bone marrow uptake (Fig. 5).

Differences among different groups of hematologic diseases-radiation absorbed dose (fig.6)

Liver: At the $p \leq 0.10$ level of significance, we did not observe significant differences in the comparison of multiple myeloma group versus lymphoma group; however, we observed lower liver radiation dose for AML/MDS patients compared to multiple myeloma ($p \leq 0.1$) and to the lymphoma group of patients ($p \leq 0.10$).

Spleen: At the $p \leq 0.05$ level of significance, we observed differences when comparing multiple myeloma versus lymphoma. At the $p \leq 0.10$ level of significance, we observed differences between multiple myeloma versus AML/MDS. However, we did not see significant differences when comparing AML/MDS group versus the lymphoma group ($p \leq 0.01$).

Red Marrow: At the $p \leq 0.05$ level of significance, we did see significant differences when comparing AML/MDS versus lymphoma. We did not observe significant differences in comparing multiple myeloma versus AML/MDS, or multiple myeloma versus lymphoma at the $p \leq 0.10$ level of significance.

Differences based on the protein concentration administered (Figs. 7A, 7B)

We also compared the biodistribution of radiolabeled antibody in patients who received 0.5 mg/kg (multiple myeloma and AML/MDS groups of patients) versus 0.75 mg/kg (lymphoma group of patients). At the $p \leq 0.10$ level of significance, we did not observe differences in the initial uptake of liver or marrow, but we did observe a greater splenic uptake for the group that received 0.5 mg/kg (multiple myeloma plus AML patients) compared to the 0.75 mg/kg (lymphoma group patients).

Regarding the radiation absorbed dose at the $p \leq 0.05$ level of significance, we do have significant differences in comparing protein concentration (0.5 mg/kg versus 0.75 mg/kg), for dose to spleen and dose to marrow (cGy/mCi administered), but we do not have significant differences at the $p \leq 0.10$ level for dose to the liver. Therefore, protein concentration did not influence the liver dose.

DISCUSSION

Preclinical studies on the biodistribution of radiolabeled anti-CD45 were published previously (16). For example, the biodistribution of ^{90}Y-labeled anti-CD45 antibody was demonstrated in a nonhuman primate model (macaques) a model that also predicted ^{131}I -labeled anti-CD45 antibody biodistribution in humans (17). The results showed that the ^{90}Y-labeled anti-CD45 antibody BC8 can deliver relatively selective radiation to hematopoietic tissues, with similar ratios of radiation delivered to target versus nontarget organs, as compared with the ^{131}I-immunoconjugate in the same animal model. Another study performed with mice employed 30F11, an antibody with a slightly different structure (rat anti-CD45 antibody IgG2b) (18).

Targeting with 30F11 also showed a favorable biodistribution with effectively targeted bone, marrow, and spleen, with minor uptake in nonhematologic organs. In humans, prior studies with anti-CD45 antibody were performed, either with a ^{90}Y-conjugated rat IgG2a monoclonal Ab (YAML568) or with a murine anti-CD45 IgG1antibody (BC8).

Given that yttrium-90 is a pure beta-emitting radioisotope, in our clinical studies, a different radiotracer (^{111}In bound to DOTA-BC8) has been used as a surrogate to determine ^{90}Y-antibody biodistributions necessary for calculating internal radiation doses as previously performed with other radiolabeled antibodies (19, 20). After the dosimetry step was performed using ^{111}In-DOTA-BC8, the patients included in our analysis received a treatment dose calculated by escalating the maximum normal organ dose by 2 Gy per group. The maximum dose received by the dose-limited normal organ was set at 32 Gy for the multiple myeloma group (14 patients) and lymphoma group (19 patients), and 28 Gy for the AML/MDS group of patients (15 patients) (21). No dose-limited toxicities were observed. One patient from multiple myeloma and one from AML/MDS group included in our analysis did not receive treatment because of developing HAMA antibodies after the trace (low-level) labeled imaging dose of In-111-BC8. One subject from lymphoma group had grade 4 hypotension during and after infusion.

Dosimetry showed that the radiolabeled antibody ([111]In -DOTA-BC8) was retained in the patient with a very long or infinitely long biological retention half-time (corrected for physical decay of ^{111}In) in liver, spleen, red marrow and kidneys resulting in highest doses calculated for spleen and liver. The long biological retention half-times (approaching 10 days and longer) resulted in a more efficient delivery of radiation to the patient, because decay occurred *in vivo* rather than after excretion. Long biological retentions were common to all patients from the four studies included in this analysis. The reason for this behavior is unknown however it is probably due to the fact that the ^{111}In remains conjugated to the antibody and is not metabolized or catabolized. This was not seen in the animal model when AC8 or 30F11 were used. Also, this result was not seen in clinical studies when biodistribution of radiolabeled anti-CD20 antibody (^{111}In-Ibritumomab) was determined (20, 22, 23) or when radiolabeled andi-CD45 antibody [131]I -BC8 or YAML568 dosimetric calculations where made (24, 25). We were able to achieve desired doses to the non-target limiting organ (liver in all the patients) 32 Gy for multiple myeloma patients and 28 Gy for AML/MDS and lymphoma patients without dose-limiting toxicity seen. Also, our results showed a higher calculated radiation dose to the liver compared to the bone marrow which was not seen on preclinical studies or clinical studies which used [111]I-BC8 or YAML568. For instance, when ^{90}Y-AC8 antibody was used in preclinical studies, delivered estimated radiation absorbed doses was five to seven times higher to spleen and two to four times higher to marrow than to lungs or liver lungs (17). However, the murine anti-human antibody used (BC8) has a structure that is different from the murine anti- CD45 antibody called 30F11 and the nonhuman primate anti-CD45 antibody AC8. This might be explained by the difference in antibody structure or different species (18). Another potential explanation is that the cold antibody was not used prior to administration of the labeled one which is known to cause

changes in the biodistribution. Addition of supplemental unlabeled antibodies was shown to be necessary to achieve optimal biodistribution when another anti-CD45 monoclonal antibody with a different structure than BC8, called YAML568 was used (26). However, the unlabeled (cold) antibodies were not given in these four clinical trials since in human, prior biodistribution studies using ^{131}I-BC8 without preloading dose of unlabeled antibodies showed a favorable distribution with highest dose to the bone marrow and spleen followed by the normal organs (liver was the highest dose limited normal organ). (24, 25)

Since the patients with multiple myeloma and AML/MDS received 0.5 mg/kg amount of protein and lymphoma patients received 0.75 mg/kg we also analyzed differences in biodistribution based on the protein concentration. This comparison is limited because there is no change in the protein concentration within the one group of patients. Comparison of the initial uptake and radiation absorbed dose for the liver between these two groups (0.5 mg/kg vs 0.75 mg/kg) did not show a statistically significant difference for liver initial uptake or (average) liver radiation absorbed dose. This is an important information since liver was the dose-limiting organ in all 3 group of patients and therefore the radiation absorbed dose to the liver was used to calculate the amount of treatment dose.

Initial uptake in the spleen was higher for MM and AML/MDS group (which received 0.5 mg/kg) compared to lymphoma group (lymphoma group with 0.75mg/kg). It is possible that although the amount of protein in lymphoma patients increased splenic uptake in patients with splenic involvement since higher protein amount improved tumor dosimetry (12) but not to the level observed in AML patients, likely because of the increased cellularity in leukemia. Differences in biodistribution based on different groups of disease was also performed and there was higher initial uptake for the spleen in leukemia patients when compared to lymphoma and multiple myeloma patients probably due to also high percentage of patients with enlarged spleen due to disease infiltration with possibly because of the number of target sites is greater in spleen of leukemia patients. Even though the amount of BC8 protein was greater in the lymphoma patients compared to leukemia patients, the over-riding factor appears to be the greater number of binding sites in the leukemia patient spleen. Thus, the effect of higher number of target sites in leukemia patients in the spleen is stronger than merely the mg of protein administered. However, when the radiation absorbed dose was calculated, a higher splenic radiation absorbed dose was seen in multiple myeloma patients compared to AML/MDS and lymphoma patients likely because radiation absorbed dose is inversely proportional to the mass.
Radiation absorbed dose in the liver was higher for multiple myeloma patients compared to AML/MDS patients. Similarly, for bone marrow there was a higher radiation absorbed dose in AML/MDS patients compared to lymphoma patients.
In patients treated with ^{111}In-DOTA-BC8, our group have previously published data regarding the influence of splenic size on the bone marrow dose received in patients treated with ^{111}In-DOTA-BC8. Increasing spleen size reduced the bone marrow dose, but measurement uncertainties associated with biopsy specimen marrow content may have reduced the correlation coefficient (r = 0.25). The spleen acts as a natural sink for radiolabeled antibody which reduces uptake and retention of radiolabeled antibody in red marrow. (27) Other authors also discussed the possible role of spleen in antibodies biodistribution (28).

CONCLUSIONS

Compared to other radiolabeled anti-CD45 antibodies, ^{111}In-DOTA-BC8 was retained longer in liver, spleen, red marrow and kidneys, with the highest doses calculated for spleen and liver. These long biological half-times (approaching 10 days and longer) result in a more efficient delivery of radiation to the patient because decay takes place in vivo rather than after excretion. This pattern of biodistribution was not seen on preclinical or clinical studies that targeted CD45 (using other radiolabeled antibodies) and might be partially due to DOTA chelator which is present in the structure of this radiolabeled antibody.

Liver represented the critical non-target organ for all patient cases with highest calculated radiation absorbed dose after spleen and was the designated limiting normal organ for treatment planning for determining administered activity. This might have been related to the DOTA chelator presence and the fact that in these studies a cold antibody pretreatment was not given. Regarding the protein concentration (0.5 mg/kg versus 0.75 mg/kg) we did not observe significant differences for radiation absorbed dose to the liver (at the $p \leq 0.10$). Therefore, protein concentration did not influence the liver dose.

Few differences were observed in ^{111}In-DOTA-BC8 biodistribution by malignancy type. The exception was greater initial splenic uptake among the AML/MDS group when compared to lymphoma and multiple myeloma groups.

Oncoresponse; has equity ownership in AnaptysBio, Blaze Bioscience, EpiThany, Inipharm, Oncoresponse, Mavupharma; and was formerly employed by Mavupharma.

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No other potential conflicts of interest relevant to this article exist.

Key Points

Question:

Can the treatment with preformed antibodies using Y90-CD45 radioimmunotherapy deliver safely the desired radiation doses without significant side effects?

Pertinent Findings: After the dosimetry step was performed using [111]In- DOTA-BC8, the patients included in our analysis received a treatment dose calculated by escalating the maximum normal organ dose by 2 Gy per group. The maximum dose received by the dose-limited normal organ was set at 32 Gy for the multiple myeloma group (14 patients) and lymphoma group (19 patients), and 28 Gy for the AML/MDS group of patients (15 patients) (21). No dose-limited toxicities were observed.

The long biological half-times observed using [111]In- DOTA-BC8 for dosimetry estimates (approaching 10 days and longer) result in a more efficient delivery of radiation to the patient because decay takes place in vivo rather than after excretion.

Implications for Patient Care:

Radioimmunotherapy using preformed antibodies (like the one used in these 4 clinical trials that is a preformed antibody against CD45 antigen) have the potential to treat patients that failed other treatments for hematologic diseases. It has the advantage of using passive immunotherapy (preformed antibodies) without the risk of activating the immune side effects which is seen with some of the active immunotherapies.

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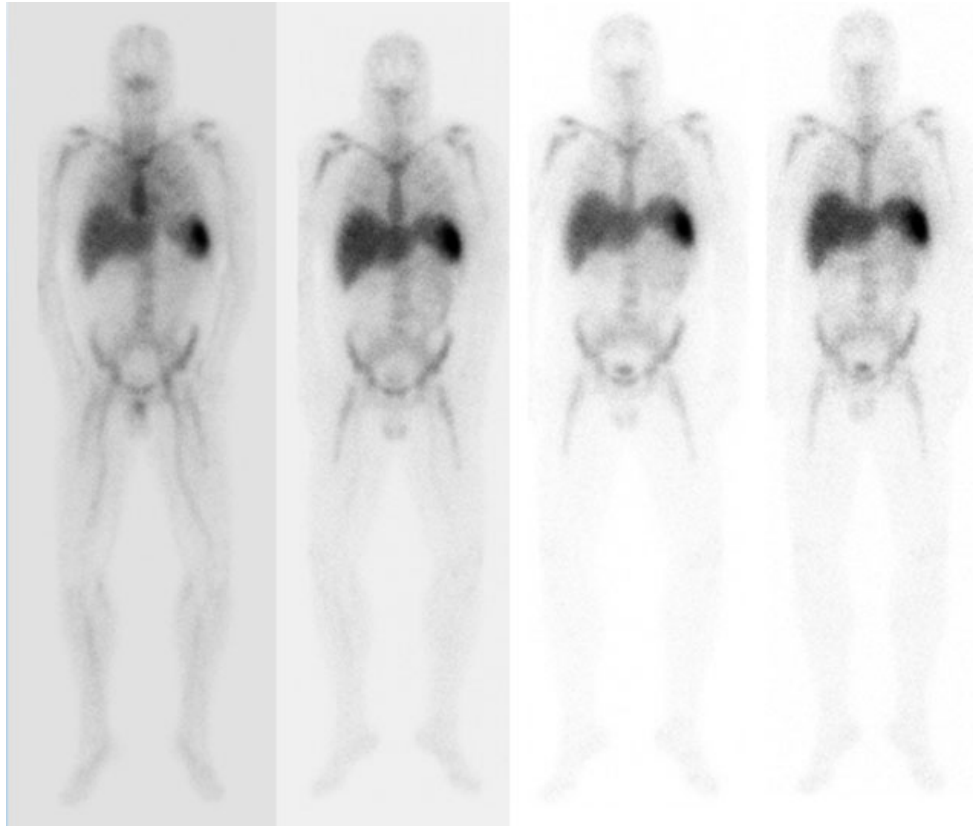
Figure 1. Whole body anterior view planar images obtained in a patient with B-cell non-Hodgkin lymphoma after injection of a low activity of ^{111}In - DOTA-BC8 for the step of dosimetric calculations before treatment with Y-90-DOTA- BC8.

Figure 2. Imaging step necessary for dose calculation. Counts obtained from the regions of interest (ROI) over the liver, spleen and kidneys drawn on the anterior (a and d) and posterior (b and c) planar In111- DOTA- BC8 images were obtained. This information was used for dosimetry estimations together with the counts per gram tissue obtained from the measurement of bone marrow biopsy specimen.
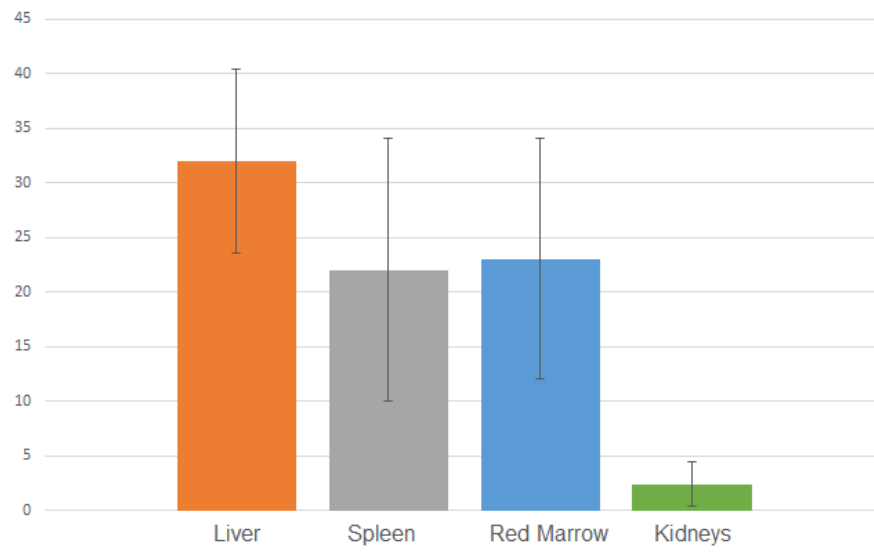
Figure 3. Chart illustrating the initial post-infusion uptake in the main organs of biodistribution.
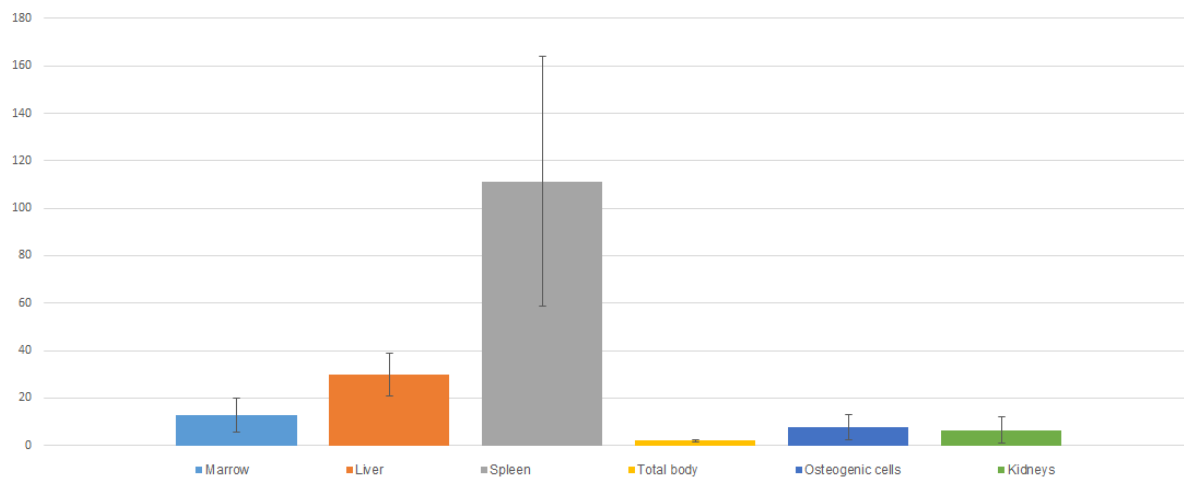
Figure 4. Absorbed doses per unit administered activity (cumulative data for all groups of patients). Liver was the dose-limiting normal organ in all the patients; the maximum dose received for dose-limited normal organ was 32 Gy for the multiple myeloma and lymphoma and 28 Gy for the AML/MDS group of patients. No dose-limited toxicities were observed.
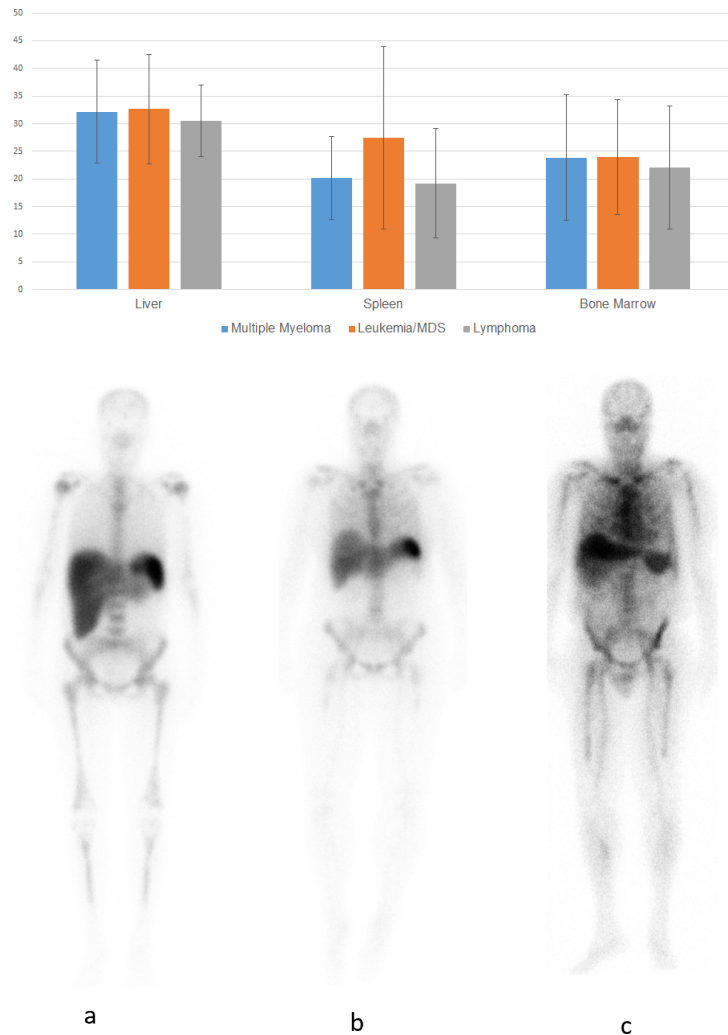
Figure 5. A. Percent of initial uptake for different groups of patient population. Initial splenic uptake was higher in AML/MDS group when compared to lymphoma group ($p \leq 0.05$) and multiple myeloma group ($p \leq 0.1$). No significant differences were observed between the three groups for liver initial uptake and bone marrow uptake ($p \leq 0.10$).
B. Anterior view whole- body images obtained immediate after In-111- DOTA-BC8 infusion (time 0-initial uptake) in 3 different patients one with acute myeloid leukemia (a), one with multiple myeloma (b), and one with diffuse large B cell lymphoma (c). Although for the liver there were no significant differences regarding initial uptake, we did found a lower radiation dose (at $p \leq 0.1$) for the group of acute myeloid leukemia/myelodysplastic syndrome patients compared to the other 2 groups (probably because radiation absorbed dose is inversely proportional to the mass).
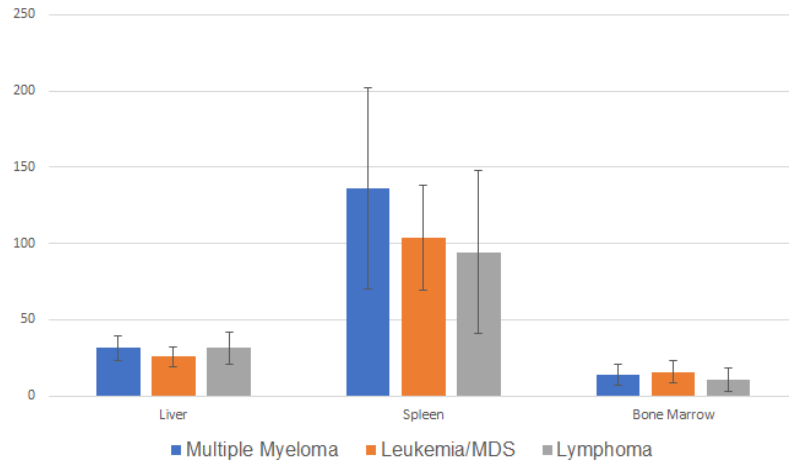
Figure 6. *Differences in radiation absorbed dose among different groups of hematologic diseases.* For the spleen, we observed higher radiation absorbed dose for multiple myeloma when compared to lymphoma ($p \leq 0.05$) and for the bone marrow there was a higher radiation absorbed dose for the AML/MDS group compared to lymphoma ($p \leq 0.05$).
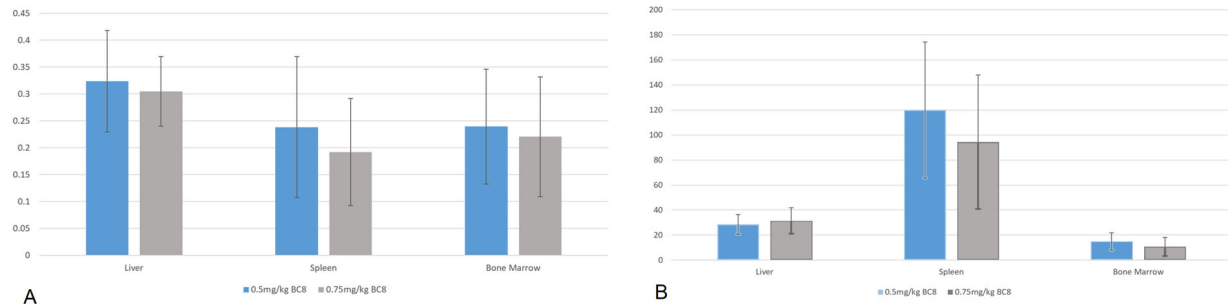
Figure 7. *Differences regarding initial uptake and radiation absorbed dose based on the protein concentration* (0.5 mg/kg vs. 0.75 mg/kg). **A**. Statistical significance was not reached (p was higher than 0.05) for the differences in the initial uptake in the liver, spleen or bone marrow; **B**. Regarding radiation absorbed dose, no statistical significant differences based on protein concentration was obtained for the liver radiation absorbed dose (which was the critical limiting non-target organ for all the patients).

Table 1. Clinical Protocol and Characteristics.

Protocol	Type	Patient Population	Treatment Combinations
2728	Phase I/II	B-NHL, T-NHL, HL	^{90}Y-DOTA-BC8, BEAM chemotherapy*, Autologous peripheral blood stem cell transplantation
2450	Phase I	Multiple myeloma	^{90}Y-DOTA-BC8, Fludarabine, TBI**, HLA-Matched Blood Stem Cell Transplant
2468	Phase I	AML, MDS	^{90}Y-DOTA-BC8, Fludarabine, TBI (2 Gy), Allogeneic Stem Cell Transplantation
2361	Phase I	B-NHL, T-NHL, or HL	^{90}Y-DOTA-BC8, Autologous peripheral blood stem cell transplantation

*BEAM chemotherapy includes: Carmustine, Etoposide, Cytarabine, and Melphalan
**TBI-total body irradiation
AML and MDS refer to acute myeloid leukemia and myelodysplastic syndrome

Table 2. Patient Demographic Data.

Demographics	Total
Number of patients	52
Age, median (range)	55 y (26- 76 y)
Gender	
Female	24
Male	28
^{111}In-DOTA-BC8 dose (MBq), median (range)	329 (176-406)
Antibody concentration	
0.5 mg/kg	15 patients, multiple myeloma 16 patients, AML/MDS patients
0.75 mg/kg	21 lymphoma patients
Patients with multiple myeloma	15
Patients with AML/MDS	13 AML/3 MDS
Lymphoma	21

Table 3. Calculated absorbed doses per unit administered activity for ^{90}Y-DOTA-BC8 in selected target organs.

Target organ	Mean absorbed dose (cGy/mCi)	Range (cGy/mCi)
Bone marrow	12.8 ± 7.35	0.276 - 27.6
Spleen	111.39 ± 52.8	0.987 - 327
Liver	29.67± 8.95	13.9 - 63
Lung	0.448 ± 0.46	0 -1.3
Kidneys	6.4 ± 5.5	0 - 22.5
Osteogenic cells	7.77 ± 5.4	0 - 22
Stomach	0.55 ± 0.349	0 - 1.3
Small intestine	0.448 ± 0.349	0 - 1.3
Large intestine	0.448 ± 0.349	0 - 1.3
Bladder wall	0.448 ± 0.349	0 - 1.3
Total body	2.02 ± 0.53	1.05 - 3.74