Dosimetric Approaches for Radioimmunotherapy of Non-Hodgkin Lymphoma in Myeloablative Setting

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Abstract

Radioimmunotherapy (RIT) is a safe and active treatment available for non-Hodgkin lymphomas (NHLs). In particular, two monoclonal antibodies raised against CD20, i.e. Zevalin® (^{90}Y-ibritumomab-tiuxetan) and Bexxar® (^{131}I-tositumomab) received FDA approval for the treatment of relapsing/refractory indolent or transformed NHLs. RIT is likely the most effective and least toxic anticancer agent in NHLs. However, its use in the clinical setting is still debated and, in case of relapse after optimized rituximab-containing regimens, the efficacy of RIT at standard dosage is suboptimal. Thus, clinical trials were based on the hypothesis that the inclusion of RIT in myeloablative conditioning would allow to obtain improved efficacy and toxicity profiles when compared to myeloablative total-body irradiation and/or high-dose chemotherapy regimens. Standard-activity RIT has a safe toxicity profile, and the utility of pre-therapeutic dosimetry in this setting can be disputed. In contrast, dose-escalation clinical protocols require the assessment of radiopharmaceutical biodistribution and dosimetry before the therapeutic injection, as dose constrains for critical organs may be exceeded when RIT is administered at high activities .

The aim of the present study was to review and discuss the internal dosimetry protocols that were adopted for non-standard RIT administration in the myeloablative setting before hematopoietic stem cell transplantation in patients with NHLs.

1) Introduction

Mature lymphoid neoplasms comprise a number of malignant tumors of the lymphoid tissue that can be divided into three main categories: B-cell neoplasms, T-cell and NK-cell neoplasms, and Hodgkin's lymphomas (HL). Lymphomas other than HL are also commonly referred to as non-Hodgkin lymphomas (NHL). Overall, mature B-cell neoplasms account for >90% of all lymphoid neoplasms. Follicular lymphoma (FL) and Diffuse large B-cell lymphoma (DLBCL) are the most common types of lymphoma, representing about 60% of all NHLs[1].

HL can be cured in most cases with a combination of chemotherapy and external beam radiotherapy (EBRT)[2]. In contrast, NHLs have heterogeneous clinical courses and prognosis, and their clinical management ranges from watchful waiting and/or localized EBRT to myeloablative, high dose chemotherapy (HD-CT) followed by autologous (auto-SCT, indicated also as ASCT) or allogenic (allo-SCT) stem cell transplantation [3]. Standard chemio-immunotherapies, although very active, are accompanied by adverse side effects in many cases[4].

Among the treatment strategies available for NHLs there is the so called Radioimmunotherapy (RIT). In particular, two CD20-targeting radiolabelled full IgG antibodies, namely Zevalin® (^{90}Y-ibritumomab-tiuxetan) and Bexxar® (^{131}I-tositumomab) received FDA approval at the beginning of this century for the treatment of relapsing/refractory indolent or transformed NHLs. Zevalin® was also approved in Europe with the same clinical indications[5,6,7]. Ten years after FDA approval, in 2014, Bexxar® was withdrawn from the market for commercial reasons. In some countries, other CD-20 targeting RIT agents, such as ^{131}I-rituximab, were tested clinically[8,9,10].

RIT is arguably the most effective and least toxic anticancer agent in NHLs. In patients with FL, 87% and 97% overall response rates (ORR), including 56% and 75% complete responses (CR), were obtained after a single frontline infusion of Zevalin® and Bexxar®, respectively[11,12,13]. However, in case of relapse after optimized rituximab-including treatments, the efficacy of RIT was reduced[14,15].

RIT was tested in diverse clinical settings including, among the others, frontline (FL)[11,12], consolidation of advanced-stage FL[16,17] or DLBCL[18], salvage treatment for relapsing DLBCL[19] or, as part of conditioning regimens prior to SCT[20]. In the pre-transplant setting, RIT was given at standard[21,22,23,24,25] or increased activities[26,27,28,29,30,31,32,33,34,35,36,37], with or without a combination of myeloablative chemo/radiotherapy. These clinical trials were based on the hypothesis that the inclusion of RIT in myeloablative conditioning, either at standard or at high injected activities, would show improved efficacy and toxicity profiles compared to classical myeloablative total-body irradiation (TBI) and/or high-dose chemotherapy regimens[38,39,40].

Standard-activity RIT has a generally safe toxicity profile and the utility of pre-therapeutic dosimetry in this setting can be disputed. In contrast, dose-escalation clinical protocols require the assessment of radiopharmaceutical biodistribution and dosimetry before the therapeutic injection, as dose constrains may be exceeded for critical organs when RIT is administered at high activities[41].

The aim of the present study was to review and discuss the internal dosimetry protocols that were adopted for non-standard RIT administration in the myeloablative setting before hematopoietic SCT in patients with NHLs.

2) High-dose RIT in stem cell transplant conditioning: clinical protocols and results

Following the results of the PARMA study, bone marrow ablation followed by auto-SCT is the established standard-of-care for chemosensitive relapses of DLBCL[42]. For patients with refractory disease, or for patients who relapse after auto-SCT, allo-SCT can be considered as a curative option. In FL, auto-SCT is usually offered to patients relapsing after two or three previous lines of chemo - immunotherapies. The correct timing and indication to the use of allo-SCT in FL is controversial, although allo-SCT remains the only curative option for this disease[43]. The best conditioning regimen for either auto- or allo-SCT has not been established yet, and the choice might also be subject to local availability of chemotherapeutics[44,45,46]. For the purpose of the present work, only studies including high-activity (or high-dose) RIT (HD-RIT) in SCT conditioning were reviewed. A summary of these studies is given in Table 1.

Myeloablative radioimmunotherapy with ^{131}I-Bexxar® and ^{131}I-Rituximab.

Press and co-workers pioneered the use of HD-RIT with anti-CD20 antibodies as conditioning regimen before auto-SCT. In their phase I study, patients with various relapsed B cell NHLs showing favourable Bexxar® biodistribution, defined as a dose to the tumor higher than that of the liver, lung and kidneys, were treated with dose escalated Bexxar® (at that time called ^{131}I-anti-B1). The protocol was designed to deliver from 16.75 up to 30.75 Gy to the dose-limiting organs, respectively[47]. Auto-SCT was performed when radiation exposure was <0.02 mSv/h at 1 meter distance. Hematological toxicity was managed by stem cell rescue, and the study established that the administration of HD-RIT delivering more than 27 Gy to the dose-limiting organ, usually the lungs, was the toxicity limit. The ORR of 95%, including 84% CR, together with a median duration of response >11 months were considered very encouraging and prompted further

phase II studies designed to deliver between 25 and 31 Gy to the organ receiving the highest dose, which was most often the lungs or, occasionally, the kidneys. Projected 2-year overall survival (OS) and progression-free survival (PFS) were 93% and 62% respectively, with better PFS estimates obtained in patients receiving more than 20 Gy to the dose-limiting organ[48]. Further follow up analysis of the 29 treated patients showed 4-years projected OS and PFS of 68% and 42%, respectively. Early death occurred in two patients. Two patients developed second solid neoplasms; none developed myelodysplasia or acute leukemia. Late toxicities included chronic thrombocytopenia (n=1), hepatitis (n=1), chronic renal (n=1), cardiac (n=1) and pulmonary (n=2) insufficiency. Elevation of TSH levels was observed in 60% of patients[49]. The strategy of delivering 25-27 Gy to the critical organ with HD-RIT Bexxar® followed by auto-SCT proved to be safe in patients older than 60 years (median age 64 years, range: 60-76 years) as well, with no treatment-related mortality and only two grade 4 non-haematological toxicities in 24 treated patients. Survival outcomes in this fragile patient population were also satisfactory, with 3-year estimated OS and PFS of 59% and 51%, respectively[27].

The same group in Seattle, designed a trial to establish the maximum tolerated absorbed dose of Bexxar® to be safely combined with high-dose etoposide (60 mg/kg) and cyclophosphamide (100 mg/kg) followed by auto-SCT for the treatment of patient with relapsed CD20-positive NHLs. Fifty-two patients (n=38 FL, n=8 de novo or transformed DLBCL, n=6 mantle cell lymphomas (MCL)) were divided in four groups, receiving 20, 23, 25 and 27 Gy to the dose-limiting organ, respectively, in addition to high-dose chemotherapy. The highest dose level of 27 Gy proved to be excessively toxic, with three life-threatening events occurring in 8 patients including one death. Therefore the maximum tolerated dose delivered by Bexxar® in this setting was considered to be 25 Gy to the dose-limiting organ. Two-year projected OS and PFS were 83% and 68%, respectively, which resulted significantly advantageous over historical controls treated with TBI-including conditioning[50]. The 10-year follow-up results of this conditioning regimen in 101 treated patients showed 62%, 64% and 43% PFS in n=29 aggressive NHLs, n=45 indolent NHLs, and n=33 MCL, respectively, with 2.8% non-relapse mortality at 100 days[36].

HD-RIT with Bexxar® delivering up to 27 Gy to the critical organ was tested in combination with escalating dosages of fludarabine prior to auto-STC in 36 patients older than 60 years (median: 65 years, range: 60-76) with relapsing/refractory B cell NHLs, including n=23 MCL and n=8 de novo or transformed DLBCL. No treatment-related deaths were observed, and grade 4 non-haematological toxicities were observed in 2 patients only. Three-year estimated OS and PFS were 54% and 53%, respectively[28].

Additionally, the anti-CD20 antibody Rituximab was radiolabeled with ^{131}I and used in some countries[8,9,10]. ^{131}I-Rituximab was tested with various combinations of high-dose chemotherapy as auto-SCT conditioning. Results of the first two original reports, obtained in a small number of patients, were encouraging in terms of survival outcomes, but showed significant toxicities[33,35].

Myeloablative radioimmunotherapy with ^{90}Y-Zevalin®.

The inclusion of HD-RIT with Zevalin® in auto-SCT conditioning was firstly adopted by Nademanee et al. in patients with poor-risk or recurrent CD20-positive B-cell NHL, including FL, DLBCL and MCL[29]. Patients were ruled out if the tumor dose was inferior to that of any other organ excluding spleen and bone marrow, unless patients were in complete remission (CR) at the time of treatment. The activity to be administered was designed to deliver a maximum of 10 Gy to any organ excluding the spleen and the bone marrow, with a pre-determined maximum limit of 3.7 GBq. A median activity of 2.7 GBq Zevalin® was injected at day -14, followed by high-dose etoposide and cyclophosphamide. Autologous stem cells were reinfused at day +1, unless the bone marrow absorbed dose was determined to be >50 mGy. Of the 41 patients enrolled, 31 underwent the full therapeutic procedure. The treatment resulted in satisfactory 2-year survival outcomes, and the toxicity profiles observed, with 3% transplantation-related mortality, were similar to historical controls using TBI in addition to high-dose etoposide and cyclophosphamide MCL[29].

A different strategy was pursued by Ferrucci et al.[31] at IEO in Milan. The Authors demonstrated feasibility and safety of auto-SCT conditioning based on HD-RIT with Zevalin® alone in NHL patients unfit for high-dose chemotherapy because of age or co-morbidities. Thirteen patients (median age: 68 years) with refractory/transformed B-cell NHL (n=8 DLBCL, n=3 MCL, n=1 FL and n=1 marginal lymphoma) were divided in three groups receiving 30 MBq/kg, 45 MBq/kg or 56 MBq/kg, respectively. Autologous stem cells were reinfused at day +13. Based on dosimetry, two patients were assigned to activity levels lower than initially planned without personalized dosimetric data. Similarly, bone marrow engraftment was delayed in one patient treated with the highest activity schedule. A trend towards higher haematological toxicity was found in patients with more than three previous lines of chemotherapy and reduced bone marrow reserve. One heavily pre-treated patient developed a myelodysplastic syndrome two years after treatment while being in continuous CR. Acute non-haematological toxicities were manageable in all cases.

Devizzi et al.[32] enrolled 30 patients (median age: 62 years) with various CD20-positive NHLs (including, among the others, n=10 DLBCL, n=12 FL and n=3 MCL) who underwent induction chemotherapy and stem cell harvesting, followed by a single consolidation treatment with HD-RIT Zevalin® before auto-SCT. Most patients (n=19) were ineligible for conventional autografting. Zevalin® was given at 30 MBq/kg or 45 MBq/kg in n=17 and n=13 patients, respectively, followed by two tandem infusions of autologous stem cells, on day +7 and + 14, respectively. Neutrophil and platelets counts fully recovered 7 and 14 days after auto-SCT, respectively. No non-haematological toxicities greater than grade 3 were observed. In the overall population, 30-month projected OS and event-free survival were 87% and 69%, respectively[32].

Winter et al. showed the feasibility and the safety of combining dose-escalated Zevalin® with high-dose BEAM (carmustine, etoposide, cytarabine and melphalan) conditioning before auto-SCT in 44 patients with relapsing/refractory CD20-positive NHLs (n=33 de novo or transformed DLBCL, n=4 FL, n=7 MCL), including 30% of patients who had achieved less than a partial remission after their most recent salvage therapy, and would have been considered non-eligible for auto-SCT[30]. Administered therapeutic activities of Zevalin® were targeted to deliver increasing absorbed doses (range 1-17 Gy) to the critical organs. There were two dose-limiting non-haematological toxicities including one patient death of septic pneumonia at the 17 Gy dose level, therefore the maximum tolerated absorbed dose to the critical organ (liver) was set at 15 Gy. Additional grade 4 toxicities included infections, obstructive uropathy, pulmonary embolism, and veno-occlusive disease. Survival outcome profiles compared favourably to historical data of similar cohorts[30].

More recently, Wahl and colleagues[37] proposed a hybrid approach (SPECT/CT and planar images) for dosimetry-based dose-escalated RIT with Zevalin® followed by auto-SCT in 18 patients with chemo sensitive relapses of CD20-positive NHLs. Patients were divided into four groups, targeted to receive 18, 24, 28 and 30.5 Gy to the liver, respectively. Stem cells were infused when the predicted bone marrow dose rate was < 10 mGy/h. Haematological toxicity was mild and reversible. No liver toxicity was observed. One patient died of pneumonia 27 days after auto-SCT. The study showed that a dosimetry-based protocol could safely deliver Zevalin® activities up to five times higher than the maximum prescribed standard. Unfortunately, the study was terminated prematurely for commercial reasons and only one patient could be enrolled at the highest dose level of 30.5 Gy and the maximum tolerated dose could not be established. Response rates were encouraging (88% ORR, with 13 CR and 3 PR), although of short duration, and no correlation was shown with the Zevalin® administered activity[37].

HD-RIT Zevalin® was also tested as part of reduced intensity conditioning (RIC) before allo-SCT in 20 patients with aggressive CD20-positiveNHLs with a median of four previous therapy courses including auto-SCT[34]. Patients were assigned receive either 22 MBq/kg (n=10) or 30 MBq/kg (n=10) Zevalin® at day -14, followed by fludarabine, melphalan and alemtuzumab before allo-SCT at day 0. Non-relapse mortality was 0% at day 100, and 30% at 3 years. The authors concluded that these features do not represent an increased toxicity compared to RIC without RIT in patients with these characteristics[34].

3) Dosimetry protocols

In the myeloablative RIT setting, several dosimetric protocols were adopted, depending both on the radiopharmaceutical characteristics and on the specific authors' approach. All of these protocols refer to the widely accepted MIRD approach [51,52]. Most protocols are based on the whole body planar images (two-

dimensional, 2D) acquired at different time points post tracer injection (p.i.) [51,52]. The MIRD 16 pamphlet suggests to improve the accuracy of activity measurements by correcting 2D-images for several factors (geometric mean of anterior and posterior view, background, attenuation, scattering etc.) however, no standard protocol including such corrections has been defined[51,53]. Moreover, the 2D approach presents several pitfalls, such as overlapping of structures, partial volume effect and uncertainties contouring the region of interest[53]. For these reasons, several studies promote hybrid or full three-dimensional (3D) protocols based on SPECT/CT[37,53,54,55].

In myeloablative RIT, bone marrow suppression represents the wanted treatment effect. Consequently, dosimetry evaluations focused mostly on secondary critical organs. Nevertheless, bone marrow dosimetry can be used to identify the adequate time for SCT ensuring cell engraftment[47,29,37]. Appendix A summarizes the different bone marrow dosimetry approaches reported in literature. Owing to the large interpatient variability of normal tissues dosimetry, in myeloablative RIT it is not possible to identify a safe maximal activity to be administered or a single dose-limiting organ for all patients. Therefore, an individual dosimetry approach is suggested[31,32,37,56,57,58,30]. In the following, the main dosimetry protocols adopted with either ^{90}Y-Zevalin® or ^{131}I-labelled anti-CD20 antibodies Bexxar® and Rituximab are detailed.
A summary of the previsional dosimety methods used by different authors for NHL RIT is reported in Table 2.

Studies with ^{131}I-labelled antibodies.

To perform previsional dosimetry studies of Bexxar® and/or ^{131}I-rituximab, a tracer amount of the same therapeutic radiopharmaceutical is used, owing to the gamma emissions of ^{131}I. Given the highly penetrating ^{131}I gamma radiation which is easily detectable by thyroid probe or gamma scintigraphy, whole body radiation dose has been suggested to replace red marrow constraints. For previsional dosimetry, tracing activities of **^{131}I-**Bexxar® or ^{131}I-rituximab are measured longitudinally after pre-loading with the cold antibodies tositumomab and rituximab, respectively. In their early studies with Bexxar®, Wahl and co-workers proposed a whole-body dosimetry approach based on sequential thyroid NaI probe measurements, which was later replaced by sequential gamma-camera imaging[59]. The dosimetric protocol based on the thyroid probe counting consisted of six or more time-points measurements over 5-8 days, while the imaging-based protocol consisted of whole-body planar scans acquired at three time points over 6-7 days. The conjugate-view method was used to calculate the total body count at each time point, corrected for the background contribution. No information about other corrections was reported. The main assumption of the whole body approach is that the radiopharmaceutical remained uniformly distributed throughout the patient's body after the injection. For standard RIT treatments, the activity to be

administered was targeted at delivering a total-body dose of 0.75 or 0.65 Gy in patients with platelet count ≥ or ≤ 150000/ml, respectively[59,60].

In the dose escalation study described by Press and co-workers, the dosimetric protocol consisted of sequential whole body images acquired at 0, 48, 96 and 120 h post injection; no information were reported about the corrections applied[47]. In other studies of the same group, quantitative ^{131}I imaging was performed daily for seven days and data were corrected for whole body thickness, attenuation, radioactive decay, and electronic drift[61,62].

The same approach was adopted with minor variations in all later HD-RIT studies performed by the same group (Table 2) Image-based dosimetry was used to determine the administered Bexxar® activity to deliver absorbed doses in the range of 25-31 Gy to the organ receiving the greatest dose (lungs, liver or kidneys), depending on the high-dose chemotherapy conditioning regimen used in combination with HD-RIT. SCT was performed when whole-body radiation exposure was <0.02 mSv/h at 1 meter distance[48,50,27,28,36].

Dosimetry of standard-activity ^{131}I-rituximab consisted of sequential whole-body scans acquired 1h, 4 and 7 days p.i. to determine the effective half-life of the radiopharmaceutical. Some patients were enrolled in more extended hybrid dosimetry protocols including the acquisition of a single SPECT/CT scan at 5-7 p.i., or 3D dosimetry after therapy based on SPECT/CT acquisitions. The whole-body clearance rate and the lean body weight were used to determine the injected activity to deliver 0.75 Gy to the whole-body, which ensured that red marrow dose never exceeded 2 Gy [55].

Dose calculations were based on the two following assumptions: a) the activity concentration (activity/kg) based on the lean body weight is the same as the activity concentration in red marrow and b) the whole-body and red marrow residence times are equal. The Bolch et al.[63] approach was used to compute energy-dependent absorbed fractions for red marrow since the approach proposed in MIRDOSE3 underestimates the absorbed fractions for low electron energies. Therefore, the red marrow self-dose included ^{131}I contributions from both the non-penetrating absorbed fraction in the spine and that from photons, taking into account the expected cellularity fraction in the spine.

Hohloch and co-workers treated nine patients with myeloablative BEAM chemotherapy plus auto-SCT, followed by dose-escalated HD-RIT with ^{131}I-rituximab rescued by a second auto-SCT[33]. After the first auto-SCT, patient-specific dosimetry was performed to individualize the injected activities in order to keep kidney and lung absorbed doses below 25 Gy. Serial planar scans were acquired at different times points p.i. however, the corrections performed were not specified (Table 2). Red marrow dosimetry was based on the blood method[64], assuming a non specific uptake[65]. The second SCT was performed after the total body activity of the patients had decreased to < 555 MBq (20 days p.i., on average) [33].

Wagner and co-workers performed a phase I/II study escalating ^{131}I-rituximab injected activities to target the kidneys up to 27 Gy in combination with different high-dose chemotherapy protocols and auto-SCT[35]. For dosimetry evaluations the conjugate-view technique suggested by MIRD was applied, and planar scans were acquired up to 168 hours p.i. The corrections applied, as well as the method for organ segmentation were not reported[35].

Studies with ^{90}Y-Zevalin.

Dosimetry protocols of ^{90}Y-Zevalin® were based on the injection of tracing amounts (185 MBq) of the surrogate radiopharmaceutical ^{111}In-tositumomab tiuxetan, after pre-loading with the anti-CD20 cold antibody rtuximab (Mabthera®), 250 mg/m^2 [58].

In the Wiseman protocol[58], serial whole body scans were acquired up to 6 days p.i. Attenuation correction was applied by using an average correction factor estimated from the first whole body image. No further corrections other than individual organ masses (measured from CT scans) were applied. The coniugate-view method was applied to estimate the activity concentration in lung, liver, spleen, kidney, and bone marrow. The absorbed doses evaluation was performed using the MIRDOSE 3.1 software. Dose to the red marrow was estimated by using both the Sgouros blood-based method[64] and the sacral image-derived method[66], using patient-specific red marrow masses. Median absorbed doses to the patients resulted well below protocol-defined maximum limits (3 Gy to red marrow and 20 Gy to other organs), with spleen receiving the highest dose (7.4 Gy). No toxicities were observed lungs and kidneys; hepatic dysfunction was detected in a few patients, but attributed to other factors than RIT. Hematologic toxicity was reversible and transient and the maximum tolerated activity without SCT was set at 1.85 GBq[58].

A different protocol was adopted by Nadamanee et al. in their phase I/II trial using HD-RIT with Zevalin® combined with high-dose etoposide and cyclophosphamide, followed by auto-SCT[29]. For dosimetry, a hybrid approach was adopted, with serial planar images up to 144 h p.i. and two SPECT images at 4, 47-72 h p.i. No other corrections were specified. Blood samples were collected at 2, 4-6 h p.i. and at the same planar image timing to determine antibody clearance and red marrow absorbed dose. However, after the therapeutic injection, the biopsy method[64] (see the specific paragraph below) was adopted to estimate the actual dose and the correct timing for SCT, given a constraint of ≤ 50 mGy to the red marrow. Liver was the main organ at risk[29].

A similar constraint on SCT timing (RM dose < 50 mGy) was adopted by Cremonesi et al.[56], while Chiesa et al.[32,57] verified this condition before performing the second ASCT in a TANDEM reinfusion approach. These authors adopted a planar-only approach with a different image acquisition timing (Table 2). Since bone

marrow trephine biopsies were negative, red marrow dosimetry was performed based on the blood model[64]. The attenuation correction was performed using a transmission scan with a ^{57}Co source. Images were also corrected for scatter and background with two different approaches. Chiesa et al. adopted the pseudo-extrapolation number method[51] for scatter correction instead of the energy windows method used by Cremonesi et al. [56]. For the background correction, Cremonesi et al. [56] performed an integral subtraction, while Chiesa et al. a partial subtraction only, based on the Bujis method[67]. The main role of dosimetry in these studies was to prevent toxicity verifying that dose constraints were respected. In particular, Cremonesi et al assumed a dose constraint of 20 Gy to organs-at-risk excluding the red marrow. As in the work of Nadamanee et al.[29], the liver was identified as the main organ at risk[56,57].

In the phase I study of Winter et al. combining HD-RIT with BEAM chemotherapy before auto-SCT, different activities of Zevalin® were injected to deliver absorbed doses to critical organs ranging from 1Gy to 17Gy. The dosimetry was based on serial planar scans acquired up to 144h p.i.(Table 2). The same corrections reported by Wiseman et al were applied[58]. The recommended maximum tolerated dose to critical organs was finally set at 15 Gy. The main critical organ was the liver in all patients but four for whom it was the kidney[30].

A similar approach based on dose constraints was recently adopted by Whal et al.[37], who proposed a patient-specific, dosimetry-driven absorbed dose escalation allowing the adjustment of the injected activity as a function of different absorbed dose to the liver. For this reason, the accuracy of the dosimetry was a major focus in this study. In each patient, the authors implemented a hybrid dosimetric approach based on both serial planar and one SPECT/CT images. The SPECT/CT was used to rescale the time-activity curve derived from planar images and to calculate both the attenuation correction factors and patent specific organ masses. Both blood and image based methods were implemented for red marrow dosimetry. Even in this protocol, the red marrow dosimetry was used to estimate the appropriated time for stem cells infusion, defined at a red marrow dose rate < 10 mGy/h (Figure 3).

In the study of Bethge et al.[34] combining HD-RIT with RIC before allo-SCT, Zevalin® injected activities were escalated empirically, and not based on dosimetry. Nevertheless, sequential whole-body scans were acquired up to 6 days following the injection of ^{111}In-ibritumomab tiuxetan. The study does not specify whether corrections were applied, or if individual organ masses were calculated.

4) Evolution of Dosimetric approaches for red marrow dosimetry

The bone marrow architecture is complex, therefore several bone marrow dosimetry models with varying degrees of complexity were developed over the years. So far, more refined bone marrow-specific dosimetry models have failed to show a clear superiority over simpler ones as regards dose/response correlations. Under the assumption of non-specific uptake, Sgouros et al.[64] was the first to focus on red marrow dose models in RIT, based on either blood samples collection or bone marrow biopsies. The method based on biopsy sampling is considered the gold standard but it implies high patient compliance and high expertise for activity measurements and specific corrections for each biopsy component (See details in the Appendix). The blood-based method is simpler, and allows to estimate the red marrow dose assuming an equal activity concentration in both plasma and the extracellular fluid volume.

Ferrer et al.[68] highlighted the importance of considering the specific red marrow uptake also in case of limited bone marrow disease in NHL patients treated with the anti CD22 antibody ^{90}Y-epratuzumab-tetraxetan. The authors compared the blood-based method (with rescaling for the patient-specific haematocrit) with an image-based approach that quantifies the uptake in L2-L4 vertebrae, under the assumption that the red marrow mass in L2-L4 is 6.7% of the total red marrow mass. Image-to-blood dose ratios of 2 were found, on average[68] (Figure 2). Dose results from image-based methodology were able to predict the haematological toxicity observed better than blood-based methods.

All the above described methods assume a red marrow homogeneous distribution. The data from a single region (either blood sample, single biopsy or imaged bone region) are considered adequate to represent the whole red marrow dose estimation. However, inter- and intra-patients differences in red marrow distribution may occur and largely impact on dosimetry evaluation[69,70,71,72]. Sgouros et al.[73] demonstrated the importance of considering such variability, although for a different antibody (^{131}I-labeled HuMl95, Anti-CD33). In particular, some marrow regions were identified and the total dose to the red marrow was calculated using three different image-based approaches: a) assuming a red marrow homogeneous distribution; b) using a volume-weighted average of the local marrow cumulated activity concentration; c) using a weighted average absorbed dose of the considered regions. Large differences were observed among patients in all regions and results showed a large inter- and intra-patient variability, leading to the conclusion that a patient-specific approach is needed for a more accurate RM dose estimate (Figure 2).

The Sgouros' study [73] also shows the influence of different S-factors for red marrow self-irradiation in the dose evaluation. In fact, different models have been implemented over the years[74]. Spiers et al[75,76] evaluated the dose conversion factors (DFs) for marrow irradiation by beta-emitting radionuclides within the trabecular bone by statistical evaluations of the electron path in experiments with trabecular bone samples. Cristy and Eckerman[77] improved the low-energy evaluations (previously underestimated), developed different phantoms, and provided regional and skeletal average dose conversion factors, implemented in the MIRDOSE3 software. Finally Bouchet et al.[78] developed a new model to generate S-

364 factor for 22 skeletal sites, employing a 3D Monte Carlo code (EGS4). However, the Eckerman model
365 underestimated the absorbed fractions at photon energies < 200keV, while the Bouchet model
366 overestimated these values at energies higher than 20keV. Thus, an adjusted model, combining the
367 previous results at different energy ranges, was proposed [79,80,81]. Despite these efforts, we should point out
368 that the improved S factors show a negligible impact on the red marrow dosimetry with respect to the
369 influence related to the blood- or image-based dosimetric approach.

370

371 5 Discussion

372 Although direct comparisons in phase III randomized trials are not available, the use of HD-RIT in
373 myeloablative conditioning seems to be less toxic than more used conditioning regimens based on high-
374 dose chemotherapy and TBI. Ultimately, less toxicity is leading to improved survival outcomes[39,40]. Elderly
375 or fragile patients, considered non-suitable for high-dose chemo/radiotherapy, were successfully treated
376 with HD-RIT-based conditioning followed by SCT. In HD-RIT myeloablative protocols rescued by SCT, red
377 marrow irradiation and/or toxicity is not the major concern. In contrast to standard-activity RIT, other
378 organs become at risk. Due to the very high activities administered, dosimetry analysis was often included
379 in HD-RIT clinical trials as a tool to establish the safe dose constraints allowing activity-escalation. In
380 particular, the activity to be administered was calculated to accomplish specific dose limits to the organs
381 receiving the highest dose, namely the lungs, the liver and the kidneys.

382 A summary of the most important clinical studies of HD-RIT followed by SCT is reported in Table 1. The
383 experience gained from standard RIT was often a useful starting point to optimize the HD-RIT dosimetry
384 methods in terms of acquisition timing, data collection and analysis. For this reason, we have also briefly
385 summarized the dosimetry methods and some results of the most relevant studies using standard RIT
386 (Table 2). The histograms in Figure 1 (a, b) report the median absorbed dose values for the most relevant
387 organs obtained with either ^{131}I- or ^{90}Y-labelled radiopharmaceuticals. In case of escalation studies, the
388 dose values reported refer to the group receiving the highest absorbed dose to the organ at risk or the
389 highest activity/kg of body weight, according to the protocols' outlines summarised in Table 2. The various
390 studies differ regarding the rationales, methodologies, activity levels, and dose constraints, which makes
391 the comparison between the absorbed dose values reported in Figure 1 a difficult task. An actual
392 dosimetry comparison should be based, instead, on absorbed dose per unit activity values. However, only
393 few authors provided such information for organs other than the red marrow. A common evidence
394 emerging from all studies is the large variability of the absorbed doses within the patient cohorts. Table 3
395 reports the range of dose variability factors related to the major source organs, in terms of ratio between
396 the minimum/maximum dose and the median dose (activity escalation protocols) or and the ratio between

the minimum/maximum activity and the median activity for a same dose constraint (dose escalation protocols). The data in Table 3 highlight a very high variability in almost all organs however, the organs at risk deserve a special focus.

For standard RIT treatments the major concern is the red marrow irradiation. In contrast, the major organs at risk for HD-RIT are the liver, the kidneys and the lungs depending on the radiopharmaceutical adopted. The corresponding variability factors for each organ among all authors are 0.5-2.1 for the liver, 0.6-1.64 for kidneys and 0.5-1.6 for the lungs.

Concerning the red marrow, Figure 2 shows the absorbed dose per unit of activity (Gy/GBq, range) for the most representative studies exploring different dosimetric approaches. The absorbed doses for Zevalin at standard and high activities are comparable, being based on the blood method. It was also shown that, for the ^{90}Y-epratuzumab-tetraxetan, the imaging method provides higher dose estimates than the blood method in the same patients. The study by Sgurous et al.[73] highlights the variations of dose estimations depending on the bone region used to extrapolate imaging data. All these studies show a quite relevant inter-patient variability. Although the most appropriate approach for red marrow dosimetry has not been established yet, there is some evidence showing that dosimetry obtained with the imaging method could better predict the toxicity data of standard RIT[68]. We should point out that, in the majority of the studies, the dosimetry data reported are based on 2D images, whose pitfalls are well known. The recent developments of equipment technology and computational models for dosimetry will certainly provide more accurate results than in the past. Hybrid approaches combining 2D and 3D imaging of activity distribution in organs at risk, adopted by some authors[37,55,82] are highly recommended. In case of ^{131}I-labelled radiopharmaceuticals, the use of the positron-emitting ^{124}I as a surrogate radioisotope for dosimetry would be desirable, although the costs and the availability are still demanding.

A further issue that deserves attention in the myeloblative RIT is the appropriate timing for SCT. In fact, to be on the safe side for a successful engraftment, the radiation dose to the reinfused stem cells should be as low as possible. Different authors provided several empirical dose constraints for the proper time of SCT.

In particular, an absorbed dose ≤ 50 mGy (T_1) to the Reinfused Stem Cells (RSC) or a dose rate ≤10 mGy/h to the red marrow (T_2)[37] were proposed. The criteria are depicted in Figure 3 based on the blood curve of a representative patient treated with HD-RIT ^{90}Y Zevalin[56]. For the first constraint, some Authors[56] assumed that RSC receive the same irradiation of the red marrow from the time of SCT to infinity (Figure 3c, pink triangle). However, considering that the RSC circulate in the blood pool for a certain time (Δ) before homing in the bone marrow, a potentially more accurate model should consider two different sources of irradiation in two time intervals: the first source of irradiation during the Δ time would be the blood, the second being the red marrow up to infinity (Figure 3d).

Finally, we would like to emphasise that, besides any possible improvements of dosimetry accuracy and standardization, the absorbed doses are just one of the multiple parameters needed to predict the effects of therapy in term of both toxicity and efficacy. It is well known that, in radiation oncology, the clinical outcomes depend not only on the adsorbed dose but also on the tumour biology and on patient conditions. Today, novel molecular and genetic tests are available and may guide the choice of the most appropriate drug or immunotherapy. Currently available molecular and genetic biomarkers, along with personalised dosimetry, may enable to select the best candidates for HD-RIT. The final goal of precision nuclear oncology is to minimize acute and late toxicity whilst preserving efficacy.

Conflict of Interest

The authors declare no conflict of interest with regard to this paper.

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Appendix A

a. Bone marrow dosimetry without specific uptake

In their model, Sgouros et al.[64] assume a rapid equilibrium in both plasma and extracellular fluid and the absence of specific uptake, i.e the absence of binding between the administered antibodies and any component of the blood, marrow, or bone. As a consequence, an equilibrium of agents is rapidly achieved after injection. Under the assumption of non-specific uptake, Sgouros et al. [64] proposed two methodologies for red marrow dose estimation, based respectively on blood samples and red marrow biopsy.

The simplest method is the one based on the red marrow-to-blood concentration ratio. It relates the activity concentration in blood $[A]_{BL}$ to the one in plasma $[A]_P$ by the hematocrit (*HCT*):

$$[A]_P = \frac{[A]_{BL}}{1 - HCT} \quad \text{Eq. 1}$$

Since the activity concentration in plasma is assumed equal to the one in the extracellular volume of the red marrow, the activity concentration in marrow is simply expressed as:

$$[A]_{RM} = \frac{[A]_P \cdot V_{RMECF}}{V_{RM}} \quad \text{Eq. 2}$$

where V_{RMECF} = red marrow extracellular fluid volume and V_{RM} = red marrow volume.

Thus the red marrow-to-blood activity concentration ratio (*RMBLR*) is:

$$RMBLR = \frac{[A]_{RM}}{[A]_{BL}} = \frac{V_{RMECF}}{V_{RM}} \cdot \frac{1}{1 - HCT} = RMECFF \cdot \frac{1}{1 - HCT} = \frac{0.19}{1 - HCT} \quad \text{Eq. 3}$$

where *RMECFF* is the red marrow to extracellular fluid fraction[83].

The second method proposed by Sgouros et al.[64] is based on the time-activity concentration curve extracted from bone marrow biopsy. This method is considered the gold standard but, while in the first case it is sufficient to take small amounts of blood, in this case it is necessary to sample the marrow to calculate the concentration of activity in the red marrow. The marrow biopsy is composed of a thickness of cortical bone at both ends and an internal region of trabecular bone. This latter part contains in its honeycomb structure red marrow, fat (yellow marrow) and blood. Therefore, when the marrow activity concentration is obtained from the complete biopsy, different correction factors taking into account the biopsy components have to be applied. In fact, under the assumption that radiolabeled antibodies do not bind to these components, the activity concentration in marrow may be underestimated if the marrow mass is overestimated.

If the cortical bone is present in the biopsy, the cortical bone correction factor (*CBC*) can be expressed as:

$$CBC = \frac{[A]_{RM}}{[A]_{BIOPSY}} = \left[1 + \left(\frac{CBF}{1 - CBF}\right)\frac{\rho_{CB}}{\rho_{RM}}\right] \quad \text{Eq. 4}$$

where $[A]_{BIOPSY}$ = activity concentration in red marrow, *CBF* = volumetric fraction of the cortical bone in the biopsy, ρ_{CB} = cortical bone density and ρ_{RM} = red marrow density. *CBC* baseline value is 1.42 and it ranges from 1.1 to 1.9 for *CBF* of 0.06-0.32[84].

When the cortical bone portion is removed from the biopsy, the presence of trabecular bone should be considered anyway. Similarly to the cortical bone, the trabecular bone conversion factor (TBC) can be expressed as:

$$TBC = \frac{[A]_{RM}}{[A]_{BIOPSY}} = \left[1 + \left(\frac{TBF}{1 - TBF}\right)\frac{\rho_{TB}}{\rho_{RM}}\right] \quad \text{Eq. 5}$$

where *TBF* = trabecular bone volumetric fraction in the biopsy and ρ_{CB} = cortical bone density. *TBC* baseline value is 1.66 and it ranges from 1.3 to 2.1 for *TBF* of 0.12-0.38[84].

Given a completely bone-free biopsy, a certain component of the sample is composed by yellow marrow. Therefore, a fatty tissue correction factor (*FTC*) can be expressed as:

$$FTC = \frac{[A]_{RM}}{[A]_{BIOPSY}} = \left[1 + \left(\frac{FTF}{1 - FTF}\right)\frac{\rho_{FT}}{\rho_{RM}}\right] \quad \text{Eq. 6}$$

where *FTF* = yellow marrow volumetric fraction in the biopsy and ρ_{FT} = yellow marrow density. *FTC* baseline value is 1.37 and it ranges from 1.1 to 1.7 for *FTF* of 0.08-0[84].

In case of a completely bone- and fat-free biopsy, only the blood contamination remains, which may lead to an overestimation of the marrow activity concentration. In this case, the activity concentration in the red marrow can be expressed as:

$$[A]_{RM} = [A]_{BIOPSY} \cdot \left[1 + \left(\frac{BLF}{1 - BLF}\right)\frac{\rho_{BL}}{\rho_{RM}}\right] - [A]_{BL} \cdot \left[\frac{BLF}{1 - BLF} \cdot \frac{\rho_{BL}}{\rho_{RM}}\right] \quad \text{Eq. 7}$$

where *BLF* = blood volumetric fraction in the biopsy and ρ_{BL} = blood density.

This equation can be directly used to correct the biopsy activity concentration, as the blood concentration in the sample can be easily obtained. The blood correction factor (*BLC*) can be also expressed by substituting $[A]_{BL}$ from Eq. 3:

$$BLC = \frac{[A]_{RM}}{[A]_{BIOPSY}} = \left[\frac{1 + \left(\frac{BLF}{1-BLF}\right)\frac{\rho_{BL}}{\rho_{RM}}}{1 + \left(\frac{1-HCT}{RMECFF}\cdot\frac{BLF}{1-BLF}\right)\frac{\rho_{BL}}{\rho_{RM}}}\right] \quad \text{Eq. 8}$$

734 *BLC* baseline value is 0.85 and it ranges from 0.96 to 0.69 for *BLF* of 0.02-0.24[84].

735 For an untreated biopsy sample, containing all the contamination components, the appropriate correction
736 factor is the product of the correction factors for each biopsy component and it converts the activity
737 concentration in the whole sample to the activity concentration in the red marrow component. For
738 standard biopsy samples baseline values of the correction factors can be used.

739 The described methods are suitable not only for radiolabeled antibodies, but for any labeled agent that
740 rapidly reaches an equilibrium within the extracellular fluid region of the red marrow and that does not
741 bind to any marrow, blood or bone component.

742

743 b. Bone marrow dosimetry with specific uptake

744 The methods for calculating activity concentration in red marrow shown above were based on the
745 assumption that radiolabeled agents did not bind to any component of bone, marrow, or blood. These
746 methods can be justified when less than 25% of red marrow is involved in dose absorption, thus assuming
747 negligible consequences in marrow toxicity. However, red marrow involvement is usually assessed by an
748 iliac crest bone marrow biopsy, which is often associated with false-negative results[85]. To overcome this
749 limitation, Ferrer et al.[68] evaluated three different red marrow dosimetric methods in B-cell NHL patients
750 that received 2 co-administrations of ^{90}Y-labeled and ^{111}In-labeled antibodies. The methods investigated are
751 one image-based method (M1) and two blood-based methods (M2, M3).

752 Based on the MIRD approach[52], the mean absorbed dose to the red marrow is expressed as:

$$D_{RM} = \widetilde{A_{RM}} \cdot S_{RM\leftarrow RM} + \sum_h \widetilde{A_h} \cdot S_{RM\leftarrow h} + \widetilde{A_{RB}} \cdot S_{RM\leftarrow RB} \quad \text{Eq. 10}$$

753

754 where $\widetilde{A_{RM}}$, $\widetilde{A_h}$ and $\widetilde{A_{RB}}$ are the accumulated activity in the red marrow, in the source organ h and in the
755 remainder of the body, respectively. Similarly, $S_{RM\leftarrow RM}$, $S_{RM\leftarrow h}$ and $S_{RM\leftarrow RB}$ are the S value for RM self-
756 irradiation, the S value for irradiation from source organ h and from the remainder of the body,
757 respectively[86]. In the two blood-based methods, $\widetilde{A_{RM}}$ is calculated as:

758

$$\widetilde{A_{RM}} = RMBLR \cdot C_{BL} \cdot m_{RM} = RMECFF \cdot \frac{1}{1-HCT} \cdot C_{BL} \cdot m_{RM} \quad \text{Eq. 11}$$

759

where m_{RM} is the red marrow mass (fixed at 1500 g[86]), *RMECFF* is 0.19, according to the Sgouros results, leading to a *RMBLR* of 0.36 for a normal value of *HCT* (0.47 for standard man)[87].

The M2 approach assumes *RMBLR* constant and equal to 0.36 for all patients, whereas in the M3 approach RMBLR depends on the patient's *HCT.* The cumulated activity in blood, C_{BL} , is calculated from the blood time-activity curve.

The image-based M1 method is more complex, requiring several imaging sessions and image/data processing, but it allows considering individual differences in marrow mass and uptake. This method assumes that red marrow mass in L_2-L_4 lumbar vertebrae is proportional to trabecular bone volume and red marrow mass in this region is 6.7% of the red marrow mass in the whole body[88]. Therefore, marrow mass considered in dose calculation is patient-specific and red marrow absorbed dose can be obtain as:

$$D_{RM} = \frac{\widetilde{A_{L_2-L_4}}}{0.067} \cdot S_{RM \leftarrow RM} \cdot \frac{V_{trab\ L_2-L_4}^{refman}}{V_{trab\ L_2-L_4}^{patient}}$$

Eq. 12

with S values from the MIRD Pamphlet 11, $V_{trab\ L_2-L_4}^{refman}$ = trabecular bone volume of the Reference Man, $V_{trab\ L_2-L_4}^{patient}$ = patient trabecular bone volume (from CT) and $\widetilde{A_{L_2-L_4}}$= cumulated activity in red marrow in L_2-L_4 lumbar vertebrae (calculated from the time-activity curve of these regions).

Combining red marrow doses with platlet and leukocyte toxicity, M1 is the method which provides the best absorbed dose-effect relation as compared with the blood-based methods. Methods M2 shows almost the same results than M3 in red marrow doses, but both seem to have no correlation at all with the observed toxicity. Therefore, even for patients with low bone marrow involvement (less than 25%) it is important to consider bone marrow uptake of the radiolabeled agents.

c. Regional variability of marrow-localizing agents

The above described methods are based on the assumption of red marrow homogeneous distribution. The data form a single region (either blood sample, single biopsy or specific bone region such as L2-L4) are used for whole red marrow dose estimation. In fact, a linear factor is used for scaling the dose estimated for a single data to the whole red marrow. However, large inter- and intra-patients differences in red marrow distribution may occur that largely impact dosimetric evaluation[69,70,71,72]. Sgouros et al.[73] demonstrated the importance of this variability. They studied three different methods to calculate the mean absorbed dose to the whole red marrow in 10 patients infused with ^{131}I radiolabeled antibodies, in order to evaluate the dosimetric impact of a non uniform distribution of the activity concentration in the marrow. After the injection of the antibodies, patients were scanned front and back with a gamma camera on the day of the injection and daily for the next 3 days. Images were corrected for the background, the attenuation and the geometric mean was used. Some regions were selected as regions of interest: liver, spleen, thyroid, all femur's head and necks, all humerus' head and necks, two lumbar vertebrae (L3 and L4) and finally the whole body. Selected marrow regions (femur's head and necks, humerus' head and necks, L3-L4 lumbar vertebrae) had the minimal overlaying of tissues. Blood samples were also acquired post injection. No statistically significant difference of half-lifes was found among femoral (mean ± standard deviation = 50 ± 20 hr), lumbar (50 ± 20 hr), humeral (50 ± 10 hr) regions, or blood samples (37 ± 9 hr) and whole body (50 ±

10 hr). However, absorbed dose differences were observed. For each region, the cumulated activity was calculated from the time-activity curve fitted with a single exponential curve. The absorbed dose to each red marrow region (rg) was calculated using the equation:

$$D_{rg} = \widetilde{A_{rg}} \cdot S_{rg \leftarrow rg} + \widetilde{A_{wb}} \cdot S_{rm \leftarrow wb} \quad \text{Eq. 13}$$

where:

- $\widetilde{A_{rg}}$, $\widetilde{A_{wb}}$ = cumulated activity in the red marrow region rg and in the whole body respectively;

- $S_{rg \leftarrow rg}$ = S-factor for the self-irradiation of the specific red marrow region rg;

- $S_{rm \leftarrow wb}$ = S-factor for the cross irradiation of the whole body to red marrow.

The S-factors of corresponding body region (*i.e.* legs, arms and spine) were rescaled from the MIRD Pamphlet 11 based on the mass of the single region considered (*i.e.* femural, humeral and L3-L4 regions respectively). This results in a large difference of mean absorbed dose among regions: 0.7 ± 0.3 mGy/MBq for the femoral region 1.0 ± 0.3 mGy/MBq for the humeral region and 2.2 ± 0.5 mGy/MBq for L3-L4. Therefore, the difference in both mass and S-values strongly impact the absorbed dose estimation beyond the similarities in half-lifes.

Then the total dose to the whole red marrow was calculated using 3 different approaches:

a) Assuming the cumulated activity concentration in the femur as representative of the whole marrow (with S-factors from MIRD Pamphlet 11);
b) Using a volume-weighted average of the local marrow cumulated activity concentration in all considered regions (with S-factors from MIRD Pamphlet 11);
c) Using a weighted average absorbed dose of all considered regions (with regional S-factors from MIRDOSE3).

This results in a mean absorbed dose to the red marrow equal to 1.7 ± 0.8 mGy/MBq, 2.2 ± 0.6 mGy/MBq and 1.4 ± 0.3 mGy/MBq with the three proposed methods respectively. The impact of lower activity concentration measured in the femoral region is evident comparing the results of Method a to Method b. Moreover, the result of Method c, compared to one of Method b, reflects the lower (regional) S-factors used in MIRDOSE3 for the marrow self-irradiation than the values implemented in MIRD Pamphlet 11. Large differences were observed among patients in all considered regions and results showed a large inter- and intra-patient variability. Moreover red marrow depletion is not uncommon during radiotherapy treatments so the dosimetry based on a single-site activity concentration measure may not properly estimate possible marrow toxicity in any patient. Since patients were affected by leukemia, such variability could be caused by the antigen-positive cell distribution (which is also patient-specific).

d. Evolution of bone and red marrow dose models (S-values)

In the last decades several approaches for dosimetric evaluation in radioimmunotherapy have been proposed and they differ for both mathematical model and phantom used to mimic the human body. As for all other organs, the red marrow conversion factors between disintegrations in some regions to

absorbed dose in a target region were influenced by the evolution of phantom definition and calculation model[74].

A first evaluation of dose conversion factors (DFs) for marrow irradiation by beta-emitting radionuclides within the trabecular bone was done by Spiers et al. from the early 1960s through the late 1970s[75,76,89]. In this model, electrons lose energy under the assumption of the continuous slowing down approximation (CSDA), irradiating both the trabecula of origin and the surrounding trabeculae and cavities containing red marrow. The electron's path through these regions was estimated by statistical evaluations of the chord length distribution in experiments with trabecular bone samples. Therefore average energy deposition in marrow from beta-emitters in bone was calculated.

Snyder et al. extended Spiers' work deriving the absorbed fractions for this case and other cases such as the bone marrow self irradiation with Monte Carlo codes. These results were used by the MIRD Committee to build S-values in MIRD Pamphlet No. 11[86]. In this Pamphlet the photon absorbed fractions for bone-marrow irradiation were conservatively high for low energy photons. Cristy and Eckerman[77] solved this problem, improving the low energy photon calculations. In particular, they independently modelled the energy deposition by secondary electrons derived from photon interactions in bone, but still relying on the chord-length distribution of Spiers. Therefore they obtained the electron absorbed fractions for different bone groups and a wide range of energies. The Cristy/Eckerman phantom model allowed to directly calculate the absorbed dose to the marrow from electrons originating in the marrow regions. Moreover, different Cristy/Eckerman phantoms were developed for both male and female and for different ages from newborns to adult age. The Cristy/Eckerman model is implemented in MIRDOSE3, which provides doses for adult males, adult females and children, as well as regional and skeletal average dose conversion factors. MIRDOSE2 software implemented the ICRP 30 phantom, mainly used for radiation protection purposes on workers because it was intended to be conservative. For this reason, it is not useful in predicting doses to red marrow in the context of patient specific dosimetry.

Bouchet et al.[78] developed a model still based on the Spiers' chord-length distribution, but employing a 3D electron transport algorithm, in both trabecular and cortical bone, using EGS4 Monte Carlo transport code. They calculated new absorbed fractions to generate new S-values for 22 skeletal sites.

The MIRD 11 model provides only the average marrow S-value for self-irradiation for reference adult male. The Eckerman et al. and Bouchet et al. models also provide local values for a specific region of the skeleton. Both models are accurate in electron transport algorithms and give good detailed internal doses. However they differ in three main points:

a) Eckerman supposed that absorbed fractions for red marrow self-irradiation should be obtained by multiplying absorbed fractions for marrow space self-irradiation by marrow cellularity, while Bouchet assumed that they were numerically equal without this multiplication. Eckerman values are 50% lower than those calculated by Bouchet.
b) Eckerman implemented 2D planar sources at the interface between the trabecular and marrow cavities, assuming the 10µm layer of soft tissue (endosteum) on the bone interface as a part of the red marrow. On the contrary, Bouchet assumed a source distribution throughout this layer of soft tissue. Dose factors in the Bouchet model for bone surface sources were about 1.5-2 times higher than the Eckerman ones.
c) Electron passing through the 10µm layer of soft tissue had a uniform distribution of angles in the Eckerman model, while in the Bouchet model had a uniform distribution of the cosine angle. Dose

factors in the Bouchet model for bone surface as a target were about 2 times higher than the Eckerman results.

The University of Florida conducted studies on these two models using 3D transport techniques in trabecular bone, based on NMR microscopy images which allowed to differentiate the active marrow (red) from the inactive marrow (yellow) regions[79,80,81]. They showed that none of the models accurately predicts the absorbed fraction for red marrow self-irradiation in the energy range from 20keV to 200keV. The Eckerman model underestimates the fraction at energies below 200keV, while the Bouchet model overestimates these values at energies higher than 20keV. Therefore they proposed an adjusted model where the Bouchet results are applied at low energies (below 10keV), while Eckerman results are applied at energies above 100keV. Intermediate values are assumed in the energy range 10-100keV.

Acronyms

A:	Attenuation
ASCT:	Autologous Stem Cell Transplantation
B:	Background
Bexxar®	^{131}I-tositumomab
BEAM:	carmustine, etoposide, cytarabine and melphalan chemotherapy.
DLBCL:	Diffuse large B-cell lymphoma
DLT:	Dose Limiting Toxicity
FL:	Follicular lymphoma
GM:	Geometric mean
HCT:	Hematocrit
HD-RIT:	High Dose Radioimmunotherapy
HL:	Hodgkin's lymphomas
MCL:	Mantle Cell Lymphomas
MTD:	Maximum Tolerated Dose
n.a.:	not available
NHL:	Non-Hodgkin Lymphoma
OM:	Organ masses
RIT:	Radioimmunotherapy
RM:	Red Marrow
RSC:	Reinfused Stem Cells
S:	Scatter
SPECT:	Single-Photon Emission Computerized Tomography
TANDEM:	Protocol combining HD-chemotherapy + ASCT and HD-RIT + ASCT
TB:	Total Body
TBI:	Total Body Irradiation
Zevalin®	^{90}Y-ibritumomab-tiuxetan

Figures' captions

Figure 1. Absorbed doses (median values, Gy) to normal organs for a) ^{131}I-MoAbs+ASCT and b) ^{90}Y-MoAbs+ASCT, reported by different authors. TB stands for Total Body.

Figure 2. Absorbed per unit activity (Gy/GBq) to the RM (median values and ranges of variability) for different therapy and dosimetry approaches (b=blood model; i L = imaging, lumbar vertebrae; i H = imaging, homerus; i F= imaging, femoral head). The absorbed doses for Zevalin at standard and high activities are comparable, despite quite high variability. The ^{90}Y-eprattuzumab tetraxetan (Ferrer et al. [68]) shows much higher evaluation when derived for imaging as compared to the blood method in the same patients. The values for by Kaminski et al.[91] For ^{131}I-Bexxar have been extrapolated from the absorbed doses provided for blood, using the blood model, with $D_{RM}= 0{,}36 \times D_{blood}$. The study by Sgurous et al.[73] refers to a different antibody but highlights the regional variability of the RM doses from imaging of I-131- MoAb.

Figure 3. Time-activity curves for blood and RM to estimate the absorbed dose to the RSC.

The black line is the Time Activity Curve for the blood with the experimental time points of blood sampling (black crosses). The red line is Time Activity Curve for the RM, extrapolated from the blood model or evaluated from imaging. The %IA is in logarithmic scale. In this example the $T_{1/2\ eff}$ = 32 h

Figure 3.a: The dashed area in black is the time integrated activity (TIA) for the blood allowing to evaluate the absorbed dose to the blood.

Figure 3.b: The dashed area in red is the TIA for the RM.

Figure 3.c: The larger pink triangle represents the TIA to the RSC under the hypothesis RSC receives the same irradiation as RM from the time ASCT to infinity. T_1 is the time that guarantees a constraint of 50 mGy to RM. T_2 is time that guarantees a constraint of dose rate to RM ≤10 mGy/h (Whal et al.[37]).

Figure 3.d:The trapezoid grey area represents the TIA to RSC due to the irradiation from the time of ASCT until the RSC homing. The smaller pink triangle represents TIA of the RSC after the homing. Δ represents the time needed for SCT homing. The total irradiation is related to the sum of grey and pink areas.

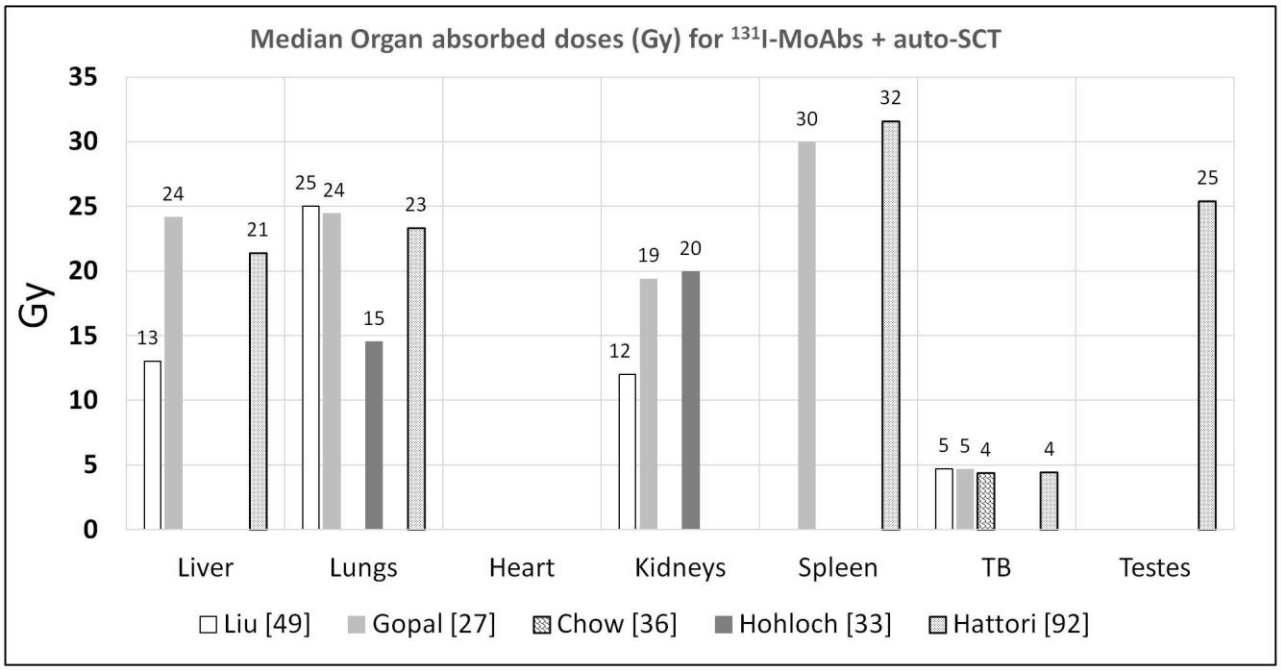
Tables' captions

Table 1. Summary of the main clinical protocol used by different authors for NHL HD RIT.

Table 2. Summary of the previsional dosimetry methods used by different authors for NHL RIT. The first four studies concern standard approaches with dosimetry for RM . The other studies refer to high activity treatments associated with ASCT.

Table 3. Ranges of variability factors related to the absorbed doses to normal organs, normalised to the median absorbed dose values.

a


Median Organ absorbed doses (Gy) for 131I-MoAbs + auto-SCT
Gy
35
30
25
20
15
10
5
0
13
24
21
25
24
15
23
12
19
20
30
32
5
5
4
4
25
Liver
Lungs
Heart
Kidneys
Spleen
TB
Testes
Liu [49]
Gopal [27]
Chow [36]
Hohloch [33]
Hattori [92]

b

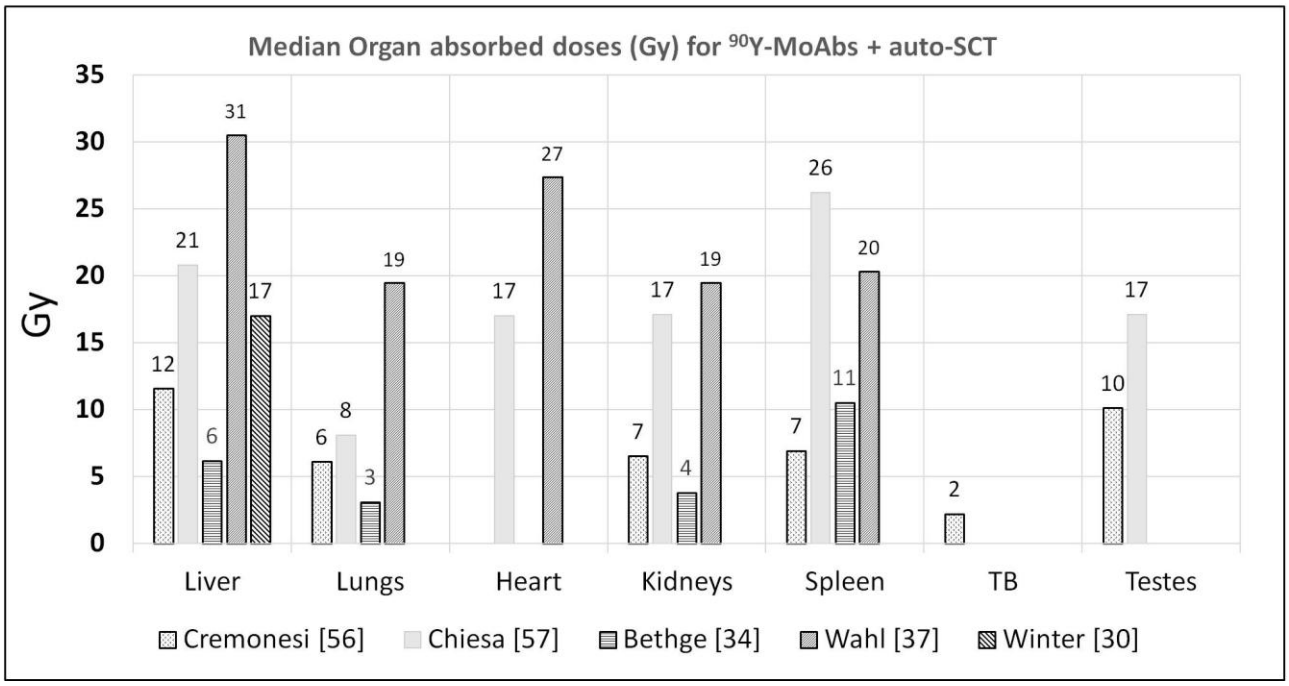

Median Organ absorbed doses (Gy) for 90Y-MoAbs + auto-SCT
Gy
35
30
25
20
15
10
5
0
12
21
6
31
17
6
8
3
19
17
27
7
17
4
19
7
26
11
20
2
10
17
Liver
Lungs
Heart
Kidneys
Spleen
TB
Testes
Cremonesi [56]
Chiesa [57]
Bethge [34]
Wahl [37]
Winter [30]

Fig. 1

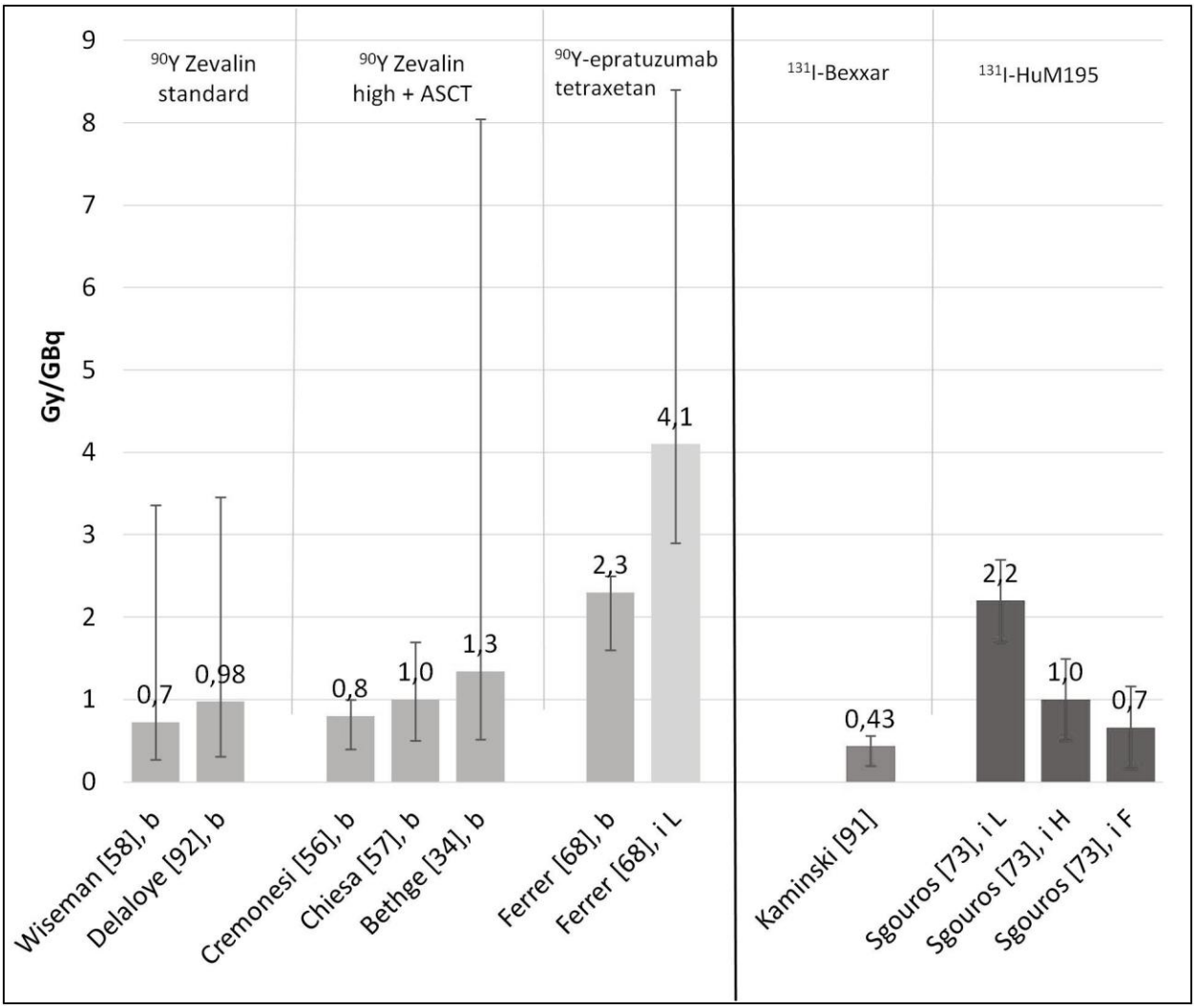

Gy/GBq
0
1
2
3
4
5
6
7
8
9
90Y Zevalin standard
90Y Zevalin high + ASCT
90Y-epratuzumab tetraxetan
131I-Bexxar
131I-HuM195
0,7
0,98
0,8
1,0
1,3
2,3
4,1
0,43
2,2
1,0
0,7
Wiseman [58], b
Delaloye [92], b
Cremonesi [56], b
Chiesa [57], b
Bethge [34], b
Ferrer [68], b
Ferrer [68], i L
Kaminski [91]
Sgouros [73], i L
Sgouros [73], i H
Sgouros [73], i F

Fig. 2

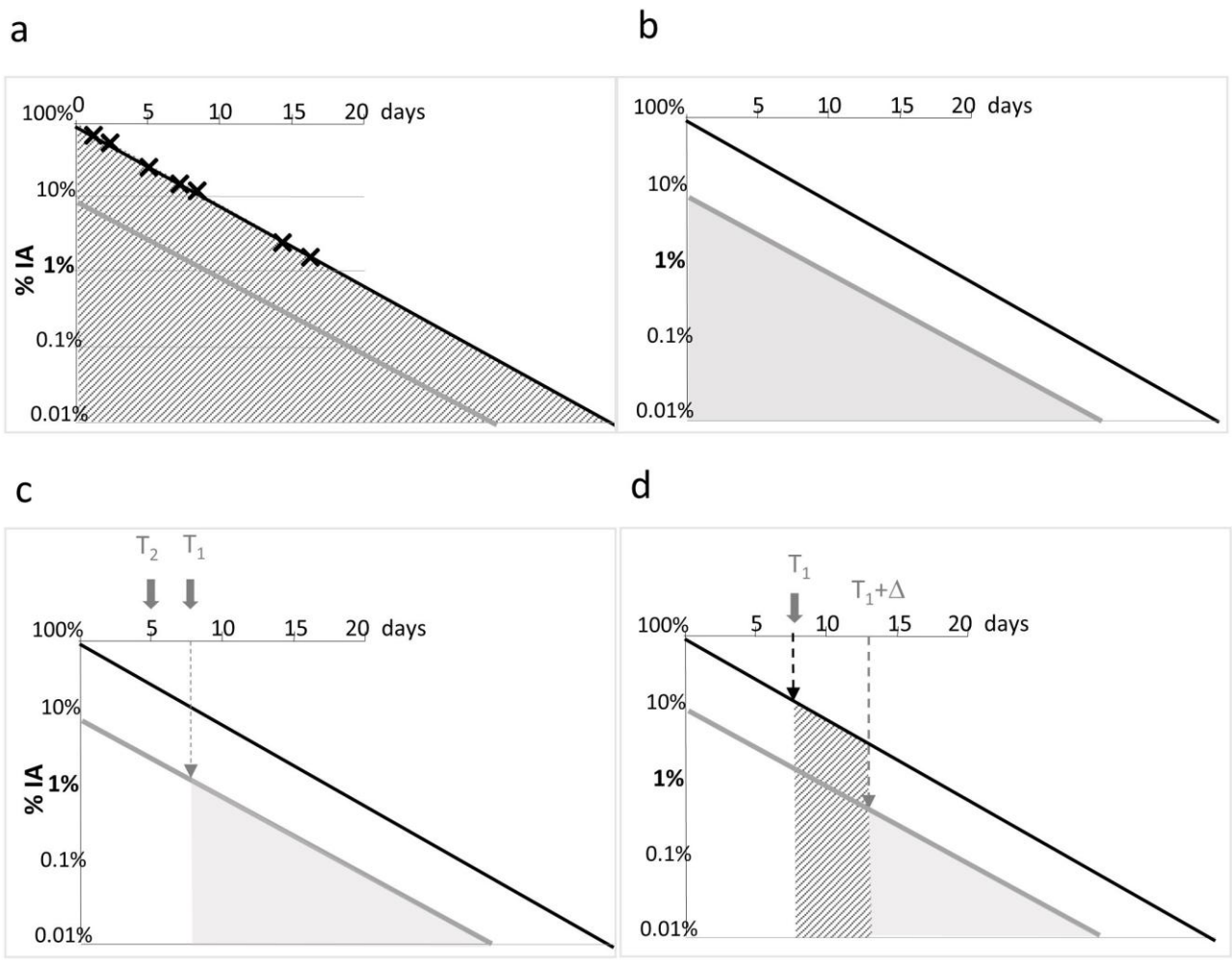


Fig. 3

Table 1. Summary of the main clinical protocol used by different authors for NHL HD RIT.

AUTHOR [ref]	Radiopharmaceutical	Cold MoAb preloading	Type of disease	No patients	Activity administered	ASCT time	Dose constrains	Major OAR	Chemiotherapy
Y-90-MoAbs									
Nademane [29]	Zevalin	rituximab 250 mg/m2	follicular lymphoma (n = 12), diffuse large B-cell (n = 14), and mantle cell (n = 5)	29	1,3 -3,9 GBq	radiation dose to RSC < 50 mGy	10 Gy to highest normal organ	Liver	high-doseetoposide (VP-16) 40 to 60 mg/kg (day -4) and cyclophosphamide 100 mg/kg (day -2)
Ferrucci[31]	Zevalin	rituximab 250 mg/m2	resistant/refractory B-cell NHL	13	Activity escalation: group I: 29.6 MBq/kg 4 patients group II: 44.4 MBq/kg for 4 patients group III: 55.5 MBq/kg 14 patients	ASCT @ 13 d p.t.***	< 20 Gy to uninvolved organs (except RM) Dose to reinfused stem cells < 50 mGy	Liver	none
Devizzi [32]	Zevalin	rituximab 250 mg/m2	relapsed/refractory or de-novo high-risk NHL	30	Activity escalation: 30 MBq/kg 15 patients 45 MBq/kg for 17 patients	ASCT @ 7 and 14 d p.t.***	No dosimetry based	Liver kidneys	PRIOR TO RIT: five chemotherapy courses, including three cycles of anthracycline- or platinum-containing regimens, one cycle of cyclophosphamide (4 to 7 g/m2), and one cycle of cytarabine (12 to 24 g/m2).
Winter [30]	Zevalin	rituximab 250mg/m2	relapsed or refractory B-cell NHL	44	Activity escalation: 9 cohort 2,2 MBq/kg 43 MBq/kg	14 days afetr RIT	90Y activities were based on dosimetry and were calculated to deliver cohort-defined radiation-absorbed dose (1 to 17 Gy) to critical organs with three to six patients per cohort.	Liver kidneys	high-dose carmustine, etoposide, cytarabine, and melphalan (BEAM)
Bethge [34]	Zevalin	250 mg/m2 rituximab before dosimetry and 250 mg/m2 before therapy	Relapsed or refractory: diffuse large B-cell (n=13), blastic mantle cell (n=2), transformed chronic lymphocytic leukemia (n=4), follicular (n=1)	20	Activity escalation: 22 MBq/kg 10 patients; 30 MBq/kg 10 patients	Allogeneic PBSC were transfused on day 14 p.t.***	Dosimetry was done for reasons of radiation safety and not used to calculate administered radiation dose, which was weight based.	RM	reduced intensity conditioning (RIC) using fludarabine, melphalan and alemtuzumab
Wahl [37]	Zevalin	375 mg/m2 weekly for 4 weeks	Relapsed or refractory: follicular (n=11), transformed or mixed follicular (n=5), mantle cell (n=5), diffuse large B-cell (n=1), others (n=2)	24 (18 proceeded to RIT)	Activity escalation: 14.8 MBq/kg (NO ASCT) and 4 cohorts from 2.46 GBq to 6.26 GBq	NO ASCT first group ASCT @ 10-15 d p.t. ***	absorbed dose from 18 to 30.5 Gy to live	Liver	none
I-131-MoAbs									
Liu [49]	Bexxar	Tositumiomab	small lymphocytic (n=2), diffuse largre-cell (n=2), immunoblastic (n=1), diffuse small cleaved-cell (n=3), follicular large-cell (n=4), follicular small cleaved-cell (n=13), follicular mixed small cleaved- and large-cell (n=4)	29	range 10,4 - 29 GBq	N.A.	< 31 Gy to critical organs	Lung kidneys	none
Gopal [26]	Bexxar	-	relapsed or refractory mantle cell lymphoma	16	Range 12-30 GBq	@ 14 days after therapy o radiation exposure < 0.02 mSv/h at 1 m	131I was calibrated to deliver 20 to 25 Gy to vital normal organs.	not reported	10 days later by administration of high-dose etoposide (30-60 mg/kg), cyclophosphamide (60- 100 mg/kg)
Gopal [39]	Bexxar	-	relapsed follicular lymphoma	27	Range 10.4-29.1 GBq	@ radiation exposure was less than 0.02 mSv/h at 1 m (RANGE 12-27 DAYS)	131I was calibrated to deliver 20 to 25 Gy to vital normal organs.	Lung kidneys	Two groups: - HD-RIT + ASCT -conventional HD chemotherapy + ASCT
Gopal [27]	Bexxar	-	Relapsed: diffuse large B-cell (n=9), mantle cell (n=8), follicular (n=6), marginal zone (n=1)	24	Range 12,1 - 42,7 GBq	ASCT @ 16 d p.t.***	< 25 to 27 Gy to critical organs	Lung liver kidneys	none
Hohloch [33]	131I-rituximab	rituximab 2.5 mg/kg	Relapsed or refractory: follicular (n=4), transformed follicular (n=6), diffuse large B-cell (n=4), mantle cell (n=1), marginal zone (n=1)	16 (9 proceeded to RIT)	median 9 GBq (range 8,6 - 13 GBq)	18–22 days.	Therapeutic activity was calculated according to the protocol in order to obtain a myeloablative dose to the bone marrow and to keep the kidney and lung doses lower than 25 Gy	Lung kidneys	Dexa-BEAM+ BEAM
Wagner [35]	131I-rituximab	rituximab 2.5 mg/kg	Relapsed or refractory: follicular (n=14), marginak zone (n=1), mantle cell (n=5), agressive B-cell lymphoma (n=3)	23	7.0–19.4 GBq, according to previous dosimetric study planning	@ body activity < 0.222GBq (median of 21 days)	Phase I dose-escalation study including 16 pts: 4 cohorts of 4 pts by level: 21, 23, 25 and 27 Gy to the kidney. 7 pts were treated in the Phase II study on the 27 Gy level.	Kidneys	Three groups: - HD-RIT+ASCT alone -(HD-RIT+ ASCT) + (EAM + RIT+ASCT) -(HD-RIT+ASCT) + (BEAM + ASCT) = TANDEM
Gopal [28]	Bexxar	-	relapsed or refractory B-NHL or mantle cell lymphoma	36	median 17.4 GBq; range 9.6 to 59.9 GBq	@ radiation exposure < 0.02 mSv/h at 1 m, (Range 12 -18 days)	absorbed dose of 27 Gy to the critical normal organ	Lung, liver, kydneys	Fludarabine was escalated from 10mg/m2 daily × 5 days (total dose 50mg/m2) to 30mg/m2 daily × 7 days (total dose 210mg/m2) without observation of a DLT.
Cassaday [90]	Bexxar	-	mantle cell lymphoma	61	median of 19.8 GBq (range: 7.6-40.7 GBq)	not rteported	in order to median 25 Gy (20-27 Gy) to critical organs	not reported	TBI in combination with chemotherapy (high-dose cyclophosphamide with or without etoposide).
Chow [36]	Bexxar	tositumomab 450 mg	relapsed or refractory NHL	107	20.6 GBq (range 6,2 - 36,5)	@radiation exposure ≤0.02 mSv/h at 1 m. (Range 7-13 days)	≤25Gy at critical organs	Lung, liver, kydneys	chemotherapy with etoposide and cyclophosphamide

ACRONYMS: RIT=radioimmunotherapy; HD=high dose; ASCT= autologous stem cell transplantation; RM=red marrow;
TBI = Total Body Irradiation
TANDEM = protocol combining HD-chemotherapy + ASCT and HD-RIT + ASCT;
BEAM = carmustine, etoposide, cytarabine and melphalan chemotherapy; DLT = Dose Limiting Toxicity.

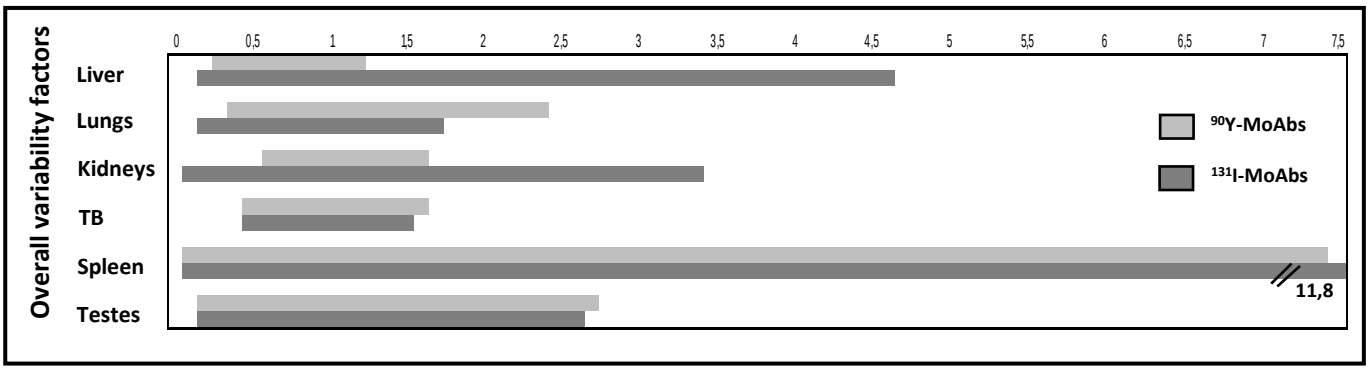
Table 2. Summary of the previsional dosimety methods used by different authors for NHL RIT. The first four studies concern standard approaches with dosimetry for RM . The other studies refer to hifght activity treatments associated with ASCT

AUTHOR [ref]	TREATMENT	RADIOPHARMACEUTICAL FOR PREVISIONAL DOSIMETRY [INJECTED ACTIVITY]	DOSIMETRY METHODS				RESULTS
			Other Organs		Red Marrow		
Sgouros [64]	RIT	---	Not performed	---	Model 1) Blood-based 2) Marrow biopsy	No RM uptake	"Blood -based model": Equation for red marrow-to-blood activity concentration ratio. Correction factors for red marrow biopsies.
Wiseman [58]	RIT	111In-Ibritumomab tiuxetan [185 MBq]	Planar @ 4–6 h, 1 d, 3 d, 6 d	Corrections: A (a same value for all organs), OM	1) Blood-based 2) Image-based: sacral	Possible RM uptake supposed uniform and checked with method 2	Both dosimetric and pharmacokinetic parameters were unable to predict observed hematologic toxicity
Ferrer [68]	RIT	111In-epratuzumab [120MBq]	Planar @ 1, 4, 24, 48 and 120 h	Corrections: A, S, B, GM	1) Blood-based 2) Image-based: L2-L4	Hypothesis of uniform RM uptake (method 2) or no uptake (method 1)	Only method 3 provides for bone marrow involvement and it better predict hematological toxicity as compared with 1 and 2.
Sgouros [73]	RIT	131I-labeled HuMl95 (Anti-CD33) antibody [300 MBq]	Planar @ day of injection, 1 and 2 d post injection	Corrections: A, B, GM	Image-based: - L3-L4 - femoral head - homerus head	Study of regional variability of RM uptake	Large inter- and intrapatient variability in marrow total dose. Dosimetry based on a single-site activity concentration measure may not properly estimate marrow toxicity.
Ferrucci [31] Cremonesi [56]	HD-RIT + ASCT	111In-Ibritumomab tiuxetan [185 MBq]	Planar @ 0, 1, 16, 24, 96 and 144 h	Corrections: A, S, B, GM, HCT, OM	Blood-based	Hypothesis of no specific RM uptake	Liver main critical organ and method 3 identified erroneous organs as critical. Individual dosimetry minimizes error sources. Choice of fitting curve crucial in dose calculations. Large inter-patient variability.
Pacilio [41]	RIT/HD-RIT	111In-Ibritumomab tiuxetan [185 MBq]	Planar @ 15 min, 1 h, 8 h, 24 h, 48 h, 72 h, 96 h and 120 h	Corrections: A, B, S, GM, OM	Blood-based	Hypothesis of no RM uptake	Liver, lung and kidney main organs at risk. Strong disagreement in dose results with Cremonesi/Ferrucci et al. [23,33] and with Wiseman et al. [53] works. Better agreement with Devizzi/Chiesa et al. [24,51].
Devizzi [32] Chiesa [57]	HD-RIT + ASCT	111In-Ibritumomab tiuxetan [median: 200 MBq]	Planar @ 0–1, 18–26, 40–48, 120–140 h	Corrections: A, B, S, GM, HCT, OM	1) Blood-based 2) Image-based in 3 patients: -sacrum -humerus -L2,L3,L4	RM uptake/uniformity checked with method 2	Large inter-patient varibility. Fixed-activity approach does not properly exploit the possibility of the treatment. Disagreement between RM dose estimations with method 1) and 2) and between L2-L4 and the other ROIs. No evident correlation between RM absorbed dose and platelet reduction.
Wahl [37]	HD-RIT + ASCT	111In-Ibritumomab tiuxetan [185 MBq]	Hybrid method: planar @ 0–1, 4, 24, 72, and 144 h + SPECT/CT @ 24 h	Corrections: A, B, S, OM	1) Blood-based 2) Image-based	Details not specified	Liver main organ at risk, but RM dose crucial for ASCT timing. MTD to liver seems to exceed 28 Gy. Large inter-patient varibaility. Hybrid approach is feasible for organ dosimetry-based HD-RIT with ASCT.
Hohloch [33]	TANDEM	131I-rituximab [370-400MBq]	Planar @ 1 h - 8 days	Corrections: GM, others not specified	Blood-based	Hypothesis of no RM uptake	Lungs and kidneys dose-limiting organs.
Gopal [28]	HD-RIT + fludarabine + ASCT	131I-tositumomab [185-370MBq]	Planar @ day of injection, 48, 96, and 120 h post injection	Corrections: A, B, GM, OM	Image-based	Details not specified	Lungs, liver and kidneys main critical organs.
Chow [36]	HD-RIT + HD chemptherapy + ASCT	131I-tositumomab [1.7mg/kg or 35mg] + unlabelled tositumomab [450mg]	Planar @ day of injection, 48, 120, 144 h post injection	Corrections: A, B, S, GM, OM	Not specified	Not specified	Lungs, liver and kidneys main critical organs.
Winter [30]	RIT (dose escalation) + HD-BEAM + ASCT	111In-Ibritumomab tiuxetan [185 MBq]	Planar @ 0, 4, 24, 72 and 144 h post injection	Corrections: A (a same value for all organs), OM	Not specified	Not specified	Large inter-patient variability underscores the importance of careful dosimetry evaluations. A dosimetry-based approach, rather than a weight-based approach, is recommended to safely deliver the highest possible dose. Liver and kidneys main critical organs.

ACRONYMS: RIT=radioimmunotherapy; HD=high dose; ASCT= autologous stem cell transplantation; RM=red marrow;
A=attenuation; B=background; S=scattering; GM=geometric mean; OM=organ masses; HCT=hematocrit; MTD=maximum tolerated dose;
TANDEM = protocol combining HD-chemotherapy + ASCT and HD-RIT + ASCT;
BEAM = carmustine, etoposide, cytarabine and melphalan chemotherapy.

Table 3. Ranges of variability factors related to the absorbed doses to normal organs, normalised to the median absorbed dose values.

	Reference	n. pts	Liver	Lungs	Kidneys	TB	Spleen	Testes
^{131}I-MoAbs	Kaminski [90]	7	0.8 - 1.3	0.7 - 1.9	0.7 - 1.6	0.6 - 1.2	0.4 -1.8	- .
	Gopal [27]	24	0.6 - 1.2	0.6 - 1.2	0.6 - 1.4	0.7 - 1.5	0.3 - 1.8	-
	Hattori [91]	67	0.3 - 1.2	0.4 - 1.2	-	0.6 - 1.5	0.1 - 7.4	0.2 - 2.7
	Chow [36]	107	-	0.4 - 2.4	-	0.5 - 1.6	-.	-
	Hohloch [33] *	9	-	0.6 - 1.2	0.6 - 1.2	-.	-	- .
^{90}Y-MoAbs	Wiseman [58]	229	0.2 - 4.5	0.2 - 1.7	0.1 - 3.3	0.6 - 1.5	0.1 - 3.0	0.3 - 1.5
	Delaloye [93]	57	0.3 -2.4	0.5 - 2.4	0.5 - 2.7	0.6 - 1.5	0.4 - 2.3	-
	Cremonesi [56]	22	0.5 - 2.8	0.2 - 1.6	0.2 - 2.0	0.5 - 1.1	0.3 - 2.3	0.2 - 2.6
	Chiesa [57]	15	0.7 - 1.4	0.7 - 1.4	0.5 - 1.3	-	0.7 - 1.4	0.5 - 1.7
	Whal [37]	18	0.5 - 1.6	0.5 - 1.6	0.6 - 1.5	-	0.5 - 11.8	-
	Bethge [34]	18	0.2 - 1.9	0.2 - 5.2	0.4 - 3.4	-	0.3 - 3.0	-



Note: For each organ, the variability factors are defined as the following ratios: min/median absorbed dose value, and maximum/median absorbed dose value. Thus, indicating with X the median value of the absorbed dose to an organ, for a range of variability factors e.g. 0.4 – 3.2, the range of the absorbed doses for a same activity administered is: (0.4·X, 3.2·X).

* Study on ^{131}I-Rituximab.