Estimates of Red Marrow Dose by Sacral Scintigraphy in Radioimmunotherapy Patients Having Non-Hodgkin's Lymphoma and Diffuse Bone Marrow Uptake

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Abstract

According to the recommendations of the Dosimetry Task Group of the American Association of Physicists in Medicine, blood-derived estimates of the red marrow (RM) dose from radiolabeled monoclonal antibodies (MAbs) are valid only if the RM is devoid of any specific uptake. There is, therefore, a clear need for an alternative method for estimating the RM dose in patients receiving MAbs that target normal or abnormal (malignant) bone marrow elements. Radiolabeled LL2, an anti-B-cell murine MAb, targets normal B cells and malignant lymphoma cells in the RM. This may result in an increased radiation dose to the RM through neighboring targeted activity. We investigated whether imaging-based estimates of the RM dose, particularly using sacral scintigraphy, correlate with myelotoxicity in non-Hodgkin's lymphoma patients who received $^{131}$I-LL2. The sacrum-based RM dose (RMs) was estimated from sacral activity as assuming that 95% of the total adult RM is contained in the sacrum. The sacrum was not used if there was focally increased or decreased sacral uptake. Myelotoxicity was assessed based on Radiation Therapy Oncology Group criteria. Twelve of 21 non-Hodgkin's lymphoma patients treated had adequate imaging, dosimetry, and follow-up to evaluate myelotoxicity. Eight of these patients had diffusely increased RM uptake on their MAb scans. The average estimated RMs in the eight patients was 168 ± 62 cGy (mean ± SD) with only 50 mCi $^{131}$I-LL2. Six of these patients (75%) developed grade 3 or 4 myelotoxicity. In contrast, the average RMs in the four patients who did not have any enhanced uptake on their scans was 71 ± 30 cGy (P < 0.02). None of these patients developed grade 3 or 4 toxicity. These results suggest that image-based estimates of the RM dose may be predictive of myelotoxicity and should be used in patients with diffuse RM uptake on their scans.

Introduction

Patients with NHL who receive RAIT and who have diffuse bone marrow metastases are more likely to develop dose-limiting toxicity than patients without bone marrow involvement (1). This may be due partially to a reduced RM reserve in these patients, caused by lymphomatous involvement of their marrow and/or extensive prior therapies. However, it also could be related to irradiation of normal bone marrow elements by radiation from neighboring tumor cells or clusters targeted by the radiolabeled antibodies (1, 2).

According to the recommendations of the Dosimetry Task Group of the American Association of Physicists in Medicine, blood-derived estimates of the RM dose from radiolabeled MAbs are valid only if the RM is devoid of any specific uptake due to the targeting of normal or abnormal bone marrow elements (2, 3). Several radiolabeled antibodies are being used increasingly for the treatment of hematological malignancies (1, 4–9). Most of these antibodies react with normal cells that reside in the bone marrow, in addition to bone marrow leukemia or lymphoma, thus potentially resulting in increased bone marrow uptake evident on the antibody scan. In these circumstances, blood-derived calculations are inadequate to estimate the RM dose and may not be expected to predict myelotoxicity, because these estimates will be too low. Thus, there is a clear need for an alternative method for estimating the RM dose in such patients.

Image-based methods to estimate the RM dose were suggested previously as more adequate than those derived from blood (10–13). These methods would be particularly important in NHL or leukemia patients with diffuse bone marrow uptake. Unfortunately, however, none of these methods has found widespread use in this clinical setting. We hypothesized that the use of sacral scintigraphy may provide a simple method of estimating the RM dose, and possibly a better predictor of myelotoxicity, in patients with relatively diffuse, but not focal, bone or bone marrow uptake. In patients with diffuse uptake, a ROI over the sacrum, as a representative of RM, could provide a reasonable and useful estimate of the RM dose.

Imaging of B-cell NHL with radiolabeled LL2 anti-CD22 MAb has a high sensitivity for targeting diffuse RM involvement with lymphoma, as seen by a markedly increased uptake on the antibody scans (4, 5). However, there also may be other reasons for increased diffuse RM uptake with antibodies reactive with hematopoietic cells, such as hyperproliferating RM after cytotoxic therapy (i.e., a hyperproliferative B-cell population; Ref. 5). Thus, enhanced targeting of bone marrow with an antibody reactive with hematopoietic cells may not always be indicative of tumor. There also may be situations in which the use of low antibody protein doses could show enhanced marrow uptake due to reaction with normal B cells (5). Thus, increased bone marrow uptake may not be of diagnostic significance, but it may be important for predicting myelotoxicity if the radiolabeled antibody is used for therapy. In this respect, we examined the role of sacral scintigraphy for predicting RAIT-induced myelotoxicity in patients who show enhanced, diffuse marrow activity.

Materials and Methods

Patients. Twenty-one patients with confirmed NHL who were referred for treatment with $^{131}$I-LL2 anti-CD22 antibody were studied. Adequate imaging and dosimetric studies were available in 17 patients. Patients were eligible for this trial if they had failed previous conventional therapy, had normal renal and hepatic function, had not been treated for 4 weeks, and were free from other active medical problems. Patients were excluded if they had allergies to mouse protein or iodine, had circulating HAMA, or had prior radiation to a maximal tolerable level of any normal organ. Patients without or with biopsy-proven bone marrow involvement were eligible for treatment. They received one or more cycles of therapy, with each cycle consisting of two injections of 30 and 20 mCi $^{131}$I-LL2 IgG or F(ab')2, over a 1-week period.

Imaging. Scans were acquired using a Sopyh DS-7 or DS-X camera (Sopyh Medical Systems, Columbia, MD). Anterior and posterior planar images of the head, neck, chest, abdomen, and pelvis were obtained 3 h after the injection and then on a daily basis (minimum of 3 days) for up to 1 week after injection. A high-energy collimator and 15% energy window centered on the $^{131}$I energy peak of 364 keV were used; 500,000 counts were collected using a $128 \times 128$ matrix. SPECT images of the chest, abdomen, and pelvis were obtained routinely in all patients on at least two occasions, usually on days 2 and 3, with a $64 \times 64$ matrix and 64 projections in a 360° circular orbit. A minimum of 50,000 counts was collected for each projection. Reconstruction was performed using a Hamming-Hann filter. The images were interpreted by at least two reviewers.

References

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3. The abbreviations used are: NHL, non-Hodgkin’s lymphoma; RAIT, radioimmunotherapy; MAb, murine monoclonal antibody; RM, red marrow; RMs, absorbed radiation dose to red marrow based on sacral scintigraphy; ROIs, regions of interest; SPECT, single-photon emission computed tomography; CLL, chronic lymphocytic leukemia.
Dosimetry. The method for determining the RM dose by sacral scintigraphy has been described previously (10). The sacrum was chosen for the scintigraphic method, because it contains a known fraction of RM (9.9%; Ref. 14) and is easily identifiable in nuclear medicine images of the pelvis. The sacrum was not used in patients who exhibited focally increased sacral uptake. Although such focal uptake is indicative of focally enhanced marrow localization, it may not be representative of uptake in the entire marrow and, therefore, cannot be used to make an assessment of the average RM dose. A photopenic sacral region usually caused by prior sacral X-ray irradiation also excluded the use of the sacrum for dose calculations. The same applies to lower pelvic masses such as lower bowel tumors or extensive adenopathy obscuring the sacral ROI. In these cases, ROIs of other marrow-containing areas, such as the lumbar vertebrae, may be used. In our pilot study, ROIs other than the sacrum were not explored. ROIs around the sacrum were used to quantitate activity uptake as a function of time, using the conjugate-view counting method. The anterior and posterior planar images of the pelvis obtained at multiple time points during imaging with the radiolabeled LL2 antibody were used for drawing the sacral ROI. An inverted triangular ROI encompassing the area between the internal iliac vessels, with exclusion of the bladder, was used to identify the sacrum to minimize the count contribution to the sacral counts from the blood vessels and ureters within the ROI. A bone marrow scan with \( {\text{\textsuperscript{99m}}\text{Tc}}\) sulfur colloid or a bone scan with \( {\text{\textsuperscript{99m}}\text{Tc}}\) methylene diphosphonate was used to delineate the sacrum in patients without discernible uptake on the antibody scan. An example of the ROI is shown in Fig. 1. Appropriate background ROIs were drawn for each sacral region. A computer-generated gray scale was used in the selection of the background for the sacrum. This minimizes the possibility of choosing areas with increased radiolabeled antibody uptake. The background ROIs were usually drawn lateral to the sacrum.

Cumulated activity in the RM was determined by curve integration and division by 0.099, because, as previously stated, 9.9% of the total RM is contained in the adult sacrum. RM doses were then obtained by multiplying the cumulated activities by the appropriate S factors obtained from Medical Internal Radiation Dose pamphlet 11 (15). These were \( 2.3 \times 10^{-4} \text{ cGy/\mu Ci/h} \) for RM to RM and \( 1.1 \times 10^{-5} \text{ cGy/\mu Ci/h} \) for total body to RM. The total sacrum-based RM dose was calculated for a single cycle of RAIT (50 mCi) and is reported as such in "Results."

Toxicity. Myelotoxicity was evaluated according to the standard Radiation Therapy Oncology Group grading. Weekly complete blood counts, with differential and platelet counts, were obtained following each therapy infusion. If grade 3 or 4 toxicity occurred, then the counts were obtained more frequently until resolution of toxicity. Blood counts were collected for a minimum of 8 weeks or until 2 consecutive weeks demonstrated full recovery to stable or baseline counts.

Results

Thirteen of 17 patients in this study exhibited increased RM uptake based on the \( {\text{\textsuperscript{131}}\text{I}}\)-LL2 MAb scan at 24 h or later after the antibody infusion (Table 1). The average RMs (per 50 mCi) in these patients was \( 153.7 \pm 63.7 \text{ cGy (mean \pm SD)} \). Ten of the 13 patients with enhanced uptake had RMs doses >100 cGy; however, 3 patients had RMs doses of 48, 77, and 85 cGy, respectively. These patients had very large spleens, which may have acted as potent "antigenic sinks," thus reducing the radiolabeled antibody amount available for other sites. Eight of the 13 patients had biopsies that confirmed bone marrow involvement with lymphoma. An example of a patient with biopsy-proven bone marrow involvement with diffusely increased uptake on the LL2 scan is shown in Fig. 2. Bone marrow biopsies were negative in 2 patients and were not obtained in the remaining 3 patients, but 1 patient had a magnetic resonance imaging study and a bone marrow scan with \( {\text{\textsuperscript{99m}}\text{Tc}}\)-sulfur colloid that failed to detect any bone marrow involvement. Although it is conceivable that the antibody imaging study may be more sensitive for detecting tumors in the marrow of patients with tumor-negative marrow biopsies, other possibilities must be considered. For example, increased bone marrow uptake may be due to hyperproliferative RM recovering from cytotoxic therapy. This was demonstrated in one patient by a bone marrow scan that indicated regenerative RM with expansion in the periphery (Fig. 3). Such conditions may be confirmed by a bone marrow biopsy demonstrating hypercellular RM but no evidence of lymphoma.

Table 1. Relationship between RMs, RMs (absorbed radiation dose to RM based on blood clearance), bone marrow biopsy, and MAb scan findings

<table>
<thead>
<tr>
<th>Patient</th>
<th>RM dose (cGy) by sacrum/50 mCi</th>
<th>Bone marrow biopsy for tumor</th>
<th>Scan results for bone marrow uptake</th>
<th>Toxicity grade after 1 full cycle of RAIT (50 mCi)</th>
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a) Not done or not determined.
b) Not assessable; patient already had grade 3 toxicity prior to RAIT.
enhanced bone marrow uptake in an antibody imaging study should be correlated with the results of a bilateral bone marrow biopsy.

As expected, the 4 patients without visually increased bone marrow uptake on their antibody scans had lower RMs than that of the 13 patients with visibly enhanced specific bone marrow uptake (70.9 ± 30.1 versus 153.7 ± 63.7; P < 0.05). Three of these 4 patients had tumor-negative bone marrow biopsies; a biopsy was not performed in the fourth patient.

A key issue for RAIT is whether the RM dose can predict myelotoxicity. If such a prediction were proven to be reliable, RAIT doses could be individualized, based on a pretheraputic imaging/dosimetry study. In all 4 patients without increased bone marrow uptake, myelotoxicity after a single cycle of RAIT of 50 mCi 131I-LL2 was no greater than grade 2. Only 8 of the 13 patients with enhanced bone marrow uptake had sufficient follow-up for determination of the nadir blood counts so that myelotoxicity could be graded. Six of these patients (75%) developed grade 3 or 4 toxicity. Here again, the mean RMs dose in the 8 evaluable patients with enhanced antibody uptake in the RM was significantly higher than the mean RMs dose in the 4 patients without enhanced uptake (168.1 ± 61.5 versus 70.9 ± 30.1; P < 0.05). One of the 8 patients had only a slight drop of platelets from 182,000 to 133,000, but this patient with low-grade lymphoma received only 77 cGy to his RM and had no prior chemotherapy. However, another patient who received 179 cGy to the RM by sacral scintigraphy also had only a transient drop of platelets from 201,000 to 124,000, which is still considered a grade 0 toxicity. However, this patient had CLL, with 80% of his marrow infiltrated with lymphocytes, and it is, therefore, feasible that a substantial portion of the radiation dose was delivered to the malignant leukemic cells with only a small contribution to normal hematopoietic elements.

Similar results were found in a subgroup of eight patients, in whom both increased bone marrow uptake was seen on the antibody scans and biopsy-proven bone marrow disease was documented. Five of these patients could be evaluated for myelotoxicity, and four (80%) had grade 3 or 4 toxicity after a single cycle of treatment. This compares well with a subgroup of three patients in whom both a negative bone marrow biopsy and no bone marrow uptake were documented and who developed grade 2 or less myelotoxicity. Thus, these results strongly suggest that imaging-based estimates of the RM dose predict myelotoxicity in patients with diffuse bone marrow uptake or bone marrow involvement.

Discussion

Estimates of absorbed radiation dose to the RM can be obtained by several methods: photon emissions from the whole body (16); mean whole-body dose (17); circulating blood mass of the RM (18); equivalent RM and blood activity concentration (19); RM: blood activity concentration ratios of less than 1.0, mostly 0.25 (1–3); and scintigraphy (10–13). We have estimated the RM dose based on blood previously by assuming equal activity concentrations of RM and blood, as suggested by Bigler et al. (19). Most recently, we have instituted the use of a marrow:blood ratio of 0.36 to be more consistent with the recommendations of the Dosimetry Task Group of the American Association of Physicists in Medicine (1–3), suggesting a marrow:blood activity concentration ratio of 0.2–0.4. We have also used sacral scintigraphy as an alternative, imaging-based, method to estimate the RM dose (10, 11) in patients with solid tumors given 131I-labeled anticarcinoembryonic antigen or anti-α-fetoprotein MAbs. In these patients, the RMs was 21–38% lower than that based on blood. However, these blood-based RM doses were computed with the assumption of equal marrow and blood activity concentration, and these results, therefore, were expected, because the activity concentration in the RM may be a only fraction of that in the blood (1–3, 20, 21). Most importantly, these patients did not have diffuse RM involvement with cancer, their RM elements did not react with the antarcinoembryonic antigen or anti-α-fetoprotein antibodies, and, therefore, specific bone marrow uptake was not expected. In these circumstances, either imaging- or blood-based methodology may be adequate for estimating the RM dose.

Patients with hematological malignancies, including leukemia, stage IV Hodgkin’s or non-Hodgkin’s disease, and multiple myeloma, commonly have diffuse bone marrow involvement of variable degrees. Moreover, the antibodies used in the targeting and treatment of these malignancies react with malignant and normal cells. Although targeting of malignant cells in the marrow is desirable, the concomitant targeting of normal cells is likely to be undesirable, because this could lead to increased irradiation of the marrow elements essential for the reestablishment of normal marrow activity. Depending on the antigen marker, the number of normal cells recognized by an antibody could constitute a significant portion of the marrow. Therefore, it would be preferred if markers could be selected that are on a subpopulation of normal cells with minimal residency in the marrow. For example, the CD22 antigen recognized by the LL2 antibody is found on the surface of mature B cells, which are found in only a low concentration in the normal marrow (4). This is confirmed by the usual lack of any significant uptake in the marrow with radiolabeled LL2. However, patients who are recovering from chemotherapy, or who received treatment with cytokines or other marrow-enhancing agents, may have hyperproliferating bone marrow. Under these conditions, the number of normal cells expressing the CD22 antigen may be increased, and enhanced radioantibody uptake may be expected. This was very apparent in one patient included in this study. Thus, enhanced diffuse antibody uptake in the marrow may not be able to discriminate between tumor involvement or marrow hyperactivity, but it may be a useful procedure for screening patients to determine the need for a bone marrow biopsy. Thus, it will be important in the future to assess the sensitivity of antibody imaging for detecting diffuse bone...
Fig. 3. A, anterior and posterior whole-body scans with $^{131}I$-LL2 F(ab')2 in a patient with hyperproliferative bone marrow. Magnetic resonance imaging did not demonstrate lymphomatous bone marrow involvement. The patient was infused with 30 mCi $^{131}I$-F(ab')2 and imaged 24 h later. B, Posterior spot views of the chest, abdomen, and pelvis in the same patient as in A. C, Bone marrow scan posterior spot views of the chest, abdomen, and pelvis in the same patient, clearly demonstrating hyperactive RM. The scan was obtained 20 minutes after the injection of 5 mCi $^{99m}$Tc-sulfur colloid.

marrow involvement. In this study, routine pathological and cytological testing was used to detect tumors in the marrow biopsies. With the potential for enhancing the sensitivity of detecting malignant cells by flow cytometry and PCR analysis, it will be essential to include these methods to determine the sensitivity of antibody imaging in diagnosing bone marrow involvement.

As expected, the average RMs dose was higher in patients with NHL or CLL and diffuse antibody uptake in the marrow than in
patients with only nonspecific marrow uptake. Moreover, patients with the higher RM doses were at a higher risk of developing more severe myelotoxicity when given the same radioactive dose as patients with lower RM doses. Similar results were obtained by Macey et al. (12) in six patients with NHL and CLL who were treated with $^{131}$I-labeled Lym-1 anti-B-cell antibody. These investigators also used an imaging-based method for estimating the RM dose, using data from three lumbar vertebrae for their calculations. A greater hematological toxicity was predicted using this method than would be anticipated from radiation doses estimated by using the traditional blood and total-body contributions (12).

Although it is likely that as we continue to assess the correlation between RMs and myelotoxicity, a strong relationship will be found, more research needs to be done to define the tolerance of patients who have received chemotherapy and radiation therapy prior to nonmyeloablative RAIT treatment. This is especially true for patients who had extensive prior exposure to myelotoxic agents. Thus, methods need to be established that will reflect more accurately the marrow reserve in patients, so that radioantibody dosages can be adjusted accordingly. It also is reasonable to assume that hyperproliferative RM is more radiosensitive than normally active RM, and, therefore, steps must be taken to avoid initiating RAIT until such a condition is resolved. Thus, although the RM dose is a very important parameter in determining myelotoxicity in NHL patients, other factors should be considered as well.

The use of the sacral ROI in patients with relatively uniform diffuse RM uptake may be adequate for determining the RM dose. However, there are limitations to the exclusive use of the sacral region as a representative portion of the entire RM. In addition to the possibility that overlying sacral disease or other problems may limit its use, there is also an assumption that the percentage of lymphoma involvement is similar throughout the entire RM. This assumption is made currently when bone marrow biopsies are performed. Although biopsies are performed in the iliac crest regions, it is assumed that the degree of RM involvement is similar throughout the RM. Other investigators have used several ROIs and a weighted average to calculate a mean RM dose (13). In this regard, MAb imaging may provide a better picture of the extent of marrow involvement. Studies are underway in our laboratory to compare a region-weighted result obtained using several ROIs with the value obtained when using the sacral ROI alone. In addition, SPECT may be used for a better delineation of the sacral ROI. One should recognize, however, that all of these image-based estimates are based on the assumption that the radiation dose is homogeneously distributed between microscopic tumor areas and normal RM elements within the bone marrow mass, thus providing an “average” dose in this region. This assumption may lead to an overestimation of the radiation dose to the normal RM. This limitation is explained partially by the limited spatial resolution of the nuclear imaging techniques, including SPECT. However, although microdosimetric calculations may be important to determine the “exact” dose to the normal RM, information regarding the exact spatial distribution of the micrometastases may not be available, even when using multiple bone marrow biopsies. Moreover, due to the diffuse nature of micrometastatic deposits in lymphoma and their generally small average diameters (~450 μm) compared with the path length of $^{131}$I, the dose distribution may be partially “evened out” (22). Nevertheless, because the average RM estimates by sacral scintigraphy seem to predict myelotoxicity in lymphoma patients better, it seems reasonable to use this estimate in the clinical setting. This study confirms that an image-based estimate of the RM dose should be used in patients with diffuse bone marrow uptake on their scans and that it may be predictive of RAIT-induced myelotoxicity in this group of patients. Studies are underway to confirm this finding in a larger number of patients.

References


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