Blood-Based Red Marrow Dosimetry: Where's the Beef?

TO THE EDITOR: We read with great interest the recent article by Wessels et al. (*1*). The article purports to propose a clinically relevant, standard method for the blood-based estimation of red marrow absorbed dose for radiolabeled antibody therapy as a benchmark for intercomparison purposes. We believe that the proposed model contains a mathematic error and that, even if corrected, the method may have limited clinical relevance.

The Mathematic Error: Treatment of Remainder-of-Body Component

The absorbed dose to red marrow due to ^{131}I activity in the remainder tissues of the body is given as (*1*):

$$D_{RM}^{Cross} = \left\{ \tilde{A}_{WB} - [\tilde{A}]_{bl} \times \left(\frac{RMECFF}{1 - HCT} \right) \times \left(\frac{1.5}{70} \right) \times M_{WB-patient} \right\} \times S(RM \leftarrow RB)_{patient},$$

where:

$$S(RM \leftarrow RB)_{patient} = S(RM \leftarrow WB)_{MD11} \times \left(\frac{M_{WB-patient}}{M_{WB-patient} - M_{RM-patient}} \right) - S(RM \leftarrow RM)_{MD11} \times \left(\frac{M_{RM-patient}}{M_{WB-patient} - M_{RM-patient}} \right)$$
$$= 8.258\text{E}-07 \times \left(\frac{1}{1 - (1.5/70)} \right) - 1.727\text{E}-05 \times \left(\frac{(1.5/70)}{1 - (1.5/70)} \right)$$
$$= 4.66\text{E}-07 \text{ (mGy/MBq-s)}.$$

This S value differs from that given in the article because an incorrect value for $S(RM \leftarrow TB)_{MD11}$ was used, leading to a miscalculation. More important, contrary to their stated intent, the authors' approach has resulted in a remainder-of-body S value that is patient mass independent, when it should be mass dependent.

In order to add the necessary mass dependence, the 2 S values themselves must be mass adjusted (*2*). Each S value should be multiplied by $M_{RM-MD11}/M_{RM-patient}$, which may be approximated by $M_{WB-MD11}/M_{WB-patient}$, leading to a multiplicative factor of $70/M_{WB-patient}$. Therefore:

$$S(RM \leftarrow RB)_{patient} = 4.66\text{E}-07 \times 70/M_{WB-patient} = 3.26\text{E}-05/M_{WB-patient}.$$

It has previously been shown that ignoring this mass dependence may lead to significant calculational errors (*2*).

Establishing a Clinically Relevant, Standard Method for Red Marrow Dosimetry

Although most institutions have adopted the 2-component approach to red marrow dose calculation, the methods used are only similar, not identical. Wessels et al. (*1*) suggest that this lack of standardization caused many investigators to use a dosing metric based on administered activity, when in reality these nondosimetric methods have been proven effective. Although variations in dosimetry methods will certainly contribute uncertainty to red marrow dose estimates, the small sample set (consisting of datasets containing only 2 patients for 6 of the 7 participating institutions) included in the article (*1*) makes it difficult to comprehend the true range of uncertainty, and therefore the reported "benchmarking" is of limited value.

There are 3 major mathematic features that require standardization in the blood-based estimation of red marrow absorbed dose. We have already discussed the remainder-of-body S value; the other 2 are conversion of blood data to red marrow data, and phantom choice.

Conversion of Blood Data to Red Marrow Data. A commonly used, practical method to estimate the ratio of cumulated activity concentration in red marrow to that in blood uses the term red marrow extracellular fluid fraction/(1 − hematocrit), as proposed in the article (*1*). The red marrow extracellular fluid fraction is assumed to have a constant value of 0.19, a value obtained from a study of the albumin space in the red marrow of rabbit femur and, importantly, a value not intended for use in patients whose marrow has been compromised by therapy (*3*). Because the majority of patients receiving radiolabeled monoclonal antibody therapy (using either commercially available or investigational agents) have undergone prior therapies resulting in vastly differing marrow reserves and radiosensitivities, assigning a constant value, such as 0.19, may not be a clinically relevant approach because it does not adequately address these other variables in a manner to reduce the variation in hematologic toxicity that is generally encountered.

Phantom Choice. MIRD Pamphlet No. 11 S values and phantom masses (*4*) for ^{131}I were used in the article (*1*). Patients treated with ^{186}Re were included in the investigation, but the phantom choice was not specified for these patients (^{186}Re does not appear in MIRD Pamphlet No. 11). A review of the literature indicates that more investigators have used MIRDOSE (*5*) than MIRD Pamphlet No. 11. It would seem more reasonable to use MIRDOSE, or potentially OLINDA (organ level internal dose assessment) (*6*), S values and phantom mass values to accommodate a standard method for both ^{131}I and ^{186}Re.

In conclusion, we believe that the clinically relevant standard method for the blood-based estimation of red marrow absorbed dose presented by Wessels et al. (*1*) contains a mathematic error and uses a phantom that does not include both radionuclides presented in the article. Thus, the method can hardly be viewed as a benchmark standard. We do, however, strongly endorse the idea that marrow dosimetry should be standardized, but in terms of not only parameters of absorbed dose but also parameters of marrow status (i.e., the ability of individual patients' marrow to tolerate

additional myelosuppressive treatment), especially in heavily pretreated patient populations (*7,8*).

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REPLY: With the exception of the specific points considered below, the primary concerns raised by Siegel et al. center on use of the word *benchmark.* As the title of the paper indicates, its focus was a multiinstitutional comparison (*1*). As such, the conclusions of the paper remain valid. Regarding the specific points:

1. The correspondents have noted that a value used in Table 1 differs from their own calculation. The discrepancy lies in the number of significant figures used in the calculation. In converting to SI units and using *S(RM ← WB)* to derive *S(RM ← RB),* my coauthors and I rounded the published MIRD Pamphlet No. 11 (*2*) value of 1.1E−05 to 1E−05. The difference in the values for *S(RM ← RB)* is, therefore, due to a truncation error resulting in an overall 3%–7% underestimate in dose values calculated for institutions using ^{131}I in Table 2. When other errors involved in dosimetry calculations are considered, the conclusions drawn from Table 2 remain unchanged. The correct Table 1 values for *S(RM ← WB)* and *S(RM ← RB)* are 8.261E−07 and 4.660E−07 mGy/MBq-s, respectively.
2. As has been previously recognized in MIRD Pamphlet No. 11 (*2*), there is no simple approach to mass scaling of an S factor that includes combined electron and photon contributions, such as *S(RM ← WB).* Although phantom models and S values have been updated in MIRDOSE3.1 and organ level internal dose assessment (OLINDA) codes (*3,4*), no systematic study has been published that provides us with further information on how to perform this scaling. In fact, MIRD Pamphlet No. 11 indicates that for target organs sufficiently distant from source organs, one would expect the specific absorbed fraction and the S value to be independent of mass (i.e., increases in patient size result in compensating increases in both organ mass and cross-organ photon absorbed fraction). MIRD Pamphlet No. 11 states that the photon contribution from the target self-dose varies as $M^{-2/3}$ and electron self-dose as M^{-1}. The scaling suggested by Siegel et al. and used by Stabin et al. (*5*) has yet to be validated to support the approach of applying a linear mass correction (M^{-1}) to the photon cross-dose contribution. Notably, strict adherence to the guidance provided by MIRD Pamphlet No. 11 regarding mass correction was properly applied in the OLINDA code (*4*). OLINDA documentation cites an earlier Snyder publication (*6*) in which the particulate component of the self-dose varies as M^{-1}, photon self-dose varies as $M^{-2/3}$, and photon cross dose is mass independent. Hence, the mass correction methodology used in the present work remains consistent with MIRD Pamphlet No. 11 recommendations. It remains the method of choice pending new studies using variable-mass patient phantoms that would substantiate any further change in patient mass scaling.

   Nevertheless, if such a mass correction were to be included in the cross-dose term (Eq. 11) of the article and at a power of M^{-1}, the result would be a 2%–6% change to any of the values appearing in Table 1. This change is similar to the change one would arrive at for using lean body mass and less than if MIRDOSE3 S values were used. However, the text used to describe Equations 9–11 in the article is unclear and a clarification will be included in an erratum.

   Large uncertainties noted by Siegel et al. are dominated by the electron contribution from the self-dose term for the physically relevant data presented in the article and were appropriately mass corrected in Equation 8. This is discussed by Shen et al. (*7*), for whom a mathematically correct derivation showed an apparent canceling of mass dependence for the self-dose term when the blood concentration was used. One is reminded that the dominance of a mass adjustment for the self-dose term remains because blood concentration automatically scales this term to be patient specific.
3. Regarding sample size, we certainly would have preferred to analyze a greater number of patients per institution. However, total patient number ($n = 21$) is well within nominal standards that have been traditionally used for MIRD dose estimate reports. As noted in the article, a greater number of patients were submitted by all institutions. Several of these patients, however, did not meet our inclusion criteria for data entry into the study or remain to be analyzed. Because the emphasis of the paper is on an interinstitutional comparison of calculations relative to a standardized approach given the same dataset, the most critical *n* value is the number of institutions. The reproducibility of calculation methodology at any individual institution is a secondary to the specific aims as stated above.

We had 7 institutions participating and believe that the conclusions of the paper are not invalidated by the sample number for each institution.

4. Comments regarding variations in red marrow extracellular fluid fraction, MIRDOSE S values, prior therapies, and marrow reserve have already been extensively addressed in this article. As Siegel et al. point out and as was discussed in our paper, it is important to understand the limitations of the blood-based remainder-of-body dosimetry formulation. The correspondents are correct. ^{186}Re S value was adopted from MIRDOSE3.1. A similar approach was taken by the contributing institution but using MIRDOSE2.

To summarize, Siegel et al. have identified errors in the article that lead to at most 10% differences in the final published results, well within the error associated with radionuclide dosimetry calculations. Nevertheless, corrections will be published via an erratum. Suggested mass corrections to the cross-dose term do not agree with MIRD Pamphlet No. 11 methodology and the OLINDA program and have no experimental basis supported in the literature. It is our opinion that this paper makes a meaningful contribution and that the validity of the conclusions is inconsistent with the concerns raised in the letter.

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REPLY: I respectfully dissent from the majority opinion offered regarding point 2 in the response of Wessels to the letter of Siegel et al. I remain in agreement with the position that "with measured blood activity concentration, red marrow dose may be represented by a *patient mass-independent term,* involving red marrow self dose, and a *patient mass-dependent term,* involving dose from the remainder of the body" (*1*). This position is also shared by Shen et al. (*2*) and was reiterated recently by Siegel (*3*). I believe this approach to be the most correct and accepted current method to perform patient-specific corrections to standardized marrow dose calculations. The article of Wessels et al. (*4*) treats both terms as being patient mass independent and thus treats all patients as if they are of standard size and mass. Correct accounting for the electron and photon contributions from activity in the remainder of the body is important, especially when the cumulated activity ratios for remainder of body to red marrow are high. This may result in differences in calculated marrow dose from standardized models of much larger than 2%–6%, as claimed by Wessels in his response; our calculations indicated that patient-specific marrow doses might be different from those calculated using standard phantoms by 20%–70% (Table 2 of Stabin et al. (*1*)). The arguments raised by Wessels in his response to eliminate the patient specificity of the second term, regarding mass-based corrections to absorbed fractions, apply most correctly to discrete (not distributed) organs in the body. Whether this type of correction can be applied to values of $S(RM \leftarrow RB)$ could be tested and might produce some interesting results for future study. I do not, however, believe that a sufficient scientific basis exists to support this argument (and I tried to point this out to the other authors in the spring of 2003). I enthusiastically applaud the efforts of the authors to encourage multiinstitutional comparisons of marrow dose in order to study dosimetry and possible dose–effect relationships. I suggest, however, that if patient-specific modifications are undertaken, they be applied with consistent and widely accepted methods and include patient-specific corrections for target region masses when possible.

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Advantage of ^{188}Re-Radiopharmaceuticals in Hepatocellular Cancer and Liver Metastases

TO THE EDITOR: We read with great interest the paper from Lambert et al. (*1*) about the treatment of hepatocellular cancer using a mean activity of 3.6 GBq of ^{188}Re-labeled 4-hexadecyl-1,2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol/lipiodol (^{188}Re-HDD/lipiodol) in 11 patients.

We would like to comment on the relatively high urinary excretion rate that was reported in this paper. The authors described a urinary excretion rate of 44.1% ± 11.7% of administered ^{188}Re-HDD/lipiodol within 72 h, which is ineffectively high and comparable to the treatment of bone metastases using radioactive labeled diphosphonates (*2*). This high urinary excretion rate corresponds to an effective half-life of 14.3 ± 0.9 h in the whole body.

For the purpose of radioembolization, ^{188}Re-human serum albumin (HSA) microspheres were developed and the labeling procedure was improved (*3,4*). High stability of the radiopharmaceutical could be demonstrated in in vitro studies. The first human applications, in 8 patients (14 treatment sessions) with hepatocellular cancer or liver metastases of colon cancer, revealed a low urinary excretion rate for ^{188}Re-HSA microspheres (8.5% ± 3.6% of administered activity within 96 h). This rate resulted in an effective half-life of 15.7 h in the whole body.

^{188}Re-HDD/lipiodol has some other disadvantages, compared with ^{188}Re-HSA microspheres. Lambert et al. (*1*) reported a total radiochemical yield of 53% ± 4.5% for ^{188}Re-HDD/lipiodol. In our studies was observed a high radiochemical yield, greater than 95% in vitro, for ^{188}Re-HSA microspheres. ^{188}Re-HDD/lipiodol also showed a relatively high radiolysis (*5*). This fact was reflected by the instant thin-layer chromatography analysis performed by Lambert et al. (*1*), which found a high rate of ^{188}Re-perrhenate in urine. In animal studies using ^{188}Re-HSA microspheres (*3*), an in vivo stability > 90% and an in vitro stability > 88% were observed (investigated in human plasma, blood, and saline for 30 h) (*4*). Another interesting radiopharmaceutical is ^{90}Y-glass microspheres, but urinary excretion rates were not described (*6*)

Lipiodol, as an emulsion of iodized ethyl esters of fatty acid of poppy-seed oil, is more a "chemical" embolization agent with a high viscosity (*7*). Intraarterial injected lipiodol flowed retrograde into the portal venules through hepatic sinusoids and flowed antegrade through the peribiliary vascular plexus (*8*). This fact indicates only a weak fixation of this agent in the tumor capillary. In contrast, HSA microspheres are "physical" embolization agents, which embolized the capillary vascular plexus. The mean particle diameter of about 25 μm (*4*) and the uniform size are optimal for embolization (*4*), and this radiopharmaceutical is widely used in perfusion scanning of the lung.

In view of the relatively high urinary excretion rate, low radiochemical yield, and weak stability of ^{188}Re-HDD/lipiodol, we propose the use of ^{188}Re-HSA microspheres for the radionuclide treatment of hepatocellular cancer and liver metastases to increase the tumor dose and reduce unnecessary radiation exposure to patients.

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REPLY: My coauthors and I thank Drs. Liepe and Kotzerke for their interesting comments on our paper (*1*). Urinary excretion of ^{188}Re is 60% ± 12% 48 h after injection of ^{188}Re-hydroxyethylidene diphosphonate injection but 44.1% ± 11.7% 76 h after treatment with ^{188}Re-labeled 4-hexadecyl-1,2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol/lipiodol (^{188}Re-HDD/lipiodol [iodized oil; Guerbet]) (*2*). However, it seems more relevant to compare the urinary elimination of ^{188}Re in this context with the results obtained using ^{131}I-lipiodol. If the shorter physical half-life of ^{188}Re (16.9 h) is considered, our value of 44.1% over 76 h compares favorably with the observations of Raoul et al. and Nakajo et al. with ^{131}I-lipiodol (*3,4*).

It was not specified how the ^{188}Re-labeled human serum albumin (HSA) microspheres were administered. We applied an administration in the proper hepatic artery or both left and right branches, aiming at whole-liver treatment. Other authors have proposed injection as close to the tumor-feeding artery as possible (*5*). The administration protocol might have an impact on clearance of the radiopharmaceutical. Second, we assume that the presence of arteriovenous shunting in the liver affects elimination of the radionuclide after intraarterial administration. The degree of shunting depends on the underlying liver disease and, for patients with hepatocellular carcinoma and cirrhosis, is expected to be considerably higher than for patients with colorectal metastasis without underlying cirrhosis (*6*). Hence, the relatively low value of 8.5% of injected ^{188}Re retrieved in the urine after administration of ^{188}Re-labeled HSA microspheres in a mixed patient population (hepatocellular carcinoma and liver metastasis) is difficult to compare with the results obtained in our series, consisting of cirrhotic patients with hepatocellular carcinoma.

In addition, low urinary excretion of radionuclide does not guarantee good liver or tumor retention of the radiopharmaceutical. It would have been more relevant to compare the effective liver half-life rather than the effective half-life in the whole body. Was fecal elimination checked in the clinical study?

We agree that the low radiochemical yield of the ^{188}Re-HDD/lipiodol labeling procedure is an important drawback to implementing high-activity treatment routinely. Probably, the kit presented by Wunderlich et al. (*7*) is also safer from a radioprotection

point of view. In addition, the ^{188}Re-labeled HSA microspheres have several interesting features such as a homogeneous particle size of 25 μm, an only-temporary occluding effect on the blood vessels, and a production cost that is probably lower than that for ^{90}Y-labeled microspheres.

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Radioiodine Therapy and Pregnancy

TO THE EDITOR: While reading the European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine (SNM) procedure guidelines for therapy with ^{131}I (*1*,*2*), I was concerned to find that both organizations recommend the use of pregnancy testing (type unspecified) a few days before ^{131}I treatment. The implication is that the pregnancy test will preclude pregnancy, which is contraindicated because of the high radiation dose to the embryo or fetus.

Standard pregnancy tests are intended to assess pregnancy status after a missed period rather than to exclude pregnancy at other points in the menstrual cycle. The standard pregnancy tests detect human chorionic gonadotropin (hCG) in the urine with a sensitivity of ~20–50 mIU/mL. Using such tests, urinary hCG is detectable only from ~3 d after the fertilized ovum is implanted in the uterine wall. Typically, implantation occurs ~21 d into the cycle, so that it is ~24 d before measurable urinary hCG is produced. However, even a urinary hCG assay 100 times more sensitive than the standard assays failed to detect 10% of pregnancies on the first day after a missed period (i.e., ~29 d after the last menstrual period [LMP]) and 3% of pregnancies 7 d after a missed period, presumably because of variability in times of fertilization and implantation (*3*).

Therefore, if we look at the expected performance of a standard pregnancy kit for urinary hCG throughout the cycle, from the early phase of the cycle until day 10 after LMP, it is considered reasonable to assume that the woman has not ovulated and is not pregnant and that, therefore, a standard pregnancy test would yield a true-negative result. If we assume that the ovulation and fertilization occur ~11–14 d after LMP, then from that time until ~day 24, a standard pregnancy test is likely to yield a negative result although the woman is pregnant, that is, a false-negative result. Thereafter, the findings would become increasingly true positive, although as indicated above, false negatives can occur even up to 7 d after a missed period. Therefore, if our aim is to exclude pregnancy before therapy, a standard pregnancy test is likely to mislead us for approximately half the menstrual cycle. With a more sensitive serum assay for hCG, the period of uncertainty might be reduced but not eliminated.

The other way in which we try to exclude the possibility of pregnancy is to ask the patient if she can categorically state that she is not pregnant. There is at least one reference in the literature where, despite a pretherapy negative pregnancy test and a written signed declaration stating that she was not pregnant, the woman in question was subsequently found to be pregnant after radioiodine therapy (*4*). The typical patient's assessment of her own pregnancy status may be inaccurate, perhaps because she overestimates the efficiency of the method of contraception used. Because many methods of "reversible" contraception, such as contraceptive pills or condoms, are not 100% efficient, it is unlikely that a woman who has had intercourse "mid cycle" and is using "reversible" contraception can categorically state that she is not pregnant. This is supported by an interesting statement in a recent paper on contraceptive failure to the effect that "half of all pregnancies in the United States are unintended. Of these, half occur to women who were practicing contraception in the month they conceived" (*5*).

Our practice to date has been to ask the woman to sign a declaration that she is definitely not pregnant. If she has done this, we have proceeded with the therapy; however, if she is in any doubt, we have applied the "10-d rule"; that is, performed the therapy during the 10 d after the onset of a period (*6*). Maybe we should apply the 10-d rule across the board for all sexually active women of childbearing age undergoing radioiodine therapy, irrespective of whether they indicate they are pregnant. Even this protocol will not be foolproof, given that thyrotoxicosis can be associated with menstrual cycle irregularities and that cycle variability generally affects the earlier follicular phase of the cycle, or the phase associated with our "10 d," rather than the later luteal phase (*7*). Thus, the 10-d rule might be too long for someone with a short cycle.

The considerations above indicate the difficulties in being proscriptive when administering radioiodine to female patients of childbearing age. Therefore, perhaps it would be best to administer therapies on the basis on the 10-d rule but modified as required after the prescribing physician asks detailed questions about the patient's menstrual history. This protocol would require modifications to both EANM and SNM guidelines.

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REPLY: Dr. Watson correctly makes 3 points regarding the inherent difficulties of absolutely excluding pregnancy before the administration of radioactive iodine in all women of childbearing age.

First, pregnancy testing alone will not exclude all early pregnancies. However, if pregnancy testing were not performed, it is reasonable to expect that more pregnant hyperthyroid patients would receive ^{131}I therapy than is the case when pregnancy testing is done. The Society of Nuclear Medicine (SNM) guidelines are deliberately not too specific regarding method and timing of the pregnancy test. Of interest, the American College of Radiology (ACR) Practice Guideline for the Performance of Therapy with Unsealed Radiopharmaceutical Sources (effective Jan.1, 2001) also states that "pregnancy may be ruled out by a negative hCG [human chorionic gonadotropin] test obtained within 48 hrs prior to administration of the radiopharmaceutical, or by documented history of hysterectomy or tubal ligation, by a postmenopausal state with absence of menstrual bleeding for 2 years, or by premenarche in a child" (*1*). Institutions should have their own policies for excluding pregnancy and can make them more stringent than what is found in the guidelines. However, the SNM guidelines reflect the consensus opinion of numerous practitioners from various regions of the United States who were involved in the writing, review, and approval of this document.

Second, historical data also are not perfect. The SNM guidelines state, "Occasionally, when historical information clearly indicates pregnancy is impossible, a pregnancy test may be omitted at the discretion of the treating physician." All physicians should know that condoms and birth control medication are fallible. Again, all institutions should have their own specific criteria.

Third, likewise, limiting radioiodine therapy to the first 10 d of the menstrual cycle will also not exclude all pregnancies for the reasons given by Dr. Watson. This and the limitations of even the highly sensitive serum β-hCG testing in the earliest stages of pregnancy (approximately 7 d after conception) underscore the value of the treating physicians' clinical interview and judgment. Some practitioners ask the patient to abstain from intercourse for a week before therapy and still obtain a pregnancy test just before treatment.

We believe that Dr. Watson's practice of relying on the patient's "declaration that she is definitely not pregnant" is insufficient in the current regulatory and medicolegal environment in the United States. Aside from the obvious goal of never administering ^{131}I therapy to a potentially pregnant patient, in the United States, fetal exposure greater than 50 mSv (which is likely to occur with ^{131}I therapy) must be reported to regulatory agencies; thus, it seems reasonable to take every measure to minimize the likelihood of this occurrence.

Strictly adhering to the policies outlined in our first and second points, plus having the patient sign a consent stating she is definitely not pregnant, will make the occurrence of treating a pregnant woman with radioiodine an exceedingly rare event. Obviously, the given criteria must be rigidly followed.

REFERENCE

1. ACR practice guideline for the performance of therapy with unsealed radiopharmaceutical sources. Available at: www.acr.org/s_acr/bin.asp?CID=1074&DID=12298&DOC=FILE.PDF. Accessed June 15, 2005.

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