Magnetically enhanced protection of bone marrow from beta particles emitted by bone-seeking radionuclides: Theory of application

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Utilization of radiopharmaceuticals that directly target radioactivity to tumors for treatment has a great deal of promise. Ideally, lethal doses of radiation could be delivered precisely to areas of disease, while, for the most part, sparing normal tissues. This potential, however, has not yet been fully realized. Current limitations of this approach are low tumor uptake of radiopharmaceuticals and dose-limiting radiotoxicity. In an effort to offset low uptake, radionuclides that emit high average-energy electrons have been proposed. Unfortunately, use of these radionuclides increases myelosuppression on a per decay basis. In order to allow for the utilization of high doses of this class of high-energy beta emitters, we propose the application of a strong static homogeneous magnetic field to constrain the beta particles. Monte Carlo computer simulations indicate that application of a 10 T magnetic field can decrease the total radiation dose from bone-avid tracers to marrow located in shafts of human long bones by 14%. More significantly, however, the penetration depth of high-energy electrons from the bone surface into the marrow can be reduced by up to 74.6%. Preservation of marrow in areas distal to the bone has previously been shown to facilitate relatively rapid recovery from pancytopenia produced by radiation damage to trabecular marrow (without marrow transplantation). Magnetically enhanced protection of bone marrow, therefore, may allow administered doses of high-energy beta-emitting radionuclides to be increased. By raising the limits on injected quantities of such highly ionizing radionuclides, amounts of the radiation dose absorbed by both soft and calcified tissue tumors will be increased, compared to conventional treatments. Hence, it is possible that this technique will, in part, aid in the realization of the promise of radionuclide therapy by permitting the delivery of therapeutic levels of radiation exposure to tumors.

Key words: magnetic fields, radionuclide therapy, bone marrow, dosimetry

I. INTRODUCTION

Utilization of radiopharmaceuticals to treat cancer is an extremely attractive concept. Therapeutic doses of radiation could be delivered preferentially to tumors after injection, while sparing the majority of normal tissues; in contrast to traditional external beam irradiation. Unfortunately, much of the promise of radiopharmaceutical therapy has not been realized. Among the reasons for this failure are subtherapeutic radiation absorbed doses caused by low (and sometimes inhomogeneous) tumor uptake of the radiopharmaceutical, and limitations on the injected amount of radionuclide because of hematopoietic toxicity due to bone marrow irradiation.

Attempts to offset low tumor (and sometimes heterogeneous) uptake by utilizing high-energy beta-emitting radionuclides, such as ^{90}Y, have had limited success, mainly because of increased myelosuppression at high radiation doses.[1-7] The increased bone marrow toxicity of high-energy emitters is produced by two factors. Higher-energy beta particles deposit more radiation dose in bone marrow (increased dose deposition is also why these radionuclides may be more effective in treating disease). Also, the long range in the tissue of electrons emitted from these radionuclides can result in energy deposition deep into bone marrow cavities.[8] In addition, many high-energy beta emitters are radiometals that, when separated from their conjugates, can preferentially accumulate in bone.[9,10] For example, Stewart *et al.* demonstrated that ^{90}Y liberated from the human milk fat globule 1 (HMFG1) monoclonal antibody against papillary ovarian carcinomas was accumulated in bone and produced excessive myelosuppression at relative low injected doses (~444 MBq).[1] Efforts to reduce bone uptake by preadministering calcium disodium EDTA to chelate free Yttrium have had only limited success.[1,6] While more stable conjugation methods for radionuclide binding to monoclonal antibodies have been developed, the amount of administered activity can still be limited by radiometals dissociating from the antibody.

Thus, there is a dilemma in radionuclide treatment of soft tissue tumors: Low tumor uptake and heterogeneous distribution of radiopharmaceutical can be partially offset by utilizing radionuclides that emit higher-energy electrons, but less radiolabeled agent can be injected due to enhanced bone marrow radiation dose produced by these substances. Presently, the most successful treatments utilize ^{131}I as the radiolabel; a radionuclide that is excreted in urine and not accumulated in bone following metabolism or deiodination.[11]

Palliation of pain from bone metastases with radiopharmaceuticals has been somewhat more successful. Treatments with agents labeled with ^{153}Sm,[12,13] ^{186}Re,[14,15] ^{32}P,[16,17] and ^{89}Sr[18,19] have been demonstrated to reduce the level of pain in many patients. This success rate is due, primarily, to high accumulation of these radioagents in bone; although the exact mechanism of the therapeutic effect is not certain. But, as

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TABLE I. Dosimetric properties of electrons emitted by the four radionuclides utilized in the computer simulations. Shown are the average energies of the emitted electron spectra, mean number of electrons emitted per nuclear transformation, and mean absorbed dose per unit cumulated activity.

Radionuclide	Average energy (MeV)	Number of electrons per decay (n_i)	Δ_i (Gy kg/MBq s)
^{153}Sm	0.20	0.35	1.11×10^{-8}
	0.23	0.44	1.59×10^{-8}
	0.27	0.21	8.79×10^{-9}
^{166}Ho	0.65	0.48	4.99×10^{-8}
	0.69	0.52	5.68×10^{-8}
^{188}Re	0.74	0.24	2.81×10^{-8}
	0.81	0.76	9.46×10^{-8}
^{90}Y	0.93	1.00	1.50×10^{-7}

with soft tumor treatments, the injected dose of these agents is limited by myelosuppression. Indeed, the injected dose is more of a concern due to the proximity of the intended site of accumulation to the radiosensitive bone marrow. Hence, closeness of the bone marrow to the site of accumulation exacerbates the problems associated with utilizing high-energy beta emitters, which are otherwise desirable because of their high efficiency in delivering a radiation dose.

In general, radiometals and bone-seeking radiopharmaceuticals are not actually deposited directly in bone; instead they are absorbed by the thin endosteal membrane that covers trabecular bone and the outer edge of the marrow cavity in long bones. Emissions from the radiolabels irradiate bone marrow in spaces within the trabecular and long bone marrow cavities, hence damaging the highly radiosensitive active marrow cells. Bone marrow suppression that can be fatal may ensue if radiation doses are too high. Recovery of hematopoiesis without the aid of marrow transplantation, however, is possible. The probability of this recovery has been found to be dependent upon the energy of beta particles emitted from the radionuclide. This effect was demonstrated in two studies by Appelbaum. In the first investigation, escalating doses of up to 1110 MBq/kg of ^{153}Sm-EDTMP were administered to Beagle dogs.[20] Results showed that even in dogs given the maximum dose (estimated to deliver 30 Gy to red marrow), which produced complete aplasia of the trabecular bone marrow in the humeral head, spontaneous recovery from bone marrow suppression without bone marrow transplantation was observed. In these animals, marrow in the trabeculae was aplastic by day 28 of the experiment, even though peripheral blood counts had returned to normal. It was discovered that bone marrow in the shafts of long bones (a region that normally supports little hematopoiesis) displayed modest activity by day 14 and abundant hematopoiesis by day 21. Appelbaum concluded that the low average energy electrons emitted from ^{153}Sm were not able to reach marrow cells in the center of the shaft of long bones. It was these areas that became active in response to pancytopenia caused by radiation damage to trabecular marrow. To test this theory, Appelbaum repeated his previous experiment, replacing ^{153}Sm with ^{166}Ho.[21] In contrast to ^{153}Sm, electrons emitted from ^{166}Ho possess high-average energies (refer to Table I). Hence, per nuclear transformation, a greater fraction of marrow in the shaft of the long bones should be exposed to more ionizing radiation, resulting in a reduction of hematopoietic support from these regions. Results revealed that ^{166}Ho-EDTMP doses of 740–1110 MBq/kg produced fatal pancytopenia in splenectomized dogs. Thus, it appears that recovery from radiation-induced myelosuppression can be facilitated by sparing marrow cells in long bones from significant doses of radiation.

We propose to protect marrow in long bones from high-energy electrons emitted by bone-avid agents by constraining their range with a strong static magnetic field. A similar technique, Magnetically Enhanced Radionuclide Therapy (MERiT), has been previously proposed to enhance radionuclide therapy of small tumors utilizing high-energy beta emitters.[22] The magnetic field substantially confines therapeutic electrons to trajectories that remain largely within the boundaries of the tumor. Radiation dose is, thus, increased to the small lesion, while surrounding normally tissue is protected. Additionally, large structures, such as most organs, do not receive significantly higher absorbed radiation doses. Although it is not possible to significantly reduce radiation dose to marrow in trabecular spaces (these cavities are too small[22–24]), the application of a magnetic field should be able to minimize the radiation dose to bone marrow in the central region of the long bone shaft. Therefore, reduction of bone marrow exposure produced by magnetic confinement may allow the benefits of using high-energy beta-emitting radionuclides to be realized. In this paper, we present the theoretical basis for such a therapeutic approach.

II. MATERIALS AND METHODS

A charged particle in motion in the presence of a magnetic field will experience a force. If the field is uniform and static, and there is no electric field present, the force is given by

$$\mathbf{F}_{\mathrm{Lor}} = q\mathbf{V}\times\mathbf{B}. \tag{1}$$

Equation (1) is known as the magnetic component of the Lorentz force, where V is the particle's velocity vector, B is the magnetic field vector, and q is the particle's charge. The symbol $\times$ signifies the cross-product vector operation. Its cross-product nature ensures that the magnetic Lorentz force is always directed perpendicular to the particle's path. Hence, a static magnetic field cannot do work on a moving charged particle. Since the force is also directed perpendicular to the magnetic field's direction, the path of the particle is curved about the field's axis. A particle moving parallel to the field will experience no force. For the most common case of a particle moving at an angle to the axis of the magnetic field, a helical path results. The radius of this helix in centimeters is given by

$$R = \frac{0.334}{B}\sqrt{(2\cdot m_e\cdot E_t)+E_t^2}, \tag{2}$$

where B is the magnetic field in Tesla (T) ($1T = 10\,000$ G), m_e is the rest mass of the electron in MeV, and E_t is the component of the kinetic energy perpendicular to the magnetic field, also in MeV. As electrons move through matter, they collide with other electrons present in the absorbing material. As a result, an emitted electron loses energy, reduc-

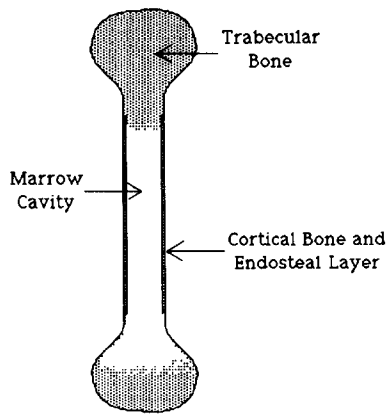

FIG. 1. Schematic drawing of a human long bone.

ing the radius of the helix and producing a corkscrew path. The electrons, therefore, are constrained to regions closer to their point of origin. From Eq. (2), it is clear that the degree of confinement is dependent upon the magnetic field strength and electron energy.

Much of the hematopoietically active red bone marrow in adults is located in the trabecular bone of the spinal column, sternum, pelvis, and ribs. Additional active marrow is contained also in trabecular bone of long bones, such as the femur. Of concern to this investigation is normally inactive or moderately active bone marrow that resides in the shafts of long bones. Shafts of long bones were modeled by assuming that the marrow cavity had a diameter of 2 cm, and that the cortical bone surrounding the shaft is 0.25 cm thick.[8,25] The length of the shaft was set to 20 cm, which is a representative size for adult long bones. Furthermore, based on past studies, radionuclides were assumed to be absorbed by the 10 μm thick endosteal layer located on the inner surface of the cortical bone[8,23,26] (Fig. 1). We assume that most of the myelosuppressive effects are due to absorbed rather than circulating radionuclide. This assumption is based on the conclusion by Stewart *et al.* that much of the myelosuppression observed in his experiments was due to ^{90}Y absorbed in bone, and not the circulating radionuclide.[1] This assumption is also supported by Appelbaum *et al.*'s findings that Beagle dogs could tolerate up to 1110 MBq/kg of ^{153}Sm circulating in blood without developing fatal pancytopenia.[20]

Energy deposition in the marrow was determined using Monte Carlo computer simulation software developed at the University of Michigan Medical Center.[22] Briefly, this computer code generates electron energies utilizing the von Neumann rejection method and the Fermi theory of beta decay. Distances between electronic collisions are calculated using the continuous-slowing-down approximation. The energy loss at each collision point is determined by the Bethe–Bloch equation. Due to the sharp density gradient at the bone–marrow interface, the spatial position of each electron is utilized to determine the proper parameters (density and ionization energy) for calculation of energy loss. Scattering angles are sampled from a Gaussian distribution whose width is a function of energy loss. The spatial position of each particle is also utilized to calculate the amount of energy deposited in thin regions located at various distances from the inner edge of the cortical bone inside the marrow cavity. These target regions are annuli arranged concentrically about the axis of the bone shaft. The thickness of these annuli were 0.05 cm for high-energy beta emitters (^{166}Ho, ^{188}Re, and ^{90}Y) and 0.025 cm for the low-energy emitter (^{153}Sm).

The mean radiation absorbed dose to an individual annulus of bone marrow is given by the equation

$$\bar{D}(r_a \leftarrow r_b) = \frac{\tilde{A}_b}{m_a} \sum_i \Delta_i \phi_i(r_a \leftarrow r_b), \tag{3}$$

where $D(r_a \leftarrow r_b)$=mean absorbed dose to target annulus (Gy), $\tilde{A}_b$=cumulated activity in endosteum (MBq s), m_a =mass of target annulus (kg), Δ_i=mean energy emitted per unit cumulated activity (kg Gy/MBq s) and $\phi_i(r_a \leftarrow r_b)$ =fraction of emitted energy absorbed in target annulus. The simulation determines the fraction of emitted energy absorbed by individual target annuli for each of the beta emission modes [$\phi_i(r_a \leftarrow r_b)$]. From these values a parameter defined as the mean absorbed dose per cumulated activity is calculated for each annulus (S_a). S_a is given by

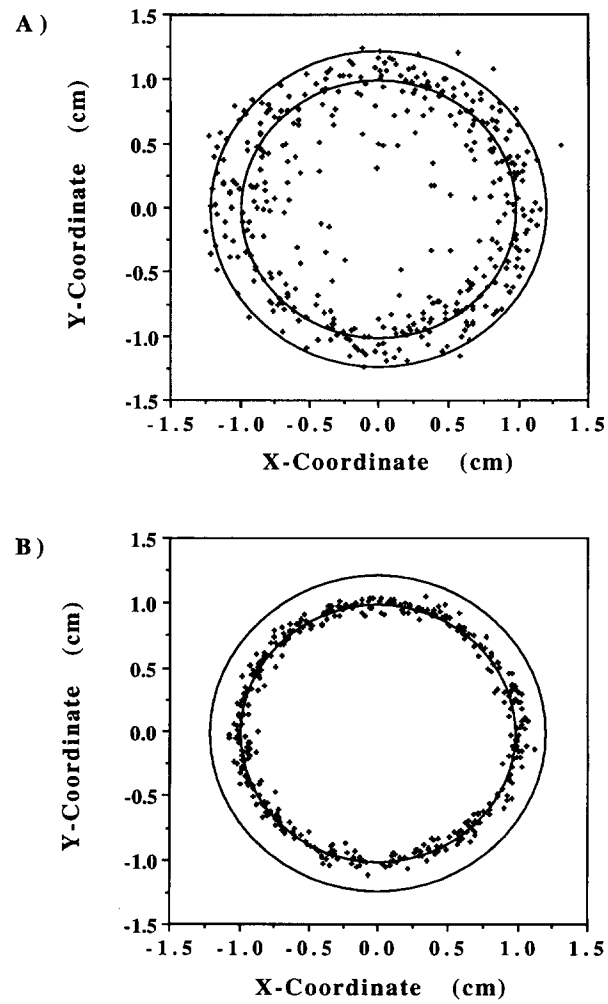

FIG. 2. End point locations for electrons emitted by ^{90}Y located in the endosteum. (a) No magnetic field present; (b) 10 T magnetic field directed into the page.

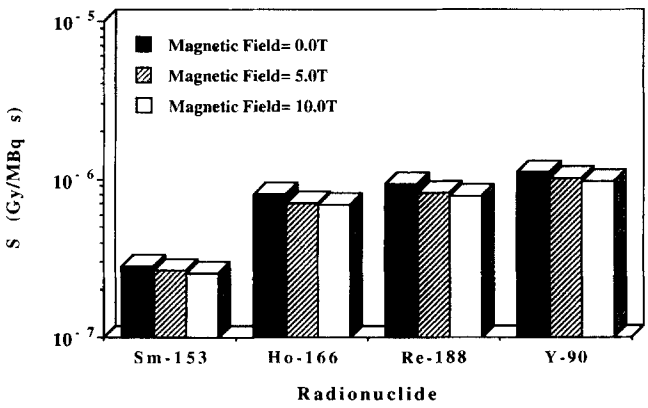

FIG. 3. S values for the entire marrow cavity calculated at 0, 5, and 10 T.

$$S_a = \sum_i \Delta_i \frac{\phi_i(r_a \leftarrow r_b)}{m_a}, \tag{4}$$

where the definitions of the symbols are identical to those used in Eq. (3). S values were determined for four radionuclides: ^{153}Sm, ^{166}Ho, ^{188}Re, and ^{90}Y. Calculations were performed for magnetic field strengths of 0, 5, and 10 T. The radiation dose due solely to electron emissions were considered, as the photon component (that usually contributes a small fraction of the radiation dose to bone marrow) would not be affected by the magnetic field. Energy losses and radiation exposure due to synchrotron radiation and bremsstrahlung are small and were therefore not considered. For example, a 2 MeV electron will lose 3.28×10^{-9} MeV/cm from synchrotron radiation[27] and lose 0.027 MeV/cm from bremsstrahlung in bone marrow;[28] compared to the 1.82 MeV/cm lost in collisions with other electrons.[28]

III. RESULTS

The effect of magnetic constraint on the paths of electrons emitted from a bone-avid agent deposited in the endosteal layer is demonstrated in Fig. 2. Panel (a) shows the end points of electrons emitted from ^{90}Y when no magnetic field is present. Panel (b) shows the end points when a 10 T magnetic field is applied coaxial with a long bone. Clearly, the penetration of the electrons into the marrow cavity is greatly reduced. It is also interesting to note that the electrons rarely exit the cortical bone itself. This is due to the higher density of cortical bone compared to bone marrow. Figure 3 displays the S values for the whole marrow cavity. Notice that these values change very little with the application of 5 and 10 T magnetic fields (the maximum reduction in total marrow radiation dose is 14% for ^{90}Y at 10 T). The total radiation dose to bone marrow is decreased at the expense of increased dose to cortical bone and the endosteum. The curvature of the electron trajectories induced by the magnetic field causes electrons to exit the marrow cavity and enter cortical bone sooner than when no magnetic field is present and the paths are more linear. Since the radius of curvature of the electrons decreases with the application of stronger magnetic fields [refer to Eq. (2)], the cortical radiation bone dose increases (with a concomitant decrease in marrow dose) when strong fields are applied. Also note that the radiation dose to marrow at all magnetic field strengths increases with increasing average energy per particle (refer to Table I). Alterations in radiation dose due to changes in the distribution of synchrotron radiation and bremsstrahlung as a function of magnetic field should be small, and were not considered.

Although the total radiation dose to bone marrow is only slightly reduced, the distribution of dose is significantly altered by the application of a magnetic field. Figure 4 demonstrates this change in radiation exposure. S values calculated for each annulus are plotted as a function of its distance from the outer edge of the marrow cavity. For example, in panel (a) the first point ($x=0$ cm) represents data obtained for an annulus of bone marrow with an outer radius of 1 cm and an inner radius of 0.975 cm; keeping in mind that the assumed marrow cavity radius is 1 cm. It is important to note that in all of the plots displayed in the Fig. 4 application of a magnetic field reduced the amount of marrow tissue exposed to the radiation dose. Changes in penetration depth can be gauged by the positions where the S values reach a certain level. For example, electrons emitted from ^{153}Sm attain an S value of 10^{-7} Gy/Mbq s at a distance of 0.131 cm from the endosteum when no magnetic field is present. With the application of a 10 T magnetic field, this distance becomes 0.064 cm (a 53.6% reduction), compared with a reduction in the penetration distance from 0.516 to 0.131 cm (74.6% change) for electrons emitted by ^{90}Y with the application of a 10 T magnetic field. Another significant feature of these curves is the fact that the radiation dose to marrow close to the endosteal layer is increased with the application of a magnetic field. Clearly, this is due to the confinement of the electrons to areas adjacent to the bone–marrow interface. Changes in marrow cavity dimensions and cortical bone thickness did not significantly alter the shapes of the curves.

The results generated by the software were compared with findings reported by Johnson *et al.*[8] This group utilized the EGS4 (Electron Gamma Shower) and PRESTA (Parameter Reduced Step Algorithm) computer codes to calculate the spatial distribution of the radiation dose absorbed by long-bone marrow. Our results were in good agreement with Johnson's. For example, the mean absorbed dose per cumulated activity (S) calculated 1 mm from the endosteum of a long bone with the same dimensions used in our investigation and containing ^{166}Ho was reported to be 1.18×10^{-6} Gy/MBq s, compared to 1.21×10^{-6} Gy/MBq s, calculated at 0 T by the University of Michigan software.

Finally, in Fig. 5 the S values for ^{90}Y are plotted as a function of distance from the endosteum for a wide range of magnetic field strengths. From this plot it is evident that application of a magnetic field with a magnitude less that approximately 5 T produces little change in the spatial distribution of a radiation dose in the bone marrow cavity. It is also clear that little change in relative dose distribution occurs at magnetic field strengths above approximately 12.5 T.

IV. DISCUSSION

A major factor hindering the success of radionuclide-based treatments of cancer and, to a lesser extent, associated bone pain is the limited amount of radiopharmaceutical (es-

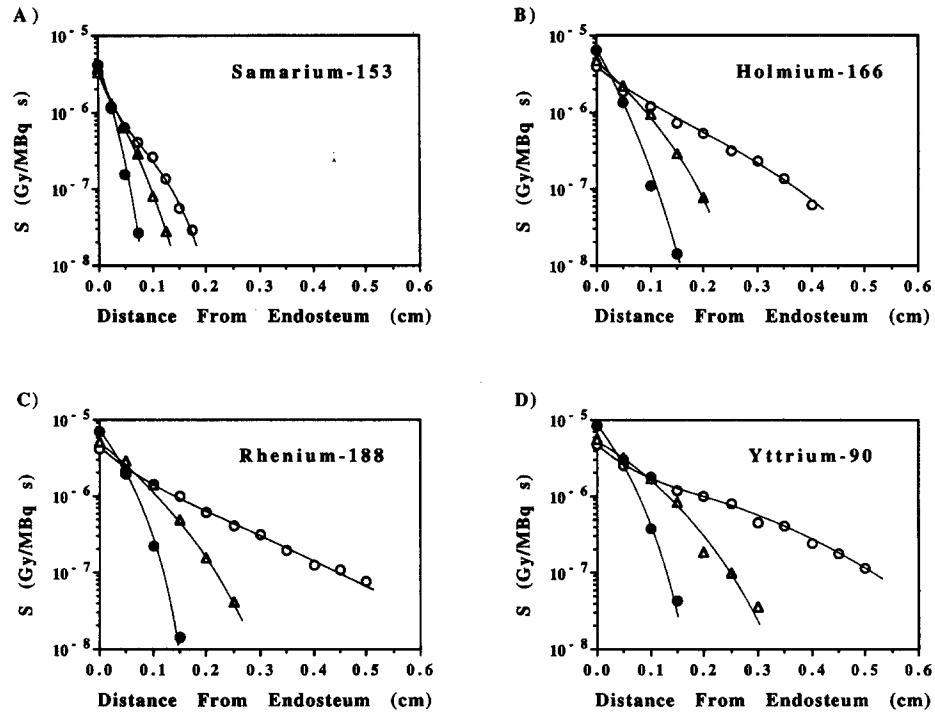

FIG. 4. Spatial distribution of the radiation dose inside the marrow cavity. Results for magnetic field strengths of (○) 0 T, (△) 5 T, and (●) 10 T are shown.

pecially those labeled with high-energy beta-emitting radionuclides), which can be safely administered, primarily due to myelosuppression. The work of Appelbaum suggests a possible solution to this problem. He and his colleagues demonstrated that normally inactive marrow in the shafts of long bones can become active during periods of radiation-induced pancytopenia. As long as these regions did not receive significant radiation exposure, normal blood counts could be sustained by the newly activated marrow after a short period of time. Based on our simulations, we believe that this important marrow can be, at least, partially preserved through the application of a magnetic field.

Figure 2 demonstrates our concept of magnetic constraint of electrons applied to the problem of long-bone marrow

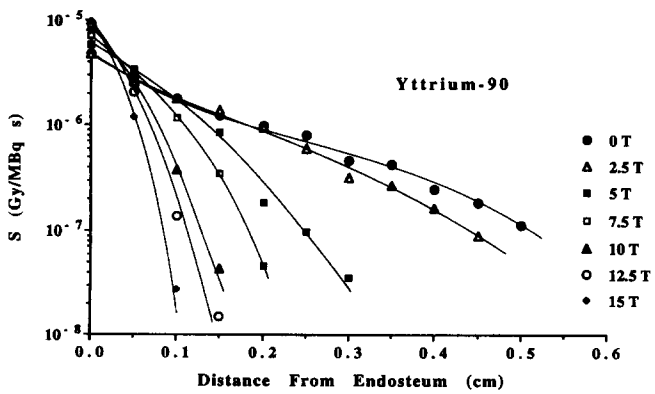

FIG. 5. Spatial distribution of the radiation dose inside the marrow cavity from electrons emitted by ^{90}Y. Plots for magnetic fields ranging from 0 to 15 T are shown.

radiotoxicity. Electrons emitted from radionuclides absorbed in the endosteum deposit energy in the bone marrow located in the shafts of long bones [panel (a)] and trabecular marrow cavities. Depth of penetration into the marrow is related to the average energy of these particles: The higher the energy the more marrow exposed. Application of a strong static magnetic field (10 T in this case) along the axis of the bone is predicted to significantly reduce the depth of penetration. Thus, the amount of bone marrow subject to significant radiation exposure is reduced.

Total radiation dose to bone marrow is significantly but only moderately reduced by the application of a magnetic field, as demonstrated by the plot in Fig. 3. Magnetic fields of the magnitude considered in this investigation are not capable of preventing electrons from entering the marrow space. These magnetic fields are only able to confine the emitted particles to areas close to and at times within the cortical bone, thus the small change in total dose. But, as demonstrated by Appelbaum, the total radiation dose to this marrow is not the most important factor in hematopoietic recovery. Instead, the spatial distribution of the dose is critical in predicting future recovery from radiation-induced pancytopenia. The plots in Fig. 4 display how magnetic constraint is predicted to reduce the amount of bone marrow exposed to particulate radiation damage.

It is apparent from the results presented in Fig. 4 that the presence of a magnetic field affects the electrons from each radionuclide differently. This is due to the differences in emitted electron energy spectra. For example, a 10 T field reduces the depth of penetration for electrons emitted from ^{153}Sm by 53.6%, while the reduction is 74.6% for ^{90}Y. Since ^{153}Sm emits, on the average, lower-energy electrons, they are

not able to penetrate very deeply into the marrow cavity. Hence, confinement of these electrons to smaller regions with a 10 T magnetic field produces a proportionately smaller change in penetration distance than is obtainable for deeper penetrating electrons, such as those emitted by ^{90}Y. The amount of marrow penetration reduction produced by a magnetic field is related not only to the strength of the field, but it is also dependent upon the energy of the electron. More energetic particles are more difficult to constrain. These factors must be considered when choosing the application that will benefit most from utilizing this technique. Applications that must utilize agents labeled with low-energy beta emitters will not achieve as large a change in marrow dose distribution as will those that use higher-energy emitters.

Furthermore, results presented in Fig. 4 show that electrons emitted by ^{90}Y at 0 T penetrate deeper in the marrow cavity than ^{166}Ho. Therefore, the toxicity of ^{90}Y should be higher than that reported for ^{166}Ho by Appelbaum,[21] making ^{90}Y a somewhat less attractive choice for radionuclide therapy, at least in terms of marrow toxicity. Application of a 10 T magnetic field, however, reduces depth of penetration to magnitudes comparable to ^{153}Sm at 0 T. This finding is likely very important, since Appelbaum reported that subjecting bone marrow at this depth to very high radiation dose levels did not prevent spontaneous recovery of hematopoiesis. This result also indicates that the administration of larger quantities of high-energy beta-emitting radionuclides (amounts that currently produce unacceptable levels of pancytopenia) may be possible. The increase in the radiation dose to marrow contiguous (distance=0 cm on the plot) with the endosteum is not likely to be significant, since, as previously mentioned, high radiation doses to this region do not hinder the future restoration of blood counts. The long-term effects of the radiation dose to the endosteum appears to be negligible. This conclusion is drawn from studies involving survivors of bone marrow transplantation whose bone marrow was ablated with total body irradiation prior to transplant. These investigations revealed no serious long-term side effects.[29,30] Confirmation of these findings for radionuclide ablation, however, is desirable in order to fully resolve this issue. Indeed, application of higher radiation doses to this region might aid in the treatment of the disease located in the edges of cortical bone. The mechanism of pain relief produced by radiopharmaceutical therapy of bone metastases is not completely understood. Therefore, the effect of magnetic confinement of particle range on pain palliation cannot be fully resolved. Studies suggest, however, that radiolabels that emit short-range beta particles can achieve significant pain palliation,[12,13] indicating that reducing particle penetration depths with a magnetic field should not significantly diminish pain palliation, though this requires further study.

Results shown in Fig. 5 indicate that, for a high-energy electron emitter, a magnetic field of at least 5 T is required to significantly reduce the amount of bone marrow exposed to ionizing radiation. There also appears to be a point were the magnetic constraint of the emitted electrons saturates. For electrons emitted by ^{90}Y and for a long bone of the dimensions utilized in this study, application of a magnetic field greater than approximately 12.5 T results in relatively little additional reduction in the amount of bone marrow spared from radiation exposure. Therefore, it may not be necessary to apply the highest magnetic field available to achieve the maximum effect. Indeed, it may be possible that the amount of bone marrow protected by much lower field strengths is sufficient to facilitate recovery of hematopoiesis. Determination of the optimal field cannot be made solely by computer simulation; it must be based on experimental measurements of the relationship between hematopoietic recovery and magnetic field strength.

The amount of bone marrow exposed to ionizing radiation is largest for applications utilizing ^{90}Y, since of the four radionuclides studied it emits the highest average energy electrons. Results for the other high-energy emitters (^{166}Ho and ^{188}Re) are somewhat better in that the maximum depth of penetration at 10 T is less than that of ^{153}Sm at 0 T. Furthermore, use of radiometals, such as ^{90}Y and ^{188}Re, may hold an advantage over the utilization of radionuclides from other chemical groups. Several studies indicate that radiometals are retained by tumors, following catabolism of their conjugates, longer than many members of the halogen group, such as ^{131}I.[31,32]

As with all newly proposed techniques, the subject of practicality must be addressed. The first concern is availability and cost of a 10 T magnet. Advances in material engineering in the past decade have made it possible to build a 10 T magnet with a 20 cm diam spherical isocenter for approximately one million dollars. It should be noted that the field uniformity requirements for these magnets are much less stringent than for imaging magnets; this aids in limiting cost. Larger bore 10 T magnets can be constructed, but at a higher expense. It is anticipated that future advances in magnet and materials technology may make magnets required for this procedure more accessible. In addition, magnet costs can be further reduced if it is found that magnetic field strengths lower than 10 T are capable of protecting sufficient amounts of bone marrow.

There are also concerns about the length of time a patient must spend in the magnet. Proper treatment planning would have the subject inserted into the magnet only after the radionuclide concentration has reached its maximum level in the target site. This should minimize patient time in the magnet. In addition, utilization of a relatively short-lived radionuclide can significantly decrease the required amount of magnet time. It was for this reason that ^{188}Re was included in this study. Its 16.8 h half-life could reduce magnet exposure time to less than two and one-half days. Furthermore, ^{188}Re emits high-energy electrons (E_{ave}=0.24 and 0.76 MeV), and has been used to label monoclonal antibodies;[33] it could also possibly be used to replace ^{186}Re in bone pain palliation applications. Since the marrow targeted for protection is located in the long bones, it may be necessary to only apply the magnetic field to certain bones instead of the whole body. For example, position the subject such that just the legs (femur, tibia, and fibula) are in the magnet. This configuration could aid in reducing patient discomfort. Finally, computer simulation studies by Kinouchi *et al.* indicate that exposures to 10 T magnetic fields should not affect normal cells.[34] Experiments involving human subjects, however, have only ex-

plored the effects of up to 40 h exposures to a 4 T magnetic field. Except for some minor transient effects, such as nausea, no lasting physiological effects were reported.[35] While few physiological effects are predicted for humans in strong fields,[36] decisions concerning the safety of therapeutic magnetic fields must be based on results from future human trials.

In conclusion, we have demonstrated, with the utilization of a computer model, that a magnetic field can confine the trajectories of high-energy electron emissions from radionuclides absorbed on the inner surfaces of long bones. Hence, the radiation dose to central regions of the marrow cavities are predicted to be greatly reduced. Preservation of marrow in these areas has been shown to facilitate recovery of hematopoietic function. The use of this technique, therefore, may allow for the increase in amounts of radiolabel administered without the need for marrow transplantation, possibly leading to more effective treatments of a variety of cancers.

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