A Strategy to Reduce Red Marrow Dose for Intraperitoneal Radioimmunotherapy[1]

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Abstract

The aim of this study was to determine whether shorter-lived radionuclides can reduce red marrow (RM) toxicity for i.p. radioimmunotherapy (RIT). The potential radionuclides, which included Lu-177, I-131, Y-90, Re-186, Re-188, and Ho-166, were attached to antibody CC49. Each radiopharmaceutical was assumed to have identical *in vivo* pharmacokinetics. Blood and whole body retention data acquired from 26 patients who received i.p. RIT with Lu-177 CC49 were used as input. The average biological half-time of Lu-177 CC49 in the whole body was 280 h, and the average Lu-177 concentration in plasma increased to a maximum at 2 days postinfusion, followed by steady clearance. The residence time and RM doses were calculated for each radionuclide. In the current model, Re-188 was found to deliver the lowest RM dose, primarily because it had the shortest half-life, whereas Y-90 delivers the highest dose. Re-188 delivers 60% of the RM dose as compared with Lu-177 and can increase the dose to metastatic sites in the i.p. space by a similar factor. Based on limiting the RM dose to 200 cGy, the maximum administered activity of each radionuclide is as follows: (*a*) 106 mCi, Lu-177; (*b*) 58 mCi, I-131; (*c*) 34 mCi, Y-90; (*d*) 70 mCi, Re-186; (*e*) 169 mCi, Re-188; and (*f*) 110 mCi, Ho-166. Because of the delayed steady leakage of radiopharmaceuticals from the i.p. cavity to the plasma, short-lived radionuclides may offer special advantages for i.p. RIT.

Introduction

Bone marrow toxicity is the dose-limiting factor for i.p. RIT[3] today. This toxicity is associated primarily with radioactivity that leaks from the i.p. cavity to the plasma and delivers a significant absorbed dose to the RM. Prudent selection of radionuclides for i.p. RIT could reduce the absorbed dose to the RM. The efficacy and toxicity of radionuclide therapy are usually interrelated, because the most desirable spatial and temporal patterns of energy delivered to targeted tumor cells are generally associated with enhanced toxicity. Selecting a suitable radionuclide requires careful consideration of many physical factors such as half-life, type/energy of particles/

photons emitted, and availability, together with matching radiochemical properties. Results from modeling nine commonly available radionuclides for RIT indicated that Re-186 and Y-90 were the optimum candidates (1). In another report, based on time-dose fractionation and the linear-quadratic model, longer-lived radionuclides (P-32 and Y-91) were shown to offer superior therapeutic advantages compared with shorter-lived radionuclides such as Y-90 (2). More recently, proliferation of tumor cells and critical bone marrow tissues has been incorporated in these models, and the advantages of longer-lived radionuclides have been reiterated (3). In practice, longer-lived radionuclides are also limited because of the lower dose rate, and the amount of radionuclide bound to the carrier may be limited for longer-lived radionuclides.

Clinical RIT trials for ovarian cancer involve i.p. administration of radiopharmaceuticals to the i.p. space, where the radiolabeled antibodies bathe the surface of tumor deposits that are growing in the i.p. fluid and are attached to the surfaces of the i.p. wall. After i.p. administration of Lu-177 CC49 to 26 ovarian cancer patients, the concentration of radioactivity detected in blood increases steadily to reach a maximum at 2 days, followed by monoexponential clearance with a biological half-time of about 72 h (4). Similar results for i.p. therapy in patients have been reported for antibodies labeled with I-131 (5) and Re-186 (6). This leakage of radiopharmaceutical from the i.p. space to plasma in i.p. RIT interferes with the radionuclide selection criteria used for i.v. administration. Significant toxicity has been reported with i.p. RIT, and this report is concerned with exploiting the special advantages of shorter-lived radionuclides that will have decayed significantly by the time they move from the i.p. fluid to plasma.

Clinical trials with Lu-177-labeled CC49 i.p. therapy in ovarian cancer patients have established that the concentration of this radionuclide reaching plasma peaks at about 48 h postinfusion, followed by a steady clearance as the radioactivity is localized in various organs and excreted via the urine (6). Because the radioactivity exiting the i.p. space is considered to be the major contributor to bone marrow toxicity, choosing a radionuclide with a shorter half-life seems attractive. Ho-166, for example, has a half-life of 26.8 h and would have decayed by a factor of about 4 before it reached a maximum concentration in the plasma.

The objectives of this study were: (*a*) to compare RM doses for i.p. RIT with Lu-177, I-131, Y-90, Re-186, Re-188, and Ho-166, assuming they have *in vivo* pharmacokinetics identical to those of Lu-177 CC49; and (*b*) to predict the maximum activity (in mCi) of each radionuclide that can be administered without exceeding a dose of 200 cGy to the RM.

Materials and Methods

The model that describes the temporal distribution of i.p. infused radiopharmaceuticals in various compartments is shown in Fig. 1. The radiopharmaceutical is distributed throughout the
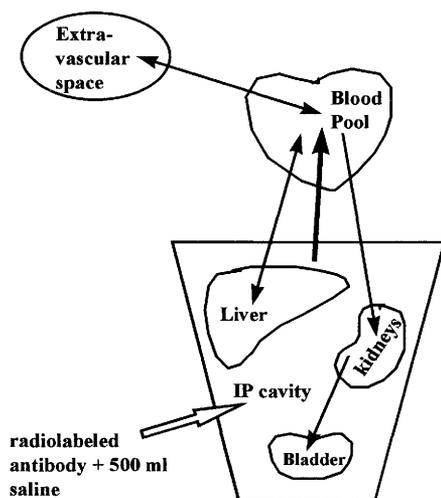

Fig. 1 Qualitative schematic of assumed antibody kinetics used to derive radiation-absorbed doses to RM and whole body for i.p. RIT. At 7 days postinfusion, approximately 60% of radioactivity leaves the i.p. cavity and is localized in the remainder of the body or excreted.

Fig. 2 Average uptake and clearance pattern of Lu-177 CC49 in plasma measured from 26 ovarian cancer parents. The PIA data for the five other radionuclides were calculated from the data measured for Lu-177.

i.p. cavity, and serial gamma camera images can trace the movement of more than 50% of the infused radioactivity from the i.p. space to the rest of the body over about 7 days. The significant leakage and difficulties inherent in trying to determine the fraction in the i.p. space make it difficult to use the dosimetry model described for i.p. administration of radionuclides (7). Infusion involves the injection of the radiolabeled antibody in a few milliliters to the i.p. cavity, followed by 500 ml of saline. Mixing and distribution of the radiolabeled antibody in the i.p. cavity are promoted by movement of the abdomen while the patient is supine. The input data for this study was serial plasma and whole body retention data measured after an infusion of Lu-177-labeled CC49 in 26 ovarian cancer patients at the University of Alabama at Birmingham. Plasma samples were collected at 6 and 12 h and days 1, 2, 3, 4, and 7 after patients received 15–45 mCi/m^2 Lu-177 CC49 as an i.p. infusion in a total volume of 500 ml of saline. Whole body Anger camera images were acquired at 4 days postinfusion to validate that the radioactivity was uniformly distributed in the i.p. space and to visualize tumors/organs in which the Lu-177 CC49 was preferentially localized.

The average PIA of Lu-177 in the total plasma volume measured at various times postinfusion was converted to expected radioactivity for each radionuclide, assuming that the biological half-life for each radiopharmaceutical was identical. The RT for each radionuclide was calculated using the trapezoidal rule. The area from the last measured point to total decay was measured by extrapolating to a point along the time axis set at 10 times the effective half-life of the clearance region of the plasma PIA curve. A similar procedure was used to convert the PIA for the whole body data measured with Lu-177 CC49 to RT for the six radionuclides. In general, the whole body retention data measured with a gamma probe/spectrometer placed 4 meters from the surface of each patient was monoexponential, and the RT for each radionuclide was simple to calculate.
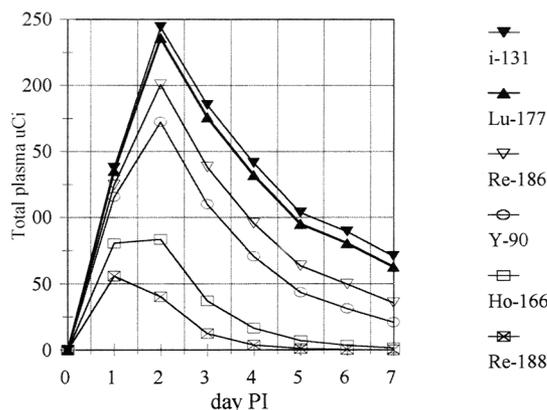
The RM dose for each radiopharmaceutical was calculated from two sources of radioactivity: (*a*) plasma; and (*b*) the remainder of whole body. No specific uptake of the radiopharmaceutical or degradation products in the bone marrow or skeletal tissues was assumed for this model. The RT for bone marrow was calculated assuming the concentration of radionuclide in the RM was 0.19 of that in the plasma (8). Because S values for all of the radionuclides in this study were not available in MIRD11 S tables or the PC program MIRDOSE3, the source code for MIRDOSE2 was modified by Dow Chemical[4] (Freeport, TX) with permission from Oak Ridge.[5] This was used to provide RM dose estimates for the six radionuclides selected. Based on the results and setting the RM dose limit at 200 cGy, the maximum quantity of each radionuclide for i.p. therapy was calculated using

$$A_{max} = \left[\frac{200}{RM\ dose}\right]_{radionuclide} \quad (A)$$

where A_{max} is the maximum administered activity (in mCi) of each radionuclide, and RM dose is the dose to the RM (in cGy/mCi) calculated for each of the radionuclides compared.

Results

This radionuclide selection model indicates the advantage of using shorter-lived radionuclides for i.p. RIT. The average radioactivity level detected in plasma from infusing 1 mCi of each radionuclide for i.p. RIT is depicted in Fig. 2. The concentration of the radionuclide in plasma is proportional to physical half-life of each radionuclide. The corresponding RTs for each radionuclide in plasma are depicted in Fig. 3. The half-life of each radionuclide represents the order of magnitude. The

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[4] MIRDOSE2, modified version supplied by Dr. Jim Simon (Dow Chemical Branch, Freeport, TX).
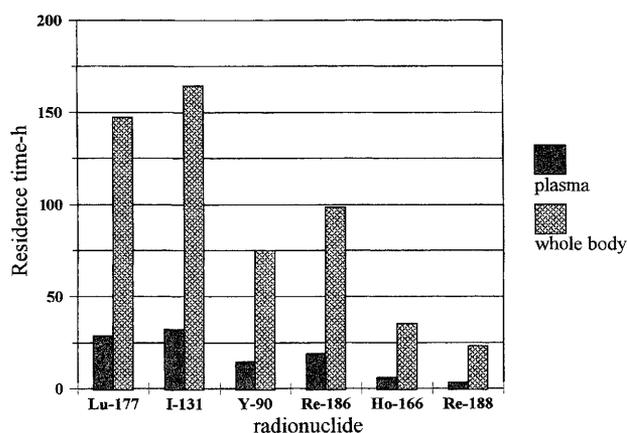[5] M. G. Stabin, Oak Ridge Institute for Science and Education, TN.

Fig. 3 RT-h for plasma (■) and whole body (▨) calculated from data acquired with i.p. RIT for Lu-177 and extrapolated to five other radionuclides.
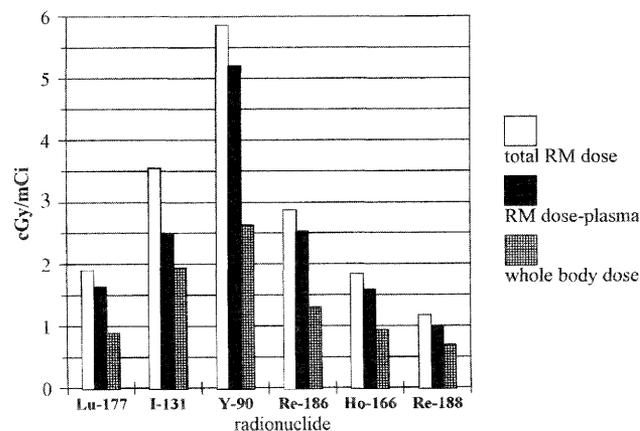

Fig. 4 RM dose (total dose and self-dose) and whole body dose (in cGy/mCi) estimated for i.p. RIT with each radionuclide. Re-188 delivers the smallest dose to RM, whereas Y-90 delivers the largest dose. Total RM dose, □; RM dose-plasma, ■; whole body dose, ▦.

Table 1 Maximum administered activity predicted for i.p. RIT with each radionuclide attached to CC-49, based on limiting the RM dose to 200 cGy

Radionuclide	Maximum activity predicted for i.p. RIT (mCi)
Lu-177	105
I-131	58.3
Y-90	34.1
Re-186	89.9
Re-188	170
Ho-166	110

Discussion

Although the goal for i.p. RIT is to restrict the radiolabeled antibody to the i.p. space, Anger camera images of every ovarian patient confirmed that a significant fraction of Lu-177 was outside the i.p. cavity. At 7 days postinfusion, approximately 60% of Lu-177 was estimated to be outside the i.p. cavity. Special techniques will be required to distinguish between the radioactivity localized in the liver from plasma-borne radioactivity and the radioactivity that is attached to the surface of this and other organs in the i.p. cavity.

The specific advantages offered by shorter-lived radionuclides for i.p. RIT cannot be assessed simply from a comparison of RT alone. Because the energy emitted from different radionuclides varies by a factor of 3 or more, the magnitude of RT alone does not provide the best estimate. Shorter-lived radionuclides usually also provide higher doses/dose rates to tumor volumes in the i.p. cavity, reduce RM doses from radioactivity that leaks out of the i.p. space into plasma, reduce exposure to hospital personnel, and may reduce the length of hospital stay for patients if the revised patient release criteria can be implemented.

These simplified modeling studies have indicated that Re-188 delivers the lowest RM dose for i.p. RIT, followed by Ho-166, Lu-177, I-131, Re-186, and Y-90. In theory, Re-188 could be supplied from a W-188 generator in therapy amounts, which would have a significant impact on the cost of i.p. RIT. The absorbed dose to tumor deposits in the i.p. cavity can be increased by a factor ≤ 3 for short-lived radionuclides that also emit longer range βs than Lu-177 and I-131, such as Re-188 and Ho-166. This approach is similar to methods described to estimate the bladder wall dose (9). Although there is some correlation between ranking the predicted amounts of I-131, Re-186, and Y-90 that have been administered for RIT, specific uptake of Y-90 in the skeletal tissues is likely to reduce the amount that can be administered for therapy.

Further refinement of the present model used to compare these six radionuclides for i.p. RIT should include doses to a tumor *versus* RM. Also, separating the contributions of dose from radioactivity in the i.p. space and the remainder of the body should provide more accurate estimates, because the photon contribution to total RM dose will be significantly lower than the values predicted, especially for low-energy photons emitted by Ho-166. If specific uptake of the radionuclide in the skeletal tissues could be visualized in Anger camera images (9), estimates of RM dose will be especially important, because this

cGy/mCi delivered to the RM from radioactivity in the plasma and whole body for each radionuclide is depicted in Fig. 4. For radionuclides such as I-131 that emit a larger fraction of high-energy photons, the marrow self-dose represents a smaller fraction of the total marrow dose. The rankings found depend on a combination of physical half-life and energy emitted/disintegration for each radionuclide. These estimates include corrections for radioactivity in the remainder of the body, and although these absorbed dose estimates are larger than would be predicted using MIRD11 S values, their rankings will remain the same, regardless of which version of MIRDOSE or S tables are used. Table 1 lists the maximum activity calculated for the present model with each radionuclide *versus* empirical values for I-131, Re-186, and Y-90. When the maximum plasma activity reaches 25% of infused activity at 48 h, the absorbed dose contribution from the self-dose to RM was found to be about 84% (range, 70–89%) of the total RM dose.

contribution has been identified to have the strongest correlation with bone marrow toxicity (10).

References

1. Wessels, B. W., and Rogus, R. D. Radionuclide selection and model absorbed dose calculations for radiolabeled tumor associated antibodies. Med. Phys., *11:* 638–645, 1984.

2. Howell, R. W., Gokha, M. S., and Rao, D. V. Application of the linear-quadratic model to radioimmunotherapy; further support for the advantage of longer-lived radionuclides. J. Nucl. Med., *35:* 1861–1866, 1994.

3. Howell, R. W., Goddu, S. M., and Rao, D. V. Proliferation and the advantage of longer-lived radionuclides in radioimmunotherapy. Med. Phys., *25:* 37–42, 1998.

4. Meredith, R. F., Partridge, E. E., Alvarez, R. D., Khazaeli, M. B., Plott, G., Russell, C. D., Wheeler, R. H., Liu, T., Grizzle, W. E., Schlom, J., and LoBuglio, A. F. Intraperitoneal radioimmunotherapy of ovarian cancer with lutetium-177-CC49. J. Nucl. Med., *37:* 1491–1496, 1996.

5. Stewart, J. S., Hird, V., Snook, D., Sullivan, M., Myers, M. J., and Epenetos, A. A. Intraperitoneal ^{131}I- and ^{90}Y-labeled monoclonal antibodies for ovarian cancer: pharmacokinetics and normal tissue dosimetry. Int. J. Cancer, *3* (Suppl.): 71–76, 1988.

6. Breitz, H. B., Durham, J. S., Fisher, D. R., and Weiden, P. L. Radiation-absorbed dose estimates to normal organs following intraperitoneal ^{186}Re-labeled monoclonal antibody: methods and results. Cancer Res., *55* (Suppl.): 5817–5822, 1995.

7. Watson, E. E., Stabin, M. G., Davis, H., and Eckerman, K. F. A model for the peritoneal cavity for use in internal dosimetry. J. Nucl. Med., *30:* 253–255, 1989.

8. Sgouros, G. Bone marrow dosimetry for radioimmunotherapy. Theoretical considerations. J. Nucl. Med., *34:* 689–674, 1993.

9. DeNardo, D. A., DeNardo, G. L., O'Donnell, R. T., Lim, S. M., Shen, S., Yuan, A., and DeNardo, S. J. Imaging for improved prediction of myelotoxicity after radioimmunotherapy. Cancer (Phila.), *80* (Suppl.): 2558–2566, 1997.

10. Macey, D. J., DeNardo, S. J., DeNardo, G. L., DeNardo, D. A., and Shen, S. Estimation of radiation absorbed doses to the red marrow in radioimmunotherapy. Clin. Nucl. Med., *20:* 117–125, 1995.