

Planning Time for Peripheral Blood Stem Cell Infusion After High-Dose Targeted Radionuclide Therapy Using Dosimetry

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Myelotoxicity can be ameliorated by peripheral blood stem cell (PBSC) infusion. Continuous irradiation by radioactivity retained in the body after high-dose radioimmunotherapy can damage PBSCs if they are transfused too early. Previously, infusion time was predetermined using the radioactivity concentration in the blood. This study proposes to plan PBSC infusion time based on noninvasive dosimetry that considers damage of PBSCs during PBSC circulation and residence in organs with high radioactivity. **Methods:** The method considers a time-varying distribution of PBSCs and radioactivity in tissues. Five breast cancer patients received ¹¹¹In-2IT-BAD-m170 for imaging, and 3 of the 5 received high doses of ⁹⁰Y-2IT-BAD-m170 therapy followed by PBSC infusion. ⁹⁰Y concentrations in tissues were extrapolated from quantitative imaging of ¹¹¹In, and ⁹⁰Y blood concentrations were determined from ⁹⁰Y in serial blood samples. The radiation dose to PBSCs was determined by time integration of the organ dose rate and PBSC distribution rate. The radiosensitivity of PBSCs was determined by measuring survival of granulocyte-macrophage colony-forming units with ⁹⁰Y in cell culture. **Results:** The mean effective half-life of ⁹⁰Y within the imaging period (up to 6 d) was 3.7 d for liver, 2.4 d for spleen, 2.1 d for kidneys, 1.8 d for lungs, and 1.6 d for blood. The survival fractions of PBSCs in patients were determined as functions of the infusion time and the injected dose of ⁹⁰Y-2IT-BAD-m170. To achieve 90% PBSC survival rate for a 2.0-GBq injection dose, PBSC dosimetry suggested a time interval of 13 d after radioimmunotherapy for PBSC infusion. In contrast, the simple blood concentration method suggested an interval about 7 d for the same PBSC survival rate. In our clinical practice, an interval of 2 wk has been used and worked well. **Conclusion:** A noninvasive dosimetry method was developed for optimizing the time interval for PBSC infusion after high-dose radionuclide therapy. Our studies suggested that the PBSC dosimetry method was more effective than the blood concentration method in determining the optimal time to reinfuse PBSCs for radiopharmaceuticals that have much a higher activity concentration in organs than that in the blood.

Key Words: treatment planning; peripheral blood stem cell; bone marrow; radiation dosimetry; radioimmunotherapy

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Targeted radionuclide therapy, including radioimmunotherapy, is an innovative approach that systemically delivers localized radiation using target molecules directed to cancer cells. Encouraging results have been obtained in radioimmunotherapy for lymphoma (1–4). However, the efficacy of radiolabeled antibodies for solid tumors such as breast cancer has been limited by several factors, including (a) slow accumulation of antibodies at tumor sites, (b) relatively slow clearance of antibodies from the blood, and (c) relative radioresistance of solid tumors compared with lymphoma. Consequently, whereas tumors often receive insufficient radiation for a significant response, radiation dose to the radiosensitive normal organ, marrow, can readily reach the tolerable limit. Myelosuppression can be ameliorated with autologous bone marrow transplantation or peripheral blood stem cell (PBSC) infusion, as illustrated first by Press et al. in treatment of lymphoma (2) and followed by others in treatment of breast cancer (5–9), colon cancer (10), and lymphoma (11). These studies suggested that a higher tumor response rate was associated with a higher radioactive injection dose followed by bone marrow reconstitution.

In treatments having PBSC support, the time interval between the radioactive dose injection and PBSC infusion is an important parameter for optimal patient management. Although PBSCs can be injured by continuous irradiation from exposure to irradiation from radioimmunotherapy if they are transfused too early, patients can also develop serious complications from low levels of neutrophils or platelets if PBSCs are transfused too late. Previously, the time interval for PBSC infusion was determined by a calculation method based on blood radioactive concentration (5). The blood activity concentration threshold was deter-

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mined from an in vitro study in which rates of PBSC survival were measured at various radioactivity concentrations. However, our initial clinical results on hematopoietic reconstitution after ^{90}Y radioimmunotherapy were unsatisfactory when the PBSC infusion time was determined by ^{90}Y concentrations in the blood. Recovery of blood counts was delayed even when ^{90}Y concentration in the blood was well below the activity concentration threshold determined in vitro.

Radioactivity concentration in the liver, spleen, and kidneys can be much higher than that in the blood, so that PBSCs can be damaged during their circulation through these organs. PBSCs can be further damaged after homing (a process in which PBSCs migrate from peripheral blood to bone marrow) if marrow or bone has radioactive uptake. Therefore, the radiation dose from radioactivity in the blood is only one part of the total radiation dose to PBSCs. To address the issues described here, we propose a new, non-invasive method for planning PBSC infusion time based on imaging and radiation dosimetry. The proposed method considers (a) time-varying radiation dose rate to PBSCs from radioactivity in the blood and other source organs, (b) time-varying PBSC distribution in the body during the homing, and (c) radiation dose to PBSCs from radioactivity in bone and marrow after PBSC homing.

MATERIALS AND METHODS

Radiopharmaceuticals

Monoclonal antibody 170H.82 (m170) is a murine monoclonal IgG1 antibody that is reactive with the synthetic Thomsen-Friedenreich antigen family. It was obtained from Biomira. m170 was 95% monomeric IgG by polyacrylamide gel electrophoresis and met U.S. Food and Drug Administration guidelines for administration to patients. m170 binds to a variety of human adenocarcinomas, including breast cancer (12,13). m170 was radiolabeled with ^{90}Y or ^{111}In via DOTA-2IT-BAD (2-iminothiolane-2-[p-(bromoacetamido)benzyl]-1,4,7,10-tetraazacyclododecane- $N,N',N''N'''$ -tetraacetic acid).

Patients

Five patients with previously treated metastatic breast cancer were enrolled in this study. These patients had failed at least one combined chemotherapy regimen and had measurable tumors that were reactive to m170 by immunoperoxidase staining. All patients who participated in the study signed written informed consents for the protocol that was approved by the University of California, Davis, Institutional Review Board for studies involving human subjects and the Radiation Use Committees, under a physician-sponsored Investigational New Drug authorization from the U.S. Food and Drug Administration (FDA). As required by the FDA, treatment was initiated until imaging studies were completed for the first 3 patients. Therefore, 2 of first 3 patients were not treated. All patients received ^{111}In -2IT-BAD-m170 for imaging and 3 received high-dose ^{90}Y -2IT-BAD-m170 followed by PBSC infusion. The protocol planned for 3-cycle fractionated treatments; only 1 fraction was given to each of 3 patients (2.0, 2.3, and 1.4 GBq) due to progressive disease, human anti-monooclonal antibody (HAMA), and patient decision due to lack of an objective response

(disease was stable) (13). All patients had normal complete blood counts before ^{90}Y -2IT-BAD-m170 therapy and had Karnofsky performance scores of $\geq 70\%$. Patients were 41–50 y old.

PBSC Mobilization and Collection

Patients received granulocyte colony-stimulating factor at $10 \mu\text{g/kg/d}$ subcutaneously. On the fifth day, PBSCs were harvested by apheresis as described previously (5,7). The goal was to collect a total of 6×10^5 granulocyte-macrophage colony-forming units (GM-CFUs) and 6×10^6 CD34+ cells per kilogram of patient weight to support the 3 planned therapy cycles. PBSCs were harvested using a Cobe Spectra system (Cobe BCT). Aliquots of at least 1 apheresis per patient were evaluated for tumor cells by a sensitive immunoperoxidase assay that can detect approximately 1 tumor cell in 1 million cells (BIS Laboratories). Cells were cryopreserved and stored in liquid nitrogen. At least 2×10^6 CD34+ cells per kilogram were transfused to patients after ^{90}Y -2IT-BAD-m170 therapy.

PBSC Survival with ^{90}Y In Vitro Cell Cultures

The effect of ^{90}Y concentration on PBSC survival rate was evaluated by sequential counting of GM-CFUs from PBSCs in vitro. Whereas GM-CFUs represent committed progenitor cells and not primitive multipotential precursors, this cell population contributes predominantly to early engraftment. Five cell cultures were prepared with culture trays having ^{90}Y concentration levels of 0.0, 0.37, 3.7, 37, and 370 kBq/mL. Each culture tray had 4 wells with identical ^{90}Y concentration. All 20 wells (in 5 trays) were inoculated with the same initial number of cells from a PBSC collection. The volume of ^{90}Y solution in each well (5-mm height, 16-mm diameter) was 0.5 mL. The trays were placed in an incubator at 37°C with 100% humidity for 15 d to allow for colony formation. The number of GM-CFUs was counted using an inverted microscope as described previously (7).

The ^{90}Y radiation dose to the PBSCs in the well was determined by:

$$D_{\text{PBSC}} = \int_0^{15\text{d}} A \cdot \phi \cdot \Delta_{90\text{Y}} \cdot \exp(-0.693 \cdot t/2.67) dt, \quad \text{Eq. 1}$$

where A is ^{90}Y concentration (kBq/mL) in the well, ϕ is the fraction of ^{90}Y energy absorbed in PBSCs from 0.5-mL ^{90}Y solution in the well, $\Delta_{90\text{Y}}$ is the total mean ^{90}Y energy emitted per nuclear transition ($1.50\text{E}-13 \text{ Gy kg/Bq s}$), and 2.67 d (64 h) is the physical half-life of ^{90}Y . Based on numeric integration of all voxels (0.001 mm^3) using ^{90}Y percentile data (14), an absorbed fraction of 0.49 was determined for the radiation dose from ^{90}Y uniformly distributed in 0.5-mL solution to PBSCs settled in a methyl cellulose layer at the bottom of the well about 0.2-mm thick. The PBSC survival was described by a linear-quadratic formula (15):

$$\ln \left(\frac{N_{15\text{d}}}{N_0} \right) = -\alpha \cdot D_{\text{PBSC}} + \frac{0.693 \cdot 15\text{d}}{T_{\text{pot}}}, \quad \text{Eq. 2}$$

where $N_{15\text{d}}$ is the number of cells surviving after 15-d irradiation, N_0 is the initial number of cells, α is the coefficient of nonrepairable damage per gray, and T_{pot} is the doubling time for PBSC proliferation. The coefficient of repairable damage, β , is assumed to be zero as bone marrow stem cells do not exhibit a late radiation effect (16). As the initial cell numbers were identical in the control and irradiated wells, Equation 2 can be simplified as:

$$\ln \left(\frac{N_{15d}}{N_{control}} \right) = -\alpha \cdot D_{PBSC}, \quad \text{Eq. 3}$$

where $N_{control}$ is the number of cells in the control well in which ^{90}Y activity was zero.

Dosimetry Data Collection and Analysis

Imaging and blood data collection and analysis have been described in detail previously (13,17,18). Briefly, planar conjugate views were acquired with a Bodyscan dual-detector camera (Siemens Medical Systems, Inc.). Medium-energy collimators were used with energy windows centered at 171 and 245 keV with 15% width for ^{111}In . Whole-body scans and static images of the skull, chest, abdomen, and pelvis were acquired immediately and at approximately 4, 24, 48, 72, and 144 h.

Liver, spleen, lungs, kidneys, and lumbar vertebrae (L2–L4) were visualized above body background tissue and their uptake of ^{111}In -2IT-BAD-m170 was quantified. The operator reviewed CT images to facilitate region-of-interest (ROI) determination. ROIs for the whole body and the organs were manually defined based on visual boundary. The geometric-mean quantification was used for liver and lungs. The attenuation correction factor for liver and lung was determined using transmission scan images obtained with a rod source containing about 93 MBq ^{111}In . The effective-point-source quantification was used for spleen, kidneys, and lumbar vertebrae L2–L4 for marrow (19–21). Photon attenuation was corrected using measured μ values that matched the small source geometry. A 10-mL calibrated source of 7.4 MBq ^{111}In was used to convert ROI counts to megabecquerels of ^{111}In and ^{90}Y , assuming identical distributions in all organs except for bone marrow. Cumulated ^{90}Y activity and effective clearance half-life (T_{eff}) were determined by fitting the organ activity data to a monoexponential curve. Liver, spleen, kidney, and lung radiation doses from ^{90}Y were calculated using S values from MIRDOSE3 software (22). S values for source and target in red marrow and bone endosteum were obtained from a revised model based on the Eckerman and Stabin model and the Bouchet and Bolch model for high-energy β -particles of ^{90}Y (23–25).

Serial blood samples were collected after dose injection of ^{90}Y -2IT-BAD-m170 at approximately 0.083, 0.5, 1, 2, 4, 24, 48, 72, and 144 h. An aliquot (1 mL) of each sample was counted in a γ -well counter calibrated for ^{90}Y to determine ^{90}Y concentration (kBq/mL) in the blood. The cumulated activity was determined by fitting data to a biexponential curve with α - and β -clearance phases. Time-dependent radiation dose to PBSCs from blood was predominated by the β -clearance phase at the time of PBSC infusion.

PBSC Dosimetry

After intravenous infusion of PBSCs, stem cells circulate in the blood through various organs before they migrate into the cellular compartment of the marrow. Thus, radiation doses to PBSCs from ^{90}Y in major organs need to be considered (Fig. 1). The radiation dose to PBSCs in the organ, $D_{PBSC \leftarrow \text{organ}}$, can be described as a function of time for PBSC infusion T_{infu} ($T_{infu} = 0$ at ^{90}Y injection):

$$D_{PBSC \leftarrow \text{organ}}(T_{infu}) = R_{organ}(T_{infu}) \cdot \int_0^\infty \exp(-0.693 \cdot t/T_{eff}) \cdot PBSC_{organ}(t) dt, \quad \text{Eq. 4}$$

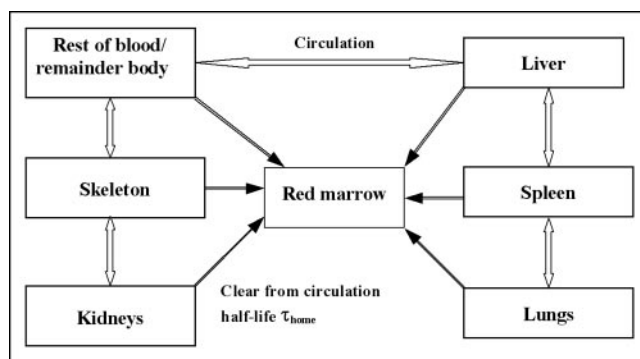


FIGURE 1. Schematic diagram to illustrate circulation of PBSCs in major organs and migration of PBSCs to marrow with a half-life of τ_{home} cleared from blood.

where $R_{organ}(T_{infu})$ is the organ dose rate at the time of PBSC infusion, T_{eff} is the organ effective clearance half-life, and $PBSC_{organ}(t)$ is the fraction of PBSCs in the organ at time t after PBSC infusion ($t = 0$ at PBSC infusion). The cumulated dose was integrated from the time of PBSC infusion.

For a τ_{home} half-life for PBSCs cleared from circulation, the PBSC distribution in the organ, except for red marrow, can be described as function of time:

$$PBSC_{organ}(t) = F_{organ} \cdot \exp(-0.693 \cdot t/\tau_{home}), \quad \text{Eq. 5}$$

where F_{organ} is the fraction of total blood volume in the organ. The blood volume in the liver, spleen, lungs, kidneys, bone, and marrow can be found in the literature for the Reference Man (Table 1) (26). The volume of the remainder of the blood was determined by subtracting blood volume in the liver, spleen, kidneys, lungs, marrow, and bone from the total blood volume. The τ_{home} was estimated to be 55 h based on a reported measurement that 20% of stem cells migrate to the murine marrow 18 h after stem cell infusion (27).

The amount of PBSCs that accumulate in the red marrow can be determined by:

$$PBSC_{red\ marrow}(t) = F_{red\ marrow} + (1 - F_{red\ marrow}) \cdot (1 - \exp(-0.693 \cdot t/\tau_{home})) = 1 - (1 - F_{red\ marrow}) \cdot \exp(-0.693 \cdot t/\tau_{home}). \quad \text{Eq. 6}$$

RESULTS

PBSC Survival in ^{90}Y -Treated Cell Culture

The GM-CFU survival fraction as a function of ^{90}Y concentration is shown in Figure 2. The natural logarithms of survival fraction data were least-square fitted to the activity concentration up to 37 kBq/mL. Data for 370 kBq/mL concentration could not be included in data fitting because there were no GM-CFUs found at a concentration level of 370 kBq/mL and, mathematically, $\ln(0)$ is uncertain ($-\infty$). Only part of the ^{90}Y energy was deposited to PBSCs. Based on numeric integration, 0.5 mL of 37 kBq/mL ^{90}Y solution delivers a mean dose of 0.88 Gy in 15 d to PBSCs in a methylcellulose layer at the bottom of the well. The fitted value for the coefficient of nonrepairable damage (α_{PBSC}) was 0.744 Gy^{-1} when the survival rate was ex-

TABLE 1

Organ Mass and Fraction of Total Blood Volume in Organ of Reference Man

Organ	Mass (g)	Fraction of total blood volume (%)
Liver	1,800	10.0
Spleen	150	1.4
Lungs	1,200	12.5
Kidneys	310	2.0
Skeleton	10,500	7.0
Bone	5,500	
Cortical bone	4,400	1.2
Trabecular bone	1,100	0.8
Red marrow	1,170	4.0
Remainder of body	59,040	67.1
Remainder of blood		67.1
Total blood		100

Data are from (26).

TABLE 2Mean T_{eff} and ^{90}Y Radiation Dose for 5 Patients Receiving ^{111}In -2IT-BAD-m170

Tissue	T_{eff} (h)	Dose (mGy/MBq)
Liver	NA	4.8
Spleen	58	2.8
Kidneys	50	1.9
Lungs	43	1.7
Marrow (imaging L2–L4)	60	1.6
Body	55	0.61
Blood	38	7.1*

*This is accumulated activity concentration (7.1 kBq h/MBq/g) in blood as actual blood dose is complicated by various blood vessel sizes.

NA = not available as uptake in liver typically increased during 6-d imaging period.

pressed as $\exp(-\alpha D)$ or 0.664 Gy^{-1} if the survival rate was expressed as $\exp(-0.064 - \alpha D)$.

PBSC Dosimetry for Individual Patients:

Example of Calculation

The mean T_{eff} and radiation dose for ^{90}Y -2IT-BAD-m170 were determined for liver, spleen, kidneys, lungs, marrow (by imaging L2–L4), blood, and body in 5 patients (Table 2). To illustrate the process for planning infusion time, the detailed calculation for 1 patient was as follows:

After completing 6 d of an ^{111}In -2IT-BAD-m170 imaging study, 1 patient received 2.0 GBq of ^{90}Y -2IT-BAD-m170. Seven days (168 h) after injection of the dose, the ^{90}Y concentration in the blood was 7.4 kBq/mL. The effective β -clearance half-life was 31 h. What is the radiation dose to PBSCs if PBSCs are transfused at 168 h after injection?

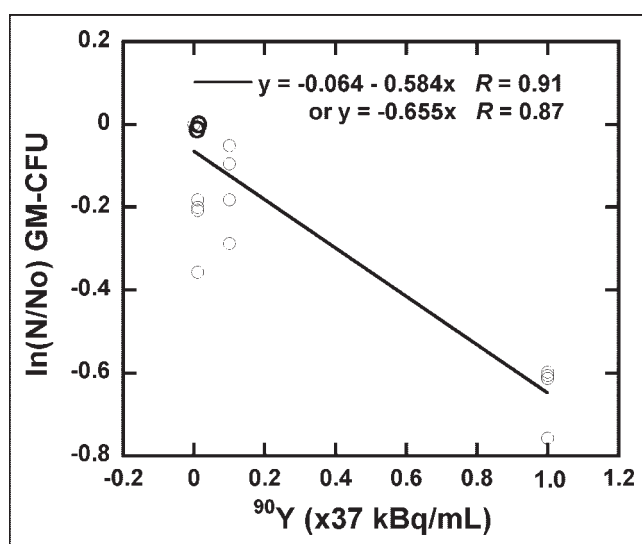


FIGURE 2. Effect of ^{90}Y concentration on survival of GM-CFUs from stem cells in cell cultures.

When should PBSCs be transfused if killing of PBSCs is to be kept $<10\%$?

Organ Effective T_{eff} , Uptake, and Concentration of ^{90}Y at 168 Hours After Injection. The T_{eff} for the liver could not be determined by monoexponential curve fitting, as the liver uptake was increased from 10 %ID (percentage injected dose) immediately after injection to 20 %ID 144 h after injection (last imaging time point). An effective half-life of 64 h (physical half-life of ^{90}Y) was assumed after 144 h in the liver, assuming a constant biologic uptake after the last imaging time point (Table 3). The effective half-life of the remainder of the body was derived from the effective half-life of liver, spleen, kidneys, lungs, marrow, bone, and total body.

An ^{90}Y concentration of 5.2 kBq/g in bone (Table 3) was estimated on the basis of the reported difference in ^{111}In and ^{90}Y concentration in bone or marrow biopsy (28) adjusted for the difference in chelation (29). The amount of ^{90}Y in cortical bone and trabecular bone was determined on the basis of the reported ratio of trabecular-to-cortical bone surface area (10.5:6.5) (26).

The radiation dose in the remainder of the blood was considered to be 2 parts: (a) 100% absorption of ^{90}Y energy for 1.4 kBq/g in the blood as the ^{90}Y concentration in the remainder of the body without blood was 1.4 kBq/g (Table 3); and (b) for the remaining 3.5 kBq/g of ^{90}Y in the blood, an absorption fraction value of 0.54 was determined using reported ^{90}Y absorption fractions for various blood vessels in the arterial and venous systems (30), excluding the pulmonary system.

Organ Dose Rate at 168 Hours After Dose Injection: Dose to PBSCs. Except for bone and red marrow, the organ dose rate was contributed from ^{90}Y located in the organ itself. At 168 h after dose injection, the dose rate to marrow was 0.49 cGy/h from ^{90}Y in marrow and 0.20 cGy/h from ^{90}Y in bone. The dose rate to bone was 0.27 cGy/h from ^{90}Y in bone and 0.31 cGy/h from ^{90}Y in marrow. In the total

TABLE 3
Dosimetry Data for 1 Patient Given 2.00 GBq of ^{90}Y -2IT-BAD-m170

Organ	T_{eff} (h)	Uptake at 168 h (MBq)	Concentration at 168 h (kBq/g)	Organ dose rate at 168 h (cGy/h)	PBSC dose (cGy)
Liver	64	65	36	1.9	8.3
Spleen	58	4.0	27	1.4	0.82
Kidneys	60	5.4	18	0.94	0.78
Lungs	42	6.1	5.1	0.27	1.2
Red marrow	55	24	21	0.69	29
Bone	64	29	5.2	0.58	0.48
Cortical bone	64	11	2.5		
Trabecular bone	64	18	16		
Total blood	31	27	4.9		
Remainder of blood	31	19	4.9	0.25	4.9
Total body	55	240	0.0033		
Remainder of body	46	100	0.0016		
Remainder of body, no blood	49	83	1.4		

To illustrate the computing process, uptake in cortical bone, trabecular bone, total blood, total body, remainder of body, and remainder of body without blood was listed but was not needed for organ dose rate and PBSC dose.

radiation dose to PBSCs, 65% of the dose was contributed from ^{90}Y in the marrow and bone, 12% was contributed from ^{90}Y in the remainder of the blood, and 11% was contributed from ^{90}Y in the liver (Table 3).

Similarly, using the same computing procedures, the radiation dose to PBSCs would be 50.4 cGy (12.4 cGy from liver, 31.2 cGy from marrow, 4.5 cGy from remainder of the blood or body) for patient 2 receiving 2.1 GBq ^{90}Y if PBSCs were infused 7 d after ^{90}Y injection. The radiation dose to PBSCs would be 32.2 cGy (8.5 cGy from liver, 15.9 cGy from marrow, 6.2 cGy from remainder of the blood or body) for patient 3 receiving 1.4 GBq ^{90}Y if PBSCs were infused 7 d after ^{90}Y injection.

PBSC Survival and Infusion Time. The PBSC survival rate was determined as $e^{-0.744D}$ as described. For a given injection dose, the PBSC survival could be determined as a function of PBSC infusion time (Fig. 3). For treatment planning before dose injection, physicians can review patient-specific isosurvival curves as a function of injection dose and the time interval for PBSC infusion (Fig. 4). For example, for the 2.0-GBq dose injection to this illustrated patient, 80% PBSC survival requires a time interval at least 9 d, and 90% survival requires a time interval at least 13 d (Fig. 4). In our clinical practice, an interval of 2 wk has been used. This infusion time interval worked well, as all 3 patients demonstrated evidence of hematologic recovery.

DISCUSSION

Radiation-induced myelotoxicity is often dose limiting in radionuclide therapy that does not include bone marrow reconstitution. For treatment without marrow reconstitution, the challenges in marrow dosimetry have been discussed extensively in the literature (20,23,31–37). However, in high-dose treatment with marrow reconstitution, there has been no detailed analysis of radiation damage to PBSCs

during circulation and after homing that can cause a delayed blood count recovery.

After PBSC infusion, several critical events determine the final engraftment results. These events include the time that PBSCs freely circulate in blood vessels, time that PBSCs traverse the endothelial barrier, time that PBSCs migrate into tissue spaces, and, finally, residence in one particular tissue space. In each of these events, PBSCs can be damaged by irradiation from radioactivity located in the tissues. In the current study, we proposed a noninvasive method to calculate radiation dose to PBSCs that accounts for time-varying distributions of PBSCs and radioactivity in tissues.

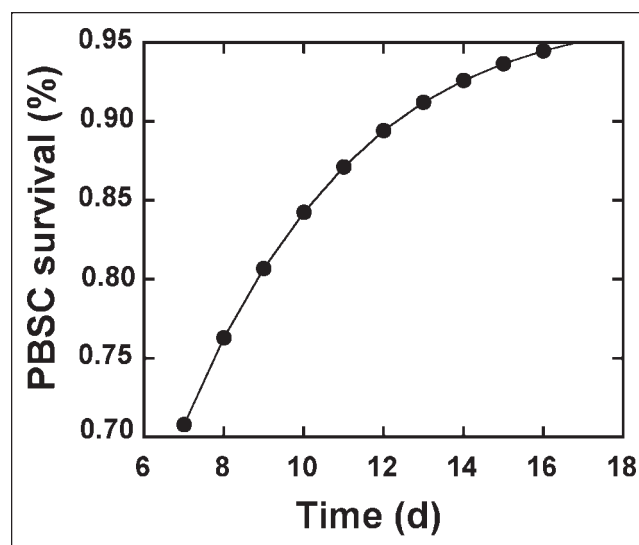


FIGURE 3. Calculated PBSC survival as function of infusion time for patient receiving 2.0 GBq ^{90}Y -2IT-BAD-m170, given patient-specific tissue effective half-lives and radiation doses (Table 3).

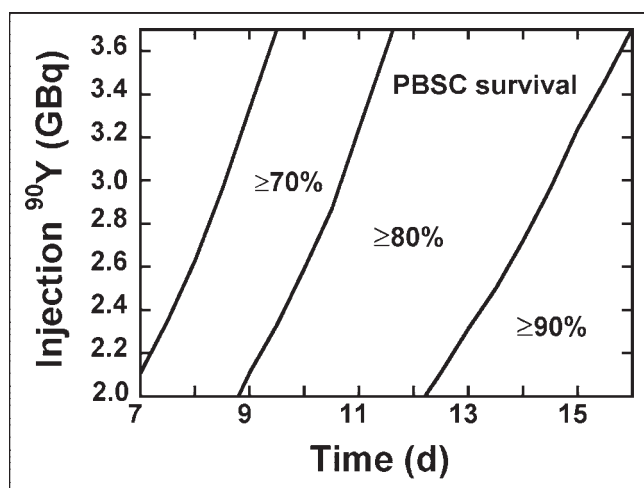


FIGURE 4. Isosurvival curves for planning time for PBSC infusion. Isosurvival curves of 70%, 80%, and 90% were determined as function of injection dose and infusion time.

Initially, we estimated the time interval for PBSC infusion based on the ^{131}I concentration level in the blood in breast cancer patients treated using ^{131}I -labeled chimeric L6 antibody (5). In limited observations of patients receiving high-dose ^{131}I -labeled chimeric L6, the PBSC infusion time based on the ^{131}I concentration in the blood worked reasonably well. However, in patients receiving high-dose ^{90}Y -2IT-BAD-m170, the results were unsatisfactory when the time for PBSC infusion was based on the ^{90}Y concentration in the blood. Recoveries of blood counts were unexpectedly delayed in 1 transfused patient when the blood level of radioactivity was below the threshold determined in vitro. This prompted further analysis of other possible contributions to the irradiation of the infused PBSCs. In the current analysis, it is quite clear that the dose from ^{90}Y in the blood accounts for only a portion of the total dose to PBSCs. Although the remainder of the blood has 74% blood volume (Table 1), it contributes 12% of the total dose to PBSCs (Table 3).

In our illustrated case, the majority of the radiation dose to PBSCs was from ^{90}Y in marrow and bone as PBSCs accumulate in marrow over time. In treatment with ^{90}Y -labeled targeted molecules, the radiation dose to PBSCs in the marrow is contributed from ^{90}Y in the blood and ^{90}Y in the bone if there is no active uptake of target molecules by the marrow. The DOTA chelator used in this study has been shown to hold ^{90}Y and ^{111}In stably (29,38). Although minimal ^{90}Y and ^{111}In can escape from the chelator, lumbar vertebrae were still visible in ^{111}In -2IT-BAD-m170 images. It is quite common to visualize lumbar vertebrae in ^{111}In -labeled antibody images of patients without known marrow malignancy (21,39), although ^{111}In or ^{90}Y is still held by the chelator.

Therefore, in the current proposed method, we estimated ^{111}In uptake in the marrow using the imaging method to include ^{111}In that was distributed in the blood and in the

marrow. The difference between the ^{111}In amount in marrow and the ^{90}Y amount in bone was considered using data reported for patient core biopsies that showed that the mean difference between ^{90}Y and ^{111}In concentration in bone and marrow was 0.003 %ID/g with MX-diethylenetriaminepentaacetic acid (methylbenzyl-DTPA [MX-DTPA]) chelator (28). To adjust the difference between the MX-DTPA chelator and the DOTA chelator, a value of 0.0016 %ID/g was estimated based on reported autoradiographic measurements in mice that the mean ^{90}Y uptake in bone with MX-DTPA chelator was 1.88 times higher than that with the DOTA chelator (29). This 0.0016 %ID/g corresponds to 5.2 kBq/g in bone at 168 h after injection in our calculation example (Table 3). Image quantification in the lumbar vertebrae region (19,20) assumes that the regional activity concentration in vertebrae can represent the mean activity concentration in total marrow. This assumption could be problematic if patients have marrow involved with cancer. In the current patient population, there was no hot spot in or near the L2–L4 lumbar vertebrae ROI. Nevertheless, if there are hot spots in the skeletal region, selection of the ROI for these particular patients should be carefully evaluated on a case-by-case basis.

The ^{90}Y concentration in bone and marrow can be directly determined from bone marrow biopsy. Wong et al. used bone marrow biopsy to estimate the ^{90}Y radiation dose to autologous stem cells (9). Initially, they transfused 25% of the stem cells at 5 d after ^{90}Y injection (0.56 GBq/m²) regardless of the variation in ^{90}Y distribution among the patients. The remaining 75% of the stem cells were transfused at the time point at which the estimated remaining marrow dose was ≤ 5 cGy, as determined by patient-specific bone marrow biopsy. Their protocol was modified for a dose level of 0.83 GBq/m², at which 25% of the stem cells were transfused when the remaining marrow dose was ≤ 5 cGy, and the remaining 75% were transfused when the absolute granulocyte count was $< 1,000/\mu\text{L}$. Their transfusion schedules worked well as all patients demonstrated evidence of hematologic recovery. According to the current analysis, the sum of radiation doses from liver, spleen, kidneys, lungs, and the remainder of the blood was about half of the dose from marrow and bone (Table 3), and 5 cGy to PBSCs would damage only 3.7% of the total PBSCs. Therefore, dose contribution from other major organs and blood may be ignored if a low threshold value for marrow dose is selected deliberately. Although bone marrow biopsy provides a direct, patient-specific, measurement of radioactivity, its accuracy often suffers from large variations dependent on sampling. The current imaging method is noninvasive and is not limited by the potential sampling error.

Regeneration of the hematopoietic system is complex. There are many factors other than radiation dose that may affect the final engraftment results, including the number and “quality” of stem cells harvested, particularly in heavily pretreated patients, or production of inhibitory cytokines—

for example, in association with infection that interferes with hematopoietic cell proliferation. These factors are beyond the scope of a method that is based on “a typical” patient. The current proposed method considers the radiation damage to PBSCs from all sources and provides a practical method to determine the infusion time under a typical patient condition. The success of engraftment is dependent on the short-term (~4 wk) repopulating cells to provide transient protection, and irradiation from radionuclide therapy is typically during this short term; therefore, radiation damage to PBSCs should be kept insignificant. It seems that a 90% PBSC survival rate is appropriate to determine infusion time. This corresponds to an infusion time interval of ~2 wk in our patients receiving 1.4–2.1 GBq ^{90}Y -2IT-BAD-m170 and it worked well, as all 3 patients demonstrated evidence of hematologic recovery. The calculation of radiation dose to PBSCs can be easily implemented using spreadsheet software, such as Excel (Microsoft). Once the spreadsheet program has been established, the PBSC dose and survival rate can be calculated instantly by simply entering patient-specific tissue effective half-lives and radiation doses into the spreadsheet.

CONCLUSION

PBSC infusion is a critical component of many high-dose targeted radionuclide therapies. A noninvasive dosimetry method was developed for planning the time for PBSC infusion after high-dose radioimmunotherapy. The method calculates the radiation dose to PBSCs from radioactivity in all sources with time-varying distributions of PBSCs and radioactivity. Our studies suggested that the PBSC dosimetry method was more effective than the blood concentration method in predicting the best time to reinfuse PBSCs for radiopharmaceuticals that have a much higher activity concentration in organs than that in the blood.

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