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Internal Microdosimetry for Single Cells in Radioimmunotherapy of B-Cell Lymphoma

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ABSTRACT

Patients with B-cell lymphoma may have disease manifestations ranging in size from more than a 1000 cm^3 down to the volume of a single cell. If targeted radionuclide therapy is to become a curative treatment, all individual tumor cells must also be eliminated. Given the vast differences in particle energy of different electron-emitting radionuclides, one questions whether the mean absorbed dose is a relevant parameter for use in single-cell dosimetry and whether it would not be more accurate to adopt a stochastic approach to dosimetry. Monte Carlo simulations were performed of energy deposition from 1000, 300, 100, or 10 electrons uniformly distributed in a sphere with a radius of 7.7 μm. The simulated electrons were monoenergetic (18 keV, 28 keV, 141 keV, or 935 keV). The absorbed dose per emitted electron, the absorbed fraction, the fraction of the cellular volume in which energy is deposited, and the dose-volume histograms were calculated. Absorbed fractions varied between 0.60 (18 keV) and 0.001 (935 keV), and the absorbed dose to the cell per electron emitted varied by a factor of 10, from 0.898 mGy (18 keV) to 0.096 mGy (935 keV). The specific energy varied between 0 and 46 mGy for the case showing the best uniformity (1000 18-keV electrons). The nonuniformity of the absorbed dose to a cell increases with increasing electron energy and decreases with the number of decays inside the studied volume. The wide distribution of energy deposition should be taken into account when analyzing and designing trials for targeted radionuclide therapy.

Key words: microdosimetry; radioimmunotherapy, lymphoma

INTRODUCTION

Approximately 25% of the patients diagnosed with non-Hodgkin's lymphoma exhibit malignant cells in the circulation,[1] which means that these patients can have disease manifestations ranging in volume from more than 1000 cm^3 down to the volume of a single cell. This large spread in the volume of tumors within one and the same patient will present a challenge in treatment optimization and will place special demands on the dosimetry and the choice of radionuclides for therapy.

Radioimmunotherapy (RIT) is an established form of treatment for B-cell lymphoma. In spite of significantly higher remission rates, the duration of remission was not found to be longer fol-

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lowing RIT (^{90}Y-labeled antibody combined with cold antibody) than when using cold antibody alone in a large, randomized study.[2] This is an unexpected finding, as the quality of remission (i.e., complete remission or partial remission) has been reported to be correlated to the duration.[3] A possible explanation could be that the energy from the beta-particle emitted from ^{90}Y is deposited outside the small tumor-cell clusters or single cells. In order to achieve a cure or a longer remission in lymphoma, it might be necessary to deliver a higher absorbed dose to single tumor cells. This might not only be relevant when treating minimal residual disease in different subtypes of lymphoma, but also when treating the most common type of lymphoma, B-cell chronic lymphocytic leukemia (B-CLL), with a large number of malignant cells in the circulation.

Dosimetry, in terms of the mean absorbed dose for the tumor cells circulating in peripheral blood, can be performed by the use of the Medical Internal Radiation Dose (MIRD) cellular S-values.[4] S-values are generally calculated from a uniform activity distribution,[5] but a uniform activity distribution is no prerequisite for a uniform deposition of energy.[6] One reason for nonuniformity in the deposited energy could be the presence of very few atoms per cell. Very few atoms per cell, or a very low activity in a small volume, will make the stochastic effects in the specific energy (as defined in ICRU report 60) more apparent. One question that arises is, therefore, how many (or few) radioactive atoms have to deposit their energy in a cell for the absorbed-dose concept to be a relevant parameter on a cellular level. Another question that must be raised is the influence of the beta-particle's energy on the absorbed dose and specific energy. Even if the absorbed dose to the cell (as calculated by the use of the MIRD cellular S-values) is a representative value, the energy deposition in the cell should be uniform if the absorbed dose is to serve as a relevant value for the assessment of the biological effect. In this study, we assumed a uniform activity distribution. Although this is not likely to be the case, it might be a reasonable approximation for rapidly internalizing antibodies that are used, or have potential use, in the treatment of lymphoma (e.g., epratuzumab and the anti-CD74 antibody). Based on a previous study of single-cell activity uptake,[7] we performed Monte Carlo simulations for low numbers of atoms per cell and different electron energies to assess the mean absorbed dose and the distribution of deposited energy in the cell.

MATERIALS AND METHODS

Monte Carlo simulations were carried out in a sphere with a radius of 7.7 μm, which is the size of the cell in a commonly used B-lymphoma cell line (Raji cells).[8] The sphere was subdivided into 7700 shells of 1 nm in thickness. The point of origin of each simulated electron was uniformly randomized inside the sphere to mimic a uniform activity distribution. In order to model different numbers of atoms incorporated into a cell, simulations were carried out with different numbers of electrons (10, 100, 300, and 1000) with their point of origin inside the cell. These numbers of incorporated atoms were based on measurements of the cellular uptake in a lymphoma patient published earlier.[7] The Monte Carlo simulations were performed for 4 electron energies, well dispersed throughout the energy interval used in RIT. The monoenergetic electron energies chosen were 18 keV (the mean electron energy per decay for ^{125}I), 28 keV (the mean electron energy per decay of ^{123}I), 141 keV (the mean beta energy per decay of ^{67}Cu), and 935 keV (the mean beta energy emitted by ^{90}Y). The continuous slowing-down approximation (CSDA) range for these monoenergetic electrons is 7.1 μm, 15.6 μm, 255 μm, and 4020 μm, respectively, and should be compared to the cellular radius of 7.7 μm assumed in this study. The CSDA ranges were calculated from data in ICRU Report No. 37.[9]

Stochastic simulations of electron tracks, in order to calculate the spatial distribution of energy deposition (and absorbed dose) within the target-cell volume, were accomplished with a hybrid transport scheme using a previously developed Monte Carlo code. Detailed documentation of the code, together with the physical models and databases used, can be found in Emfietzoglou et al.[10–13] In this paper, only a brief description will be given.

For electrons with a kinetic energy below 10 keV, a detailed history scheme is employed (i.e., event-by-event simulation of all interaction processes based on random sampling from probability distributions (cross-sections) characterizing the individual elastic and inelastic collisions, the latter encompassing the various discrete (excitation) and continuum (ionization) transitions). In this scheme, the generation of each electron (i.e., primary and secondaries) is individually followed down to the ionization threshold of water ($\sim$10 eV), and the stochastics of their tracks are fully accounted for in a self-consistent manner. How-

ever, because of the large number of collisions involved, the detailed history scheme is generally not applicable to higher-energy electrons, as computer time would become prohibitively long. Therefore, a condensed-history, random-walk scheme was implemented at higher energies where elastic collisions are still individually simulated, based on the relevant cross-sections, while energy losses are considered to be continuous and are given by the product of the stopping power and the length of the (random) path between successive elastic events. Although energy-loss straggling is neglected in this scheme, the simulation of individual elastic events will, for the most part, preserve the stochastics of angular deflection and, consequently, the spread-out pattern of the track. Therefore, this scheme is more realistic than simply using a range-energy relationship and linear tracks.

Based on the above hybrid scheme, we were able to perform full slowing-down simulation (down to 10 eV) of electrons of initial energy as high as 1 MeV. The electrons were assumed to originate at random positions with random orientations within the target-cell volume. However, the simulation also followed electrons outside this volume, as electrons are capable of re-entry because of large-angle scattering.

Dose-volume histograms (DVH) and the mean absorbed dose to the whole cell were calculated for all Monte Carlo simulations (i.e., for 4 electron energies and 4 number of atoms per cell). The absorbed fraction was calculated as the ratio of the mean absorbed energy from the Monte Carlo simulations to the kinetic energy of the electrons. The volume in which energy was deposited was defined as the sum of the volumes of the shells in the sphere that had received any energy. The specific energy, z, was calculated as:

$$z = \frac{\varepsilon_{shell}}{m_{shell}}$$

where ε_{shell} is the deposited energy in a 1-nm shell, as given by the Monte Carlo simulations and m_{shell} is the mass of that 1-nm shell.

Table 1. Absorbed Fraction and Mean Absorbed Dose per Decay in a Cell for Monoenergetic Electrons (the Radius of the Cell is 7.7 μm)

Electron energy [keV]	*Absorbed fraction*	*Absorbed dose per decay [mGy]*	*MIRD S value [mGy/Bq s]*
18	0.60	0.898	0.875
28	0.26	0.619	0.598
141	0.01	0.156	—
935	0.001	0.096	—

The MIRD cellular S values, which have been scaled by mass to a cellular radius of 7.7 μm, for monoenergetic electrons are given for comparison. MIRD, Medical Internal Radiation Dose.

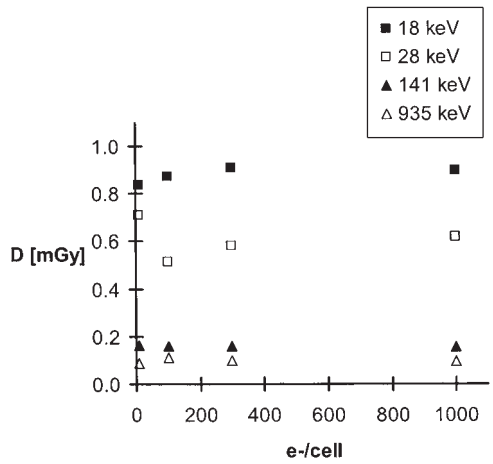

Figure 1. Mean absorbed dose (D) to a cell (radius, 7.7 μm) per decay for various number of decays in the cell for 4 electron energies.

RESULTS

Table 1 lists the absorbed fractions and the absorbed dose per decay for monoenergetic electrons uniformly distributed inside a Raji cell. A large variation in the absorbed fractions can be seen, from 0.001 for the mean energy of electrons emitted from ^{90}Y (935 keV) up to 0.6 for the mean energy of electrons emitted from ^{125}I (18 keV). For comparison of the results in this study, the MIRD cellular S-values (scaled by mass, i.e., by assuming a constant absorbed fraction) for monoenergetic electrons are also given in Table 1.

The stochastic fluctuation (owing to the small number of atoms per cell) in the mean absorbed dose to a cell per electron emitted is small in these examples, even for electrons with a high energy and a low number of simulated electrons, as shown in Figure 1.

The fraction of cellular volume that is irradiated decreases with the decreasing number of

atoms in the cell, and decreases with increasing energy of the emitted electrons. The following 2 examples show the extremes. The fraction of the volume of the cell in which energy is deposited for 1000 simulated 18-keV electrons is almost 100% (99.7%), while it is nearly 0% (0.1%) for 10 simulated electrons with a kinetic energy of 935 keV (Fig. 2).

Figure 3A shows the differential DVHs for electron energies of 18 keV, 28 keV, 141 keV, and 935 keV. The DVHs of varying numbers of simulated electrons inside the cell for electrons with an energy of 18 keV can be seen in Figure 3B. Ideally, the mean absorbed dose in the DVH should be as high as possible and the differential DVH should show as narrow a peak as possible. As can be seen in Figure 3, the DVHs for 1000 electrons with an electron energy of 18 keV show the best resemblance to the best situation. In Figure 4, the stochastic fluctuations in the specific energy in each of the 7700 shells can be seen as a function of the mass for the ideal situation (1000 simulated 18-keV electrons). The stochastic fluctuation around the expectation value (the absorbed dose) increases as the mass decreases and the range of the specific energy is 0–46 mGy, with the expectation value of 0.898 mGy.

DISCUSSION

The mean absorbed dose per decay increases as the electron energy decreases (Table 1). This is a reasonable result, as the energy deposition per unit distance increases with decreasing electron energy. A comparison of our results of the mean absorbed dose per decay to the—by mass—scaled MIRD cellular S-values for monoenergetic electrons shows that they are within 4% (Table 1). One reason for the difference is the scaling by mass of the MIRD S-values (i.e., the assumption that the absorbed fraction is constant).

Our results are based on simulations of monoenergetic electrons and they could serve as a first approximation of radionuclides (18 keV-^{125}I, 28 keV-^{123}I, 141 keV-^{67}Cu, and 935 keV-^{90}Y). The ratio of our results of the absorbed dose per decay in Table 1 and the—by mass—scaled MIRD S-values for these radionuclides varies from 0.45 to 1.26. The difference is, however, significant and shows the error introduced by approximating the whole electron spectrum emitted by the radionuclides to a monoenergetic electron.

The mean absorbed dose on a cellular level for the examples in Figure 2 does not seem to be very sensitive to statistical fluctuations in the deposited energy (caused by having very few atoms per cell) and, therefore, the MIRD cellular S-values used to calculate the mean absorbed dose to a cell should be applicable irrespective of the electron energy or the cellular uptake of the radiopharmaceutical.

The absorbed dose nonuniformity increases, however, with increasing electron energy and decreasing number of decays inside the volume. The specific energy is, as seen in Figure 4, caused by large fluctuations, which are, in turn, caused by both stochastic and spatial effects. This is an in-

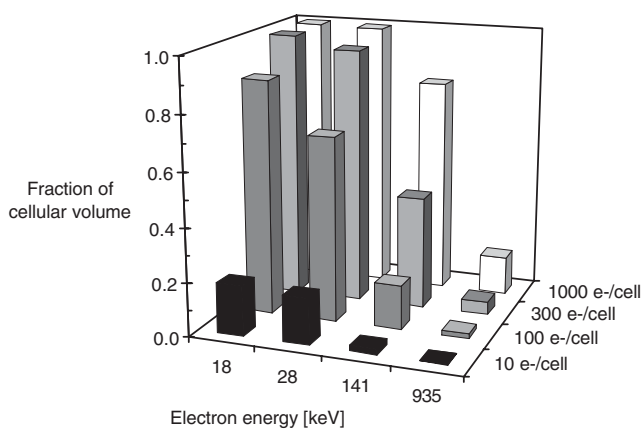

Figure 2. Fraction of the cell volume in which energy is deposited for 4 electron energies for various numbers of simulated electrons emitted inside the cell.

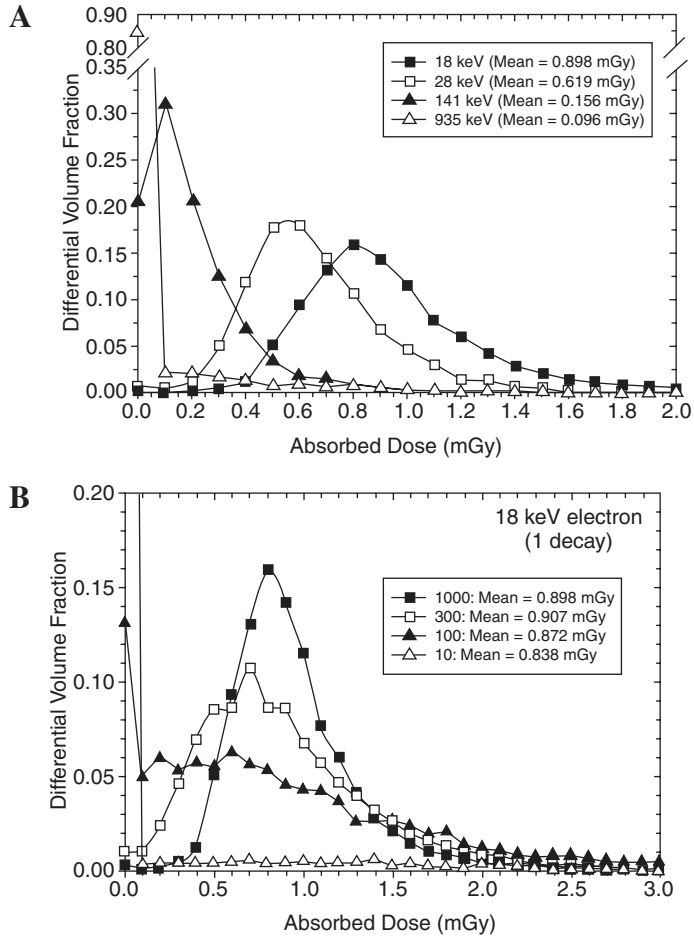

Figure 3. Dose volume histogram for a sphere (radius, 7.7 μm) for 4 electron energies (**A**) and dose volume histogram in a sphere (radius, 7.7 μm) for different numbers of 18-keV electrons (**B**).

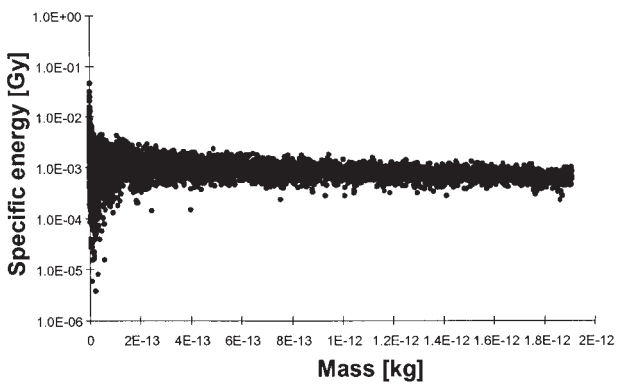

Figure 4. Specific energy in the 1-nm thick shells in the modeled cell as a function of mass for 1000 simulated 18-keV electrons. The stochastic variation around the expectation value, 0.898 mGy, increases as the mass decreases.

dication that the qualitative diagram showing specific energy as a function of mass proposed by Rossi[14] is more relevant for volumes smaller than a cell (i.e. on the subcellular level). These large fluctuations will probably have a significant effect on the correlation between the mean absorbed dose to a cell and the radiobiological effect.

The cross-absorbed dose was not considered in this study. However, the total absorbed dose to a cell is the sum of the self-absorbed dose (absorbed dose from activity in the target region) and the cross-absorbed dose (absorbed dose from activity in a source region different from the target region). The contribution from the cross-absorbed dose for a tumor cell in the setting of minimal residual disease may be low in, for example, B-CLL, so for single cells it should be reasonably correct to assume that the total absorbed dose equals the self-absorbed dose. For a large tumor, however, the cross-absorbed dose between cells must also be included. The error arising from neglecting the cross-absorbed dose will increase with increasing electron energy.

In this study, it was assumed that the activity distribution in the cell is uniform. This assumption may represent the situation for RIT with internalizing radiolabeled antibodies reasonably well.

The Monte Carlo simulation that best resembles the clinical situation during RIT today is the case with 300 simulated 935-keV electrons. Recalculations from our previous single-cell study assuming the antigen expression of Raji cells[7] showed that a maximum of 480 atoms of ^{90}Y were present per tumor cell circulating in the blood. For the single-cell case, Humm,[15] however, showed that 361,000 disintegrations of ^{90}Y on the cellular surface were required for 99% tumor-cell sterilization. According to experimental results,[7] 361,000 disintegrations per cell seems to be an unrealistically high number in RIT. For 300 emitted electrons, only 5% of the volume of the cell is irradiated (Fig. 2).

CONCLUSIONS

Twenty-four Gy, delivered by external beam radiotherapy, is an absorbed dose that is used to cure some indolent B-cell lymphomas. To deliver the same absorbed dose to single tumor cells using antibodies labeled with ^{125}I would require 27,000 decays per cell (as calculated from data in Table 1). This may be feasible in the clinical situation as, LL1, for example, is a MAb that has been reported to be able to internalize 10^7 antibodies per 24 hours.[16]

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