Biokinetic Modeling and Dosimetry for Optimizing Intraperitoneal Radioimmunotherapy of Ovarian Cancer Microtumors

Stig Palm[1], Tom Bäck[1], Börje Haraldsson[2], Lars Jacobsson[1], Sture Lindegren[1], and Per Albertsson[3]

[1]Department of Radiation Physics, Institute for Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden; [2]Department of Clinical and Molecular Medicine, Institute of Medicine, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden; and [3]Department of Oncology, Institute for Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

A biokinetic model was constructed to evaluate and optimize various intraperitoneal radioimmunotherapies for micrometastatic tumors. The model was used to calculate the absorbed dose to both anticipated microtumors and critical healthy organs and demonstrated how intraperitoneal targeted radiotherapy can be optimized to maximize the ratio between them. **Methods:** The various transport mechanisms responsible for the biokinetics of intraperitoneally infused radiolabeled monoclonal antibodies (mAbs) were modeled using a software package. Data from the literature were complemented by pharmacokinetic data derived from our clinical phase I study to set parameter values. Results using the β-emitters ^{188}Re, ^{177}Lu, and ^{90}Y and the α-emitters ^{211}At, ^{213}Bi, and ^{212}Pb were compared. The effects of improving the specific activity, prolonging residence time by introducing an osmotic agent, and varying the activity concentration of the infused agent were investigated. **Results:** According to the model, a 1.7-L infused saline volume will decrease by 0.3 mL/min because of lymphatic drainage and by 0.7 mL/min because of the transcapillary convective component. The addition of an osmotic agent serves to lower the radiation dose to the bone marrow. Clinically relevant radioactivity concentrations of α- and β-emitters bound to mAbs were compared. For α-emitters, microtumors receive high doses (>20 Gy or 100 Sv [relative biological effect = 5]). Since most of the tumor dose originates from cell-bound radionuclides, an increase in the specific activity would further increase the tumor dose without affecting the dose to peritoneal fluid or bone marrow. For β-emitters, tumors will receive almost entirely nonspecific irradiation. The dose from cell-bound radiolabeled mAbs will be negligible by comparison. For the long-lived ^{90}Y, tumor doses are expected to be low at the maximum activity concentration delivered in clinical studies. **Conclusion:** According to the presented model, α-emitters are needed to achieve radiation doses high enough to eradicate microscopic tumors.

Key Words: radioimmunotherapy; targeted alpha therapy; alpha-emitters; ovarian cancer; intraperitoneal therapy

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At diagnosis, ovarian cancer has often spread within the peritoneum. Treatment with advanced surgery and consolidated chemotherapy can appear successful, as many patients are declared tumor-free after a second laparoscopy. However, most of these patients will relapse and eventually die. To increase treatment success, adjuvant or consolidating therapies involving radionuclides have been attempted. Intraperitoneal radioimmunotherapy has the potential to irradiate micro- or subclinical tumors that have spread within the peritoneum. Many promising experiments have been performed with β-emitting radionuclides. Although a multicenter phase III clinical trial of adjuvant ^{90}Y-monoclonal antibody (mAb) did not show any survival benefit (*1*), various β-emitting radionuclides have shown other promising effects on minimal tumor growth, such as decreased tumor size at repeat operation (*2*), complete remission at third-look evaluation (*3*), and prolonged time to intraperitoneal recurrence (*4*).

The high-linear-energy transfer and short range of α-particles (50–100 μm) facilitates more concentrated irradiation of microscopic tumors. Various α-emitters have thus been evaluated for several cancer types (*5*). Our group used preclinical experiments to study the therapeutic effect and toxicity of the α-emitters ^{211}At and ^{213}Bi for intraperitoneal treatment of microscopic tumors and found high tumor doses consistent with possible cure (*6–8*). The promising results led to the initiation and completion of a phase I clinical study of intraperitoneally infused ^{211}At-MX35 F(ab′)$_2$ (*9*). Patient kinetic studies showed that for activity amounts that could be therapeutic, normal-tissue radiation doses were low to moderate and there was no acute toxicity. However, the estimated long-term risk is not negligible (*10*). It is therefore important to optimize therapy in order to maximize the ratio between dose to microtumors and dose to healthy tissues.

The aim of the current work was to build a physiology-based biokinetic model of the transport of intraperitoneally infused antibodies that describes distribution to healthy tissues and binding to microtumors of various sizes. Together with dosimetry, the model should predict the dose to both tumors and critical healthy tissues for various radionuclides and infused solutions. Ideally, the model would explain the results of previous therapies involving both β- and α-emitters and could be used to guide and optimize future intraperitoneal radioimmunotherapies.

MATERIALS AND METHODS

Compartmental Modeling

Most relevant transport mechanisms (Fig. 1) were simulated using the software package STELLA (ISEE Systems, Inc.). The resulting

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For correspondence or reprints contact: Stig Palm, Department of Radiation Physics, University of Gothenburg, Gula Stråket 2B, SE-413 45 Gothenburg, Sweden.
E-mail: stig.palm@gu.se
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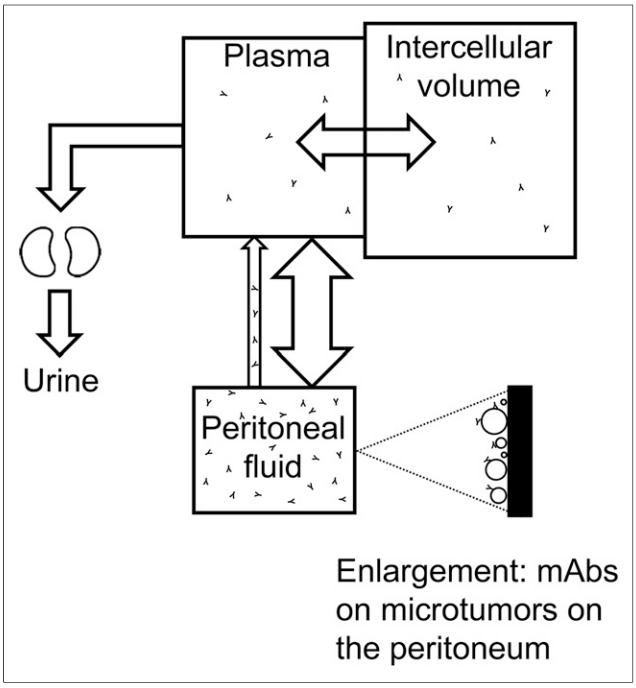

FIGURE 1. Schematic illustration of the main transports included in model. Unidirectional arrow from peritoneal fluid symbolizes lymphatic absorption, which includes mAb transport. Two-headed arrow between peritoneal fluid and plasma reflects transcapillary absorption.

time-dependent biodistribution was then used as input for dosimetry. At the time of intraperitoneal infusion, all radionuclides were assumed to be bound to antibodies. We further assumed that the radioimmunoconjugate was stable within the peritoneum and only slowly degraded in the circulation. To construct the model, we adopted a prior model (*7*) for estimates of antibody binding to cells and added elements that described transport of antibodies from the peritoneal cavity to the circulation.

Model Parameters

The uptake kinetics of microtumors were based on in vitro data generated using the cell line NIH:OVCAR-3 and were determined by the association constant, the number of available antigens on the cell surface, and the concentration of mAbs in the peritoneal fluid. Because the in vitro data indicated a negligibly small dissociation constant, this parameter was set at 0 in the model. The radiotherapeutic agent was expected to be infused intraperitoneally in a 1.7-L volume, the average used for patients enrolled in our clinical study (*10*). For modeling the peritoneal fluid transport, we expected two types of simultaneous absorption: lymphatic and transcapillary.

Lymphatic Absorption. Removal of antibody from the intraperitoneal fluid was assumed to be entirely due to direct absorption by the diaphragmatic lymphatics. A constant rate of this absorption was used as a free parameter in the model. A value of 0.3 mL/min yielded model results that best fitted the plasma concentrations of the patients enrolled in our previous trial. Because this value also agreed with what was found in the literature (*11*), it was used in the model.

Transcapillary Absorption. For infused saline, additional absorption of water due to tissue in contact with the peritoneal fluid was set at 0.7 mL/min to match an expected total absorption rate of 1 mL/min (*11*). A residual peritoneal fluid volume of 200 mL was assumed, representing the level of intraperitoneal fluid remaining after about 25 h. At that time, the flow in the model was instantaneously reversed to match the constant rate of absorption by diaphragmatic lymphatics, that is, 0.3 mL/min.

For an infused icodextrin solution, the flow rate into the peritoneum was assumed to be proportional to the icodextrin concentration. The value of the proportionality constant was set so that the model results fitted the mean peritoneal fluid concentrations of the patients enrolled in our clinical study. The resulting modeled flow rate varied from 3.2 to 1.5 mL/min in the first 24 h, which agreed reasonably well with the 4-h data published for icodextrin (*12*). Our patients' peritoneal fluid was emptied 24 h after infusion, but this procedure did not alter the main results of the current work.

The modeling further involved a range of parameter settings that were either drawn from literature (*11–14*) or based on our own clinical experience. Additional settings involved free parameters that were set so that the results of the model would match the time-dependent plasma and intraperitoneal fluid concentrations of the patients enrolled in our clinical trial. The parameters are summarized in Table 1.

Concentration of mAbs in Plasma and Intercellular Volume

We expected some delay for antibodies that had departed from the peritoneal cavity before they appeared in plasma. This delay was modeled, with a randomly drawn transit time (normal distribution; mean, 5.0 h; SD, 6.0 h) being assigned for each small amount of departed antibodies, that is, those that departed during the last 0.01 h. Once the antibodies reached the circulation, we assumed that they were instantaneously distributed throughout the plasma volume, constituting 3.6% of the body weight (*15*). A distribution volume, fixed at 9.1% (*16*) of the body weight, was simulated.

The subsequent 2-way kinetics for molecules transported in and between plasma and the intercellular volume were then modeled using a transport rate of 6.5%/h from plasma, as reported for radiolabeled albumin (*17*). Use of the same transport rate for intercellular volume to plasma provided model results that were a good fit to the patients' measured plasma concentrations.

Dosimetry

After the number of radionuclide atoms bound to a single cell was determined, the MIRD-cell application (*18*) was used for tumor dosimetry. Absorbed dose and equivalent dose were used to predict the radiation effect for all evaluated radionuclides even though a detailed microdosimetric evaluation of the α-emitters, including the number of events in individual cell nuclei of the microtumors, would likely be a better predictor of effect. Three microtumor geometries, spheres with radii of 9, 30, and 50 μm, were selected on the basis of preclinical findings from a relevant tumor model (*6*). A tumor was simulated as a homogeneous tissue-equivalent sphere of 1 g/cm^3. The sphere surface was covered with antigens of a density of 688/μm^2, equal to that for a single cell. A single point on the surface of the tumor sphere was attached to a flat plane, simulating the peritoneum. It was assumed that there were no neighboring tumors contributing to crossfire. The cell-bound radiolabeled mAbs were distributed on the surface of the tumor sphere where the decays were simulated to occur. The free radiolabeled mAbs in the surrounding fluid were simulated as randomly distributed. Because no radionuclides were simulated outside the peritoneal plane, the half-space surface geometry allowed the dose contribution to the tumor sphere from radiolabeled mAbs in the peritoneal fluid to be estimated by assigning half the intraperitoneal fluid electron equilibrium dose to the tumor. The dose contribution to the tumor sphere from free α-emitting radiolabeled mAbs in the peritoneal fluid was determined using an in-house–developed Monte Carlo program (*19*), because MIRD-cell does not support this irradiation geometry.

The radiolabeled mAb concentration in plasma will directly translate to bone marrow dose. The time-dependent concentration in red

TABLE 1
Summary of Model Parameters

Parameter	Amount/rate	Comments	Reference
Fluid			
Plasma	2.3 L	36 mL/kg of body weight	(*15*)
Distribution volume in tissue	5.9 L	91 mL/kg of body weight	(*16*)
Administered intraperitoneal fluid	1.7 L		
Residual intraperitoneal fluid	0.2 L		
Intraperitoneal fluid transport			
Lymphatic drainage (intraperitoneal fluid ⇒ plasma)	0.3 mL/min	Mean delay, 5 h (±6 h; SD)	Model fit
Water reabsorption (intraperitoneal fluid ⇒ plasma)	0.7 mL/min	Peritoneal fluid > 200 mL	Model fit
Water inflow at equilibrium (intraperitoneal fluid ⇐ plasma)	0.3 mL/min	Peritoneal fluid = 200 mL	Model fit
Water inflow; osmotic effect (intraperitoneal fluid ⇐ plasma)	3.1–1.5 mL/min	Proportional to intraperitoneal icodextran concentration, 0–24 h	Model fit
mAb conjugate transfer coefficients			
TER (plasma ⇔ intercellular volume)	0.065 h^{-1}		(*17*)
Degradation/excretion (plasma ⇒ urine)	0.0096–0.03 h^{-1}	Radiolabel-dependent	Model fit
mAb binding parameters			
Association constant (intraperitoneal fluid ⇒ tumor cell)	44,000 M^{-1} s^{-1}		(*6*)
Dissociation constant (tumor cell ⇒ intraperitoneal fluid)	0 s^{-1}		(*6*)
Number of sites per cell	700,000		(*6*)

TER = transcapillary escape rate.

bone marrow was determined from a fixed ratio of 0.19 (*20*), although this ratio has been shown to vary with time and among patients (*21*). The absorbed dose to bone marrow was then calculated by multiplying the cumulated activity by the average α- or β-particle energy emitted per decay. An absorbed fraction of 1 for the α-particles and electrons was assumed, whereas the contribution from γ-particles was considered negligible.

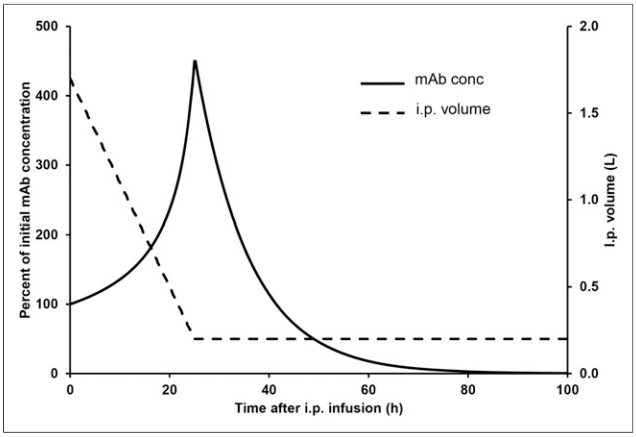

FIGURE 2. Simulated intraperitoneal fluid volume (dashed line) and relative mAb concentration (solid line) after intraperitoneal infusion of 1.7 L of saline. Rapid change in mAb concentration is due to reversal of flow when residual intraperitoneal fluid volume of 200 mL is reached. i.p. = intraperitoneal.

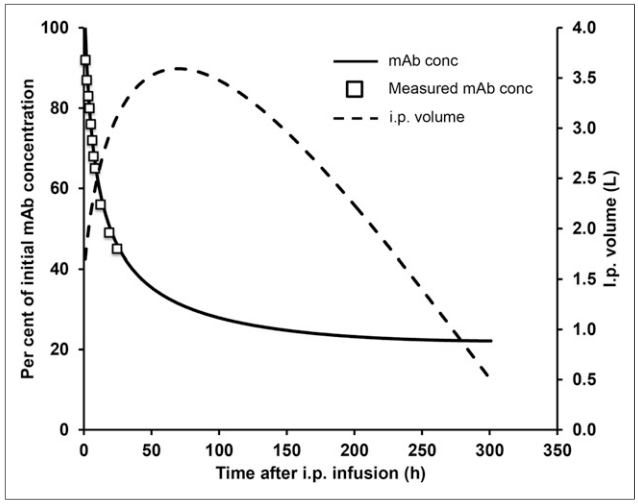

FIGURE 3. Simulated intraperitoneal fluid volume (dashed line) and relative mAb concentration (solid line) after intraperitoneal infusion of 1.7 L of 7.5% icodextrin solution. Measured data from patients' intraperitoneal fluid samples are presented as open squares. i.p. = intraperitoneal.

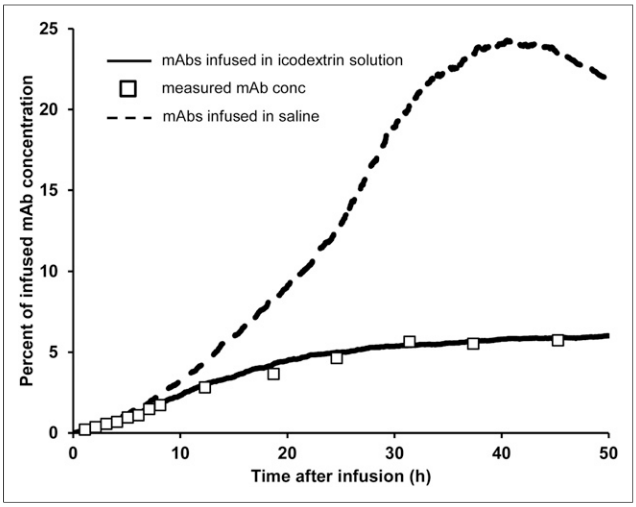

FIGURE 4. Concentration of mAb in plasma after infusion of 1.7 L of mAb in saline (dashed line) or 7.5% icodextrin solution (solid line). Measured samples from patients enrolled in our phase I clinical study are presented as open squares.

RESULTS

Peritoneal Fluid Volume

The 1.7-L infused saline volume decreased by 0.3 mL/min because of lymphatic drainage and by 0.7 mL/min because of the transcapillary convective component. Because larger molecules diffuse slowly and their passage across capillary walls is restricted, their concentration was initially increased. As the residual fluid volume of 200 mL was reached, the net influx by the transcapillary component became equal to the constant lymphatic drainage. At that point, the mAb concentration decreased as it was slowly diluted (Fig. 2).

With the addition of the osmotic agent, the transcapillary component was reversed and an initial net influx of water into the peritoneal cavity occurred. Because the osmotic effect gradually decreased, the maximum intraperitoneal fluid volume was reached at about 70 h after infusion, after which lymphatic drainage caused a net decrease in volume. The initial net influx of fluid resulted in dilution of the mAb. The results agreed with measured data from our patients' intraperitoneal fluid samples (Fig. 3).

Antibody Concentration in Plasma

Antibodies reached the circulation solely by lymphatic drainage of the intraperitoneal fluid. The mAb concentration in plasma is presented in Figure 4 as the percentage of initial mAb concentration in the 1.7 L of intraperitoneally infused fluid. The results for saline were within the broad ranges presented in the literature. The higher concentration in plasma seen after an isotonic infusion was due to the higher mAb concentration in intraperitoneal fluid (Fig. 2). The data agreed with measured plasma samples from patients enrolled in our phase I clinical study.

Bone Marrow Dose

Table 2 lists the estimated bone marrow doses after intraperitoneal infusion of mAbs with various radiolabels and hypertonic infused fluid. Because the concentration of mAbs in plasma is significantly higher for an isotonic intraperitoneal infusion (Fig. 4), the resulting bone marrow dose is higher, illustrating how adding the osmotic agent lowers the radiation dose to bone marrow.

Microtumor Uptake

The average number of mAbs bound per tumor cell was calculated. Two examples are shown in Figure 5. One is 300 MBq of ^{211}At-mAb (0.56 mg), with a specific activity translating to 1 of 200 mAbs labeled with an ^{211}At atom, intraperitoneally infused in a volume of 1.7 L. The other was 3,000 MBq of ^{213}Bi-mAb (0.59 mg), which also had a specific activity translating to radiolabeling of 1 of 200 mAbs. The small difference in the number of cell-bound mAbs between isotonic and hypertonic infused fluid is shown in Figure 5. The results were used to calculate the average number of ^{211}At or ^{213}Bi atoms per cell and the cumulative number of decays—that is, cumulated activity—per cell.

Microtumor Dosimetry

Dosimetry was performed for single cells and spheric cell clusters with diameters of 60 and 100 μm. A relative biological effect of 5 was used to calculate the equivalent dose from α-particle irradiation (*22*). Table 2 lists results for specific activities and activity amounts

TABLE 2
Model Results from Using 1.7 L of Intraperitoneally Infused Radiolabeled mAbs in Osmotic Agent

Nuclide	Fraction of mAbs radiolabeled	Administered activity (MBq)	Decays per cell (*n*)	Equivalent dose (Sv) (RBE, 5 for α-particles and 1 for electrons)							
				Bone marrow	Peritoneal fluid	Tumor (from cell-bound mAbs)			Tumor (total)		
						D, 18 μm	D, 60 μm	D, 100 μm	D, 18 μm	D, 60 μm	D, 100 μm
^{177}Lu	1/270	3,900	2,561	0.94	17	0.43	0.34	0.30	8.9	8.8	8.8
^{90}Y	1/270	1,100	2,580	0.61	26	0.13	0.12	0.12	13	13	13
^{188}Re	1/270	6,300	2,561	1.02	68	0.22	0.18	0.17	34	34	34
^{211}At	1/200	300	2,602	0.14	24	231	278	264	244	292	275
^{213}Bi	1/200	3,000	953	0.02	43	71	80	93	94	104	114
^{212}Pb	1/200	300	2,995	0.36	37	244	283	288	264	305	305

RBE = relative biological effect; D = diameter.

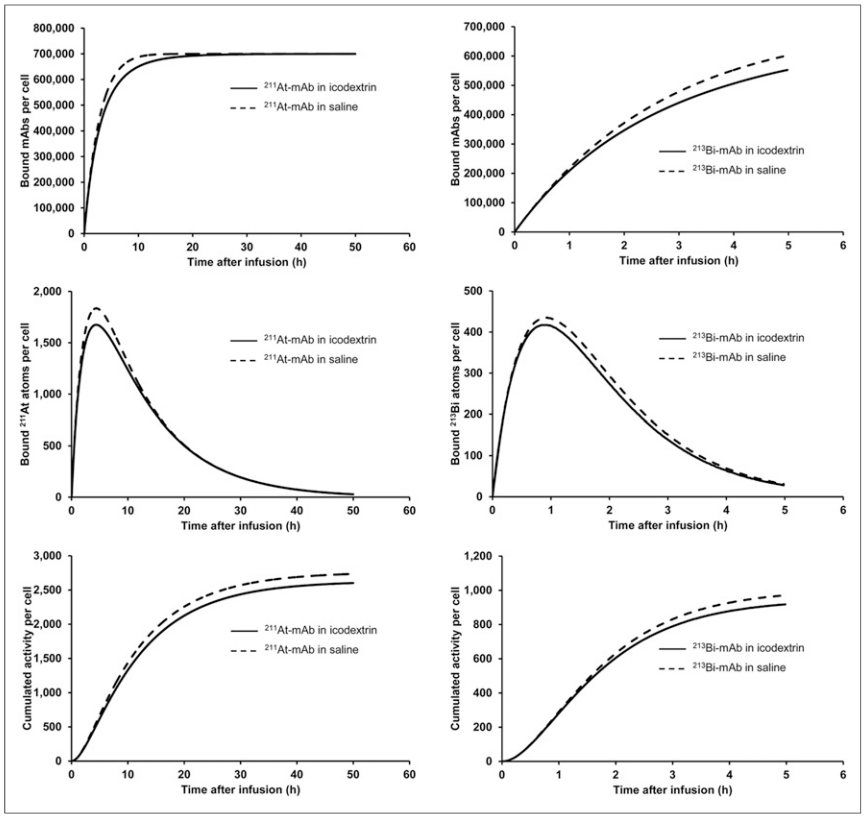

FIGURE 5. Illustration of how simulated cell-binding kinetics of radiolabeled mAbs determines absorbed dose to tumors. Top panels show total number of mAbs bound per cell. Middle panels show expected number of ^{211}At or ^{213}Bi atoms bound per cell at any specific time, that is, non–decay-corrected, assuming 1 of 200 mAbs radiolabeled at time of intraperitoneal infusion. Bottom panels show cumulated number of decays per cell, which translates to absorbed dose. Dashed lines represent results after intraperitoneal infusion of 1.7 L of saline, whereas solid lines are results for 1.7 L of 7.5% icodextrin. Figure also illustrates how use of icodextrin only slightly reduces tumor dose (but results in large decrease in dose to healthy tissues).

that are reasonably achievable today. For the α-emitters, microtumors received high doses. Because most of the tumor dose originated from cell-bound radionuclides, an increase in specific activity will further increase the tumor dose without affecting the dose to peritoneal fluid or bone marrow. Tumor doses from unbound radiolabeled mAbs in the surrounding intraperitoneal fluid were close to 50% (range, 40%–60%) of the fluid equilibrium dose for those α-emitters and tumor sizes that were investigated.

When β-emitters were used, less than 5% of the radiation dose to tumors was due to decay on tumor surfaces. The remainder of the dose, that is, more than 95%, was due to irradiation by decay occurring in the surrounding intraperitoneal fluid. For the longer-lived ^{90}Y, tumor doses are expected to be low at the maximum activity concentration delivered in clinical studies. For the shorter-lived ^{188}Re, unspecific irradiation from the peritoneal fluid would result in tumor doses of 34 Gy at a tolerable bone marrow dose (~1 Gy).

Optimization

Optimal use of radiation for therapy involves maximizing the ratio between absorbed dose to tumors and absorbed dose to critical healthy organs. Further, for cure, the absorbed dose must be high enough to eradicate the tumors. For β-emitters, the model showed that the results were best for ^{188}Re, the shortest-lived of those evaluated. Specific activity was not important since unbound radiolabeled mAbs dominated the irradiation.

Optimization for α-emitters, for which binding to tumor cells determines the tumor dose, also depends on the half-life of the radionuclide. For treatment with ^{211}At, the best gain in tumor dose was achieved by improving the specific activity of the radioimmunoconjugate (Fig. 6). If 1 of 25 mAbs can be radiolabeled, a concentration of approximately 25 MBq/L is enough to achieve therapeutic tumor doses (~20 Gy or 100 Sv [relative biological effect, 5]) for cells with 700,000 antigens and a very low dose to normal tissues, that is, at low risk. A low specific activity cannot be compensated for by using a higher activity concentration, but a higher activity concentration will improve the treatment if the specific activity is high.

DISCUSSION

In radioimmunotherapy, it is the range of the emitted particle that determines the fraction of total radiation energy absorbed in small volumes such as microtumors. Because the β-emitters used for intraperitoneal radioimmunotherapy have a relatively long range, on the order of millimeters, the absorbed dose to a cell will remain low even if a large number of radionuclides are bound to the cell surface. For the illustrative cases presented in this work, the absorbed dose from cell-bound radionuclides to cell clusters (with diameters $\leq$ 0.1 mm) is negligible in comparison to the dose received from radiolabeled mAbs in the surrounding intraperitoneal fluid. The total tumor dose is only moderate since the permissible amount of administered radioactivity is strictly limited by the resulting irradiation of critical healthy tissue, particularly bone marrow.

Sparing critical healthy tissues is, according to the presented model, particularly challenging for radionuclides with half-lives greater than about 24 h because a larger fraction will decay outside the peritoneal cavity. According to our results, the use of shorter-lived β-emitters improves the tumor–to–critical-normal-organ ratios but probably not enough to eradicate all microtumors. The β-emitters that have been clinically evaluated so far have a relatively long half-life. The restricted administered activity in combination with the long particle ranges results, according to our model, in absorbed doses not near cell sterilization levels for microscopic tumors. However, for macroscopic tumors with diameters of several millimeters, β-emitters have provided measurable antitumor effects as seen for ^{131}I (*3*), ^{186}Re (*2*), and ^{90}Y (*4*).

α-emitters have a short (50–100 μm) particle range and high-linear-energy transfer, but their half-lives can differ greatly. A short range in combination with high-linear-energy transfer is key to achieving high radiation doses to intraperitoneal microtumors but also involves irradiation of healthy tissues with uncertain biologic effects, including a long-term risk for secondary cancer that may not be negligible. Minimizing the irradiation of healthy

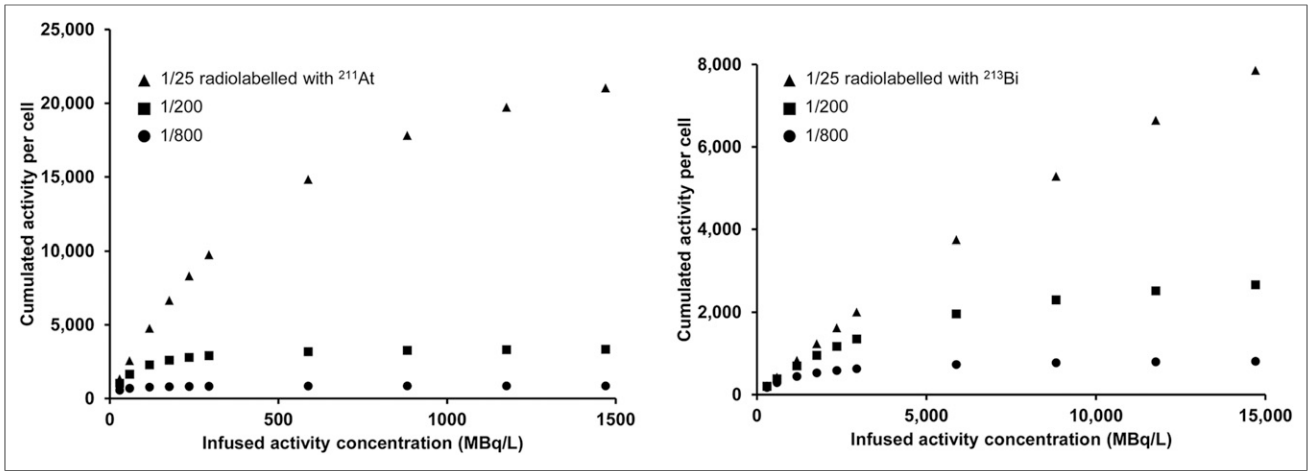

FIGURE 6. Specific activity and intraperitoneally infused activity concentration determine number of radionuclide decays per cell. Specific activity is represented as radiolabeling of 1 of 25, 1 of 200, and 1 of 800 mAbs. It is only for high specific activities of radioimmunoconjugate that increase in activity concentration of infused fluid results in significantly higher tumor doses.

tissues is therefore of the utmost importance in an adjuvant setting when long-term carcinogenic risks must be considered (*10*).

The lymphatic flow and peritoneal fluid concentration of mAbs determine the rate at which they leave the peritoneal cavity. For short-lived radionuclides with a negligible photon contribution, the resulting systemic irradiation is determined by this rate. For longer-lived radionuclides, the lymphatic flow, albeit slow, will have transported almost all radionuclides before they decay in the circulation. Any attempt to modify the rate at which radiolabeled mAbs depart from the peritoneal cavity is thus important only for shorter-lived radionuclides. In our clinical study with ^{211}At, we used icodextrin to retain a large volume of intraperitoneal fluid, primarily to guarantee several hours of complete exposure of the peritoneum. Our model showed that the diluting effect also reduced the rate of mAbs entering the circulation, reducing the dose to normal tissues by approximately 50%. The reduction in tumor dose was negligible because the dilution was slow and became significant only after tumor uptake was almost complete.

Absorbed doses to tumor cells depends both on the concentration of radiolabeled antibody within the peritoneum, that is, administered activity and fluid volume, and on specific activity. The specific activity of a radioimmunoconjugate is normally expressed as Bq/g. We chose, instead, to express it as the fraction of mAbs labeled with a radionuclide. The theoretically maximal number of radionuclide atoms bound to the cell membrane depends on this specific activity and is limited by the number of available antigens. Because some atoms decay during the binding process and cell-bound mAbs may be released, the maximum is never fully reached. According to the model results, for a fixed high specific activity, a higher infused ^{211}At-mAb activity concentration would increase tumor dose through a more rapid binding process. For a fixed low specific activity, increased ^{211}At-mAb activity concentrations would increase irradiation of healthy tissues but would only slightly increase tumor dose. To deliver high tumor doses with ^{213}Bi-mAb, cell binding must be rapid, that is, involve high mAb concentrations, and a large fraction of the mAbs must be labeled with a ^{213}Bi atom, that is, specific activity must be high.

The parameter values in the model were set from literature data or derived from pharmacokinetic data from our clinical phase I study. Thus, the model was constructed to provide perfect agreement with measured concentrations of ^{211}At-mAb in the plasma and peritoneal fluid of these patients. Because this procedure was used to set the free parameters of the model, any single value of these parameters might carry considerable error. However, the accuracy of the general conclusions drawn from the presented results is not affected.

With all feasible optimizations applied, the model predicts the best therapeutic results for ^{211}At-mAb. Good results would also be expected for ^{212}Pb-mAb but only if all, instead of the reported 65% (*23*), of the radionuclide daughters decay where the parent ^{212}Pb decay. In addition, higher activity concentrations and specific activities would be needed than those reported (*24*). Use of short-lived α-emitters such as ^{213}Bi requires high activity concentrations to eradicate microtumors. However, the short half-life will reduce normal-tissue irradiation. Excluding the dose to the peritoneum, ^{213}Bi provides a better ratio of dose to tumor relative to normal tissue than does ^{211}At. However, because the tolerance dose to the peritoneum is not known, the administered activity concentration of ^{213}Bi might be limited. Finally, if the targeted cells have significantly less antigen expression than used in the model, only ^{211}At-mAb treatment with very high specific activity would be successful for microtumors.

CONCLUSION

Through the use of physiologic data, it was possible to construct a model that fit measured radionuclide concentrations in the peritoneal fluid and blood of patients treated intraperitoneally with radiolabeled mAbs. The model is therefore useful for simulation and absorbed dose estimations of therapies with various radiolabeled mAbs.

Targeted β-emitting therapies have resulted in clinical benefit, but according to the model, α-emitters are needed to optimize treatment of microscopic tumors. High-specific-activity ^{211}At-mAbs achieve high tumor doses even for cells with a low antigen expression. With a high specific activity, sterilizing tumor doses can be achieved with a low activity concentration that spares normal tissues. Similar results can be achieved with ^{212}Pb if the radionuclide daughter–mAb complex is stable, or with high-specific-activity ^{213}Bi-mAb, but administration of several gigabecquerels of total activity would be required.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. Financial support was provided by the Swedish Research Council, the Swedish Cancer Society, the King Gustav V Jubilee Clinic Research Foundation, and the Regional Agreement on Medical Training and Clinical Research (ALF). No other potential conflict of interest relevant to this article was reported.

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