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Biokinetic modeling and dosimetry for optimizing intraperitoneal radioimmunotherapy of ovarian cancer microtumors

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ABSTRACT

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 demonstrates how intraperitoneal targeted radiotherapy can be optimized to achieve a maximum ratio between them. **Methods:** The various transport mechanisms responsible for the biokinetics of intraperitoneal (i.p.) infused radiolabeled monoclonal antibodies (mAbs) were modeled using the software package STELLA. Data from the literature were complemented with pharmacokinetic data derived from our clinical phase I study to set parameter values. Results using the beta-emitters ^{188}Re, ^{177}Lu, and ^{90}Y and the alpha-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 due to the lymphatic drainage and by 0.7 mL/min due to 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 alpha- and beta-emitters bound to mAbs were compared. For alphas, microtumors receive high doses (>20 Gy or 100 $Sv_{(RBE=5)}$). 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 the peritoneal fluid or the bone-marrow. For betas,

tumors will almost entirely receive non-specific irradiation. The dose from cell-bound radiolabeled mAbs will be negligible in 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, alpha 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

INTRODUCTION

At diagnosis, ovarian cancer has often spread in the peritoneum. Treatment with advanced surgery and consolidated chemotherapy can appear successful, as many patients are declared tumor-free after a second laparoscopy. However, the majority of these patients will relapse and eventually die. To increase treatment success, adjuvant or consolidating therapies involving radionuclides have been attempted. Intra-peritoneal (i.p.) radioimmunotherapy has the potential to irradiate micro- or subclinical tumors spread within the peritoneum. Many promising experiments were performed with beta-emitting radionuclides. Although a multi-center phase III clinical trial of adjuvant ^{90}Y-mAb did not show any survival benefit for the patients (*1*), other promising effects on minimal tumor growth have been presented using various beta-emitting radionuclides, e.g. decreased tumor size diagnosed at repeat operation (*2*); cases of complete remission at third-look evaluation (*3*); and prolonged time to i.p. recurrence (*4*).

The high linear energy transfer and short range of alpha-particles (50–100 μm) facilitates a more concentrated irradiation of microscopic tumors. Various alpha-emitters have thus been evaluated for several cancer types (*5*). Our group used preclinical experiments to study the therapeutic effect and toxicity of the alpha-emitters ^{211}At and ^{213}Bi for i.p. treatment of microscopic tumors and found high tumor doses consistent with a possible cure (*6-8*). The promising results led to the initiation and completion of a phase I clinical study of i.p. infused ^{211}At-MX35 F(ab')$_2$ (*9*). The patient

kinetic studies showed that for activity amounts that could be therapeutic, the normal tissue radiation doses were low to moderate, and no acute toxicity was observed. However, the estimated long-term risk is not negligible (*10*). It is therefore important to optimize the therapy to achieve the greatest possible 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 i.p. 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 beta- and alpha-emitters, and could be used to guide and optimize future i.p. radioimmunotherapies.

MATERIALS AND METHODS

Compartmental modeling

Most relevant transport mechanisms (Fig. 1) were simulated using the software package STELLA (ISEE Systems, Inc.). The resulting time-dependent biodistribution was then used as input for dosimetry. At the time for i.p. 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 new elements that included 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 k_{on}; the number of available antigens on the cell surface; and on the concentration of mAbs in the peritoneal fluid. Since the *in vitro* data indicated a negligibly small k_{off}, 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 modelling the peritoneal fluid transport, we expected two types of simultaneous absorption: lymphatic and transcapillary.

Lymphatic absorption. Removal of antibody from the i.p. 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. Since 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 remaining peritoneal fluid volume of 200 mL was assumed, representing a residual i.p. fluid that was reached 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, i.e. 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 was in reasonable agreement with the 4h-data published for icodextrin (*12*). Our patients were emptied 24-h post-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 i.p. fluid concentrations of the patients enrolled in our clinical trial. A summary of the parameters are found in Table 1.

Concentration of mAbs in plasma and the intercellular volume

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

The subsequent two-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*). Using the same transport rate for intercellular volume to plasma provided model results that were a good fit to the patients' measured plasma concentrations.

Dosimetry

Following the determination of the number of radionuclide atoms bound to a single cell, the MIRD-cell application (*18*) was used for tumor dosimetry. Absorbed dose and equivalent dose were used to predict radiation effect for all evaluated radionuclides even though a detailed microdosimetric evaluation of the alpha-emitters, including the number of events in individual cell nuclei of the microtumors, would likely provide a better predictor of effect. Three microtumor geometries, spheres with radii = 9, 30, and 50 μm, were selected based on pre-clinical 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 $688/\mu m^2$, equal to that found for a single cell. The tumor sphere was attached, at a single point of its surface, to a flat plane, simulating the peritoneum. No neighboring tumors contributing to crossfire were assumed. 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. Since no radionuclides were simulated outside the (peritoneum) 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 i.p. fluid electron equilibrium dose to the tumor. The dose contribution to the tumor sphere from free alpha-emitting radiolabeled mAbs in the peritoneal fluid was determined by 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 bone marrow was determined from a fixed ratio of 0.19 (*20*), although this ratio has been shown to vary with time and between patients (*21*). The absorbed dose to bone marrow was then calculated by multiplying the cumulated activity with the average alpha- and/or beta-particle energy emitted per decay. An absorbed fraction of 1 for the alpha particles and electrons was assumed, while the contributions from gammas were negligible.

RESULTS

Peritoneal fluid volume

A 1.7 L infused saline volume decreased by 0.3 mL/min due to the lymphatic drainage and by 0.7 mL/min due to the transcapillary convective component. Since 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, a net influx by the transcapillary component became equal to the constant lymphatic drainage. At this point, the mAb concentration decreased as it was slowly diluted during diffusion (Fig. 2).

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

Antibody concentration in plasma

Antibodies reached the circulation solely by lymphatic drainage of the i.p. fluid. The mAb concentration in plasma is presented in Fig. 4 as the percentage of initial mAb concentration in the 1.7 L i.p. infused fluid. The results for saline were within the

broad ranges presented in the literature. The higher concentration in plasma seen following an isotonic infusion was due to the higher mAb concentration in i.p. fluid (Fig. 2). The data agreed with measured plasma samples from patients enrolled in our phase I clinical study.

Bone-marrow dose

Estimated bone-marrow doses, after i.p. infusion of mAbs with various radiolabels and iso- or hypertonic infused fluid, are listed in Table 2. Since the concentration of mAbs in plasma is significantly higher for an isotonic i.p. infusion (Fig. 4), the resulting bone-marrow dose is higher. This illustrates how the addition of the osmotic agent serves to lower the radiation dose to the bone-marrow.

Microtumor uptake

An average number of mAbs bound per tumor cell was calculated. Two examples are shown in Figure 5. One is 300 MBq ^{211}At-mAb (0.56 mg), with a specific activity translating to 1/200 mAbs labeled with an ^{211}At atom, i.p. infused in a volume of 1.7 L; while, the other was 3000 MBq ^{213}Bi-mAb (0.59 mg), which also had a specific activity translating to radiolabeling of 1/200 mAbs. The small difference in the number of bound mAbs between isotonic and hypertonic infused fluid are 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, i.e. cumulated activity, per cell.

Microtumor dosimetry

Dosimetry was performed for single cells and spherical cell clusters with diameters of 60 and 100 μm. A relative biological effect (RBE) of 5 was used to calculate the equivalent dose from alpha-particle irradiation (*22*). Results, using specific activities and activity amounts that are reasonably achievable today, are listed in Table 2. For the alpha-emitters, microtumors received high doses. Since most of the tumor dose originated from cell-bound radionuclides, an increase in the specific activity will further increased the tumor dose without affecting the dose to the peritoneal fluid or the bone-marrow. The tumor doses from unbound radiolabled mAbs in the surrounding i.p. fluid were close to 50% (range 40–60%) of the fluid equilibrium dose for the alpha-emitters and tumor sizes investigated.

When using beta-emitters, less than 5% of the radiation doses to tumors were due to decays on the tumor surfaces. The remainders, i.e. more than 95%, were due to irradiation by decays occurring in the surrounding i.p. fluid. For the longer-lived ^{90}Y, tumor doses are expected to be low at the maximum activity concentration delivered in clinical studies. For shorter-lived ^{188}Re, unspecific irradiation from the peritoneal fluid would result in tumor doses of 34 Gy at a tolerable bone-marrow dose (approximately 1 Gy).

Optimization

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

Optimization for the alpha-emitters, where the binding to the tumor cells determines the tumor dose, depends also on the half-life of the radionuclide. For treatment with ^{211}At, best gain in tumor dose was best achieved by improving the specific activity of the radioimmunoconjugate (Fig. 6). If 1/25 mAbs can be radiolabeled, approximately 25 MBq/L was enough to achieve therapeutic tumor doses (approximately 20 Gy or 100 $Sv_{(RBE=5)}$) for cells with 700 000 antigens, and a very low dose to normal tissues, i.e. at a low risk. A low specific activity cannot be compensated for by using a higher activity concentration, but a higher activity concentration would improve the treatment if the specific activity was high.

DISCUSSION

In radioimmunotherapy, it is the range of the emitted particle that determines the fraction of total radiation energy that is absorbed in small volumes, such as microtumors. The beta-emitters used for i.p. radioimmunotherapy have a relatively long range, on the order of mm. This means that even if a large number of radionuclides are bound to a cell surface, the absorbed dose to that cell will remain low. For the illustrative cases presented in this work, the absorbed dose from cell-bound radionuclides to cell clusters (with diameters up to 0.1 mm) is negligible in comparison to the dose received from radiolabeled mAbs in the surrounding i.p. 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, in particular the bone marrow.

Sparing the critical healthy tissues is, according to the presented model, particularly challenging for radionuclides with half-lives greater than about 24h because a larger fraction will decay outside the peritoneal cavity. According to our results, the use of shorter-lived beta-emitters improves the tumor-to-critical-normal-organ ratios, but probably not enough to eradicate all microtumors. The beta emitters that have been clinically evaluated so far have all a relatively long half-life. The restricted administered activity in combination with the long particle ranges result, according to our model, in absorbed doses not near cell sterilization levels for microscopic tumors. However, for

macroscopic tumors with diameters of several millimeters, beta-emitters have provided measurable anti-tumor effects as seen for ^{131}I (*3*), ^{186}Re (*2*), and ^{90}Y (*4*).

Alpha-emitters have short (50–100 μm) particle range and high linear energy transfer, but their half-lives can differ greatly. The short range in combination with the high linear energy transfer is key to achieve high radiation doses to the intraperitoneal microtumors, but also involves irradiation of healthy tissues with uncertain biological effects, including a long-term risk for secondary cancer that may not be negligible. Minimizing the irradiation of healthy tissues is therefore of utmost importance in an adjuvant setting, when long-term carcinogenic risks must be considered (*10*).

The lymphatic flow and the peritoneal fluid concentration of mAbs determine the rate at which the mAbs leave the peritoneal cavity. For short-lived radionuclides with negligible photon contributions, 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 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 intraperitoneal fluid volume, 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

since the dilution was slow and became significant only after the tumor uptakes were almost completed.

Absorbed doses to tumor cells depends both on the concentration of radiolabeled antibody within the peritoneum, i.e. administered activity and fluid volume, and on the specific activity. The specific activity of a radioimmunoconjugate is normally expressed in terms of Bq/g. We chose, instead, to express it as the fraction of mAbs labelled 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. Since 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 due to a more rapid binding process. For a fixed, low, specific activity, increased ^{211}At-mAb activity concentrations would result in very little increase in tumor doses, but would result in increased irradiation of healthy tissues. For ^{213}Bi-mAb, the cell binding must be rapid, i.e. involving high mAb concentrations, and have a large fraction of the mAbs labelled with an ^{213}Bi atom, i.e. a high specific activity, to deliver high tumor doses.

The parameter values in the model were set from literature data or derived from pharmacokinetic data from our clinical phase I study. This meant that the model was constructed to provide perfect agreement with measured concentrations of ^{211}At-mAb in the plasma and the peritoneal fluid of these patients. Since this procedure

was used to set the model's free parameters, any single value of these parameters might carry considerable errors. This does, however, not affect the accuracy of the general conclusions drawn from the presented results.

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*), radionuclide daughters decay where the parent ^{212}Pb decay. In addition, higher activity concentrations and specific activities than those reported (*24*) would be needed. Use of short-lived alpha-emitters, e.g. ^{213}Bi, requires high activity concentrations to eradicate microtumors. However, the short half-life will reduce the normal tissue irradiation. Excluding the dose to the peritoneum, ^{213}Bi provides a better ratio of the dose to tumor relative to normal tissue than does ^{211}At. However, since the tolerance dose to the peritoneum is not known, this might limit the administered activity concentration of ^{213}Bi. 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

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

Targeted beta-emitting therapies have resulted in clinical benefit but according to the model, alpha 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, which spares normal tissues. Similar results can be achieved with ^{212}Pb if the radionuclide daughter-mAb complex is stable and with high-specific activity ^{213}Bi-mAb, but this requires administration of several GBq of total activity.

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FIGURE LEGENDS

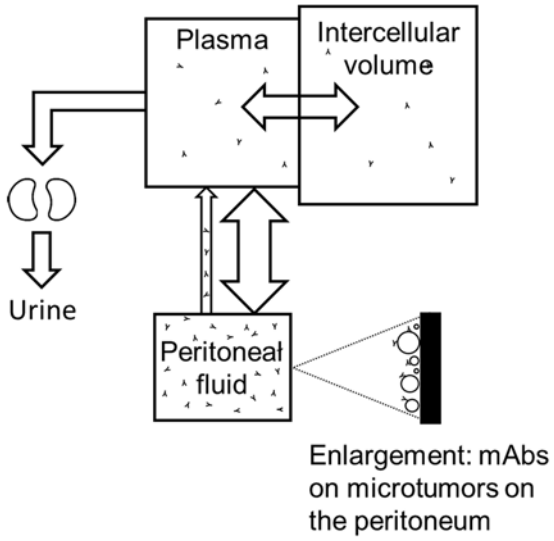

Fig. 1: Schematic illustration of the main transports included in the model. The unidirectional arrow from the peritoneal fluid symbolizes the lymphatic absorption which includes mAb transport. The two headed arrow reflect the transcapillary absorption.

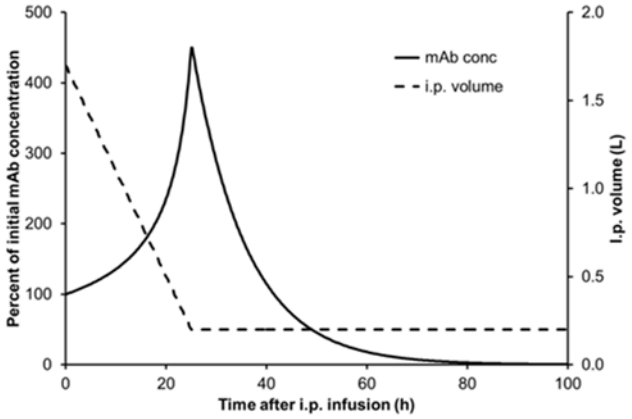

Fig. 2: Simulated i.p. fluid volume (dashed line) and relative mAb concentration (solid line) following i.p. infusion of 1.7 L of saline. The rapid change in mAb concentration is due to the model reversing the flow when a residual i.p. fluid volume of 200 mL is reached.

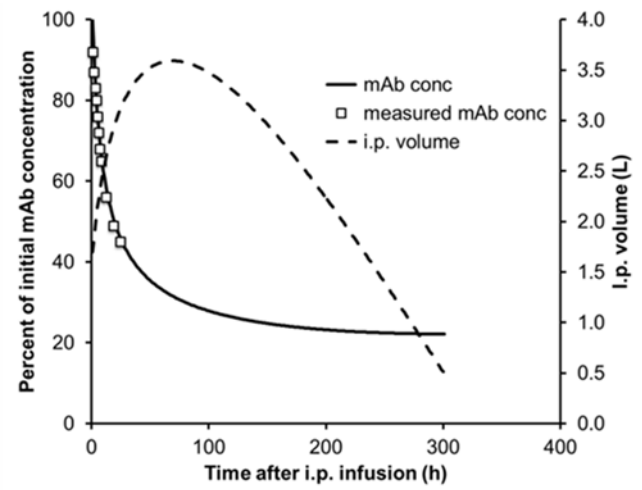

Fig. 3: Simulated i.p. fluid volume (dashed line) and relative mAb concentration (solid line) following i.p. infusion of 1.7 L of 7.5% icodextrin solution. Measured data from patients' i.p. fluid samples are presented as open squares.

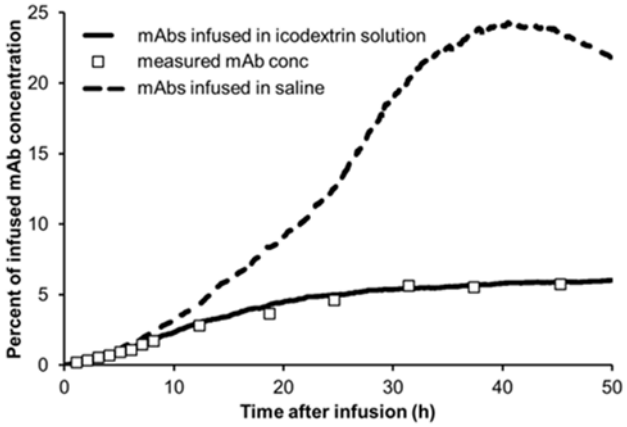

Fig. 4: Concentration of mAb in plasma following infusion of 1.7 L of mAb in saline (dashed line) or 7.5% icodextrin solution (solid line). Measured samples from patients enrolled in our phase I clinical study are presented as open squares.

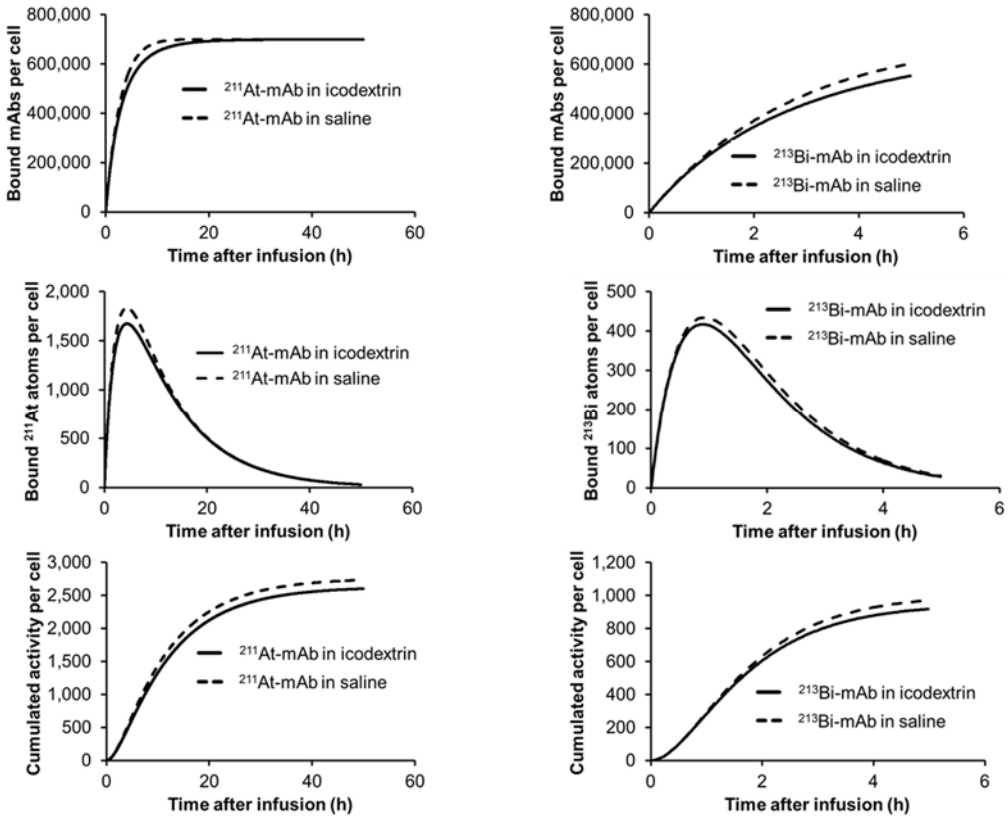

Fig 5: Illustration of how the simulated cell-binding kinetics of radiolabeled mAbs determines the absorbed dose to the tumors. Top panels show the total number of mAbs bound per cell. Middle panels show the expected number of ^{211}At or ^{213}Bi atoms bound per cell at any specific time, i.e. non-decay corrected, assuming 1/200 mAbs radiolabeled at the time for i.p. infusion. Lower panels show the cumulated number of decays per cell, which translates to absorbed dose. Dashed lines represent results following i.p. infusion of 1.7 L saline, while solid lines are the results for 1.7 L 7.5% icodextrin. The figure also illustrates how the use of icodextrin only slightly reduces the tumor dose (but result in a large decrease in dose to healthy tissues).

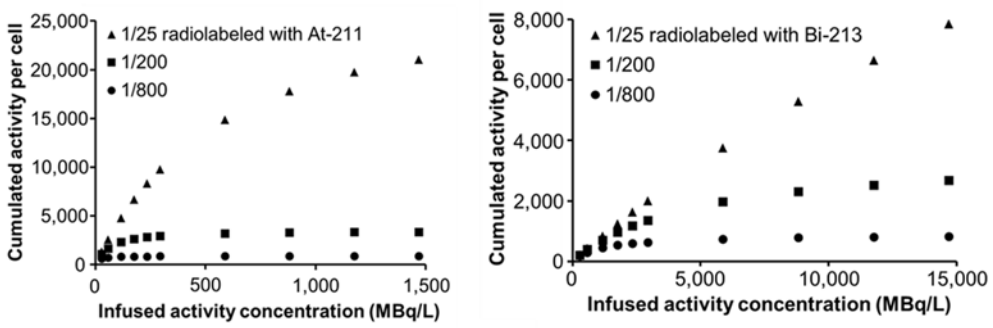

Fig. 6: Specific activity and the i.p. infused activity concentration determine the number of radionuclide decays per cell. Specific activity is represented as radiolabeling of 1/25 (triangles), 1/200 (squares), and 1/800 (circles) mAbs. It is only for high specific activities of the radioimmunoconjugate that an increase in activity concentration of the infused fluid results in significantly higher tumor doses.

TABLES

Table 1: Summary of model parameters.

Fluid volumes	**[L]**	**Comments**	**Reference**
Plasma	2.3	36 mL/kg body weight	(*15*)
Distribution volume in tissue	5.9	91 mL/kg body weight	(*16*)
Administered i.p. fluid	1.7		
Residual i.p. fluid	0.2		

I.p. fluid transport	**[mL/min]**		
Lymphatic drainage I.p. fluid ⇒ plasma	0.3	Mean delay 5 h (±6 h; standard deviation)	Model fit
Water reabsorption I.p. fluid ⇒ plasma	0.7	When >200 mL peritoneal fluid	Model fit
Water inflow at equilibrium I.p. fluid ⇐ plasma	0.3	When 200 mL peritoneal fluid	Model fit
Water inflow osmotic effect I.p. fluid ⇐ plasma	3.1–1.5	Proportional to i.p. icodextran concentration 0–24 h	Model fit

MAb conjugate transfer coefficients	**[h^{-1}]**		
TER (plasma ⇔ intercellular volume)	0.065		(*17*)
Degradation/excretion (plasma ⇒urine)	0.0096–0.03	Radiolabel dependent	Model fit

MAb binding parameters			
Association k_{on} [M^{-1} s^{-1}] Ip fluid ⇒tumor cell	44 000		(*6*)
Dissociation k_{off} [s^{-1}] Tumor cell ⇒ ip fluid	0		(*6*)
Number of sites/cell	700 000		(*6*)

Table 2. Model results from using 1.7 L i.p. infused radiolabelled mAbs in an osmotic agent.

nuclide	fraction of mAbs radiolabelled	administered activity [MBq]	decays per cell	Equivalent dose [Sv] (RBE = 5 for alpha particles; RBE = 1 for electrons)							
				bone-marrow	peritoneal fluid	tumor (from cell-bound mAbs)			tumor (total)		
						diameter = 18 μm	diameter = 60 μm	diameter = 100 μm	diameter = 18 μm	diameter = 60 μm	diameter = 100 μm
^{177}Lu	1/270	3900	2561	0.94	17	0.43	0.34	0.3	8.9	8.8	8.8
^{90}Y	1/270	1100	2580	0.61	26	0.13	0.12	0.12	13	13	13
^{188}Re	1/270	6300	2561	1.02	68	0.22	0.18	0.17	34	34	34
^{211}At	1/200	300	2602	0.14	24	231	278	264	244	292	275
^{213}Bi	1/200	3000	953	0.016	43	71	80	93	94	104	114
^{212}Pb	1/200	300	2995	0.36	37	244	283	288	264	305	305