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Clearance Kinetics and External Dosimetry of Iodine-131-labeled Murine and Humanized Monoclonal Antibody A33 in Patients with Colon Cancer: Radiation Safety Implications

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Abstract

The monoclonal antibody (mAb) A33 detects a membrane antigen that is expressed on greater than 95% of metastatic human colorectal cancers. Previous studies have shown excellent tumor-targeting of iodine-131 labeled murine and humanized forms of the mAb. A retrospective analysis of whole body clearance in the murine form was performed for comparison to the humanized form. Serial whole-body dose rate measurements were obtained for 55 treatments on 30 patients participating in phase I/II dose escalation studies of therapeutic iodine-131-murine A33 mAb. Whole-body retention fractions over time were derived. Each treatment was fit with exponential curves to determine the effective half-lives and corresponding clearance fractions. There was a large variability in the calculated mono-exponential clearance effective half-life time, with a mean value of 36.5 h $\pm$ 8.5 h. A bi-exponential fit of all combined data shows that 60% of the administered dose rapidly clears with a biological half-time of 23.9 h and 40% clears with a slower biological half-time of 101.2 h. The whole body clearance proved to be more rapid in the murine form when compared with recent studies on the humanized form of radiolabeled A33 mAb. The variability in whole body clearance reinforces the need for patient-specific tracer dosimetry for clinical care and radiation safety precautions. In addition, the slower clearance of the humanized form of the A33 mAb requires longer term radiation safety precautions than the earlier murine form. As other monoclonal antibodies progress from murine to humanized forms, radiopharmacokinetics should be evaluated for clinical and radiation safety implications.

Keywords

immunotherapy; radiotherapy; kinetics; monoclonal antibody; cancer; radiation protection

INTRODUCTION

Colorectal cancer is among the most common malignancies of the Western world and a leading cause of cancer deaths (Silverberg and Lubera 1987, Catimel et al. 1996, Heath et al.

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1997). Microdisseminated colorectal carcinoma cells are highly resistant to conventional therapy. While advances have been made in the treatment of patients with advanced disease, these have had a modest impact on overall survival and there is still a need to develop effective treatment methodologies.

The use of monoclonal antibodies (mAbs) in targeting therapeutic levels of radioisotopes to tumors continues to be an active area of clinical research (Welt et al. 1990, Chong et al. 2005). One potentially useful target for colon cancer is the surface molecule that interacts with the mAb, A33 (Welt et al. 1990, Welt et al. 1994, Catimel et al. 1996, Welt et al. 1996). The mAb A33 detects a transmembrane glycoprotein antigen that is expressed in normal human colonic and small bowel epithelium. The mAb A33 is also expressed in greater than 95% of metastatic human colorectal cancers and in approximately 50% of gastric cancers (Catimel et al. 1996, Welt et al. 1996, Heath et al. 1997, Sakamoto et al. 2000). In addition, there is an absence of circulating A33 antigen in plasma (Heath et al. 1997). After mAb binding to the A33 antigen, the antibody-antigen complex is internalized and sequestered in cytoplasmic vesicles (Daghighian et al. 1996).

Preclinical evaluations of the A33 mAb as a therapeutic reagent were explored in a nude mouse model using the human colorectal carcinoma xenograft cell line, SW1222. Transplanted tumors regressed after treatment with either ^{125}I - or ^{131}I -labeled A33 (Barendswaard et al. 2001). In phase I and II radioimmunotherapy trials in humans, radioiodinated A33 mAb, a mouse-based IgG2a, was shown to preferentially accumulate and be retained for up to 6 weeks (Daghighian et al. 1996, Welt et al. 1996) in metastases of patients with advanced colorectal cancer (Welt et al. 1990) and was shown to have anti-tumor effects without bowel toxicity (Welt et al. 1994, Welt et al. 1996).

These preliminary studies with murine mAb A33 defined the capability of this antigenic system and potential antitumor efficacy; however, full characterization of the therapeutic potential of the mouse-derived A33 antibody was impossible due to the development of human anti-mouse antibody (HAMA) responses in all pilot study patients preventing repeated treatments (Welt et al. 1994, Welt et al. 1996). The production of less immunogenic, chimeric, or humanized antibodies to reduce this immune reaction in patients would, presumably, allow antibodies to be repeatedly administered (Heath et al. 1997).

Complement determinant region (CDR) grafting is a method of humanizing antibodies in which human framework sequences are chosen from the set of human germline genes based on the structural similarity of the human CDRs to those of the mouse antibody. In order to reduce immunogenicity, a CDR grafted, humanized A33 mAb was therefore developed (King et al. 1995, Antoniow et al. 1996, Barendswaard et al. 1998, Lee et al. 2001). Clinical trials using multiple dose schedules have shown safe use and possible efficacy of radioiodinated humanized A33 mAb alone and in combination with chemotherapy regimens (Welt et al. 2003, Welt et al. 2003, Chong et al. 2005). Studies have also shown that radiolabeled humanized A33 mAb can selectively target primary and metastatic colorectal tumors and penetrate to the center of large necrotic metastatic lesions (Scott et al. 2005).

While tumor-targeting and biodistribution with ^{131}I -humanized A33 mAb is comparable to ^{131}I -murine A33 mAb, the humanized form has a longer serum half-life compared to the murine form (Welt et al. 1996, Welt et al. 2003, Chong et al. 2005). In addition, the incidence of human antihuman antibody (HAHA) response is less frequent than the incidence of HAMA generated using the murine form (Welt et al. 1990, Chong et al. 2005, Sakamoto et al. 2006).

More refined data on whole-body clearance times are essential for clinical management and for evaluating radiation safety considerations. The purpose of this paper is to evaluate the whole-body clearance kinetics of murine A33 mAb and to compare these results with existing data for humanized A33 mAb. These data should also provide information on the expected clearance values for “typical” patients and the distribution of these values over a patient population. An understanding of whole-body clearance and external dosimetry is also helpful in planning for compliance with federal regulations on the release of patients administered radiopharmaceuticals from medical licensee control (USNRC 1997, USNRC 1998).

MATERIALS AND METHODS

Patients and Treatments

This study presents a retrospective analysis of clearance kinetics based on whole-body dose rate readings obtained from measurements on 30 patients ranging from 33 to 80 years of age who participated in phase I/II studies of ^{131}I -murine A33 performed at Memorial Sloan-Kettering Cancer Center. Under the dose escalation schema, patients received between 0.9 GBq (24.8 mCi) and 6.6 GBq (178.0 mCi) per cycle of treatment, with total overall administered activity between 1.1 GBq (30.0 mCi) and 10.3 GBq (278.0 mCi). Appropriate radiation safety measures were used in order to comply with municipal, state, and federal regulations regarding monitoring, waste handling, personnel exposure, and patient release. Specific practical radiation safety practices in the treatment room included: training all staff associated with the protocol on time, distance, shielding and planning requirements, contamination control barriers, and the placement of a 2.5 cm (1 in.) thick mobile lead shield at the patient’s bedside when necessary.

Whole-Body Dose Rate Readings

As a confirmation of retained ^{131}I activity, the whole-body exposure rate was directly measured for each patient within 1 h after each infusion and approximately daily thereafter while the patients remained hospitalized. Exposure rate measurements were obtained at the surface of the anterior skin at the point of maximum exposure rate (“surface reading”) and at a distance of 1 m anteriorly from this maximum exposure-rate point (“1-m reading”). Exposure rate measurements were determined using a radiation ionization chamber survey meter (Keithley model 36100) calibrated with ^{137}Cs . This unit has an energy response that is relatively flat between the ^{137}Cs calibration energy and that of ^{131}I gamma ray energies and, therefore, no calibration-correction was required or applied to the measurements. For the purposes of this study, it was assumed that the directly measured exposure rates were

numerically equal to the absorbed dose rates at the point of measurement and are therefore referred to as “dose rate” measurements for the remainder of this paper.

Whole-Body Clearance Kinetics

Although it was expected that the 1-m readings would provide the most reliable indicator of whole-body activity, the 1-m readings taken at the later time period were below the sensitivity of the instruments used in this retrospective study (approximately $1 \mu\text{Gy hr}^{-1}$) and were not fully representative of the long lived fraction. Therefore, for the purposes of this study, the method for estimating whole-body radiation clearance kinetics assumed that the total activity in the whole body was also proportional to the maximum surface reading for the measured dose rates (Dauer et al. 2007). For this study, activity normalized surface measurements were found to be directly proportional to activity normalized 1-m readings by a factor of 22.3 ($R^2=0.96$, $p<0.0005$) indicating that this assumption is reasonable. Using these measurements, the whole-body retention fractions (WBRF) were calculated and the data for each treatment were fit to both a mono-exponential model (equation 1) and all combined data were fit to a bi-exponential model (equation 2). The whole-body time-retention curves were obtained by weighted nonlinear regression analysis with the software package Prism 4® (GraphPad, San Diego, CA) to determine the exponential time constants (k_{eff} or $k_{1\text{eff}}$ and $k_{2\text{eff}}$) and the coefficients (F or F_1 and F_2).

$$WBRF(t) = F e^{(-k_{\text{eff}} t)} \quad (1)$$

$$WBRF(t) = F_1 e^{(-k_{1\text{eff}} t)} + F_2 e^{(-k_{2\text{eff}} t)} \quad (2)$$

RESULTS

Patients

This retrospective analysis included data from 30 patients with colorectal cancer who had failed to respond to conventional chemotherapy but had not received prior external beam radiotherapy or radiopharmaceutical therapy. The median age of the patients was 59.2 y with a range of 33 to 80 y. The median weight of the patients was 70.8 kg with a range of 50.0 to 102.7 kg. Table 1 summarizes the data on age, weight, and injected activity for the 55 treatments on the 30 patients. Fig. 1 shows the distribution of injected activity (MBq) of ^{131}I -murine A33.

Whole-Body Dose rate Readings

The whole-body dose rate ($\mu\text{Gy hr}^{-1}$) was measured within 1 h after infusion and approximately daily thereafter for up to 7 d. A total of 205 whole-body dose rate readings were obtained during the 55 treatments on the 30 patients. Initial whole-body dose rates are summarized in Table 1. For the 55 treatments, the median initial maximum surface dose rate reading was $0.86 \mu\text{Gy hr}^{-1} \text{ MBq}^{-1}$ ($3.2 \text{ mrad hr}^{-1} \text{ mCi}^{-1}$) and the median initial maximum dose rate reading at 1 m was $0.036 \mu\text{Gy hr}^{-1} \text{ MBq}^{-1}$ ($0.13 \text{ mrad hr}^{-1} \text{ mCi}^{-1}$). Figs. 2 and 3 show the distribution of initial maximum dose rates on contact and at 1 m, respectively.

Estimated Whole-Body Clearance Kinetics

Of the total 55 treatments, there were 30 single-dose treatments (i.e. when patients received the first injection of ^{131}I :murineA33) and 25 multi-dose treatments (i.e. when patients received followup injections of ^{131}I :murineA33). There were a total of 53 treatments for which sufficient measurements were available for curve fitting. For these 53 treatments, mono-exponential whole-body time-retention curves were obtained by weighted nonlinear regression analysis with the software package *Prism 4*® (GraphPad, San Diego, CA) to determine the exponential time constant (k_{eff}) assuming a unity coefficient ($F=1$). Table 2 summarizes the mono-exponential fit results (mean, standard deviation, minimum, and maximum) including the mean calculated whole-body clearance effective half life (T_{eff}) of 36.48 ± 8.50 h. Overall, there was a large variability in the calculated individual clearances, T_{eff} , ranging from a minimum of 19.08 h to a maximum of 58.34 h. Fig. 4 shows the whole-body clearance of the ^{131}I -murine A33 with 95% confidence bands for the 53 treatments.

All combined data were then fit to a two-compartment clearance (equation 2) with 60% of the injected activity clearing with a $T_{\alpha\text{eff}}$ of 21.3 h (95% confidence interval = 14.5–39.9 h) and 40% of the injected activity leaving at a longer $T_{\beta\text{eff}}$ of 66.5 h (95% confidence interval = 42.3–154.9 h), where $T_{\alpha\text{eff}}$ and $T_{\beta\text{eff}}$ represent the effective half-lives (incorporating both biological and physical components) of the initial and terminal phases of disposition, respectively. This indicates a two-compartment biological clearance from the whole body of 23.9 h and 101.2 h ($T_{\alpha(\text{bio})}$ and $T_{\beta(\text{bio})}$, respectively).

DISCUSSION

Welt et al (1990) previously reported on a phase I study of 20 patients and identified a serum bi-exponential clearance of ^{131}I -murine A33 mAb with a T_{α} of 6.3 h and a T_{β} of 38.5 h. Several recent studies have reported radiopharmacokinetics results for ^{131}I -humanized A33 mAb. Scott et al. (Scott et al. 2005) conducted an open label, dose escalation, biopsy-based phase I study that included 12 patients with colorectal cancer and identified a serum bi-exponential clearance of ^{131}I -humanized A33 mAb with a T_{α} of 13.7 h and a T_{β} of 86.9 h, as well as a monoexponential whole body clearance T_{bio} of 143.9 h. Chong et al. (Chong et al. 2005) conducted a phase I trial that included 15 patients with advanced metastatic colorectal cancer and identified a serum bi-exponential clearance of ^{131}I -humanized A33 mAb with a T_{α} of 23.0 h and a T_{β} of 135.2 h, as well as a mono-exponential whole body clearance T_{bio} of 227.5 h. Sakamoto et al. (Sakamoto et al. 2006) conducted a phase I radioimmunolocalization trial of ^{131}I -humanized A33 mAb in 13 patients with gastric cancer and identified a serum bi-exponential clearance of ^{131}I -humanized A33 mAb with a T_{α} of 26.6 h and a T_{β} of 79.9 h, as well as finding that an average of 73% (range 71.4% to 75.44%) of the injected activity leaves with the longer clearance compartment. This is higher than the 60% found in this present study for ^{131}I -murine A33 mAb, indicating that the murine form of the A33 mAb clears more rapidly than the humanized form of the A33 mAb. Table 3 compares these serum and whole body radiopharmacokinetic parameters with those found in this study for ^{131}I -murine A33 mAb.

All studies have shown a slowly clearing compartment from the blood, a pharmacokinetic characteristic of whole IgG (Welt et al. 1994). It is also clear that for both serum and whole body kinetics, the murine form of the A33 mAb clears more rapidly than the humanized form of the A33 mAb. In addition, the serum clearance is typically more rapid than the whole body clearance, probably due to the localization of A33 mAb in tumor tissue, and the remarkable avidity of the antibody in such tissues. All studies also show a large variation in kinetics, probably due to considerable variation in quantitative uptake parameters within each patient's tumor (Welt et al. 1994).

There is intensive effort to evolve radioimmunotherapies from murine models to humanized models, especially because the incidence of HAMA response in humanized antibodies is typically less frequent than the incidence of HAMA generated using murine antibodies (Welt et al. 1990, Chong et al. 2005, Sakamoto et al. 2006). Since most radiation safety precautions are based on isotope photon energy as well as whole-body clearance, it is important to understand the potential implications as radioimmunotherapies shift to humanized models with the potential for longer clearance characteristics. In 1997, the U.S. Nuclear Regulatory Commission (NRC) promulgated regulations (USNRC 1997, USNRC 1998) which allow a medical licensee to release a patient with a body burden of radiopharmaceutical as long as the projected total effective dose-equivalent (TEDE) to another individual is not likely to exceed 5 mSv (0.5 rem). Given an injected activity of 2500 MBq (67.5 mCi), a T_{eff} of 36.48 h for ^{131}I -murine A33, or a T_{eff} of 104.6 h for ^{131}I -humanized A33, and a standardized patient release algorithm (Zanzonico et al. 2000), the TEDE to another individual is not likely to exceed 5 mSv (0.5 rem) as long as the patient follows specific instructions to avoid extended time in public places for approximately 1 d for murine or approximately 11 d for humanized and to sleep in a separate bed from others for approximately 3 d for murine or approximately 18 d for humanized following treatment. Therefore, treatments could take place on an outpatient basis, albeit with more restrictive precautionary instructions for the humanized form of the mAb treatment. Table 4 compares typical instructions to patients following ^{131}I -A33 mAb treatments for both murine and humanized forms.

The NRC also published alternative guidance for ^{131}I that allows a medical licensee to release a patient administered ^{131}I if the measured 1-m dose rate from that patient is less than $0.007 \text{ cGy hr}^{-1}$ (7 mrad hr^{-1}) (USNRC 2005). The maximum initial dose rates measured at 1 m for our data was $0.021 \text{ cGy hr}^{-1}$ (21 mrad hr^{-1}). We can therefore expect that the dose rate will drop below $0.007 \text{ cGy hr}^{-1}$ (7 mrad hr^{-1}) within approximately 2.5 d for murine A33 and approximately 7 d for humanized A33.

CONCLUSION

The method used in this study for estimating whole-body clearance kinetics is clinically practical and relevant (North et al. 2001, Dauer et al. 2007) and is based upon measurements of whole-body external dose rate, a quantity of concern in radiation protection. The whole-body external dose rate and the T_{eff} are relevant to both clinical research as well as practical radiation protection. Understanding these parameters is especially true in light of the rapidly expanding role of radiolabeled monoclonal antibodies in imaging and therapy.

In the case of ^{131}I -A33 mAb for colon and gastric therapy, the observed variability in whole body clearance reinforces the need for patient-specific tracer dosimetry for both clinical care and radiation safety precaution decision-making. Patient-specific tracer dosimetry should be performed by administering to the patient a tracer(diagnostic) activity of the therapeutic radiopharmaceutical and obtaining serial time-activity measurements for the total body, critical organs, the tumor, or other target tissues in order to determine an appropriate therapeutic dosage level (Zanzonico 2002). In addition, the slower clearance of the humanized form of the A33 mAb requires longer radiation safety precaution considerations than the earlier murine form.

As other monoclonal antibodies progress in development from murine to chimeric or humanized forms, the radiopharmacokinetics of subsequent radiolabeled versions will need to be carefully evaluated for both clinical and radiation safety implications.

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FIGURE 1.
Frequency distribution of injected activity (GBq) of ^{131}I -murine A33 monoclonal antibody.

FIGURE 2.

Frequency distribution of initial maximum dose rate on contact with patient anterior surface ($\mu\text{Gy hr}^{-1} \text{MBq}^{-1}$) following injection of ^{131}I -murine A33 monoclonal antibody.

FIGURE 3.

Frequency distribution of initial maximum dose rate at 1 m from patient anterior surface ($\mu\text{Gy hr}^{-1} \text{MBq}^{-1}$) following injection of ^{131}I -murine A33 monoclonal antibody.

FIGURE 4.

Whole-body clearance based on maximum surface dose rate measurements (mean, $\pm$ 95% confidence limits). Mono-exponential fit of ^{131}I -murine A33 monoclonal antibody treatments.

Age, weight, injected activity, and initial exposure rate for patients treated with ¹³¹I-murine A33 monoclonal antibody (55 treatments in 30 patients)

TABLE 1

Parameter	Age	Weight	Injected Activity ^a		Surface Reading ^b		1 m Reading ^b	
	(y)	(kg)	MBq	mCi	μGy hr ⁻¹ MBq ⁻¹	mR hr ⁻¹ mCi ⁻¹	μGy hr ⁻¹ MBq ⁻¹	mR hr ⁻¹ mCi ⁻¹
Median	62.5	73.6	2,141	57.8	0.86	3.20	0.036	0.13
Minimum	33	50	919	24.8	0.43	1.57	0.018	0.07
Maximum	80	102.7	6,592	178.0	2.94	10.89	0.16	0.58

^a Injected activity determined by radiopharmacy to within +/- 5 %.

^b Exposure rate measurements taken on an instrument with a calibration uncertainty of +/- 10% and a sensitivity of 0.1 mR hr⁻¹.

TABLE 2

Summary results of weighted mono-exponential fit of whole-body clearance data for ^{131}I -murine A33 monoclonal antibody

53 Treatments		
Parameter	K_{eff}	$T_{eff}(\text{h})$
Mean	0.0202	36.48
Std Dev	0.0054	8.50
Minimum	0.0119	19.08
Maximum	0.0363	58.34

TABLE 3
¹³¹I-murine A33 and ¹³¹I-humanized A33 monoclonal antibody radiopharmacokinetic parameters

	Murine A33 Colorectal (This study)	Murine A33 Colorectal (Welt et al. 1990)	Humanized A33 Colorectal (Scott et al. 2005)	Humanized A33 Colorectal (Chong et al. 2005)	Humanized A33 Gastric (Sakamoto et al. 2006)
Whole Body					
Mono-exponential clearance					
T (bio)	44.95 +/- 8.9 h		143.9 +/- 16.8 h	227.5 +/- 46.15 h	
Serum					
Bi-exponential clearance					
T _{1/2α}		6.3 h		23.0 h	26.6 h
T _{1/2β}		38.5 h		135.2 h	79.9 h
Whole Body					
Bi-exponential clearance					
T _c (bio)	23.9 h				
T _β (bio)	101.2 h				

TABLE 4

Typical radiation safety instructions to patients following treatment with 2500 MBq of ^{131}I -murine A33 or ^{131}I -humanized A33 mAb

Radiation safety precaution	Number of Days for Precaution	
	^{131}I -murine A33	^{131}I -humanized A33
Sleep in a separate bed for	3 d	18 d
Do not sleep with a pregnant partner or a child for	6 d	29 d
You may return to work after	2 d	13 d
Maximize distance (> 2 m) from children and pregnant women for	2 d	13 d
Avoid extended time in public places for	1 d	11 d