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# Relative Therapeutic Efficacy of $^{125}\text{I}$ - and $^{131}\text{I}$ -Labeled Monoclonal Antibody A33 in a Human Colon Cancer Xenograft

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A33, a monoclonal antibody that targets colon carcinomas, was labeled with  $^{125}\text{I}$  or  $^{131}\text{I}$  and the relative therapeutic efficacy of the 2 radiolabeled species was compared in a human colon cancer xenograft system. **Methods:** Nude mice bearing human SW1222 colon carcinoma xenografts were administered escalating activities of  $^{125}\text{I}$ -A33 (9.25–148 MBq) or  $^{131}\text{I}$ -A33 (0.925–18.5 MBq),  $^{125}\text{I}$ - and  $^{131}\text{I}$ -labeled control antibodies, unlabeled antibody, or no antibody. The effects of treatment were assessed using the endpoints of tumor growth delay and cure. **Results:** Tumor growth delay increased with administered activity for all radiolabeled antibodies. Approximately 4.5 times more activity was required for  $^{125}\text{I}$ -A33 to produce therapeutic effects that were equivalent to those of  $^{131}\text{I}$ -A33. This ratio was approximately 7 for a nonspecific, noninternalizing isotope-matched, radiolabeled control antibody. Unlabeled A33 antibody had no effect on tumor growth. Approximately 10 times more activity of  $^{125}\text{I}$ -A33 produced toxicity similar to that of  $^{131}\text{I}$ -A33, and this ratio fell to approximately 6 for radiolabeled control antibody. **Conclusion:** Treatment with  $^{125}\text{I}$ -A33 resulted in a relative therapeutic gain of approximately 2 compared with  $^{131}\text{I}$ -A33 in this experimental system.

**Key Words:** radiolabeled mAb A33; targeting; colon cancer xenograft; therapeutic efficacy

**J Nucl Med 2001; 42:1251–1256**

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**T**he effectiveness and toxicity of radiolabeled monoclonal antibody (mAb) therapy of tumors are dependent on the radionuclide used. Most clinical treatments and preclinical studies have been performed using  $^{131}\text{I}$ , primarily because of extensive clinical experience with  $^{131}\text{I}$  in the treatment of thyroid disorders but also because of its availability, ease of labeling, and convenient 8-d half-life.  $^{131}\text{I}$  emits  $\beta$ -particles, which provide the majority of the local absorbed radiation dose in targeted sites, and a 364-keV  $\gamma$ -photon. The range of the  $\beta$ -emissions of  $^{131}\text{I}$  (approximately 1 mm) is sufficient to

irradiate tumor cells not directly targeted by the radiolabeled antibody by cross fire. However, it is also sufficient to irradiate most of the blood-forming cells of the bone marrow. Moreover, the high-energy photon that permits patient imaging gives rise to nonspecific and undesirable irradiation of the whole body.

mAb A33 is a murine IgG2a that recognizes a cell-surface antigen expressed homogeneously in >95% of colon carcinomas but not in normal tissue with the exception of colon epithelium (1). In vitro studies have shown that after binding to cell-surface antigens, mAb A33 is internalized through cytoplasmic vesicles, transported to perinuclear regions, and subsequently exteriorized in an intact form (2). The whole process of uptake, internalization, and release may then repeat. Internalization of iodinated antibodies usually results in rapid deiodination and release of the radioiodine from the cell. However, this is not seen with mAb A33. Prolonged retention of radioactivity in tumor sites was observed in a clinical study of  $^{125}\text{I}$ -labeled mAb A33 (3) that showed the in vivo stability of the iodinated antibody.

Uniformity of antigen expression is a necessary but not sufficient condition to ensure the uniformity of the distribution of radiolabeled antibody. However, it is suggestive that radioimmunotherapy using radionuclides with shorter ranges than  $^{131}\text{I}$  may have a potential role. The existence of a relatively uniform antibody distribution in human tumor xenografts grown in nude mice between 4 h and 4 d after administration of 50–200  $\mu\text{g}$  humanized A33 has been reported (4). Because internalization of the antibody-antigen complex does not lead to rapid deiodination,  $^{125}\text{I}$  may be a rational choice for therapeutic radionuclide.

The decay of  $^{125}\text{I}$  by electron capture results in the emission of a large number of low-energy Auger electrons, most of which possess ranges of <2 nm in tissue. These short-range electrons and the charge buildup on the daughter tellurium atom are responsible for the high linear energy transfer (LET)-type damage produced by  $^{125}\text{I}$  decays, when incorporated directly into the DNA of target cells (5–7).  $^{125}\text{I}$  decays that occur within the cell but not in intimate contact

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Received Oct. 20, 2000; revision accepted Apr. 9, 2001.

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with DNA produce low LET-like damage—that is, cell survival curves are shouldered resembling those produced by x-ray irradiation (7,8). The K-shell Auger and internal conversion electrons possess ranges up to 17  $\mu\text{m}$  (8,9), and the L-shell electrons have a range of approximately 1  $\mu\text{m}$ . These longer range emissions do not yield high LET-type damage; however, they do reach the nuclear DNA from the cell surface. Nevertheless, intracellular accumulation of  $^{125}\text{I}$  will yield substantially greater dose to the cell nucleus (by a factor of 2–3) (2) than cell-surface accumulation. In addition, the relative importance of cross dose (i.e., from decays outside the cell of interest) is significantly less for  $^{125}\text{I}$  than for  $^{131}\text{I}$ . In the case of  $^{125}\text{I}$ , this is the result of its longer range emissions, whereas for  $^{131}\text{I}$ , decays within several millimeters (a vastly larger volume) may contribute to the cross dose.

The therapeutic effects of  $^{131}\text{I}$ - and  $^{125}\text{I}$ -A33 have been studied in phase I/II clinical trials for advanced colon cancer (3,10). The maximum tolerated activity for  $^{131}\text{I}$ -A33 was 2.78 GBq/m<sup>2</sup> (75 mCi/m<sup>2</sup>) in heavily pretreated patients, similar to other studies with  $^{131}\text{I}$ -labeled murine monoclonal antibodies. For  $^{125}\text{I}$ -A33, bone marrow toxicity was not seen after administered activities as high as 12.95 GBq/m<sup>2</sup> (350 mCi/m<sup>2</sup>).

In this study, the biologic efficacy and toxicity of  $^{125}\text{I}$ -A33 were compared with  $^{131}\text{I}$ -A33 in an SW1222 colon cancer xenograft model grown in nude mice.

## MATERIALS AND METHODS

### Cell Line

The human colon carcinoma cell line SW1222 was maintained in Eagle's medium as described (11). The cells were kept in a 37°C atmosphere (5% CO<sub>2</sub>) and harvested using 0.1% trypsin and 0.02% ethylenediaminetetraacetic acid (GIBCO, Grand Island, NY).

### Human Tumor Xenografts

Four- to 6-wk-old athymic female Swiss (*nu/nu*) mice (body weight, 20–25 g) from our in-house nude mouse facility were injected with  $10 \times 10^6$  SW1222 cells in the left thigh muscle. After 5–7 d, mice bearing tumors of 140–900 mg were selected. The radiolabeled mAb A33 or an IgG2a control antibody was injected intravenously in the retroorbital plexus after the mice were anesthetized with Avertin, which was made fresh from 2,2,2-tribromoethanol (Pfaltz and Bauer, Inc., Waterbury, CT) in a solution of 3-methyl-1-butanol (Sigma Chemical Co., St. Louis, MO) as described (11).

### Labeling of mAbs

Iodination of mAb was performed by the chloramine-T method (11). In brief,  $^{125}\text{I}$  or  $^{131}\text{I}$  was added to mAb solution in the presence of 200  $\mu\text{L}$  chloramine-T (2.0 mg/mL) for 1 min. The reaction was quenched with 200  $\mu\text{L}$  sodium metabisulfite (10 mg/mL). Labeled antibody was separated from free iodine using a NAP 25 column (Pharmacia Biotech, Piscataway, NJ).

Specific activities for  $^{125}\text{I}$ -labeled antibodies ranged from 640 to 925 MBq/mg (17–25 mCi/mg) for A33 (mean, 780 MBq/mg [21 mCi/mg]) and from 925 to 1,225 MBq/mg (25–33 mCi/mg) for the IgG2a control (mean, 850 MBq/mg [23 mCi/mg]). For  $^{131}\text{I}$ -labeled antibodies, the specific activities were between 830 and 1,110

MBq/mg (22–30 mCi/mg) for A33 (mean, 930 MBq/mg [25 mCi/mg]) and from 355 to 440 MBq/mg (9.6–12 mCi/mg) for the IgG2a control (mean, 395 MBq/mg [11 mCi/mg]).

The immunoreactivity of radiolabeled antibody was tested on antigen-positive cell pellets as described (1). Immunoreactivities ranged from 29% to 40% for  $^{125}\text{I}$ -A33 (mean, 34%) and from 36% to 55% (mean, 47%) for  $^{131}\text{I}$ -A33.

## Tumor Therapy and Control Studies

A total of 169 mice were divided into groups of 4–9 mice. Fourteen groups were administered varying amounts of mAb A33 labeled with either  $^{125}\text{I}$  or  $^{131}\text{I}$ . The activities of  $^{125}\text{I}$ -A33 ranged from 9.25 to 148 MBq (0.25–4 mCi), with antibody masses from 10 to 230  $\mu\text{g}$ . For  $^{131}\text{I}$ -A33, activities ranged from 0.925 to 18.5 MBq (0.025–0.5 mCi), with antibody masses from 3.3 to 24  $\mu\text{g}$ . Eleven groups received varying amounts of a mouse myeloma protein IgG2a, kappa UPC 10 (Sigma Chemical), nonspecific control mAb labeled with either  $^{125}\text{I}$  or  $^{131}\text{I}$ . Activities ranged from 27.7 to 92.5 MBq (0.75–2.5 mCi) for  $^{125}\text{I}$  and from 0.925 to 41.8 MBq (0.025–0.4 mCi) for  $^{131}\text{I}$ . One group was administered 250  $\mu\text{g}$  unlabeled mAb A33, and 5 groups served as growth controls. Tumor size was measured bidimensionally with calipers, and the volume was calculated assuming elliptic geometry.

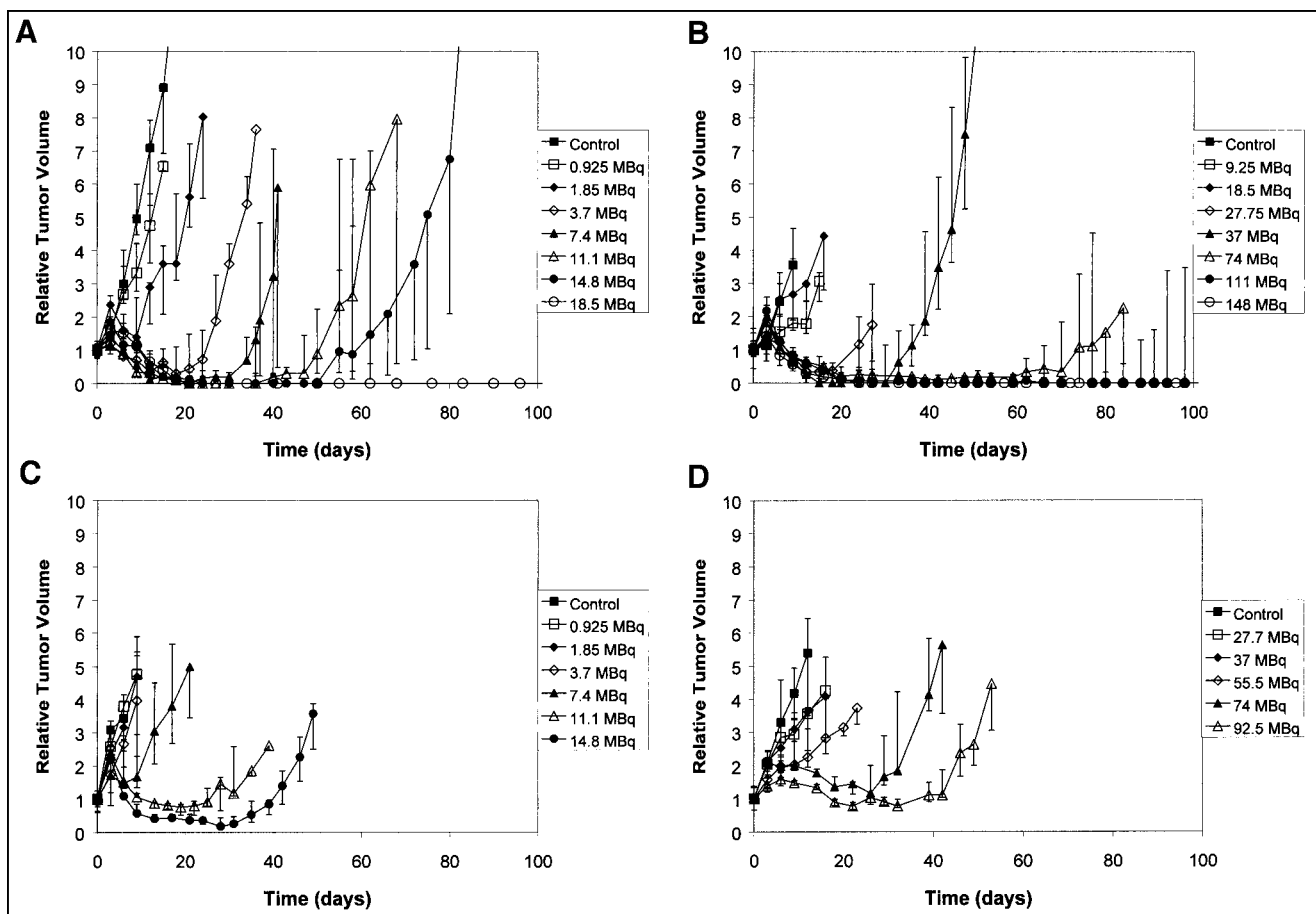
Initial tumor sizes were between 0.14 and 0.90 cm<sup>3</sup> (mean, 0.44 cm<sup>3</sup>). Mice with tumors of differing sizes were divided into each group such that the tumor size spectrum for each group was similar. In earlier localization experiments, antibody uptake did not appear to be affected by tumor size (data not shown). The tumors were measured every 3 or 4 d for 100 d or until the death of the animal. Mice were killed when the tumor caused apparent discomfort in walking or when its volume exceeded 2 cm<sup>3</sup>.

## RESULTS

### Tumor Growth Delay

The full set of tumor growth curves for each animal in the different treatment groups indicated a clear relationship between administered activity and response, although significant variability was seen within each group. The results are expressed in terms of the behavior of the median tumor volume, normalized to initial volume, as a function of time (Figs. 1A–1D). Figure 1 indicates that tumor growth was retarded after treatment to an extent that was dependent on the amount of activity administered. On the basis of these curves, we calculated the times required for the median tumor volume in each group to grow to 2.5 times its initial size. The tumor growth delay was defined as the difference between these times for the treatment groups and that for the control (untreated) group. Figure 2 shows tumor growth delay as a function of administered activity for the radiolabeled specific and nonspecific antibodies, which indicates the existence of a dose–response relationship for all radiolabeled antibodies (note the different activity scales for  $^{125}\text{I}$ - and  $^{131}\text{I}$ -labeled species). The difference in effectiveness of radiolabeled specific and nonspecific antibodies is clearly evident.

Linear regression analysis was used to estimate the average slopes of the growth delay curves versus activity curves for the specific antibodies. For  $^{125}\text{I}$ -A33 the slope was 0.97

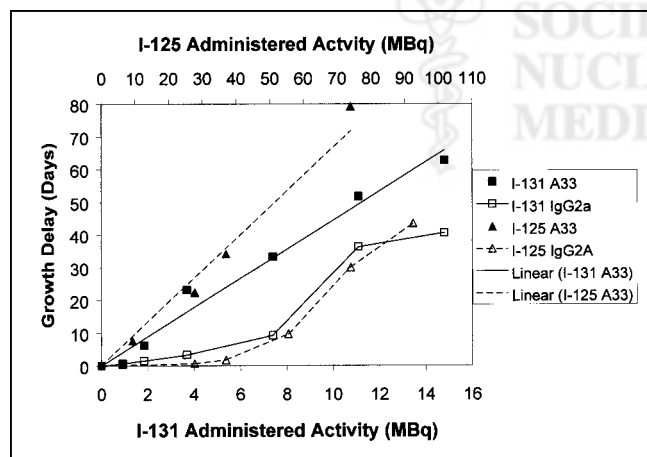


**FIGURE 1.** Median tumor volume, normalized to initial volume, as function of time in nude mice bearing SW1222 xenografts when treated with  $^{131}\text{I}$ -A33 (A),  $^{125}\text{I}$ -A33 (B),  $^{131}\text{I}$ -IgG2a (C), and  $^{125}\text{I}$ -IgG2a (D). Error bars correspond to 25 and 75 percentiles of each treatment group.

d/MBq, whereas for  $^{131}\text{I}$ -A33 it was 4.4 d/MBq. We conclude that  $^{131}\text{I}$ -A33 was around 4.5 times more effective than  $^{125}\text{I}$ -A33 in terms of administered activity for the endpoint of tumor growth delay. For the nonspecific antibodies,

the relative effectiveness was estimated by adjusting the scales of the activity axes until the response curves became coincident. As seen in Figure 2,  $^{131}\text{I}$ -IgG2a was approximately 7 times more effective than  $^{125}\text{I}$ -IgG2a on the basis of administered activity.

No apparent therapeutic effect was evident in the group treated with 250  $\mu\text{g}$  unlabeled mAb A33 compared with the growth control group (data not shown), as reported (12).

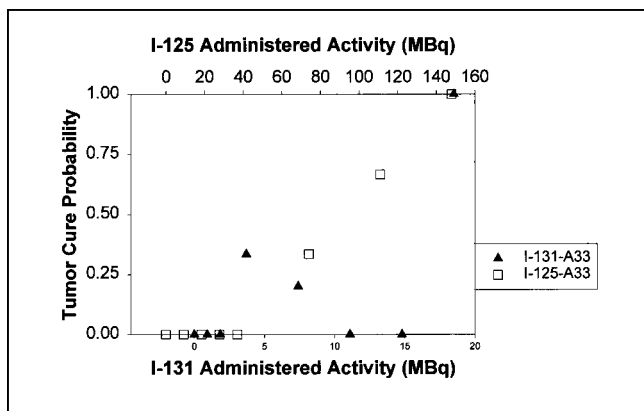


**FIGURE 2.** Tumor growth delay (d) with increasing activities of radiolabeled A33 and IgG2a. A33 data were fitted by linear regression yielding slopes of 0.97 d/MBq and 4.4 d/MBq for  $^{125}\text{I}$  and  $^{131}\text{I}$ , respectively.

### Tumor Cure

Tumors were considered cured if they failed to regrow over the period of observation (100 d after treatment). Radioimmunotherapy with  $^{125}\text{I}$ -A33 yielded a relationship between tumor cure probability and administered activity that was approximately linear (Fig. 3). For  $^{131}\text{I}$ -A33, the relationship was less predictable. Occasional tumor cures were seen at intermediate administered activities of  $^{131}\text{I}$ -A33 (3.7–11.1 MBq), but a higher value (14.8 MBq) did not produce any cures. Four of 5 tumors in this group became temporarily undetectable but subsequently recurred between day 40 and day 80. The highest activity of  $^{131}\text{I}$  administered (18.5 MBq) resulted in tumor cures in all 4 animals in that group (Fig. 3).

Neither  $^{125}\text{I}$ - nor  $^{131}\text{I}$ -labeled control IgG2a antibodies produced any tumor cures with the exception of 1 cure of 5



**FIGURE 3.** Tumor cure probability vs. administered activity for <sup>131</sup>I-A33 and <sup>125</sup>I-A33.

animals that were given <sup>131</sup>I-IgG2a at the highest activity (14.8 MBq) (data not shown).

### Toxicity of Radiolabeled mAbs on Mice

Before initiating the dose-response study, we performed a preliminary experiment to examine the toxicity induced by radiolabeled antibodies in tumor-bearing mice and to estimate the maximum tolerated activities for the different radiolabeled species. The results of this study are summarized in Tables 1 and 2. Briefly, we found that the maximum tolerated activities of <sup>125</sup>I- and <sup>131</sup>I-A33 were 185 MBq (5.0 mCi) and 18.5 MBq (0.5 mCi), respectively, in this model system. Activities of >185 MBq <sup>125</sup>I-A33 and >18.5 MBq <sup>131</sup>I-A33 caused petechiae, which became apparent after 2 d and confluent after 4 d, as well as progressive weight loss. All of these animals died within a relatively short time, during which no tumor responses were seen. No gastrointestinal toxicity was noted. Therefore, we estimated the ratio of <sup>131</sup>I- to <sup>125</sup>I-A33 activities for equivalent toxicity to be approximately 10.

Forms of toxicity that were similar to those produced by radiolabeled A33 were seen with <sup>125</sup>I- and <sup>131</sup>I-labeled control IgG2a. Animals that received  $\geq 111$  MBq (3 mCi) <sup>125</sup>I-IgG2a survived for 10–14 d. Three of 5 mice that received 18.5 MBq (0.5 mCi) <sup>131</sup>I-IgG2a died within 16 d (mean, 25 d) with similar symptoms. Therefore, for this

**TABLE 2**  
Toxicity in SW1222-Bearing Mice with  
Nonspecific Antibody

Parameter	Activity (MBq)		
	<sup>125</sup> I-IgG2a		<sup>131</sup> I-IgG2a
	111	148	18.5
No. of mice	2	2	5
No response	2	2	
Partial or complete response			5
Toxicity (weight loss or petechiae)	++	+++	+++
Mean survival (d)	14	10	25

nonspecific antibody, we estimate the ratio of activities for equal toxicity to be approximately 6.

No major toxicity was seen after treatment with antibodies labeled with either radionuclide at the levels used in the dose-response experiments.

### DISCUSSION

These results indicate that the relative efficacy of <sup>125</sup>I versus <sup>131</sup>I is dependent on the molecule to which the radioiodine is bound and also on the biologic effect under investigation. When associated with the A33 antibody, <sup>125</sup>I was approximately 4.5 times less effective than <sup>131</sup>I for the endpoint of SW1222 regrowth delay in terms of administered activity. When bound to nonspecific IgG2a antibody, the relative efficacy was around a factor of 7 for the same endpoint.

Previous studies using A33 trace-labeled with <sup>125</sup>I on the same xenograft system as we used suggested that the average absorbed dose to tumor was approximately 0.5 Gy/MBq and, by inference, the average absorbed dose to tumor from <sup>131</sup>I was estimated to be 3.7 Gy/MBq (11). The ratio of these values is approximately 7, whereas the ratio of activity for equivalent tumor effect was approximately 4.5. This finding implies that <sup>125</sup>I-A33 was more therapeutically effective than <sup>131</sup>I-A33 on the basis of average absorbed dose. When labeled to the nonspecific IgG2a antibody, the 7-fold difference in activity for equivalent therapeutic efficacy is compatible with the difference in absorbed dose for similar tumor uptake and clearance. <sup>131</sup>I-A33 was found to be

**TABLE 1**  
Toxicity in SW1222-Bearing Mice with A33 Tumor-Specific Antibody

Parameter	Activity (MBq)				
	<sup>125</sup> I-A33			<sup>131</sup> I-A33	
	185–203.5	222	233–333	22.2	27.75
No. of mice	5	2	5	2	2
No response	5	2	3	2	2
Partial or complete response			2		
Toxicity (weight loss or petechiae)	++	+++	+++	++	+++
Mean survival (d)	153	11	13.6	<10	4

approximately 10 times more toxic than  $^{125}\text{I}$ -A33 on the basis of administered activity. In contrast, for the nonspecific IgG2a, the  $^{131}\text{I}$ -labeled antibody was approximately 6 times more toxic on the basis of administered activity.

A possible interpretation of these findings is that there is a geometric enhancement of absorbed dose to the nuclei of cells that have internalized  $^{125}\text{I}$ -A33, which causes its biologic effectiveness to be greater than expected for extracellular or surface-bound activity. Although  $^{125}\text{I}$  decays in the cytoplasm will not result in a greater radiobiologic effectiveness per unit dose, the average dose per decay to the nucleus of an antigen-positive cell will be higher than that to an antigen-negative cell. The radiation dose from a radionuclide source decreases with distance according to the inverse square law and as a result of electron attenuation. Additionally, because antigen-positive tumors will accumulate radionuclide to a greater extent than antigen-negative cells, the dose enhancement will be significantly greater than from geometric factors alone. For  $^{125}\text{I}$ , the electron emission ranges are so short that the self-dose contribution can exceed that from electron cross fire and small changes in the subcellular distribution can have a significant impact on the effectiveness of the radiopharmaceutical (13). The geometric enhancement for  $^{131}\text{I}$ -A33 is insignificant because the self-dose to the targeted cell is small relative to the cross-dose contribution from the longer range  $\beta$ -emissions. S factors have been calculated for the dose to the nucleus from  $^{125}\text{I}$  decays distributed uniformly in the cytoplasm and on the cell membrane, but not specifically for distributions within extracellular space (13). For example, for a cell of 10  $\mu\text{m}$  with a nuclear diameter of 6  $\mu\text{m}$ , the calculated S factors are 6.12E-04 and 2.34E-04 Gy/Bq $\cdot$ s, respectively, a ratio of 2.6. For  $^{131}\text{I}$ , the corresponding values are 4.57E-04 and 2.63E-04 Gy/Bq $\cdot$ s, a ratio of 1.75. This indicates that the proximity of the decay to the cell nucleus is a more significant determinant of cellular self-dose for  $^{125}\text{I}$  than it is for  $^{131}\text{I}$ . In the case of  $^{125}\text{I}$ -IgG2a, internalization does not occur and the geometric enhancement is absent. The ratio of activities of nonspecific antibody for equivalent effects on tumor growth is given simply by the ratio of absorbed dose per unit administered activity.

The dose-limiting toxicities for these radiolabeled antibodies were hematologic. Differences in relative toxicity between radiolabeled antibodies are caused primarily by the higher tolerance of the animals to  $^{125}\text{I}$ -A33. If a significant proportion of the A33 antibody is in the tumor, there will be less present in the circulation and also reduced cross-fire irradiation of distant normal tissues by the short-range electrons emitted by  $^{125}\text{I}$ . The blood clearance has been reported to be significantly different between A33 and IgG2a (4). In the first 24 h, blood levels fell from 36 to 9.5 percentage injected dose per milliliter (%ID/mL) for  $^{125}\text{I}$ -A33 and from 38 to 16 %ID/mL for  $^{125}\text{I}$ -IgG2a. For  $^{131}\text{I}$ -A33 in a mouse model, the reduction in normal tissue irradiation will be less significant because of the longer range of its  $\beta$ -emissions and penetrating  $\gamma$ -photon. For the nonspecific IgG2a, a

reduced amount of antibody is bound to tumor and more is present in the circulation. The 6 times higher effectiveness of  $^{131}\text{I}$  in this context again simply reflects the differences in absorbed dose per unit administered activity.

The effects of internalizing mAbs labeled with either  $^{125}\text{I}$  or  $^{131}\text{I}$  have been studied by several other groups. Woo et al. (14) observed a dose-dependent induction of chromosome aberrations in colon cancer cells targeted by the internalizing mAb 17-1A labeled with  $^{125}\text{I}$ . These effects were not seen with noninternalizing  $^{125}\text{I}$ -labeled control antibodies. Bender et al. (15) found that the internalizing mAb 425 labeled with  $^{125}\text{I}$  was more toxic to glioma cells in vitro and xenografts in vivo than the  $^{131}\text{I}$ -labeled species. Behr et al. (16) reported superior therapeutic results in a xenograft system with  $^{125}\text{I}$ -labeled mAb CO17-A than with  $^{131}\text{I}$ -CO17-A. In this study, human colon cancer xenografts in nude mice were treated at the maximally tolerated dose. Our data are broadly in agreement with these previous studies.

Although not investigated here, the relative therapeutic efficacy of  $^{125}\text{I}$ - and  $^{131}\text{I}$ -labeled antibodies will depend on the intratumoral distribution of the targeting agent. In tumors of significant size, the delivery of radionuclides by molecular vectors may be impeded by difficulties in tissue penetration (17). For  $^{125}\text{I}$ -labeled antibody therapies to be effective, the antibody must localize on all tumor cells. Immunohistochemical studies have shown that the A33 antigen is expressed uniformly in most colorectal cancers (1) and that the A33 antibody reaches a uniform distribution within SW1222 tumors by 24 h (18). In the experiments we performed, the A33 antibody localized with sufficient uniformity to cure tumors in mice at administered activities of  $^{125}\text{I} \geq 74 \text{ MBq}$ .

## CONCLUSION

The therapeutic efficacy of  $^{125}\text{I}$ -A33 was compared with that of  $^{131}\text{I}$ -A33 in a human colon carcinoma xenograft model. Approximately 4.5 times higher activities of  $^{125}\text{I}$  were required for an equivalent tumor growth delay relative to that of  $^{131}\text{I}$ . The relative toxicity to mice injected with mAb A33 labeled with  $^{131}\text{I}$  or  $^{125}\text{I}$  was around 10:1 in terms of administered activity. On this basis, the relative therapeutic gain is a factor of approximately 2. In contrast, little difference was found between the activity ratios for equivalent biologic effects using nonspecific, noninternalizing control antibodies labeled with either  $^{125}\text{I}$  or  $^{131}\text{I}$ .

## ACKNOWLEDGMENT

This study was supported in part by National Institutes of Health grant CA 33049.

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