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Radioimmunotherapy of carcinoma of colon with [^{131}I]-labeled recombinant chimeric monoclonal antibodies to carcinoembryonic antigen

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Key words

humanized chimeric recombinant monoclonal antibody; radioimmunotherapy; colonic cancer; nude mice

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Abstract

Aim: To study the distribution of [^{131}I]-labeled anti-CEA MoAbs and its therapeutic effect on the human colonic cancer model in nude mice. **Methods:** A nude mice model of human colonic cancer was established. [^{131}I]-labeled anti-CEA MoAbs were injected intravenously into mice. The distribution of the MoAbs was then determined and the effect of RIT on human colonic cancer was observed. **Results:** The [^{131}I]-labeled anti-CEA MoAbs had a specific distribution after injection. Tumor/non-tumor ratios for [^{131}I]-labeled anti-CEA MoAbs were 10–20 times higher than [^{131}I]-labeled IgG 96 h after injection. Thirty days after injection, significant inhibition of the volume and weight of tumor was observed in the treated mice compared with the control. The tumor growth inhibition rate of 3.1 mCi/kg CEA MoAbs group (LS180, LS174T, SW1116) was 47.8%–64.0%. This was 69.6%–78.6% in the 6.25 mCi/kg CEA MoAbs group, and 81.8%–86.2% in the 12.5 mCi/kg [^{131}I]-labeled anti-CEA MoAbs group. The plasma CEA level was also lower in treated mice. **Conclusion:** The results indicate that [^{131}I]-labeled anti-CEA MoAbs can be effective in RIT on colonic cancers.

Introduction

Human colonic carcinoma is one of the most common cancers. The 5-year survival rate of patients with chemotherapy is zero. More than half of the patients with this tumor experience metastasis or reoccurrence after treatment. The liver is the most common metastasis foci[1]. Radiolabeled MoAbs offer the prospect of a localized, highly targeted radiation treatment for these cancers. The range of action for radionuclides is defined predominantly by the nature of the particle and energy of the emission. One of the earliest radioisotopes to be coupled to antibodies for therapeutic purposes was Iodine 131 (^{131}I). Its high-energy α particles can penetrate approximately three tumor cells, so it can be effective even when only deposited near the tumor cells and has minor toxicology to normal cells[2]. There are several antibodies for a variety of human tumors that have been used to localize human tumors in xenograft models as well as in patients. Several of these antigens have served as targets for testing whether MoAbs as conjugates with radionuclides can act as selective therapeutic agents. For example, antibodies directed against CEA, α-fetoprotein, ferritin, melanoma, and epithelial-specific antibody have been radiolabeled with ^{131}I and used in the treatment of human cancers[3,4].

In histological classifications, colon cancers are over 90% adenocarcinoma. CEA can be observed in either the cancer cell surface or patients blood serum in this type of tumor[5]. Until recently, three products have been approved worldwide for the treatment of tumors in patients: Bexxar, Zevalin and ChTNT. The antibody used in this experiment is a new product awaiting permission for clinical trial, provided by Beijing Second Pharmaceutical Co, Ltd (Beijing). We undertook this study to determine the antitumor effect of the [^{131}I]-labeled anti-CEA MoAbs and its distribution in nude mice bearing xenografts.

Materials and methods

Mice Athymic nude female BABL/c nu/nu mice, 4–6 weeks old, were obtained from the Institute of Laboratory Animals, Chinese Medical Science Academy. Mice were kept under

SPF conditions and were fed with a diet of sterile mice chow and water. Animals were given 10% Lugol's (5% Iodine and 10% KI) water from 2 d before the start of the experiment beginning until the experiment was completed.

Cell lines Three colonic carcinoma derivative cell lines were used: LS180 (ATCC No: CL-187) with a cell surface CEA expression rate of 81%; LS174T (ATCC No: CL-188) with a cell surface CEA expression rate of 66%; SW1116 (ATCC No: CCL-233) with a cell surface CEA expression rate of 2654 ng/10^6 cells[6]. LS180 was grown in DMEM/F-12 (Hyclone) medium, LS174T and SW1116 in MEM (Invitrogen Technologies, Inc, Carlsbad) essential medium, supplemented with 10% FBS, 2 mmol/L *L*-glutamine, 100 U/mL penicillin and 100 U/mL streptomycin.

[^{131}I]-labeled anti-CEA MoAbs [^{131}I]-labeled anti-CEA humanized chimeric recombinant MoAbs ([^{131}I]-labeled-rch24) were supplied by Beijing SaiKe Pharmaceutical. Radioactivity was 5 mCi/mg. Radiochemical purity was more than 98.5%.

Establishing colon tumors in nude mice The three tumor cells were harvested and suspended in sterile PBS at a concentration of 25×10^6 cells/mL. Cell viability was determined by trypan blue dye exclusion. Cells (5×10^6) in sterile PBS were inoculated subcutaneously into the flank of nude mice[7]. Tumors became apparent in 8–10 d.

Radiolabeled antibody treatment of tumors Mice bearing tumors were randomly divided into groups outlined in Table 1. Mice were administered i.v. in the tail vein. Antibodies were given 2 times with the interval of 10 d. The positive chemotherapy drug (5-FU) was given 2 weeks, 6 times a week.

Radiolabeled antibody effect The tumor growth rate was determined by measuring the length (a) and width (b) (mm) of each tumor using a caliper. Tumor volume=$a\times b^2/2$. The relative tumor volume (RTV), RTV=V_t/V_o. V_o is the tumor volume when the experiment started. V_t is the measured tumor volume at different experiment time. The relative tumor growth rate was calculated by % of T/C=T_{RTV} (treated group)/C_{RTV} (control group)×100%. The effective criterion is T/C (%) above or equal to 60%. Tumor growth inhibition rate was calculated by S%=(mean weight of treated group-mean weight of control group)/(mean weight of control group) ×100%[8].

To evaluate peripheral plasma CEA levels, mice in each group were bled from the eye using heparinized capillary tubes. The plasma CEA level was determined by ELISA (Hoffmann-La Roche Ltd).

Radiolabeled antibody biodistribution Two animals from each group were bled, killed, and dissected at 24 h, 48 h, or 96 h after treatment, respectively. Tissues and organs were immediately dissected, rinsed with saline, blotted dry, and placed in plastic tubes and weighed. The radioactivity of each sample of blood, liver, heart, lung, kidney, and tumor tissue was measured using a well-type gamma counter. From the data, [^{131}I]-labeled anti-CEA MoAbs biodistributions (%ID/g) were calculated: %ID/g=(tissue or organ cpm)/(total injected cpm)/ (tissue or organ weight).

Statistical analysis Differences among the groups were tested using a one-way ANOVA. Results are given as mean±SD unless indicated otherwise.

Results

Distribution studies Tables 2, 3 and 4 summarize the tumor/non-tumor ratios found with either [^{131}I]-labeled anti-CEA MoAbs or [^{131}I]-labeled-IgG in mice with tumors. The results confirmed the tumor-specific targeting and retention of [^{131}I]-labeled anti-CEA MoAbs in tumor tissues in contrast to [^{131}I]-labeled-IgG. While the percentage of injected dose per gram (%ID/g) in the normal tissues continued to

Table 1. Animal group and treatment.

	Group name	Drug and dosage
A	Model control	Saline
B	Low dosage "nude" anti-CEA MoAbs control	156.2 μg/kg
C	High dosage "nude" anti-CEA MoAbs control	625.0 μg/kg
D	Low dosage human IgG control	3.1 mCi/kg ^{131}I labeled-IgG
E	High dosage human IgG control	12.5 mCi/kg ^{131}I labeled-IgG
F	Low dosage ^{131}I labeled anti-CEA MoAbs	3.1 mCi/kg ^{131}I labeled-rch24
G	Middle dosage ^{131}I labeled anti-CEA MoAbs	6.25 mCi/kg ^{131}I labeled-rch24
H	Low dosage "nude" anti-CEA MoAbs	12.5 mCi/kg ^{131}I labeled-rch24
F	Positive chemotherapy control	5-fluorouracil (5-FU) 10 mg/kg

Table 2. Distribution of [^{131}I]-labeled anti-CEA MoAbs (LS180). $^{c}P<0.01$ *vs* IgG-low. $^{f}P<0.01$ *vs* IgG-high. $^{i}P<0.05$ *vs* 3.1 mCi/kg. $^{l}P<0.01$ *vs* 6.25 mCi/kg. n=7. Mean±SD.

Group	Time	Distribution of radioisotope in tumor and non-tumor (% ID/g)				
		IgG-low	IgG-high	3.1 mCi/kg	6.25 mCi/kg	12.5 mCi/kg
Blood	24 h	0.299±0.038	0.496±0.022	0.439±0.037^{cf}	0.656±0.075^{cf}	0.474±0.089^{cf}
	48 h	0.538±0.166	0.584±0.037	0.694±0.036^{cf}	0.834±0.037^{cf}	0.568±0.042^{cf}
	96 h	0.694±0.222	0.759±0.062	1.874±0.160^{cf}	1.325±0.179^{cf}	2.337±0.224^{cfi}
Heart	24 h	0.881±0.019	1.079±0.019^{c}	0.663±0.008^{cf}	1.255±0.007^{cfi}	1.210±0.001^{cfi}
	48 h	2.147±0.105	1.550±0.011	1.129±0.003^{cf}	1.828±0.114^{cf}	1.867±0.066^{cfil}
	96 h	2.934±0.033	3.336±0.294	3.095±0.027^{cf}	2.729±0.079^{cf}	2.839±0.004^{cfl}
Liver	24 h	0.772±0.090	1.050±0.036	0.670±0.036^{cf}	0.678±0.002^{cfi}	1.217±0.057^{cfi}
	48 h	1.324±0.035	1.203±0.093	0.946±0.042^{cf}	1.439±0.086^{cf}	1.764±0.131^{cfi}
	96 h	3.245±0.124	5.717±0.383	4.646±0.132^{cf}	3.763±0.064^{cf}	3.905±0.212^{cf}
Lung	24 h	0.528±0.024	0.688±0.016^{c}	0.426±0.016^{cf}	0.676±0.013^{cf}	0.604±0.019^{cfi}
	48 h	0.754±0.007	0.767±0.053	0.586±0.020^{cf}	0.857±0.028^{cfi}	0.829±0.059^{cf}
	96 h	1.506±0.136	2.377±0.241	2.080±0.086^{cf}	1.509±0.158^{cfi}	1.580±0.004^{cfi}
Kidney	24 h	0.972±0.089	1.256±0.047	0.935±0.144^{cf}	1.148±0.071^{cf}	1.110±0.115^{cfi}
	48 h	1.536±0.003	1.736±0.049	1.434±0.015^{cf}	2.121±0.010^{cf}	2.214±0.107^{cfi}
	96 h	2.734±0.394	5.424±0.051	5.391±0.107^{cf}	2.997±0.121^{cfi}	4.078±0.124^{cfl}

Table 3. Distribution of [^{131}I]-labeled anti-CEA MoAbs (LS174T). $^{c}P<0.01$ *vs* IgG-low. $^{f}P<0.01$ *vs* IgG-high. $^{i}P<0.05$ *vs* 3.1 mCi/kg. $^{l}P<0.01$ *vs* 6.25 mCi/kg. n=7. Mean±SD.

Group	Time	Distribution of radioisotope in tumor and non-tumor (% ID/g)				
		IgG-low	IgG-high	3.1 mCi/kg	6.25 mCi/kg	12.5 mCi/kg
Blood	24 h	0.320±0.008	0.503±0.016	0.403±0.028^{cf}	0.623±0.089^{cf}	0.530±0.038^{cf}
	48 h	0.583±0.014	0.679±0.042	0.824±0.070^{cf}	1.010±0.131^{cf}	0.619±0.023^{cfil}
	96 h	0.686±0.003	0.766±0.118^{c}	1.738±0.103^{cf}	1.196±0.049^{cf}	2.038±0.138^{cfi}
Heart	24 h	0.913±0.033	1.048±0.043^{c}	0.693±0.014^{cf}	1.277±0.015^{cfi}	1.259±0.005^{cfi}
	48 h	2.471±0.172	1.706±0.082	1.188±0.034^{cf}	1.946±0.030^{cf}	2.103±0.038^{cfi}
	96 h	3.153±0.014	3.385±0.012	3.097±0.064^{cf}	2.920±0.151^{cf}	2.915±0.096^{cfil}
Liver	24 h	0.786±0.024	1.026±0.008	0.656±0.016^{cf}	0.686±0.014^{cfi}	1.210±0.021^{cf}
	48 h	1.433±0.017	1.331±0.091	1.033±0.028^{cf}	1.577±0.049^{cf}	1.869±0.004^{cf}
	96 h	3.379±0.143	5.734±0.081^{c}	4.802±0.104^{cf}	3.766±0.079^{cf}	4.019±0.112^{cfi}
Lung	24 h	0.546±0.010	0.707±0.035^{c}	0.436±0.001^{cf}	0.686±0.001^{cf}	0.623±0.010^{cf}
	48 h	0.853±0.061	0.905±0.002	0.664±0.027^{cf}	0.923±0.120^{cf}	0.952±0.020^{cfi}
	96 h	1.433±0.019	2.441±0.209	2.153±0.058^{cf}	1.562±0.016^{cf}	1.636±0.020^{cfi}
Kidney	24 h	0.920±0.099	1.275±0.032	0.888±0.012^{cf}	1.111±0.045^{cf}	1.085±0.028^{cfi}
	48 h	1.789±0.046	1.904±0.018	1.616±0.096^{cf}	2.335±0.155^{cf}	2.575±0.049^{cfil}
	96 h	2.827±0.553	5.594±0.072^{c}	5.561±0.025^{cf}	3.073±0.017^{cfi}	4.229±0.085^{cfi}

decrease over time for both [^{131}I]-labeled anti-CEA MoAbs and [^{131}I]-labeled-IgG, the percentage of [^{131}I]-labeled anti-CEA MoAbs increased in the tumor between d 1 and 4. This caused the T/NT ratios continue to increase in this period. T/NT ratios for [^{131}I]-labeled anti-CEA MoAbs were 2–2.5 times higher than [^{131}I]-labeled-IgG on d 1 and continued to increase so that T/NT ratios were 10–20 times higher than [^{131}I]-labeled-IgG by day 4.

Inhibition of tumor growth The biological effect of [^{131}I]-labeled anti-CEA MoAbs in mice bearing three tumor types was assessed. The tumor growth curves are summarized in Figures 1, 2 and 3. The volume of both [^{131}I]-labeled anti-CEA MoAbs groups was less than the control group. As the administrative dosage increased, the tumor volume increment rate became slow or was not obvious.

The relative tumor growth rate of three tumor types was

Table 4. Distribution of [^{131}I]-labeled anti-CEA MoAbs (SW1116). $^{c}P<0.01$ *vs* IgG-low. $^{f}P<0.01$ *vs* IgG-high. $^{i}P<0.05$ *vs* 3.1 mCi/kg. $^{l}P<0.01$ *vs* 6.25 mCi/kg. n=7. Mean±SD.

Group	Time	Distribution of radioisotope in tumor and non-tumor (% ID/g)				
		IgG-low	IgG-high	3.1 mCi/kg	6.25 mCi/kg	12.5 mCi/kg
Blood	24 h	0.640±0.035	0.514±0.005*	0.437±0.068^{cf}	0.684±0.086	0.447±0.031^{cfi}
	48 h	0.641±0.026	0.735±0.096	0.561±0.022^{cf}	0.942±0.135	0.630±0.041^{cfi}
	96 h	0.831±0.048	0.760±0.169	1.865±0.111^{cf}	1.357±0.262^{cf}	0.860±0.075^{cfi}
Heart	24 h	1.886±0.022	2.314±0.035	1.420±0.003^{cf}	2.707±0.068^{cfi}	2.647±0.003^{cfi}
	48 h	2.986±0.115	2.733±0.089	1.569±0.019^{cf}	2.910±0.084^{cf}	2.795±0.089^{cfi}
	96 h	3.386±0.198	2.801±0.067	2.820±0.211^{cf}	3.278±0.049^{cfi}	2.829±0.021^{cfi}
Liver	24 h	1.644±0.137	2.250±0.101	1.438±0.059^{cf}	1.470±0.011^{cf}	2.559±0.028^{cf}
	48 h	1.831±0.034	2.300±0.111	1.529±0.096^{cf}	1.951±0.019^{cf}	2.702±0.125^{cfi}
	96 h	3.413±0.007	4.154±0.243^{c}	3.268±0.104^{cf}	3.725±0.025^{cf}	3.915±0.227^{cfil}
Lung	24 h	1.146±0.065	1.669±0.064	0.816±0.004^{cf}	1.112±0.004^{cf}	1.141±0.026^{cf}
	48 h	1.175±0.024	1.707±0.003^{c}	1.202±0.061^{cf}	1.130±0.037^{cfi}	1.145±0.043^{cfi}
	96 h	1.517±0.053	2.471±0.021^{c}	2.059±0.034^{cf}	1.539±0.064^{cfi}	1.561±0.023^{cfi}
Kidney	24 h	2.100±0.041	2.716±0.072	1.858±0.055^{cf}	2.506±0.019^{cfi}	2.417±0.114^{cfi}
	48 h	2.119±0.012	2.771±0.048^{c}	1.998±0.008^{cf}	2.819±0.101^{cfi}	3.081±0.148^{cfi}
	96 h	2.707±0.389	5.371±0.049^{c}	5.339±0.105^{cf}	2.968±0.120^{cf}	4.039±0.123^{cfil}

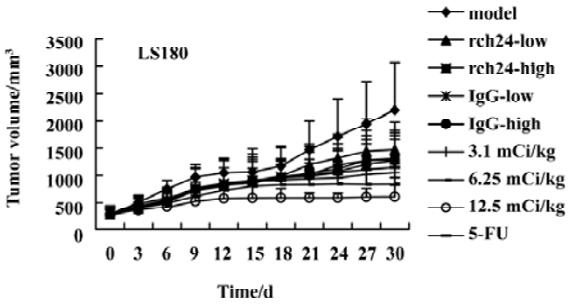

Figure 1. The effect of [^{131}I]-labeled anti-CEA MoAbs on tumor growth curve of LS180. n=7. Mean±SD.

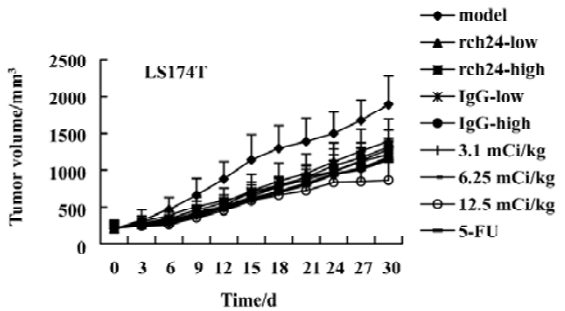

Figure 2. The effect of [^{131}I]-labeled anti-CEA MoAbs on tumor growth curve of LS174T. n=7. Mean±SD.

calculated. The growth of tumors were inhibited significantly at the dosage groups of 3.1 mCi/kg, 6.25 mCi/kg, and 12.5 mCi/kg in nude mice bearing LS180 or LS174T (T/C%<60%).

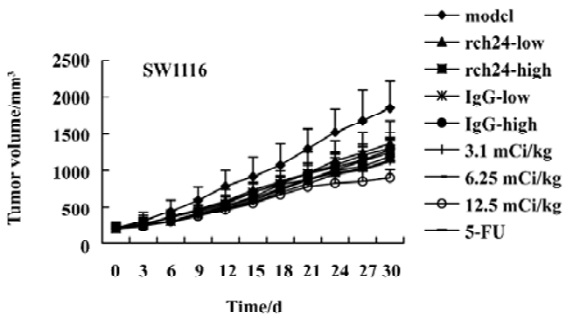

Figure 3. The effect of [^{131}I]-labeled anti-CEA MoAbs on tumor growth curve of SW1116. n=7. Mean±SD.

For SW1116, only the 6.25 mCi/kg and 12.5 mCi/kg dosages were effective. With the increasing dosage, more obvious inhibition of the tumor growth was observed.

Tumor weight and tumor growth inhibition rate (TIR) were calculated. The data is shown in Table 5. The tumor weights of three dosage [^{131}I]-labeled anti-CEA MoAbs groups were all less than that of the control. With the increase in dosage, the tumor growth inhibition rate was more obvious. The tumor growth inhibition rate of the 3.1 mCi/kg CEA MoAbs group (LS180, LS174T, SW1116) was 47.8%–64.0%. This was 69.6%–78.6% in the 6.25 mCi/kg CEA MoAbs group, and 81.8%–86.2% in the 12.5 mCi/kg [^{131}I]-labeled anti-CEA MoAbs group.

Plasma CEA level The plasma CEA level is shown in Table 6. Three groups' CEA levels were lower than the control group. This shows a relationship between the CEA level

Table 5. Tumor weight and tumor inhibition rate (TIR) of [^{131}I]-labeled anti-CEA MoAbs on mice bearing tumor. $^{c}P<0.01$ *vs* model. $^{f}P<0.01$ *vs* rch24-low. $^{i}P<0.01$ *vs* rch24-high. $^{l}P<0.01$ *vs* IgG-low. $^{o}P<0.01$ *vs* IgG-high. $^{r}P<0.05$ *vs* 3.1 mCi/kg. n=7. Mean±SD.

Group	LS180		LS174T		SW1116	
	Tumor Weight (g)	TIR (%)	Tumor Weight (g)	TIR (%)	Tumor Weight (g)	TIR (%)
Model	2.8±0.8	–	2.5±0.2	–	2.2±0.1	–
rch24-low	1.7±0.5	39.3	1.6±0.3	36.0	1.6±0.2	27.3
rch24-high	1.4±0.3	50.0	1.3±0.2	48.0	1.4±0.2	36.4
IgG-low	1.1±0.2	60.7	1.1±0.2	56.0	1.2±0.2	45.5
IgG-high	0.9±0.2	67.9	1.0±0.2	60.0	1.0±0.1	54.5
3.1mCi/kg	0.8±0.2^{cfl}	71.4	0.9±0.1^{cfl}	64.0	0.9±0.2^{cfl}	59.1
6.25mCi/kg	0.7±0.2^{cr}	75.0	0.7±0.1^{cr}	72.0	0.8±0.2^{cr}	63.6
12.5mCi/kg	0.4±0.1^{cior}	85.7	0.5±0.1^{cior}	80.0	0.7±0.1^{cior}	68.2
5-FU	1.6±0.3^{c}	42.9	1.4±0.2^{c}	44.0	1.5±0.2^{c}	31.8

Table 6. Plasma CEA levels of mice bearing different types of tumor. $^{c}P<0.01$ *vs* model. $^{f}P<0.01$ *vs* rch24-low. $^{i}P<0.01$ *vs* rch24-high. $^{l}P<0.01$ *vs* IgG-low. $^{o}P<0.01$ *vs* IgG-high. $^{r}P<0.05$ *vs* 3.1 mCi/kg. n=7. Mean±SD.

Group	CEA level (ng/mL)		
	LS180	LS174T	SW1116
Model	39.2±4.5	36.1±1.7	36.7±3.7
rch24-low	33.0±5.9	33.3±1.2	34.1±4.4
rch24-high	28.5±4.3	28.9±1.9	29.1±1.5
IgG-low	28.8±5.0	27.1±1.6	27.7±1.8
IgG-high	25.1±5.7	24.0±1.6	27.1±1.2
3.1 mCi/kg	23.4±4.1^{cf}	22.8±2.9^{cf}	24.2±2.6^{cf}
6.25 mCi/kg	21.0±4.7^{c}	20.8±1.5^{c}	21.0±1.7^{c}
12.5 mCi/kg	17.4±3.7^{cil}	17.3±1.2^{cil}	18.8±1.0^{cil}
5-FU	25.4±1.2^{c}	21.1±1.5^{c}	26.6±1.0^{c}

and dosage. Compared with the "nude" antibody and [^{131}I]-labeled-IgG, [^{131}I]-labeled anti-CEA MoAbs was more effective in lowering the CEA level.

Discussion

A new approach in radiation therapy for cancer involves the use of radiolabeled MoAbs raised against tumor-associated antigens[9]. The approach adopted in this study was the use of [^{131}I]-labeled anti-CEA MoAbs at different doses to produce tumor growth inhibition in groups of athymic nude mice bearing human colon adenocarcinoma xenografts. The two principal objectives of this study were to examine the biodistribution and antitumor activity of the [^{131}I]-labeled anti-CEA MoAbs.

Our data show that [^{131}I]-labeled anti-CEA MoAbs at different dosages can significantly inhibit the growth rate of tumors (LS180, LS174T, SW1116) in a dose-dependent manner. We are encouraged by the finding that the destruction of tumors was apparent in approximately 50% of tumors in the animals given 3.1 mCi/kg of radiolabeled rch24 antibody. This suggests that we may be able to use a low dosage to produce slight toxicity.

With one exception, most therapeutic studies with [^{131}I]-labeled antibodies in experimental animals have failed to inhibit completely the growth of well-established tumors[10–12]. However, Cheung *et al* were able to ablate 0.5–2.0 cm^3 neuroblastoma xenografts in nude mice with a single injection of 1 mCi of [^{131}I]-labeled 3F8 MoAbs[13]. Whether these results are a result of a property of the antibody, radiosensitivity of the tumor or some other factor, is unclear, but all current experimental evidence indicates that radiolabeled antibodies can be effectively used to inhibit tumor growth.

In this report we examined the distribution of [^{131}I]-labeled anti-CEA MoAbs. Targeting was observed 24 h after the drug was administered. It was more obvious 96 h after administration. The blood and liver have the main uptake and the kidney has a low uptake. Toxicity was measured by the change in bodyweight and by determination of the total peripheral white blood cells (WBC). There was no significant difference in the bodyweight and peripheral WBC counts between the treated groups and model control (data not shown).

Because [^{131}I] is not an as effective radionuclide as other isotopes, other radioconjugates are being pursued[14,15]. One of the best candidates for convenient coupling to antibodies is Yttrium-90 [^{90}Y]. But there are difficulties in the application. These include high uptake in normal tissue,

especially the liver, and problems associated with obtaining high specific activity [^{90}Y]. In addition, [^{90}Y] are known to concentrate in the bone[16]. This may cause severe problems. Each radionuclide antibody tumor system has advantages and disadvantages, but [^{131}I] label is the most promising method at present.

Overall, the results of the present study indicate that tumor growth inhibition using radiolabeled antibodies can be confirmed. Using selectively localizing antitumor antibodies conjugated with suitably cytotoxic radionuclides may provide a useful new approach to the treatment of disseminated cancers.

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