jnm/ PRELIMINARY NOTE

RADIOLANTHANIDES AS PROMISING TUMOR SCANNING AGENTS

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Based on the previous findings that some of the elements in the Group III and in the Period VI of the periodic table have a tumor affinity, the presence and extent of tumor affinity of radiolanthanides were examined using Yoshida sarcoma-bearing rats. Results indicated that all eight elements tested show some affinity for a tumor. Thulium-170 and ^{169}Yb are nuclides that can favorably compare with that of ^{67}Ga. Discovery of other good nuclides was discussed.

As a promising nuclide for clinical tumor scanning, ^{167}Tm, ^{169}Yb, and ^{175}Yb (citrate form is preferable) were suggested.

Since our success was reported in 1965 (*1*) on positive delineation of human tumors with ^{131}I-human serum albumin, the search for a good tumor-selective compound has been continued in our laboratory. Fairly good results of clinical tumor scanning were also obtained with ^{99m}Tc-albumin in 1966 (*2*), ^{203}Hg-hematoporphyrin in 1966 (*2,3*), and ^{131}I-fibrinogen in 1968 (*4*). Recent successes with ^{67}Ga-citrate by Edwards and Hayes in 1969 (*5*) and with ^{111}In-chloride by Hunter and Riccobono in 1970 (*6*) have converted our interest to simple compounds.

A series of basic experiments has been carried out on Yoshida sarcoma-bearing rats using many elements in the form of citrate, chloride, or nitrate. Elements tested so far in our laboratory number 28, including phosphorus, calcium, scandium, vanadium, iron, zinc, gallium, germanium, arsenic, selenium, strontium, yttrium, zirconium, niobium, technetium, silver, cadmium, indium, tin, antimony, iodine, cesium, barium, hafnium, tantalum, gold, mercury, and bismuth. The results have been summarized as follows from the viewpoint of tumor affinity (*7*): gallium and indium in Group III showed a very strong affinity to tumor, and scandium also showed a slight affinity to Yoshida sarcoma; mercury and bismuth in Period VI had a very strong affinity to tumor, and gold also had a very strong affinity to tumor when used as a $H^{198}AuCl_4$ solution. Considering these facts carefully in relation to the periodic table, it seems logical to select thallium and the lanthanides as key elements. The ^{202}Tl-citrate did not show any affinity to Yoshida sarcoma but some of the lanthanides, such as ^{170}Tm, ^{169}Yb, and ^{177}Lu, showed excellent tumor affinity, true to our expectations.

MATERIALS AND METHODS

Among 15 lanthanides, 8 radioactive nuclides were available: ^{140}La, ^{141}Ce, ^{153}Sm, ^{153}Gd, ^{160}Tb, ^{170}Tm, ^{169}Yb, and ^{177}Lu. All nuclides but ^{140}La (chloride) were used as citrate. Donryu rats each weighing 150–200 gm underwent subcutaneous implantation of Yoshida sarcoma (2×10^8 cells/0.5 ml) in the right thigh. Six to 7 days later an appropriate amount of radioactive nuclide was injected intravenously through the tail vein, at which time the tumor had grown to 2 cm in diam. The amounts administered to a rat were ^{140}La 3 μCi/lanthanum 40 μg; ^{141}Ce 2 μCi/cesium 7.2 μg; ^{153}Sm 3 μCi/samarium 36 μg; ^{153}Gd 2 μCi/gadolinium 0.006 μg; ^{160}Tb 2 μCi/terbium 5.4 μg; ^{170}Tm 33 μCi/thulium 3 μg; ^{169}Yb 2 μCi/ytterbium 11 μg; and ^{177}Lu 30 μCi/lutetium 3 μg, respectively. Five animals were killed 3, 24, and 48 hr postinjection, respectively. Tumor and organ specimens obtained at autopsy were assayed by a well scintillation counter. The

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retention values (percent of administered dose per gm/tissue weight) in various organs were calculated.

In the second experiment, to compare the distributions of ^{67}Ga and ^{169}Yb ions in vivo more precisely without any individual variation and tumor growth difference, we administered ^{67}Ga and ^{169}Yb simultaneously as a mixture of the same chemical form of citrate to the Yoshida sarcoma-bearing Donryu rats. The rats were killed at 3, 24, 48, and 72 hr following intravenous injection. Separate assessment of two nuclides was made using the difference of decay speeds of both nuclides with a half-life of ^{169}Yb 32 days, ^{67}Ga 78 hr. It was quite easy to compute the amount of each of the two nuclides after determination at two times: immediately and 12 days after autopsy.

RESULTS

Table 1 shows the retention values (%/gm) of each radionuclide in the tumor at 3, 24, and 48 hr after injection. Data for ^{67}Ga-citrate are shown in the last line for comparison. All radionuclides show more or less affinity to the malignant tumor, and the retention value in the tumor tissue of ^{170}Tm-citrate is the highest—1.34%/gm—and is followed by ^{169}Yb-citrate and ^{177}Lu-citrate. Generally, the lanthanides with higher atomic number have stronger affinity to a tumor than the ones with lower atomic number such as ^{140}La, ^{141}Ce, and ^{153}Sm. Results in the carefully designed second experiments (Fig. 1) showed that the retention value of ^{169}Yb-citrate in the tumor tissue itself was similar to that of ^{67}Ga-citrate. The great difference was noticed in the distribution in normal tissue between ^{169}Yb and ^{67}Ga. The ^{169}Yb-citrate is cleared from the peripheral blood more rapidly than ^{67}Ga-citrate. Retention values of ^{169}Yb-citrate in the liver and spleen were less than those of ^{67}Ga-citrate whereas accumulation of ^{169}Yb in the bone was almost two times that of ^{67}Ga. These differences may cause the lower body background in soft tissues and the denser bony image on the scintigram in the case of ^{169}Yb-citrate.

DISCUSSION

In 8 of 15 lanthanide elements, the presence and extent of tumor affinity were examined. Thulium, ytterbium, and lutetium were found to have a relatively strong affinity for tumor that was no less than that of ^{67}Ga-citrate. There still remains the possibility that another tumor-selective element will be discovered among the remaining seven elements that were not available for us at present. The possibility might be great particularly in erbium, holmium, and dysprosium, which have a relatively large atomic number.

As a possible scanning agent, thulium has many gamma-emitting nuclides: ^{165}Tm, ^{166}Tm, ^{167}Tm,

TABLE 1. DEPOSITION OF EACH LANTHANIDE AND ^{67}Ga IN YOSHIDA SARCOMA-BEARING RAT AT 3, 24, AND 48 HR AFTER INJECTION*

	Time (hr)	Tumor	Blood	Muscle	Liver	Kidney	Spleen	Bone
	3	0.52	2.20	0.035	4.90	0.42	0.59	
^{140}La-chloride	24	0.36	0.035	0.009	7.21	0.64	0.67	
	48	0.31	0.010	0.010	6.29	0.97	1.00	
^{141}Ce-citrate	24	0.38	0.016	0.025	10.23	1.26	0.54	0.55
	3	0.66	1.90	0.18	7.11	1.75	0.79	0.28
^{153}Sm-citrate	24	0.44	0.022	0.043	8.53	2.38	0.40	0.78
	48	0.45	0.008	0.052	8.05	2.54	0.23	1.04
^{153}Gd-citrate	24	0.37	0.018	0.020	2.12	1.28	0.14	2.97
^{160}Tb-citrate	24	0.41	0.021	0.056	1.42	2.16	0.21	2.94
	3	1.26	0.20	0.081	0.92	2.46	0.28	2.41
^{170}Tm-citrate	24	1.34	0.014	0.025	0.53	0.71	0.18	3.04
	48	1.30	0.012	0.017	0.34	0.51	0.10	3.10
	3	0.73	0.50	0.097	0.55	1.34	0.41	1.88
^{169}Yb-citrate	24	0.72	0.014	0.019	0.38	0.84	0.27	1.92
	48	0.73	0.013	0.019	0.44	0.74	0.29	1.75
	3	0.55	0.41	0.095	0.60	1.50	0.35	
^{177}Lu-citrate	24	0.59	0.022	0.025	0.47	0.64	0.32	
	48	0.58	0.017	0.026	0.44	0.61	0.30	
	3	0.73	1.88	0.17	0.99	0.65	0.76	
^{67}Ga-citrate	24	1.14	0.19	0.050	1.41	0.75	1.29	
	48	0.69	0.041	0.091	1.71	0.81	1.91	

* Retention values in various tissues are expressed as a percent of administered dose per gram-tissue weight. Each figure is a mean value of data of five animals.

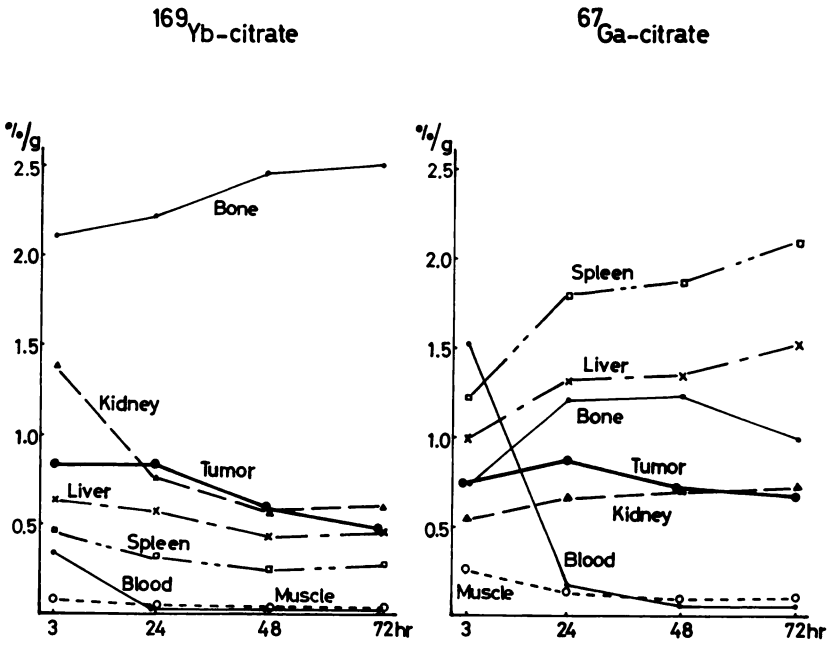

FIG. 1. Ytterbium-169-citrate and ^{67}Ga-citrate were injected simultaneously into Yoshida sarcoma-bearing rats. Ordinate is retention value of radionuclide expressed as percent of administered dose per gram-tissue weight in various tissues and tumor. Abscissa is time intervals after administration of ^{169}Yb and ^{67}Ga. Note great difference in distribution in normal tissue between two scanning agents.

^{168}Tm, ^{170}Tm, and ^{172}Tm. From the point of view of proper physical half-life, adequate energy of the principal gamma ray and no beta emission if possible, ^{167}Tm must be the nuclide of choice. It has been reported recently as a bone-scanning agent (*8*) but is not available yet in Japan. On the other hand, ytterbium has ^{166}Yb, ^{167}Yb, ^{169}Yb, ^{175}Yb, and ^{177}Yb as gamma-emitting nuclides and, of these, ^{169}Yb is most easily available and very popular in Japan as ^{169}Yb-DTPA for cisternography. For this reason, ^{169}Yb-citrate was used on trial in the patients with cancer. The clinical results of tumor scanning will be reported later. Ytterbium-175 is also a promising nuclide. Lutetium has ten gamma-emitting nuclides, but none of these are suitable for scanning.

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