

Gallium Uptake in Heterotransplanted Human Choriocarcinoma and Ovarian Carcinoma in Nude Mice (40986)

SAMUEL D. J. YEH, AND WOO S. KIM

Memorial Sloan-Kettering Cancer Center, Cornell Medical College, New York, New York 10021

Abstract. Gallium-67 citrate uptake in heterotransplanted human choriocarcinoma and ovarian tumor in nude mice was studied. Higher uptake was found in the choriocarcinoma than the ovarian tumor in terms of their percentage of uptake per dose per gram of tumor. A sixfold difference was noted in two different types of tumors transplanted to the same animal. A potential usefulness of this model is discussed.

Recently, nude mice have been used for the heterotransplantation of various human malignant tumors, and they are found to be very useful for the study of biologic characteristics of these tumors (1-3). In our laboratory we have succeeded in transplanting three strains of human choriocarcinoma (3) and ovarian carcinoma into nude mice (Kim, W. S., unpublished data). The tumors have been maintained in the nude mice by serial transfer without losing their original morphologic and biologic characteristics. All three strains of choriocarcinoma produce high levels of HCG (human chorionic gonadotropin) and have continued to do so through generations of transplantation (3). The HCG produced by transplanted tumor has also exhibited its biological effects on the gonads and other genital organs of tumor-bearing mice themselves (3). Moreover, transplanted choriocarcinomas seem to produce high levels of estradiol, progesterone, testosterone, and certain pregnancy associated glycoproteins in tumor bearing nude mice (4). In this communication, the gallium uptake in the heterotransplanted tumors is reported.

Materials and methods. The serial heterotransplantation of three different strains of human choriocarcinomas has been described previously (3). The choriocarcinoma strain used in this study was originally obtained from the metastatic pulmonary nodule of a patient who had gestational choriocarcinoma (GCC-RS strain). The ovarian carcinoma was obtained from metastatic papillary adenocarcinoma in omentum at the time of explor-

atory laparotomy. The heterotransplantation was carried out by inoculating four to five tissue blocks ($1 \times 1 \times 2$ mm) into the subcutaneous space of the right flank using 13-gauge trocar needles. Athymic, 4- to 6-week-old female nu/nu mice with Swiss background were used exclusively. The transplanted tumors started to grow within 7 to 10 days, and the animals were used for gallium studies about 20 days after implantation during the active phase of the growth cycle regardless of the variability of tumor size.

Gallium-67 citrate (10 to 20 μ Ci in 0.1 ml of saline) was injected intravenously into the retroorbital venous plexus. The animals were sacrificed 48 hr afterward. The radioactivity in various tissues was measured in a well-type gamma scintillation counter and the specific activities of various tissues were calculated. To ascertain the success of intravenous injection, some animals were imaged at the time of sacrifice in a gamma camera to assure absence of excessive accumulation of radionuclide at the sites of injection.

To compare the gallium uptake of two types of tumor heterotransplanted in the same nude mouse, choriocarcinoma and ovarian carcinoma were implanted into the flank of each side. The uptake of one type of tumor was compared with that from the other.

Since actinomycin D is one of the most effective drugs for human choriocarcinoma, attempts were also made to evaluate whether actinomycin D given over a short period may influence the gallium uptake in the choriocarcinoma. The drug was injected

TABLE I. GALLIUM UPTAKE IN NUDE MICE BEARING CHORIOCARCINOMA

Radioactivity recovered (% dose/g) ^a					
Blood	Liver	Kidneys	Spleen	Muscle	Tumor
0.45 ± 0.04	3.03 ± 0.07	2.73 ± 0.35	1.60 ± 0.11	0.26 ± 0.01	10.63 ± 1.33
	Tumor/blood	Tumor/muscle		Tumor weight (g) ^b	
	23.5 ± 1.72	41.45 ± 6.23		0.59 ± 0.11	

^a Mean ± SE in five animals.

^b The tumor weights were 0.30, 0.43, 0.54, 0.75, and 0.92 g with uptakes of 8.80, 8.70, 11.20, 15.61, and 8.85% dose/g, respectively.

intraperitoneally with a daily dose of 0.05 mg/kg for 3 days prior to the injection of gallium-67 citrate; and treatment was continued until sacrifice.

Results. The gallium uptakes in the choriocarcinoma heterotransplanted in the nude mice and in the host tissues are shown in Table I. The specific activity of gallium was highest in the tumor compared with those in the other tissues. The tumor-to-blood ratio was 24 and tumor-to-muscle ratio was even higher. Although the inoculum size, duration of implantation, and site of injection of tumor cells are the same, size of heterotransplanted tumors varied about threefold. However, the specific activity in tumor was rather constant, independent of tumor size.

The gallium uptake in the ovarian carcinoma was somewhat less than the uptake obtained in the choriocarcinoma as shown in Table II. Again, the size of tumor did not influence the specific activity of Ga-67 in the tumor.

To further study the character of gallium uptake in two types of tumor, the choriocarcinoma and ovarian carcinoma were heterotransplanted to either flank of the nude mice. Gallium uptake was again sig-

nificantly higher in the choriocarcinoma than in the ovarian carcinoma (Table III).

The effect of actinomycin D in nude mice bearing choriocarcinoma was studied. The treatment did not reduce the size of the transplanted tumor or the gallium uptake. Actinomycin D also showed no influence on gallium distribution in animals without tumor implant.

Discussion. These experiments clearly show that the degrees of gallium uptake in two different heterotransplanted tumors in nude mice were different probably due to the original biological characteristics of these tumors. Thus, one can use this model not only to evaluate the efficacy of various potentially useful tumor-localizing radiopharmaceuticals (5) but also to study certain biological behaviors in different tumors. The high uptake of gallium-67 citrate in choriocarcinoma is also in agreement with our previous observations showing increased gallium uptakes in primary or metastatic choriocarcinoma in man (6). The maintenance of original histologic and hormonal characteristics and the specific pattern of gallium uptakes in the heterotransplanted tumors in the nude mice all suggest preservation of tumor charac-

TABLE II. GALLIUM UPTAKE IN NUDE MICE BEARING OVARIAN TUMOR

Radioactivity recovered (% dose/g) ^a					
Blood	Liver	Kidneys	Spleen	Muscle	Tumor
0.29 ± 0.05	3.33 ± 0.16	1.17 ± 0.15	1.66 ± 0.13	0.33 ± 0.03	2.63 ± 0.32
	Tumor/blood	Tumor/muscle		Tumor weight (g) ^b	
	9.76 ± 2.89	7.54 ± 0.56		0.89 ± 0.37	

^a Mean ± SE in five animals.

^b The tumor weights were 0.36, 0.40, 0.49, 0.86, and 2.33 g with uptakes of 2.16, 3.41, 2.15, 3.40, and 2.02% of dose/g, respectively.

TABLE III. GALLIUM UPTAKES IN NUDE MICE BEARING TWO TYPES OF TUMORS

Radioactivity recovered (% dose/g) ^a						
Blood 0.50 ± 0.08	Liver 3.52 ± 0.17	Kidneys 2.81 ± 0.13	Spleen 1.53 ± 0.14	Muscle 0.32 ± 0.06	Choriocarcinoma 13.03 ± 1.47	Ovarian carcinoma 2.10 ± 0.20
	Choriocarcinoma	Tumor/blood		Tumor/muscle	Tumor weight (g)	
	Ovarian carcinoma	26.91 ± 2.21		47.31 ± 10.14	0.95 ± 0.27 ^b	
		4.57 ± 0.73		7.34 ± 1.18	0.25 ± 0.05 ^c	

^a Mean ± SE in five animals.

^b The tumor weights were 1.61, 1.49, 0.34, 0.37, and 0.96 g with uptakes of 15.09, 11.61, 17.75, 10.80, and 9.89% of dose/g respectively.

^c The tumor weights were 0.18, 0.18, 0.21, 0.27, and 0.42 g with uptakes of 2.87, 1.76, 1.95, 1.85, and 2.05% of dose/g respectively.

teristics in the transplanted tumor following repeated transfers.

It is not clear why actinomycin D, one of the most effective chemotherapeutic agents for choriocarcinoma, did not decrease the gallium uptake. Since the original tumor was obtained from the metastatic pulmonary nodule following multidrug therapy including actinomycin D, it is possible that the tumor cell population in our tumor model was somewhat resistant to this drug as compared to those from most clinically encountered primary tumors. Our failure to induce tumor regression and decrease hormonal levels in the tumor-bearing mice treated by actinomycin D appear to confirm this thesis (Kim, W. S., unpublished). More studies certainly are needed to substantiate this interpretation.

The differential gallium uptake in two types of tumors with different biological behaviors is one of the easily measurable and quantitated parameters. Since mechanisms of gallium uptake by soft tissue tumors have not been well established, it is possible that studies in this tumor model may elucidate our further understanding of the mechanisms and factors which may alter gallium uptakes in various tumors. Our unfruitful attempt to show actinomycin D

influence on gallium uptake is one of such factors that can be studied further. It would be important to see the response of effective chemotherapy also reflected in the gallium uptake in the tumors. Certainly, our data suggest that the heterotransplanted human tumor in nude mice can be used for screening potentially useful radiopharmaceuticals for tumor localization and comparing their efficacy with gallium-67 citrate. In view of the simplicity and reproducibility of this technic, the potential usefulness of this approach should be explored.

1. Aubert, C., Chiriceanu, E., Foa, C., *et al.*, *Cancer Res.* **36**, 3106 (1976).
2. Helson, L., Das, S. K., and Hijdu, S. I., *Cancer Res.* **35**, 2594 (1975).
3. Kim, W., Takahashi, T., Nisselbaum, J. S., and Lewis, J. L., Jr., *Gynecol. Oncol.* **6**, 165 (1978).
4. Kim, W., Dawood, M. Y., Takahashi, T., and Lewis, J. L., Jr. in "Proc. 7th Trophoblast Conference" (1977).
5. Yeh, S. D. J., Helson, L., and Grando, R., *Int. J. Nucl. Med. Biol.* **6**, 169 (1979).
6. Yeh, S. D. J., Leeper, R. D., and Benua, R. S., *Clin. Bull.* **7**, 1 (1977)

Received April 24, 1980, P.S.E.B.M. 1980, Vol. 165.