Cancer Chemother Pharmacol (1989) 23 (Suppl): S 54–S 58

Cancer Chemotherapy and Pharmacology

Radioiodinated fatty acid esters in the management of hepatocellular carcinoma: preliminary findings*

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Summary. Radioiodinated fatty acid esters, such as lipiodol or ethiodol, are localized in the hypervascular hepatocellular carcinoma (HCC) for a long time following intra-arterial hepatic injection, enabling delivery of high internal radiation to the tumor. The desired radiation can easily be delivered to small HCC, less than 5 cm in diameter, in single or multiple procedures with an 8-week interval. For larger tumors, [^{131}I]lipiodol or [^{131}I]ethiodol in conjunction with chemotherapy emulsion, Ivalon embolization or all three combinations should be considered for maximal clinical results. A strong beta emitter with shorter physical half-life, i.e. ^{90}Y will be more effective in the management of HCC if one can label lipiodol with ^{90}Y.

Introduction

It is well known that iodized fatty acid esters, such as lipiodol or ethiodol, are selectively localized within the hypervascular tumor vessels of hepatocellular carcinoma (HCC) for long periods of time, following intra-arterial hepatic administration [1, 2, 5, 12]. Many efforts have been made with lipiodol anticancer emulsions to treat HCC in recent years, and the clinical results have been fairly successful especially in Japan [3, 6, 7, 9]. For the treatment of unresectable HCC, we are investigating the effectiveness [^{131}I]lipiodol for treating HCC by means of internal irradiation. Lipiodol is labelled with radioactive iodine-131 by a simple exchange method with better than 95% labelling efficiency [8, 10, 11]. After biodistribution studies of [^{131}I]lipiodol in dogs and human subjects with HCC, 60 patients were treated with this material alone or in conjunction with Ivalon or chemoembolizations. This report describes preliminary findings of the therapeutic attempt using [^{131}I]lipiodol in patients with HCC.

Materials and methods

A total 60 patients with inoperable HCC were treated with [^{131}I]lipiodol alone or in conjunction with embolization and were followed-up for more than six months after the treatment. There were 49 male and 11 female patients, whose ages ranged from 32 years to 72 years. The diagnosis of HCC was made by cytology (NAB, 30 cases), elevated α-fetoprotein with abnormal diagnostic images (20 cases), and hepatic angiographic findings (10 cases).

A small fraction of stable iodine (^{127}I) in lipiodol was replaced with radioactive ^{131}I by a simple exchange method.

An arterial catheter was inserted into the femoral artery and was advanced into the branches of the hepatic artery supplying the tumor. Volumes ranging from 5 ml to 15 ml [^{131}I]lipiodol, in accordance with the tumor volume, were injected using an automated syringe or by hand. Tumor-to-nontumor liver or tumor-to-normal lung ratios were checked by single-photon emission computed tomography (SPECT), comparing pixel counts over these regions (Fig. 1). Quantification of the radioactivity involved obtaining the transmission factors and the system sensitivity. Effective half-lives from different regions were measured, for radiation dose calculations.

The total protracted radiation dose delivered to the tumor was aimed to be 12000 rad (120 Gy), which may be sufficient to control the tumor in those cases with HCC of less than 8 cm.

For the larger tumors, more than 8 cm in diameter, we used Ivalon embolization in conjunction with [^{131}I]lipiodol and chemotherapy emulsion, such as mitomycin or adriamycin. Response and nonresponse groups were divided after follow-up studies of computed tomography (CT), ^{67}Ga scan, angiography and serial measurements of α-fetoprotein. The response is defined as stasis or shrinkage of tumor over 6 months following the therapy, measured by CT, and the nonresponse group is that showing tumor growth following the therapy. The ^{67}Ga scan was performed especially for evaluation of tumor viability after the procedure.

Results

HCC was divided into three groups in accordance with (CT) and angiographic findings: massive, multinodular, and infiltrative types. There were 19 massive, 18 multinodular, and 23 infiltrative types, and the tumor ranged from 2.5 cm to 15 cm in diameter.

Among the 60 cases, 25 responded to our various treatment combinations of [^{131}I]lipiodol alone and in conjunction with Ivalon embolization or chemoembolization.

*This work was supported in part by Yonsei Cancer Center Research Grant

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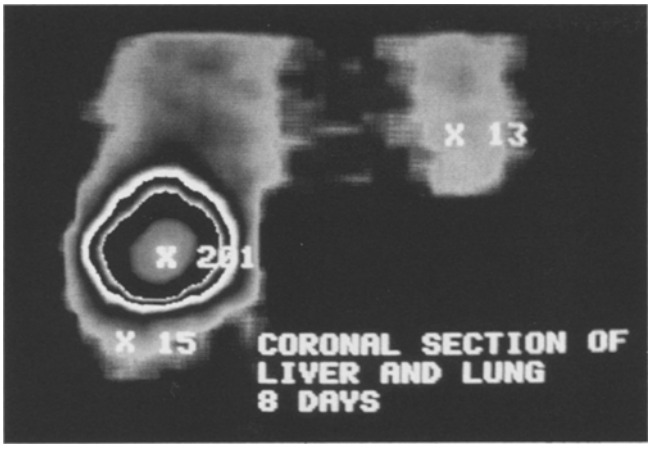

Fig. 1. Single-photon emission computed tomography (SPECT) discloses high tumor-to-normal liver and lung ratios on the same pixel counts.

Table 1. Comparison of age, sex, child class, type and size of the tumor between response and nonresponse groups

Characteristics	Response group ($n = 25$)	Nonresponse group ($n = 35$)
Age		
Mean + SD	51.8 + 9.4	51.1 + 9.4
Range	39–72	32–67
Sex (M/F)	21/4	28/7
Child class		
A	17	23
B	4	6
C	0	0
Cirrhosis (−)	4	6
Type of tumor		
Massive	14	5
Multinodular	8	10
Infiltrative	3	20
Size of tumor (cm)		
⩽5	7	3
5– 8	7	3
8–10	4	4
10⩾	7	25

Table 2. Combined modalities of response group

Modality	No. of cases
[^{131}I] Lipiodol alone[a]	15
[^{131}I] Lipiodol + Ivalon	6
[^{131}I] Lipiodol + intra-arterial chemotherapy	1
Intraoperative [^{131}I] lipiodol + hepatic artery ligation	3
Total	25

[a] Two patients had previous Ivalon embolization

Comparison of age, sex, Child class, type and size of tumor, between response and nonresponse groups, is described at Table 1. The majority (15 out of 25) of the responders were treated with [^{131}I]lipiodol alone (Table 2). The response rate was most prominent in the massive-type HCCs, which were smaller in size (less than 5 cm in diameter) (Table 3). The 35 cases of nonresponderers, whose tumors got larger, had large tumors measuring 10 cm or more in diameter (25 cases) and the majority (20 out of 35) of the tumors of this group were of the infiltrative type. Among the responders (25 out of 60), 12 patients are still alive after more than 1 year.

Table 3. Response rate according to type and size of tumor

Tumor characteristic	Total no. of cases	No. of cases responding	Response rate (%)
Type of tumor			
Massive	19	14	73.7
Multinodular	18	8	44.4
Infiltrative	23	3	1.3
Size of tumor (cm)			
⩽5	10	8	80.0
5– 8.0	10	6	60.0
8–10.0	8	4	50.0
10⩾	32	7	21.9
Total	60	25	41.7

Case reports

Case 1. A 54-year-old man was admitted to the hospital with advanced cirrhosis of the liver. On CT examination, a 5 cm low-density mass was identified incidentally in the right lobe of the liver with ascites and the mass was confirmed as HCC by an aspiration biopsy. Radiolabeled lipiodol (5 ml) containing 20 mCi radioactive iodine was infused through the tumor feeding vessel under superselection. A follow-up gamma Scintiscan revealed radioactivity confined to the tumor even 32 days after the infusion. A follow-up CT examination also showed lipiodol density only in the tumor and a 1-year follow-up angiograph disclosed shrinkage of the tumor with less vascularization and more central necrosis in comparison to the pre-embolization angiography (Fig. 2). At present the patient is alive without any clinical symptom.

Case 2. A 58-year-old man with an unresectable hepatoma was admitted to the hospital for progressive ascites and vague right upper quadrant discomfort. A CT scan disclosed a 6 cm low-density mass in the right dome of the liver and ascites. The hepatic angiogram revealed a hypervascular mass, and 30 mCi [^{131}I]lipiodol was infused through the tumor feeding vessel under superselection; the proximal right intrahepatic artery was then embolized with Ivalon. A gamma Scintiscan after 24 h of procedure revealed high levels of radioactivity confined in the tumor and only slight radioactivity was detected in both lungs, which might be caused by arterovenous shunting. A 1-year follow-up CT scan showed a contracted mass with lipiodol density remaining in the tumor, and a 21-month follow-up ^{67}Ga scan disclosed an unlabeled defect in the tumor area, which might suggest the non-viability of the tumor (Fig. 3). The patient has been without any clinical symptoms and still has no sign of recurrent disease.

Discussion

Hepatic resection is considered to be the treatment of choice for hepatocellular carcinoma but the majority of

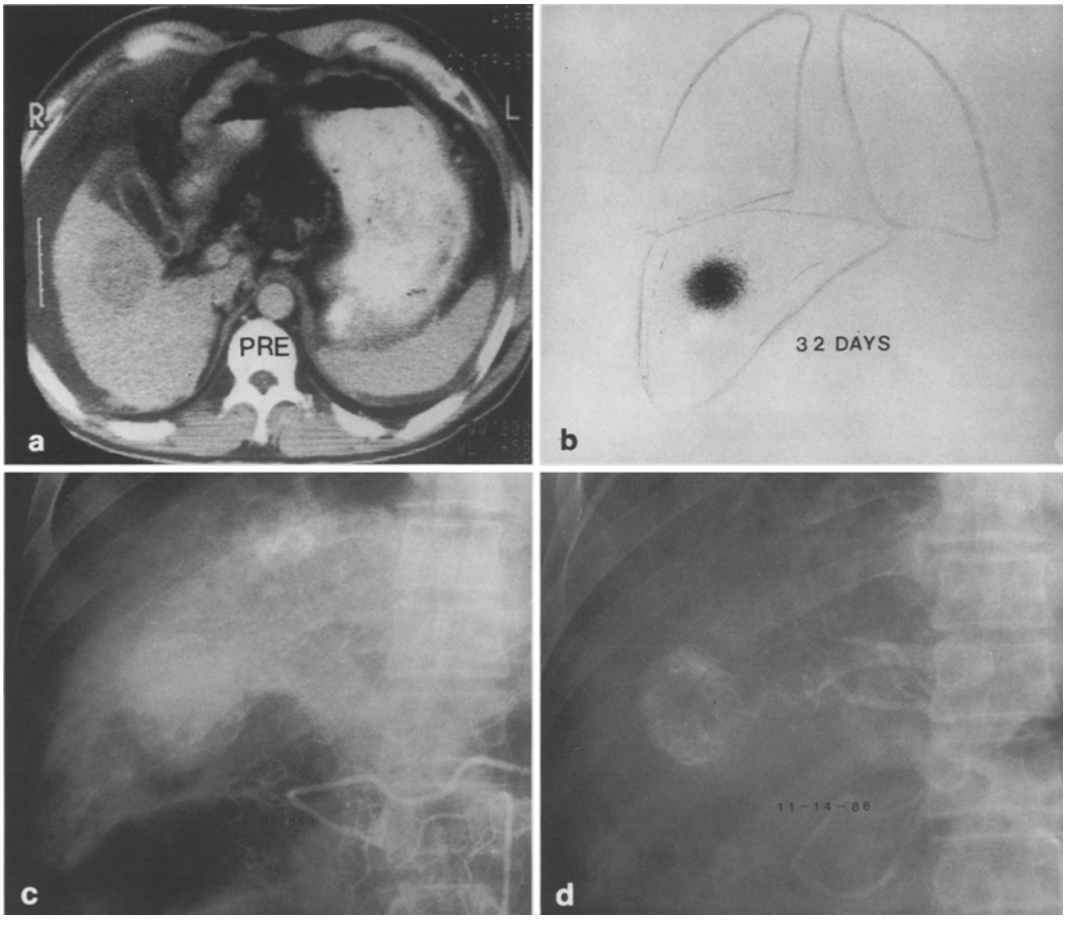

Fig. 2. a Computed tomography scan reveals well-defined low-density mass in the right lower lobe and ascites. **b** [^{131}I]lipiodol radioactivity is still seen in the tumor mass even after a 32-day follow-up period. **c** Angiography shows hypervascular mass consistent with massive type of hepatocellular carcinoma. **d** Nine-month follow-up angiography depicts contracted mass with central radiolucency suggestive of tumor necrosis

HCCs are unresectable at the time of diagnosis because of superimposed cirrhosis, the size of the tumors and portal vein involvement by the tumor. In the past, systemic chemotherapy and external radiotherapy have not been successful in the management of HCCs.

During the last 10 years, various interventional methods, such as hepatic arterial infusion, embolization and chemoembolization, have been evolved in order to improve tumor control and the patient's survival. Chemoembolization with anticancer drugs emulsified with lipiodol has been used in the treatment of HCC, especially in Japan, and the method appears to be fairly successful thus far [2–7].

We elected to try radioembolization [^{131}I]lipiodol in the management of HCC. For small tumors, a cancercidal radiation dose can be delivered using intra-arterial hepatic administration of [^{131}I]lipiodol with a radiation dose acceptable to normal liver, lung and the whole body. In our studies, where infusion was into the superselected tumor feeding vessel, we found a high tumor radioactivity, 15–20 times greater than that in the non-tumor-bearing liver and lung. When infusion was into the proper hepatic artery there was about 10–15 times higher radioactivity in the tumor than in the normal liver and lung. The effective half-life of [^{131}I]lipiodol in the tumor was about 6 days, which is long enough the deliver radioactivity [8, 10, 11]. Madsen and Park have investigated the biodistribution and kinetics of [^{131}I]ethiodol in a group of four patients of HCC. They suggested that approximately 80%–90% of the administered activity was localized within the liver, including the tumor, the remainder appearing to be in the lungs (10%–20%), and that approximately 10%–15% of the administered activity went to tumor in patients with massive and multinodular HCCs [4, 8].

Assuming that the radiolabelled lipiodol is accumulated in the tumor and that the effective half-life of [^{131}I]lipiodol is about 6 days, we can calculate the total radiation dose (D) delivered to the tumor using the following;

$$D_{\beta+\gamma} = Ct\,(73.8\,E + 0.0346\,P)\ \text{rad}$$

Where C = localized ^{131}I activity in the tumor, E = average beta energy, T = effective half-life, and P = gamma factor.

For example, if the tumor weighs 40 g (approximately 5 cm in diameter) and 1 mCi, [^{131}I]lipiodol remains in the tumor for at least 6 days, the total protracted radiation dose to the tumor would be about 2285 rad (22.85 Gy) on the basis of the following assumptions:

E = 0.18 MeV, T = 6 days, P = 2.18,
$D = 1000/40 \times 0.187 \times 6 \times 73.8 = 2070$-rad
$D = 1000/40 \times 6 \times 2.18 \times 19 \times 0.0346 = 215$-rad
$D_{\beta+\gamma} = 2070 + 215 = 2285$-rad.

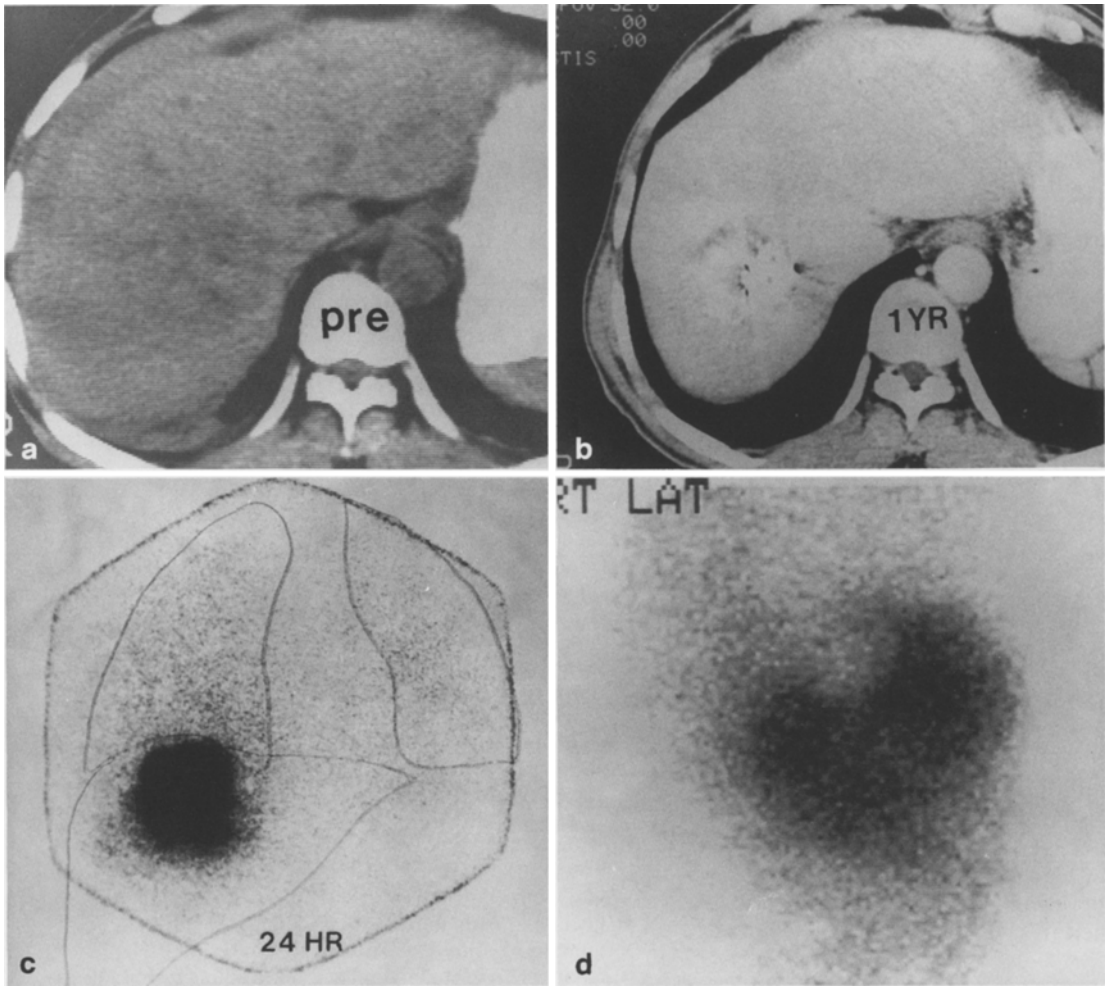

Fig. 3.a Computed tomography (CT) scan reveals 6 cm low-density mass in right dome of liver, which was confirmed as hepatocellular carcinoma (HCC) on aspiration cytology. **b** High levels of radioactivity of [^{131}I]lipiodol are seen in the tumor and slight radioactivities are noted in both lungs. **c** One-year follow-up CT scan shows confined lipiodol density and marked contraction of tumor. **d** Twenty-one-month follow-up ^{67}Ga scan reveals unlabeled defect on tumor site suggestive of nonviability of HCC

Thus, if 5 mCi radioactivity remains within the tumor, approximately 12000-rad (120 Gy) will be delivered to the tumor, and this dose might be sufficient for its destruction.

Even in cases of multinodular hepatoma or hypervascular metastatic tumors, if one can deliver 1 mCi [^{131}I]lipiodol to each vascular tumor measuring 2 cm in diameter, the total protracted radiation dose delivered to each tumor will be approximately 28500 rad (285 Gy), which should be sufficient for complete killing of tumor cells.

Table 4. Relationship among tumor size, [^{131}I]lipiodol activity and lipiodol volume (approximately 12000 rad protracted radiation was aimed at the tumor)

Tumor size (cm)	Tumor mass (g)	rad/mCi	^{131}I in tumor (mCi)	Volume of lipiodol (ml)
1	0.52	167682	0.07	1.5
2	4.18	21380	0.56	3.0
3	14.13	6.479	1.85	
4	33.49	2798	4.28	
5	65.41	1466	8.18	10
6	113.04	867	13.84	
7	179.50	558	21.50	
8	267.94	382	31.41	
9	381.51	274	43.79	
10	523.33	204	58.82	20

The relationship between tumor size, [^{131}I]lipiodol activity and lipiodol volume, in order to deliver a 12000-rad (120 Gy) tumor dose, is described in Table 4. From this table it becomes obvious that a large HCC is difficult to treat with [^{131}I]lipiodol since a larger volume of lipiodol and high ^{131}I activity are required. However, we believe that a combination of [^{131}I]lipiodol, chemoembolization and Ivalon or Gelfoam embolization will be effective in the management of such large tumors because the effective half-life might be prolonged if the tumor blood supply is interrupted by embolization materials following injection of [^{131}I]lipiodol.

The combined method will also enhance stasis of [^{131}I]lipiodol and anticancer agents and the concentration of such agents will be increased by reducing the tumor mass by Ivalon or Gelfoam embolization. The embolization would not seriously affect the oxygenation since collaterals develop rapidly following the embolization.

Non-uniform distribution of the radiolabel or chemoemulsion is expected within a large tumor. However, this

also will be less of a problem as the tumor shrinks following Ivalon or Gelfoam embolization. More effective radiation delivery to the tumor could be achieved using ethiodol labeled with ^{90}Y (exam. = 2.27 MeV, $t_{½}$ = 64 h, R_{max} = 11 mm) and ^{32}P (exam. = 1.17 MeV, $t_{½}$ = 14.3 days, R_{max} = 8 mm), with a greatly reduced shielding problem and less unnecessary radiation exposure of surrounding normal tissues from these non-photon sources.

Dosimetric comparison of ^{131}I, ^{90}Y and ^{32}P as radiolabels for lipiodol in the treatment of hepatoma reveals doses two times higher with ^{90}Y and six times higher with ^{32}P for the administration of the same quantities of radioactive isotope into the tumor [4]. The possibility of labeling lipiodol with these pure beta emitters or other elements is now being investigated.

Our present finding of selective [^{131}I]lipiodol deposition in HCC can lead to a high internal radiation delivery to the target tumor.

In conclusion, selective [^{131}I]lipiodol deposition in the tumor tissue can offer several benefits:

1. The selective delivery of the radiation to the target tumor as well as the ability to demonstrate small daughter nodules.

2. The potential for accurately determining size and tumor response by serial X-ray examination over a long period.

3. The possible destruction of tumor cells even if they one multifocal in nature, and the feasibility of using the treatment for hypervascular metastatic lesions.

4. The apparent effectiveness of the method in single expansile hypervascular hepatoma less than 8 cm.

5. The possibility of using in conjunction with other methods, such as arterial infusion chemotherapy and Ivalon embolization.

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