Cancer Chemother Pharmacol (1989) 23 (Suppl): S 42–S 44

Cancer Chemotherapy and Pharmacology

Combination chemoembolization therapy for hepatocellular carcinoma: mainly, using cisplatin (CDDP)

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Summary. Chemoembolization therapy, using the arterial injection of mixtures of various anticancer agents and lipiodol along with gelfoam particles, was carried out on 77 cases of hepatocellular carcinoma between January 1985 and March 1987, and an assessment was made on the anticancer effects of this treatment method. For the patients receiving lipiodol, the value of the longitudinal dimension multiplied by the vertical length of the tumor was calculated using a computerized tomograph before and after chemoembolization to determine the rate of tumor regression. (a) Of the 30 patients receiving chemoembolization therapy using a simple mixture of 100 mg cisplatin (CDDP) and lipiodol, the tumor regression rate was 50% or more in 10 cases (31%). (b) Of the 14 patients receiving chemoembolization therapy with a suspension of 100 mg of cisplatin, adriamycin (10–30 mg) and lipiodol, the tumor regression rate was 50% or more in four cases (29%). (c) Of the 31 cases receiving chemoembolization therapy using a suspension of adriamycin (10–40 mg), mitomycin C (10–20 mg) and lipiodol, the tumor regression rate was 50% or more in four cases (13%). (d) From these results, it can be concluded that the antitumor effect of chemoembolization using cisplatin is more significant than with other drugs.

Introduction

Transcatheter arterial embolization (TAE) was first reported by Goldstein et al. in 1976 [3] as effective therapy for hepatocellular carcinoma [1, 6, 7]. The common method employed in this therapy is the intra-arterial injection of a mixture of lipiodol with various anticancer agents followed by embolization with Gelfoam particles. This procedure is generally called chemoembolization.

There are a number of reports on chemoembolization using a variety of lipiodol preparations containing anticancer agents such as SMANCS [4], adriamycin and mitomycin C [2]. In this study we used lipiodol mixed with powdered cisplatin (CDDP) for chemoembolization and compared its anticancer effect with those of lipiodol suspensions containing multiple anticancer agents, that is, a combination of cisplatin with adriamycin, or of adriamycin with mitomycin C. The favorable results obtained by this treatment are reported herein.

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Materials and methods

Our subjects were 77 patients with hepatocellular carcinoma diagnosed over the previous 2 years by α-fetoprotein and medical imaging (Table 1). Thirty-two of these patients received chemoembolization with a simple mixture of cisplatin powder and lipiodol. Their average age was 57 years, the mean tumor size was 8 × 8 cm, and on average two TAE treatments were carried out. Fourteen patients received chemoembolization using a cisplatin/adriacin/-lipiodol suspension, their average age was 58 years, the mean tumor size was 7 × 7 cm, and on average 1.4 TAE treatments were carried out. Thirty-one patients were treated with an adriacin/mitomycin/lipiodol suspension, and their average age was 61 years; the mean tumor size was 6 × 6 cm, and on average 1.4 TAE treatments were carried out. The anticancer effects of chemoembolization with various drug mixtures were compared in following manner. The products of the longitudinal and latitudinal diameters of a slice of the largest tumor on the computerized tomograph (CT) prior to and 2–4 weeks after TAE were compared to determine the rate of tumor regression. In addition, the increase or decrease in the number and size of the daughter nodules was also compared. Chemoembolization was carried out as follows. The catheter was inserted into the proper hepatic artery and the embolic materials were injected through the catheter.

Table 1. Patients' data for 77 cases of hepatocellular carcinoma

Treatment	Age (years)	Tumor size (cm) on CT (average)
Cisplatin 100 mg/lipiodol simple mixture (32 cases)	57	8 × 8
Cisplatin 100 mg/adriamycin 10–30 mg lipiodol suspension (14 cases)	58	7 × 7
Adriamycin 10–40 mg/mitomycin C 10–20 mg suspension (31 cases)	61	6 × 6

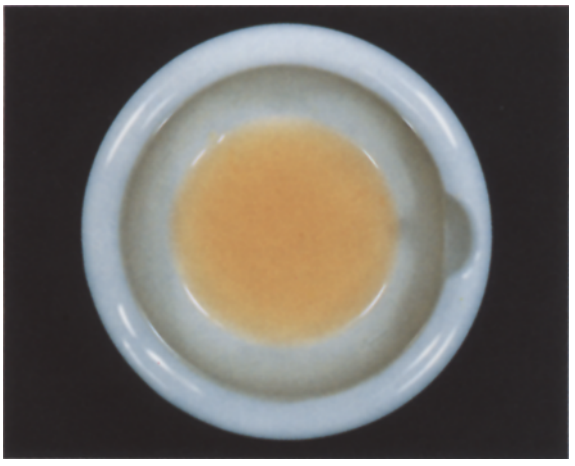

Fig. 1. Cisplatin powder is added to a lipiodol suspension and stirred well to produce a homogenized mixture

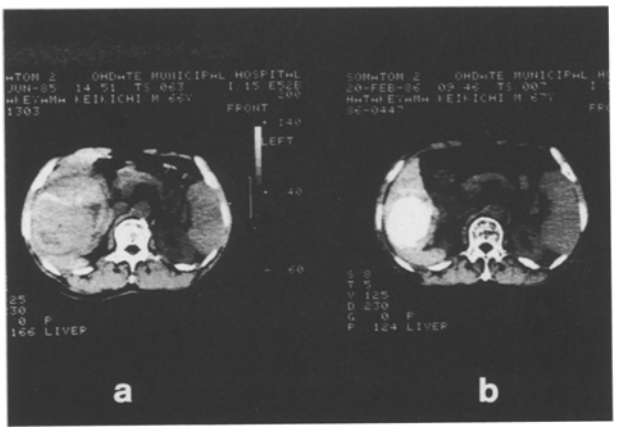

Fig. 2. Before and after the TAE CT of a 60-year-old male patient with hepatocellular carcinoma. **a** An iso-density tumor can be seen on the left-side CT before TAE therapy. **b** A dense accumulation of lipiodol can be seen on the right-side CT after TAE therapy, and the tumor has regressed well

Besides the simple mixture of lipiodol and an anticancer agent, we used a type of lipiodol suspension using aluminum stearate. The lipiodol suspension was prepared by mixing aluminum stearate with lipiodol at high speed, following sterilization. Antitumor agents were added and stirred well to produce a homogenized mixture.

The addition of cisplatin and adriamycin to this mixture produced a homogenized suspension (Fig. 1).

The cisplatin solution was concentrated through evaporation under reduced pressure, crystallized by treating it with 95% ethanol, and filtered through a glass filter to produce cisplatin powder.

Results

The antitumor effects of chemoembolization with the combinations of these embolic materials were represented by the tumor regression rate of the main tumor (Table 2).

Higher rates of tumor regression were obtained with the simple mixture of cisplatin and with cisplatin/adriamycin, indicating that the antitumor effects of these mixtures were greater than those of other mixtures. In this study, 18 of the 77 patients or about 23% of the total showed a regression rate of 50% or more. Among the patients treated with the simple mixture of cisplatin or a cisplatin/adriamycin suspension, 14 of the 46 patients or about 30% showed a regression rate of 50% or more. On the other hand, of those receiving mitomycin C/adriamycin suspension, only 4 of the 31 cases or about 13% showed a regression rate of 50% or more.

The antitumor effect of the therapy on the daughter nodules was also evaluated (Table 3). It can be seen that there was no significant difference among the three protocols, and generally the effect of chemoembolization on the daughter nodules is not significant.

Table 2. Regression rate of main tumor after TAE

Treatment	Patients showing regression rates of				Progress	Total
	100–75%	74–50%	49–25%	24–0%		
Cisplatin/lipiodol simple mixture	4 (13%)	6 (19%)	8 (25%)	11 (34%)	3 (9%)	32 (100%)
Cisplatin/adriamycin lipiodol suspension	2 (14%)	2 (14%)	4 (29%)	4 (29%)	2 (14%)	14 (100%)
Adriamycin/mitomycin C lipiodol suspension	1 (3%)	3 (10%)	13 (42%)	12 (29%)	2 (6%)	31 (100%)

Table 3. Effect of TAE for daughter nodule

Treatment	Regress	No change	Progress	Total
Cisplatin/lipiodol simple mixture	3 (12%)	11 (44%)	11 (44%)	25
Cisplatin/adriamycin lipiodol suspension	1 (11%)	2 (22%)	6 (67%)	9
Adriamycin/mitomycin C lipiodol suspension	3 (18%)	8 (47%)	6 (35%)	17

A representative case was a 60-year-old male patient with a large hepatoma in the right hepatic lobe.

An iso-density mass on the CT was visible, indicating that this was hepatocellular carcinoma. Chemoembolization was performed with a simple mixture of 100 mg cisplatin and lipiodol.

On the post-TAE CT, a dense accumulation of lipiodol was seen at the site of the tumor, which had regressed well (Fig. 2).

Discussion

In recent years, the selection of chemoembolization agents in TAE therapy against hepatocellular carcinoma has been drawing considerable attention.

There are a large number of reports on chemoembolization using adriamycin and mitomycin C, and this method has become an accepted therapy. In our study, we paid attention to the usefulness of cisplatin in the treatment of malignant tumors of the liver [5], and used this drug in its powdered form for chemoembolization against hepatocellular carcinoma, producing very good results [8]. It is noteworthy that our method was superior to the adriamycin and mitomycin C methods in the patients we treated.

A review of various reports shows that most researchers use a single agent in chemoembolization. However, from the standpoint of chemotherapy, combination chemotherapy is desirable. We therefore tested the combinations of cisplatin/adriamycin and adriamycin/mitomycin C in a lipiodol suspension, and found that there is a significant difference in the efficacy of these two combinations, the former being superior.

We shall be continuing with our study on more patients to confirm our results, and hope to provide important information on how to improve the prognosis of patients receiving chemotherapy.

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