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Targeting Chemotherapy for Hepatoma: Arterial Administration of Anticancer Drugs Dissolved in Lipiodol

T. Konno

In targeted cancer chemotherapy, Lipiodol Ultrafluid (Lipiodol) was used as a carrier of anticancer drugs, these drugs were termed as "oily anticancer agents". This arterial injection therapy with oily anticancer agents was performed for 323 patients with hepatoma. Serum alpha-fetoprotein (AFP) levels decreased in 165 (93%) of 177 AFP-positive patients. Reduced tumour size was observed in 210 (regression over 50% in 96 and less than 50% in 114) of 222 evaluable patients with unresectable hepatoma. In patients who preoperatively received a dose of styrene maleic acid neocarzinostatin (SMANCS)/Lipiodol of more than 0.7 mg/cm^2 of maximal cut surface area of the tumour, complete necrosis or necrosis of almost the entire area of tumour was found, and non-cancerous liver tissue and the gallbladder remained unaffected. The survival period of 277 patients with unresectable hepatoma who were treated with oily anticancer agents is thought to be prolonged, especially of 147 patients, excluding those with Child C liver cirrhosis, with tumour occupying all segments of the liver, or with extrahepatic spread. The 1-, 2-, 3-, and 5-year survival rates were 84, 47, 37, and 34%, respectively.
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INTRODUCTION

SURGICAL RESECTION [1], transarterial embolisation [2], bolus or continuous arterial infusion of anticancer agents, and systemic chemotherapy [3] have mainly been used to treat hepatocellular carcinoma (HCC). Because 80% of the patients with HCC had liver cirrhosis and extended spread of the tumour was observed in many patients, about 15% [4] of the patients were candidates for tumour resection, and about 50% [1] of these patients underwent curative resection. Recurrence of the tumour was observed 1 year postoperatively in 50% of the patients who underwent hepatic resection. Therefore, the majority of patients with HCC had received the other treatment modalities just mentioned. However, the results of these treatments were not satisfactory. Clear antitumour activity and reduction of damage to the cirrhotic liver are thought to be essential for successful treatment of HCC. It is thought that targeting of the anticancer agent to the tumour, which results long-lasting, selective high concentrations of the drug in the tumour, may achieve improved results.

A lipid lymphograhic agent, Lipiodol Ultrafluid (lipiodol), has been found to be selectively retained in sites of hepatic tumours and other malignant solid tumours when it is injected arterially [5, 6]. Targeted chemotherapy was attempted by using this characteristic of lipiodol. The form of the dose that is

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Table 1. Patients

	No. of patients
Treated with oily anticancer agents	
Resectable	46
Unresectable	277
Not treated with oily anticancer agents	
Resectable	79
Unresectable	45

required for such therapy with lipiodol as a carrier became clear in experimental studies [7]. The anticancer drugs styrene maleic acid neocarzinostatin (SMANCS) [8], mitomycin, aclarubicin, and doxorubicin were dissolved in lipiodol, and all proved to have essential characteristics for targeting chemotherapy; these drugs were termed "oily anticancer agents" [7]. In this study, SMANCS/lipiodol and/or a mixture of these oily anticancer agents was administered via a catheter in the celiac or the hepatic artery while X-ray monitoring was used, and their anticancer effects against hepatoma and their adverse effects were examined clinically.

PATIENTS AND METHODS

Patients

Patients had clinically established hepatoma on the basis of findings of hepatic angiography, computed tomography (CT), ultrasound, and CT after arterial injection of oily anticancer agents [5, 9], with or without increased serum alpha-fetoprotein (AFP) levels (323 total; 274 males and 49 females between 26 and 81 years old; mean age 58.4 years). The 323 patients were treated by arterial injection of oily anticancer agents. All patients or their families consented to the treatment protocol. Of these patients, 46 had resectable hepatoma and 277 had unresectable hepatoma on the basis of the spread of hepatoma and results of liver function tests, including estimation of indocyanine green (ICG) R_{max} value [10]. After an arterial injection of SMANCS/lipiodol, hepatomas of these 46 patients were resected. HCC was confirmed histologically in 36 patients; in the remaining 10 patients tumours were completely necrotic as seen on sequential slices of tumours. Histological examinations of sequential slices of resected specimens were performed for 29 of these 46 patients.

Histological examinations were performed for 30 of the 277 patients with unresectable hepatoma and all 30 tumours were revealed to be HCC. Of these 277 patients, 271 had liver cirrhosis as diagnosed by clinical findings and liver function tests including the dye (ICG) excretion test, electrophoretic serum analysis, zinc sulphate turbidity test, thymol turbidity test and cephalin–cholesterollecithin flocculation test. 94 were classified as Child A, 121 as Child B, and 56 as Child C. Angiography, CT, ultrasonography, and abdominal plain X-ray examinations were performed routinely to determine the location and size of the tumours. Of the 277 patients with unresectable disease, hepatoma was observed in one segment of the liver in 41 patients, in two segments in 87 patients, and in three segments in 59 patients. Hepatoma was observed in all four segments of the liver or with extrahepatic spread in 90 of the 277 patients (Table 1).

Preparation of oily anticancer agents

SMANCS [8] is a semisynthetic macromolecular compound that consists of an antitumour antibiotic protein, neocarzinostatin, and two chains of synthetic copolymers of styrene and maleic acid. The styrene–maleic acid copolymer exhibits hydrophobic and anionic characteristics, and the conjugated SMANCS retains these properties and becomes soluble in some organic solvents and lipid, including lipiodol. SMANCS/lipiodol was prepared by suspending 1 mg of SMANCS in 1 ml of lipiodol. Mitomycin/lipiodol (4 mg/ml), aclarubicin/lipiodol (12.5 mg/ml), and doxorubicin/lipiodol (2 mg/ml) were prepared by the method described previously [7]. Briefly, the anticancer agent dissolved in an organic solvent was mixed with lipiodol. The solvent was then removed, and aseptic filtration was performed.

Each oily anticancer agent had a homogeneous colour and did not separate into the anticancer agent and lipiodol, even if it was left to stand for 1 year. When the oily anticancer agent was mixed with saline or serum, long-lasting release of anticancer agent from lipiodol to saline or serum was observed [7]. SMANCS/lipiodol (1 mg/ml) was used as the drug of first choice. As the drug of second choice, a mixture of oily anticancer agents was used. Each oily anticancer agent was dissolved in lipiodol, so it was easy to mix each others. Carmustine, originally soluble in oil was added to the mixture. Each millilitre of a mixture of oily anticancer agents contained 0.4 mg of SMANCS, 1.6 mg of mitomycin, 5 mg of ACR (or 0.5 mg of doxorubicin), and 5.5 mg of carmustine.

Administration of agents

Selective or superselective catheterisation of the celiac artery was performed through the femoral artery under fluoroscopy by using Seldinger's method, with a No. 6.5 or 5.5 French preshaped catheter (Cook Inc., Bloomingtom, Indiana, USA) or a Target catheter (Target Therapeutics Inc., San Jose, California, USA).

The 323 patients were given a total of 1010 injections of the drug. Injections were given via the celiac artery (186 times), the common hepatic artery (305 times), the proper hepatic artery (368 times), or the left or right hepatic artery or its distal arteries (161 times). The most suitable artery for injection is the proper hepatic artery. When tumours existed only in the right or left lobe of the liver, the drug was injected in the more peripheral arteries. The drug was injected into the more proximal artery when the catherisation to the proper hepatic artery was impossible or difficult. SMANCS/lipiodol was used as the drug of first choice. For 31 patients with extremely large tumours and 52 patients with tumours that enlarged, not reduced or reduced only somewhat in size, despite administration of SMANCS/lipiodol, the mixture of oily anticancer agents mentioned above was used. Repeated administration of SMANCS/lipiodol alone was performed for 240 patients, and the mixture of oily anticancer agents was administered to the remaining 83 patients. ADR/lipiodol was used in the mixture of oily anticancer agents instead of ACR/lipiodol in 3 patients. Because the safety of injection of the mixture of these agents into the gastroduodenal artery has not been established, the proper hepatic artery or its distal artery was used. The volume of drug given in each dose depended on the size of the tumour and the artery through which it was administered; the volume was from 1 to 12 ml, with the mean of 3.8 ml. The frequency of administration varied from 1 to 12 times, with an average time of 3.5. Total dose for the patients with unresectable hepatoma ranged from 2 to 58 ml per body, with an average volume of 14 ml (9.1 ml/m^2).

The treatment was given once every 3–5 weeks until grade 4 [9] was achieved (grade 4; post-treatment CT showing the

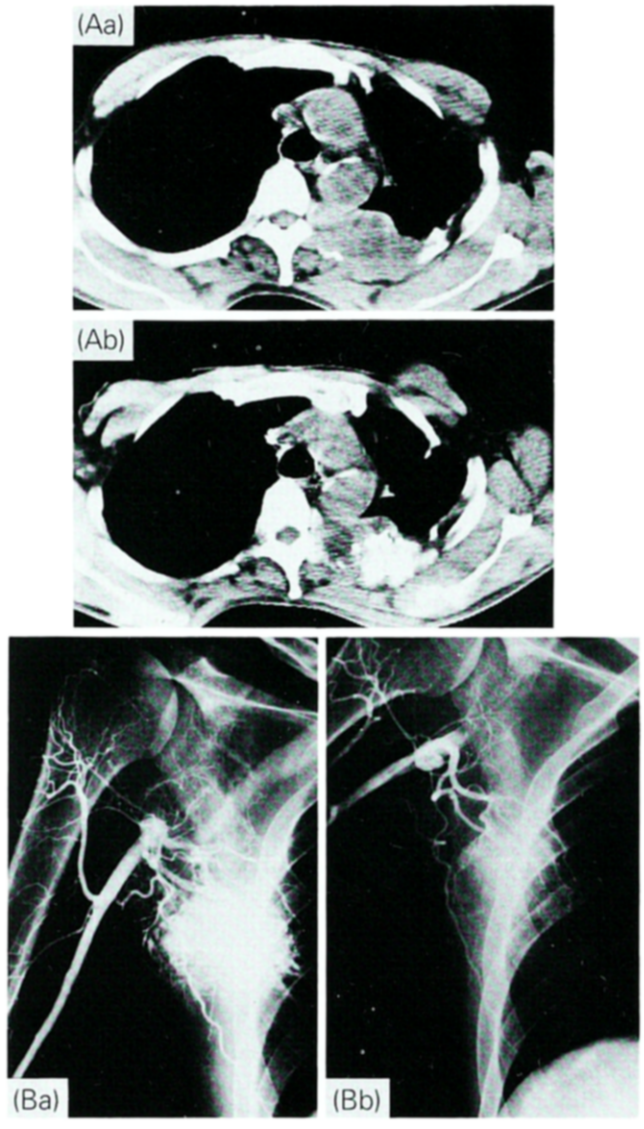

Fig. 1. Treatment of metastatic lesions. (A) Metastasis of hepatoma to the right fourth rib. (Aa) Before administration of drug. (Ab) One week after administration of SMANCS/lipiodol. Lipiodol was retained in the metastatic lesions. (B) Metastasis of hepatoma to the right scapula. (Ba) Angiogram at initial administration of SMANCS/lipiodol. (Bb) One month later, a decrease of vascularity and a reduction in tumour size were observed.

entire area of tumour filled with lipiodol). Thereafter, CT was performed once every 1 to 3 months. If the grade decreased because of washout, additional doses were given to maintain grade 4. The end point was justified by the finding that lipiodol was not increased in tumour on CT after additional injection of oily anticancer agents. For patients with resectable tumours, the drug was given once preoperatively. The time elapsed from administration of the drug to hepatic resection varied from 6 to 120 days, with an average of 33 days. For patients with extrahepatic spread of hepatoma, SMANCS/lipiodol was administered via the feeding arteries of metastatic lesions. For example, it was administered via the bronchial artery for lung metastasis, via the suprarenal artery for metastasis to the adrenal gland, and via the thoracoacrominal artery for metastasis to the scapula (Fig. 1). SMANCS/lipiodol and the other oily anticancer agents were not administered for cerebral or skin metastasis.

Evaluation of treatment response

The tumour response was evaluated by changes in the AFP level and in the size of the tumour. The histological response was assessed by examination of sequential slice of the operatively resected specimen after a single injection of SMANCS/lipiodol.

The duration of survival after the first treatment was calculated for the patients with unresectable hepatoma who were, treated by arterial injection of oily anticancer agents. For comparison, survival was also calculated for the 79 patients whose tumours were operatively resected in the same period, and for 45 patients with unresectable hepatoma who received conventional therapies such as arterial continuous infusion chemotherapy with or without ligation of the hepatic artery. For infusion chemotherapy, 5-fluorouracil (5FU) (250–500 mg/day) after one shot injection of mitomycin C (0.25 to 0.5 mg/kg of body weight) were used as long as the patients could tolerate the chemotherapy. Total dose of 5FU ranged from 750 to 32500 mg per body, with an average dose of 6786 mg. The Kaplan and Meier method and the log-rank test were used for analysis of survival.

RESULTS

Selective accumulation of lipiodol in the tumour

Selective retention of lipiodol was clearly demonstrated on the plain abdominal X-ray film and the CT scan after arterial administration of oily anticancer agents. The satellite nodules in which lipiodol remained on CT after administration of oily anticancer agents were larger than 2 mm in diameter. This phenomenon was proved also by low KVP X-ray films (Softex Instrument; Japan Softex Co., Osaka, Japan) of the resected specimens.

Tumour response

Tumour marker. AFP levels were 100 ng/ml or more (AFP positive) in 192 of the 323 patients, less than 100 ng/ml in 121 patients, and unknown in 10 patients. Sequential changes in this factor were analysed for 177 of 192 AFP positive patients; patients who did not undergo assay before or after arterial injection therapy and those with marked extrahepatic metastases were excluded. Changes in AFP levels of the patients with resectable hepatoma were calculated by comparing with AFP value before administration of only anticancer agents and that before hepatic resection. The AFP level fell in 165 (93%) of these 177 patients after arterial injection therapy, did not change in 3 (2%), and rose in 9 (5%). In the 25 patients who were initially treated with SMANCS/lipiodol and then with the mixture of oily anticancer agents, a significant decrease in AFP level was observed after administration of the mixture of agents compared with that of SMANCS/lipiodol alone (Fig. 2).

Histological tumour response. The histological tumour response was tended to be related to the dose of the agent and the size of the tumour. Necrotic changes in tumour cells occurred throughout the whole tumour in patients receiving about 0.7 mg/cm^2 or more of SMANCS/lipiodol for the maximal cross-sectional area of tumour; some patients had complete tumour necrosis (Table 2). These necrotic changes occurred not only in primary tumours but also in daughter nodules.

Tumour size. The size of the tumour could be measured by angiography and CT before and after arterial injection therapy in 222 of the 277 patients with unresectable hepatoma. For evaluation of tumour size, products of the longest perpendicular diameters were used. The tumour regressed in 210 (94%) of

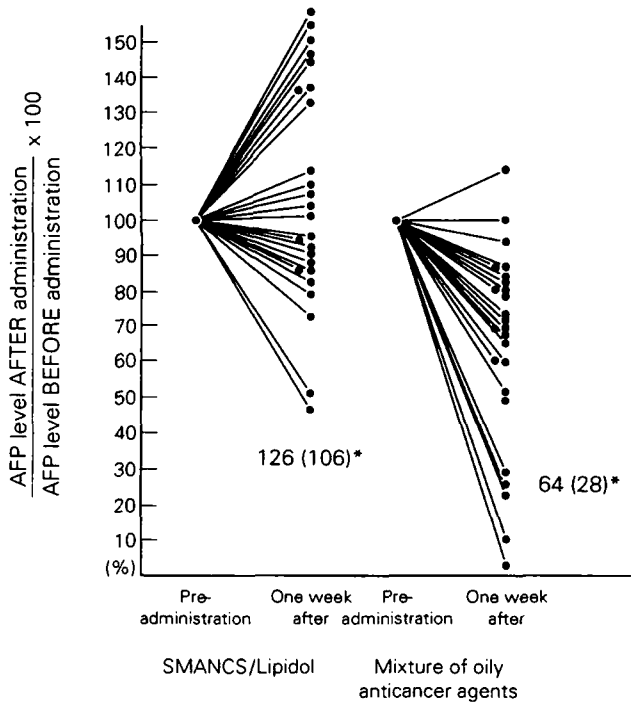

Fig. 2. Changes in AFP level of 25 AFP-positive patients who were treated initially with SMANCS/lipiodol and then with the mixture of oily anticancer agents. The AFP level decreased significantly ($P < 0.01$) after injection of the mixture compared with SMANCS/lipiodol in 25 patients. *Mean (S.D.).

Table 2. Relationship of tumour necrosis to dose of anticancer agent

	< 10% necrosis	10–50% necrosis	50–99% necrosis	Total necrosis
No. of patients	4	8	10	7
Dose of SMANCS per maximal cut surface of tumour (mg/cm²)	0.11 (0.09)*	0.14 (0.08)	0.24 (0.28)	0.72 (0.41)

*Mean (S.D.).

these 222 patients (regression over 50% in 96 and less than 50% in 114), did not change in 6 (3%), and grew in 6 (3%). The degree of reduction in tumour size and the time required for reduction are shown in Fig. 3. Almost all tumours were reduced to less than 50% of the original size 1 year after the initial administration of drug. In 35 out of 41 patients whose tumours shrank to less than 10% of initial size, follow up of size of tumour over 1 year after shrinkage (ranged from 1 to 5 years with an average of 2.2 years) could be done. All these tumours did not regrow, so such tumours were considered to be cured (Figs 3 and 4). The reduction in tumour size was observed not only in the primary tumour but also in daughter nodules and in tumours that had developed in the portal vein and the bile duct. A longer period was needed for reduction in size of larger tumours than smaller ones. Frequent administration was necessary for treatment of the larger hepatoma. While these treatments continued, it was frequently observed that new small lesions in other parts of the liver became clear and that these small

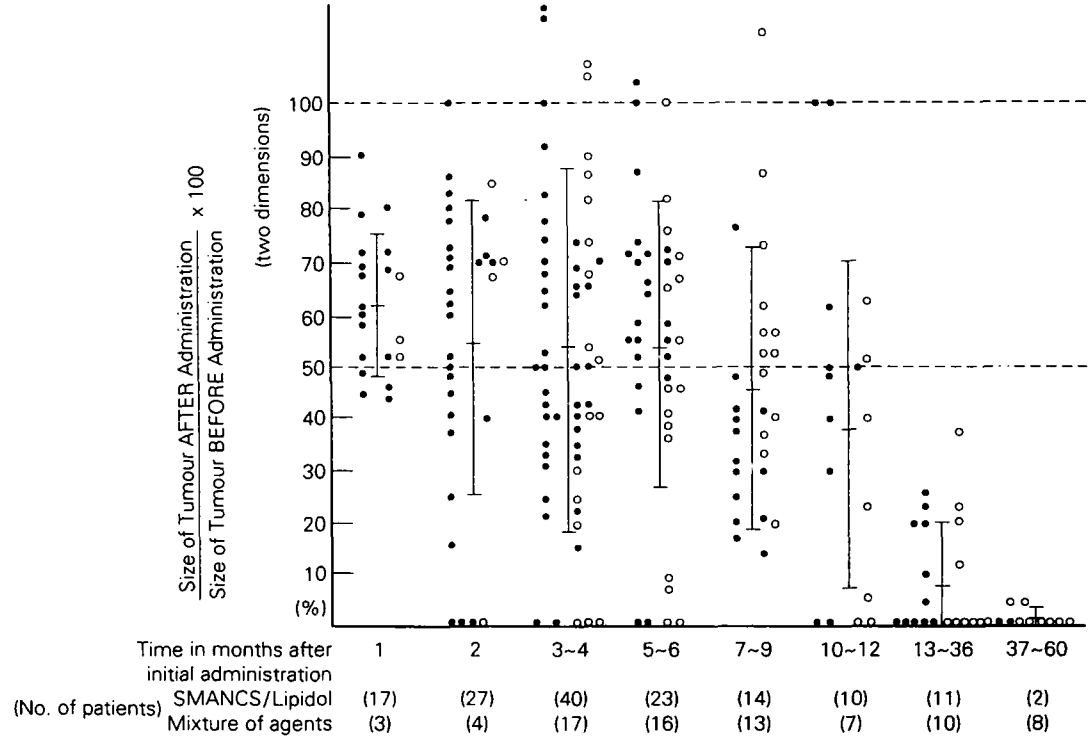

Fig. 3. Changes in tumour size after arterial administration of oily anticancer agents in patients with unresectable hepatoma. Changes in tumour size for each patient were evaluated at various times after treatment; ● = patient treated with SMANCS/lipiodol; ○ = patient treated with the mixture of oily anticancer agents. Unresectable evaluable 222 patients. Tumour size: reduced, 210 (94.6%); unchanged, 6 (2.7%); enlarged 6 (2.7%).

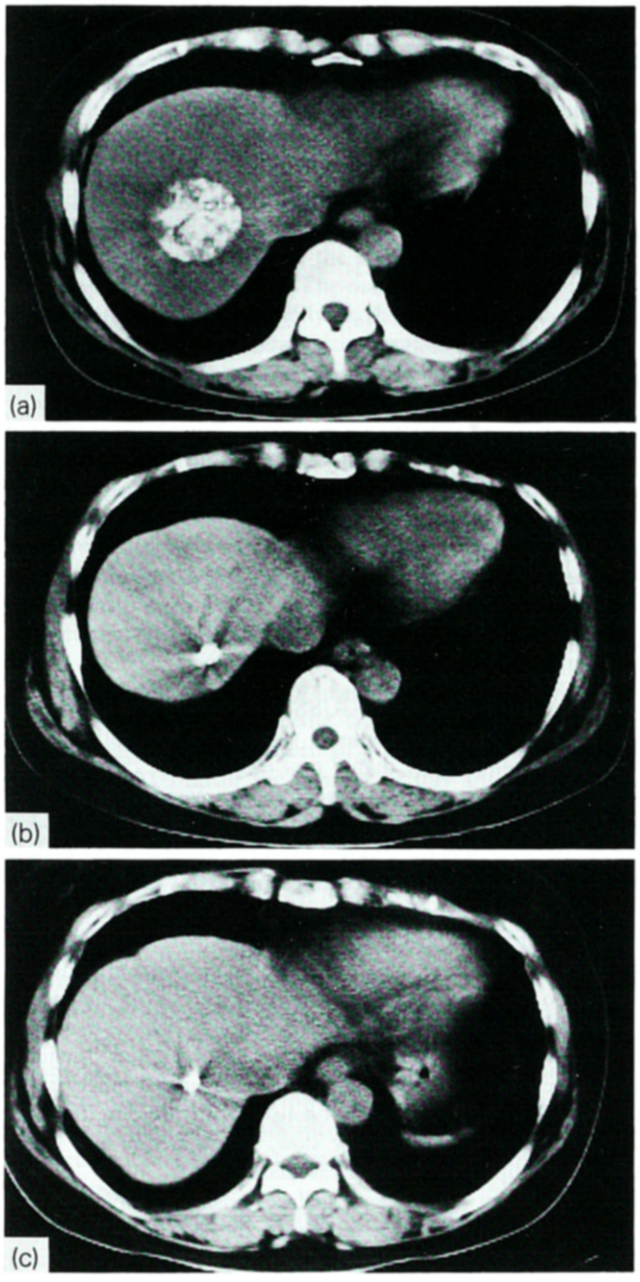

Fig. 4. Patients considered to be cured. (a) CT scan, 7 days after initial administration. (b) CT scan, 13 months after first dose. The mixture of oily anticancer agents was given six times during this period. (c) CT scan, 36 months after initial administration. The patient is alive and well 5 years after the initial dose.

lesions, which were thought to show intrahepatic metastasis or multicentric development of hepatoma, disappeared in a short period (Fig. 5). If the tumour grew despite treatment with SMANCS/lipiodol, we used the mixture of oily anticancer agents. These enlarged tumours decreased in size after injection of the mixture (Figs 4 and 5).

Survival of patients with unresectable hepatoma.

Survival of patients with unresectable hepatoma after arterial injection treatment varied according to the extent of hepatoma and the severity of liver cirrhosis. The 50% survival period of 277 patients with unresectable hepatoma, as calculated by the Kaplan-Meier method, was 15.3 months for arterial injection of

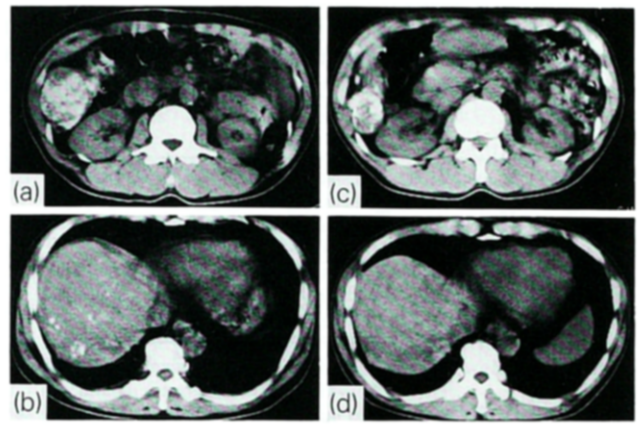

Fig. 5. Treatment of new lesions in the liver. (a) CT scan, 7 days after initial administration of drug. (b) CT scan, 14 months after the first dose. New lesions in the right upper parts of the liver were observed. Because the primary tumour was not reduced in size, the drug was changed to the mixture. (c,d) CT scans, 24 months after treatment with the mixture, the primary tumour was reduced in size, and new small lesions had disappeared.

oil anticancer agents, whereas it is 1.3 months for the conventional palliative therapies (n = 45) that we have used (Fig. 6a).

In 147 patients excluding patients with liver cirrhosis of Child C classification, with the tumour occupying all four segments of the liver or with extrahepatic spread, the 1-, 2-, 3-, and 5-year survival rates were 84, 47, 37, and 34%, respectively. Of these 147, in 30 patients having a tumour within one segment, survival of 13 patients treated with the mixture of oily anticancer agents was not significantly different from that of 17 patients treated with SMANCS/lipiodol alone. In the remaining 117 patients, survival of 49 patients treated with a mixture of oily anticancer agents was significantly better than that of 68 patients treated with SMANCS/lipiodol alone (Fig. 6b). The survival rate of these 147 patients treated with SMANCS/lipiodol and/or the mixture of oily anticancer agents is thought to be better than that of the patients whose tumour was operatively resected and better than that of patients treated with conventional palliative therapies (Fig. 6c).

Side effects

Side effects of arterial administration of SMANCS/lipiodol and the mixture of oily anticancer agents are shown in Table 3.

The major adverse reaction fever, which occurred in about half of the patients receiving the therapy. Fever was often accompanied by chills and shivering. The body temperature rose to 38–39°C in many patients, but this elevation lasted only for the day of the treatment. About 11% of the patients reported mild pain in the epigastrium. The pain occurred immediately after the arterial injection and generally eased or disappeared within 15 minutes. Hepatic function tests showed elevated aspartate aminotransferase (AST) levels in 16% of the patients and elevated alanine aminotransferase (ALT) levels in 10%. Both changes were mild and transient. The total bilirubin level rose in 14% of the patients and fell in 11%. There was virtually no bone marrow suppression, and about a half of the patients showed leukocytosis. Gastric erosion or ulcers, which might have been caused by arterial injection of SMANCS/lipiodol, were observed in a few patients, but cholecystitis and other adverse effects on the gallbladder were not observed in patients receiving these injections.

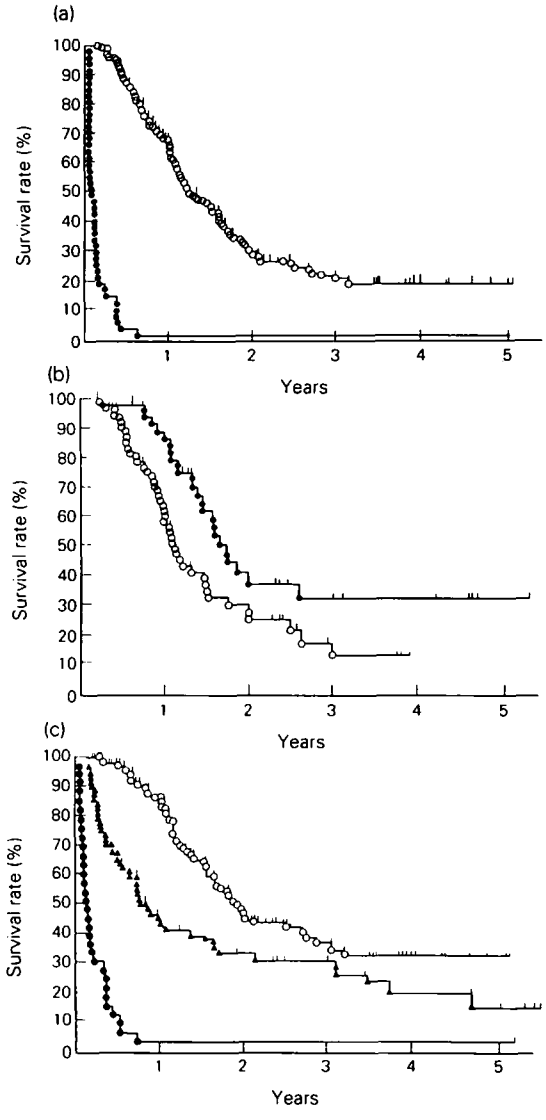

Fig. 6 (a). The survival rate of patients with unresectable hepatoma. ○–○: Survival of 277 patients who were treated with oily anticancer agents. ●–●: Survival of 46 patients who were treated with conventional palliative therapies. Survival after treatment with oily anticancer agents was significantly better than survival after treatment with conventional palliative therapies ($P < 0.01$). (b) The survival rate of patients with unresectable hepatoma occupying two or three segments of the liver and with liver cirrhosis of Child A or B class. Patients were classified according to the drugs administered: SMANCS/lipiodol alone (○–○) or the mixture of oily anticancer agents (●–●). Survival after treatment with the mixture was significantly better than that after treatment with SMANCS/lipiodol alone ($P < 0.05$) at 1.6 years. (c) The survival rate of patients with resectable or unresectable hepatoma. ○–○: Survival of patients with unresectable hepatoma who were treated with oily anticancer agents. Of 147 patients total, all had liver cirrhosis, of which 73 were classified as Child A and 74 as Child B. Hepatoma was observed in one segment in 30 patients, in two segments in 70, and in three segments in 47. ▲–▲: Survival of patients whose tumours were resected. Of 79 patients total, 59 had liver cirrhosis, of which 56 were classified as Child A and 3 as Child B. Hepatoma was observed in one segment in 46 patients, in two segments in 26, and in three segments in 7. ●–●: Survival of patients with unresectable hepatoma who were treated with conventional palliative therapies. Of 34 patients total, 33 had liver cirrhosis, of which 22 were classified as Child A and 11 as Child B. Hepatoma was observed in one segment in 5 patients, in two segments in 16, and in three segments in 13. Survival after treatment with oily anticancer agents was significantly better than survival after resection ($P < 0.01$) at 1 year and after palliative therapies ($P < 0.01$).

Table 3. Side effects of arterial administration of oily anticancer agents

Effect	No. of patients (%)		
	Total	SMANCS/lipiodol	Mixture of oily anticancer agents
Fever*	426/907 (47)	332/697 (48)	94/210 (45)
Pain†	104/910 (11)	89/707 (13)	15/203 (7)
Laboratory data‡			
AST elevation	137/837 (16)	125/642 (19)	12/195 (6)
ALT elevation	81/837 (10)	73/644 (11)	8/193 (4)
Bilirubin			
Elevation	113/780 (14)	101/595 (17)	12/185 (6)
Decrease	88/780 (11)	57/595 (10)	31/185 (17)
WBC			
Increase	345/688 (50)	246/521 (47)	99/167 (59)
Decrease	127/688 (18)	103/521 (20)	24/167 (14)

*Body temperature of 38–39°C; transitory for 1–2 days.
†Transitory for 15 min.
‡All changes were transitory.

DISCUSSION

Selective retention of lipiodol was observed in all patients with a hepatoma larger than 2 mm in diameter, "vascularised tumour" having its own neovasculature as mentioned by Folkman [11]. Selective accumulation of lipiodol in the tumour occurs because of early removal from the normal blood vessels and retention in the neovasculature and extravascular space in the tumour. An experimental study with ^{131}I-labeled lipiodol showed that the radioactivity in the tumour tissue was several thousand times higher than that in the blood 1 week after dosing [12]. The combination of the neovasculature, with its special characteristic, and the physical properties of lipiodol may contribute to selective retention of lipiodol in the tumour. Anatomically, the neovasculature lacks a muscle layer and innervation; therefore, functionally it cannot constrict. In addition, the flow of blood in it is thought to be slow. These factors may cause retention of lipiodol in the neovasculature.

The viscosity (45 cp) and surface tension of lipiodol may contribute to its selective retention; the size of the lipiodol particles is thought to be important as well. Experimentally and clinically, retention of lipiodol in the tumour did not occur after arterial injection of an emulsion of lipiodol in aqueous solution, in which the size of lipiodol particles was less than about 1–2 μm, but lipiodol was retained in the normal parenchyma of the liver (data not shown). Other factors participating in selective retention may be the increased permeability of the neovasculature and poorly developed reticuloendothelial system (RES) in the tumour. If lipiodol leaks into the extravascular space because of this increased permeability or because of necrosis of the tumour, lipiodol may be retained in the tumour for a long time. As mentioned above, selective retention of lipiodol can be easily achieved by arterial injection. To deliver anticancer drugs selectively to the tumour with lipiodol as a carrier, the following conditions are necessary: (1) the anticancer drugs must be dissolved or dispersed in lipiodol and (2) the drugs must become separated from lipiodol while lipiodol remains selectively in the tumour [7, 13].

Because lipiodol is an oil, anticancer drugs dissolved in it are protected from various hydrolytic enzymes, which would

inactivate or destroy the drugs. Anticancer drugs that become separated from lipiodol have anticancer effects. The separated drugs may be inactivated quickly, but the release of anticancer drugs from the oily anticancer agents continues for a long time [13]. Therefore, these oily anticancer agents have prolonged anticancer effects. Lipiodol acts like a reservoir of anticancer drug in the tumour.

In addition, lipiodol itself disturbs blood flow in the neovasculature by virtue of its retention. In a separate study [14], we found that the disturbance of the blood flow by lipiodol alone had some antitumour effect. The marked anticancer activity of arterial injection therapy of oily anticancer agents is thought to be due to targeting of anticancer drugs to the tumour, long-lasting anticancer effects, and peripheral blood flow disturbance.

Not only the combined effect of multiple anticancer agents but also the difference in the time of release of each drug from lipiodol may contribute to the antitumour activity of the mixture of oily anticancer agents. Namely, mitomycin diffused out completely from lipiodol to surrounding tumour tissues in 4 days, resulting in a high concentration in the tumour, and aclarubicin continued to diffuse out over 2 months [7], resulting in long-lasting antitumour activity. In experimental studies using rabbits bearing VX2 carcinoma sized 10–20 mm in diameter in the liver, complete necrosis of the tumour observed in 25% of the rabbits received an injection of 0.2 ml of SMANCS/lipiodol via the proper hepatic artery. Meanwhile complete necrosis was observed in over 80% of the rabbits received a injection of 0.05 ml of the mixture of oily anticancer agents (data not shown).

Because of the targeting of anticancer agents, the dosage of the drugs could be reduced and minimal adverse effects could be achieved. The combination of clear-cut antitumour activity and minimal damage to the liver is thought to prolong survival.

A curious result, that the survival rate of patients with unresectable hepatoma was better than that of the patients with resectable hepatoma, was noted. About 30% of the latter patients died within 3 months after resection, mainly from hepatic failure, and half of the remaining patients died of recurrence of hepatoma within 2 years. However, few patients given arterial injection therapy of oily anticancer agents died within 3 months, and recurrent lesions could be treated by frequent administration of the drug.

Clinically, antitumour activity of arterial injection therapy with oily anticancer agents against hepatoma is confirmed on the basis of the decrease in AFP level, microscopic findings of the removed specimens, reduction in tumour size, and prolonged survival of patients with unresectable tumours.

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