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Combination therapy with S-1 and interferon-α in hepatocellular carcinoma patients with lung metastasis

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Abstract. Managing extrahepatic recurrence in hepatocellular carcinoma (HCC) patients is crucial for improving prognosis. The present study aimed to investigate the effectiveness of using combination therapy with S-1 and interferon (IFN)-α in HCC patients with lung metastasis. Of the 646 patients who underwent radical surgery for HCC at our institute, 62 developed their first distant metastasis in the lung. Among these patients, 11 received S-1 combination therapy, while the remaining 51 patients received other conventional therapy, such as 5-fluorouracil and cisplatin or best supportive care. We retrospectively evaluated the toxicity and efficiency of combination therapy with S-1 and IFN-α. Hematological toxicity was observed in 5 patients and was grade 1 or 2 in all cases, except 1 patient (9.1%) who developed grade 3 leukopenia. Non-hematological toxicity was observed in 6 patients and was grade 1 in all cases, except 1 patient who exhibited a grade 2 increase of serum bilirubin levels. No patient required discontinuation of the S-1 combination therapy and no treatment-related mortality was reported during this study. Patients who received S-1 treatment exhibited significantly better survival after distant recurrence (SADR) compared to those without S-1 treatment (3-year survival rate, 81.8 vs. 43.1%, respectively; P=0.014). The multivariate analysis revealed that the S-1 treatment was prognostically significant for SADR (P=0.0091; hazard ratio = 0.343). In conclusion, combination therapy with S-1 and IFN-α may be efficient for HCC patients with lung metastasis.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common type of cancer, with >600,000 new cases reported annually (1). HCC is the third highest cause of cancer-related mortality and its incidence is increasing in the United States and Europe. Recent advancements in diagnostic modalities and efficient locoregional treatments, such as repeated hepatectomy, transcatheter arterial embolization and radiofrequency ablation, have led to improvements in intrahepatic recurrence control and prognosis (2-5). However, due to the advances in intrahepatic treatment, extrahepatic recurrence is more frequently observed. Extrahepatic metastasis is difficult to control and the prognosis remains poor; thus, it is becoming increasingly important to efficiently manage such metastases in order to improve patient outcome (6,7).

In 2008, it was first demonstrated that sorafenib may improve prognosis in patients with significantly advanced HCC (8); however, this agent was not found to be adequately effective, particularly in patients with lung metastasis (9). Lung and bone are two major sites of distant recurrence in HCC patients. Pulmonary metastastectomy is reportedly effective in certain cases with lung recurrence (10,11); however, the majority of the cases are not candidates for resection due to numerous metastatic lesions in the lungs and/or other organs. Thus, it is crucial to establish an effective regimen of systemic chemotherapy for HCC patients with lung metastasis.

In our institute, we have used combination chemotherapy with intra-arterial infusion of 5-fluorouracil (5-FU) and subcutaneous interferon (IFN)-α injection for patients with advanced HCC with portal vein tumor thrombosis (PVTT) and have reported the clinical benefits of this protocol (12,13). Recently, we used combination therapy with oral S-1 (rather than intra-arterial infusion of 5-FU) and IFN-α subcutaneous injection as systemic therapy for patients with extrahepatic metastases (14). S-1 is a novel oral combination anticancer drug consisting of tegafur and two modulators: 5-chloro-2,4-dihydroxypyrimidine and potassium oxonate (15). Following oral administration, this agent reportedly selectively accumulates in gastrointestinal tissues and suppresses the gastrointestinal toxicity induced by the phosphoribosylation of 5-FU in the gastrointestinal tract, without compromising the antitumor activity. S-1 is widely used in Japan for the treatment of several gastrointestinal malignancies, with good reported outcomes (16-19).

In the present study, we aimed to determine the feasibility of combination therapy with S-1 and IFN-α in HCC patients with lung metastasis, who are not likely to benefit significantly from sorafenib treatment. We also investigated the efficacy of S-1 combination therapy by evaluating the prognosis of the

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patients who received S-1 combination therapy compared to that of patients treated with other chemotherapeutic protocols or best supportive care.

Patients and methods

Background. This study was performed retrospectively. Between 1980 and 2007, 646 HCC patients underwent radical resection in our institute. The patients included 525 men and 121 women, with a mean age ± SD of 61.9±9.40 years. Of the 646 patients, 237 only had hepatitis B, 257 only had hepatitis C, 85 had both hepatitis B and C and the remaining 67 patients had no viral infection. According to the Child-Pugh classification, 565 patients were scored as A and the remaining 81 patients as B. All the patients underwent pathologically complete (R0) resection The 3-year and 5-year survival rates for all the patients were 75.6% and 62.4%, respectively. All the patients were regularly followed up for 52.4±44.4 months (range, 1.2-248.2 months) in our department. Of the 646 patients, 483 developed postoperative HCC recurrence [intrahepatic recurrence in 372 (57.6%) and extrahepatic recurrence, with or without intrahepatic lesions, in 111 patients (17.2%)], while 163 patients (25.2%) had no recurrence.

The study protocol was approved by the Human Ethics Review Committee of Osaka University and a signed informed consent form was obtained from each subject.

HCC lung metastasis treatment. Lung metastasis was diagnosed using a combination of imaging techniques, such as computed tomography and magnetic resonance imaging; histopathological findings, such as fine-needle biopsy; and the levels of tumor markers, such as serum α-fetoprotein and serum protein induced by vitamin K absence or antagonist-II. Pulmonary resection was indicated only when the metastatic lesions were limited to the lung and intrahepatic lesions were absent or controllable. In all other cases, systemic chemotherapy was performed based on the following criteria, as previously reported (14): Patients were required to be aged 20-75 years, with an Eastern Cooperative Oncology Group performance status of ≤2, a life expectancy of ≥12 weeks, measurable or assessable disease, adequate bone marrow function (hemoglobin concentration ≥8.0 g/dl, leukocyte count 2,500-12,000/μl and platelet count ≥80,000/μl) and adequate hepatic and renal reserve (total bilirubin ≤1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase ≤100 IU/l, blood urea nitrogen ≤30 mg/dl and serum creatinine ≤1.5 mg/dl).

Patient enrollment. Among the 111 patients with extrahepatic recurrence, with or without intrahepatic recurrence, lung metastasis was observed as the first distant metastasis in 62 patients; these patients were enrolled in the present study. The patient characteristics are reported in Table I. The patients included 46 men and 16 women, with a mean age ± SD of 60.3±10.5 years. A total of 13 patients only had hepatitis B, 26 only had hepatitis C, 12 had both hepatitis B and C and 11 had no viral infection. The average resected tumor size at primary surgery was 66.8±46.3 mm and histopathological grading revealed poorly, moderately and well-differentiated HCC in 48, 12 and 2 patients, respectively. Vascular invasion was observed in 25 patients (portal vein invasion in 17, hepatic vein invasion in 2 and both portal and hepatic vein invasion in 6 patients). Primary recurrence was manifested as an intrahepatic lesion in 42, lung lesion in 16 and both intrahepatic and lung lesions in 4 patients. The average disease-free interval (DFI) for all enrolled patients was 11.1±14.8 months,

Table I. Characteristics of enrolled patients.

Characteristics	Total (n=62)
Age, years (mean ± SD)	60.3±10.5
Gender	
Female	16
Male	46
Viral infection	
HBV	13
HCV	26
Both	12
None	11
Child-Pugh score	
A	56
B	6
C	0
Serum AFP level, ng/ml	
<400	34
≥400	28
Serum PIVKA II level, mAU	
<1,000	28
≥1,000	34
Tumor size, mm (mean ± SD)	66.8±46.3
Histological differentiation	
High	2
Moderate	12
Poor	48
Vascular invasion	
+	25
-	37
Primary site of recurrence	
Liver	42
Lung	16
Both	4
DFI, months (mean ± SD)	11.1±14.8
DRFI, months (mean ± SD)	16.2±22.4
Pulmonary resection	
+	2
-	60
S-1 treatment	
+	11
-	51

HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; PIVKA II, protein induced by vitamin K absence or antagonist-II; DFI, disease-free interval; DRFI, distant recurrence-free interval.

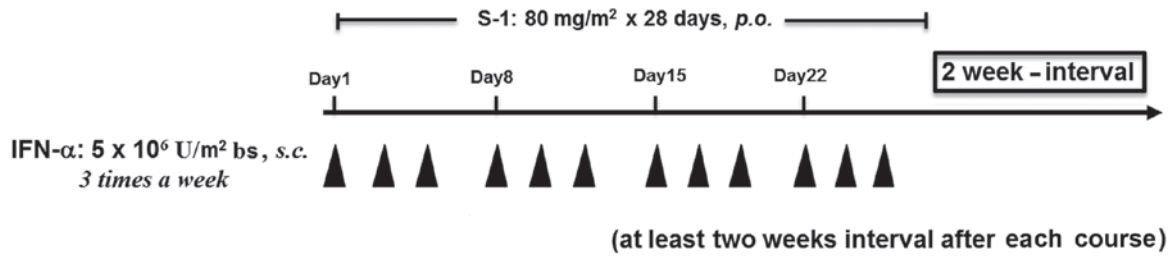

Figure 1. Schema of combination therapy with S-1 and interferon (IFN)-α. S-1 was administered orally twice daily after a meal at a total dose of 80 mg/m^2 bs. IFN-α was injected subcutaneously at a dose of 5x10^6 units (5 MU)/m^2 bs on days 1, 3 and 5 of each week. One course consisted of consecutive administration for 28 days, followed by ≥14 days of rest. The non-steroidal anti-inflammatory drug diclofenac sodium was administered prior to IFN-α injection to alleviate fever, which is a common adverse effect of IFN-α. p.o., *per os*; bs, body surface; s.c., subcutaneously.

while the distant recurrence-free interval (DRFI), defined as the period from primary surgery to the appearance of distant metastasis, was 16.2±22.4 months. S-1 treatment was administered to 11 patients (S-1 treatment group), while the remaining 51 patients (non-treatment group) received other systemic chemotherapy with a traditional regimen, such as the combination of adriamycin, 5-FU and cisplatin (CDDP). The criteria for S-1 treatment were almost identical to those for other chemotherapeutic regimens and the 51 patients who did not receive S-1 treatment were analyzed as a historical control. Two patients underwent pulmonary metastastectomy and did not receive S-1 treatment.

Schedule of S-1/IFN treatment. Combination therapy with S-1 and IFN was performed as previously reported (14). S-1 (Taiho Pharmaceutical, Tokyo, Japan) was administered orally twice daily after a meal at a total dose of 80 mg/m^2 body surface. Three initial doses of S-1 were established according to body surface area as follows: <1.25 m^2, 80 mg/day; 1.25-1.5 m^2, 100 mg/day; and ≥1.5 m^2, 120 mg/day. IFN-α (OIF; Otsuka Pharmaceutical, Tokyo, Japan) was injected subcutaneously at a dose of 5x10^6 units (5 MU)/m^2 body surface on days 1, 3 and 5 of each week. One course consisted of consecutive administration for 28 days, followed by ≥14 days of rest. The combination treatment schedule is summarized in Fig. 1. The non-steroidal anti-inflammatory drug diclofenac sodium was administered prior to IFN-α injection to alleviate fever, which is a common adverse effect of IFN-α.

Statistical analysis. Data are expressed as mean ± SD. Differences in continuous variables were evaluated by the Student's t-test. The Fisher's exact probability test was used to compare discrete variables. The DFI, DRFI and survival after distant recurrence (SADR) rates were estimated with the Kaplan-Meier method and compared using the log-rank test. The Cox's proportional hazard regression model with stepwise comparisons was used to analyze independent prognostic factors. P<0.05 was considered to indicate a statistically significant difference.

Results

Feasibility of S-1 treatment. We evaluated the toxicity of S-1 treatment according to the National Cancer Institute-Common Toxicity Criteria for Adverse Events, version 3.0 (http://ctep.cancer. goc/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf) by determining blood counts and biochemical profiles at least once every 2 weeks and monitoring patients for the occurrence of non-hematological toxicities, such as general fatigue, fever, nausea/vomiting, diarrhea, skin pigmentation, hand-foot syndrome and, particularly, depression. Hematological toxicity was observed in 5 patients (3 patients had thrombocytopenia, 2 had leukocytopenia and 1 had anemia). Toxicity >grade 3 was observed in only 1 patient (9.1%), who developed leukocytopenia but did not require withdrawal or dose reduction of either drug. Non-hematological toxicities were observed in 6 patients (4 patients had fever, 3 had increased serum bilirubin levels, 3 had general fatigue and 1 had dermatitis). All non-hematological toxicities were grade 1, except 1 patient (9.1%) with a grade 2 increase of serum bilirubin levels. There was no need for discontinuation of the combination therapy and no treatment-related mortality was reported during this study.

Differences of characteristics between the S-1 treatment and non-treatment groups. The characteristics of the S-1 treatment and non-treatment groups are summarized in Table II. There were no significant between-group differences in gender, age, viral infection status, or Child-Pugh classification. The average size of primary HCC in the S-1 treatment group was 84.4±35.7 mm and histopathological grading revealed that all HCCs were poorly differentiated and 6 were vascular invasion-positive. In the non-treatment group, the average primary HCC size was 63.0±47.7 mm and histopathological grading revealed that the HCCs were poorly, moderately and well-differentiated in 37, 12 and 2 patients, respectively, with 19 cases being vascular invasion-positive. In the S-1 treatment group, the DFI was 8.8±6.8 months and the DRFI was 14.9±11.2 months, while the DFI and DRFI of the non-treatment group were 11.6±16.1 and 16.5±24.3 months, respectively. These intervals did not significantly differ between groups. The Kaplan-Meier analysis also revealed no significant between-group differences in DRI or DRFI (Fig. 2). Pulmonary resection was performed in 2 patients who did not receive S-1 treatment.

Effect of S-1 treatment. SADR was higher among patients who received S-1 treatment compared to that in patients without S-1 treatment. All the patients in the S-1 treatment group survived for >1 year, with a 3-year survival rate of 81.8%, while the 1-year and 3-year survival rates in the non S-1 treatment group were 58.8 and 43.1%, respectively; this between-group difference was significant (P=0.0141) (Fig. 3).

Table II. Comparison of characteristics between S-1 treatment and non-treatment groups.

Characteristics	S-1 (n=11)	Non-S-1 (n=51)	P-value
Age, years	62.4±9.4	59.9±10.8	0.479
Gender			0.162
Female	1	15	
Male	10	36	
Viral infection			0.712
HBV	5	21	
HCV	1	12	
Both	3	9	
None	2	9	
Child-Pugh score			0.942
A	10	46	
B	1	5	
C	0	0	
Serum AFP level, ng/ml			0.189
<400	8	26	
≥400	3	25	
Serum PIVKA II level			0.175
<1,000	7	21	
≥1,000	4	30	
Tumor size, mm	84.4±35.7	63.0±47.7	0.167
Histological differentiation			0.142
High	0	2	
Moderate	0	12	
Poor	11	37	
Vascular invasion			0.289
+	6	19	
-	5	32	
Primary site of recurrence			0.781
Liver	8	34	
Lung	2	14	
Both	1	3	
Disease-free interval, months	8.8±6.8	11.7±16.0	0.569
Distant recurrence-free interval, months	14.9±11.2	16.5±24.3	0.831
Pulmonary resection			0.504
+	0	2	
-	11	49	

HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; PIVKA II, protein induced by vitamin K absence or antagonist-II.

Of the 11 patients receiving S-1 treatment, 1 case exhibited a good response to S-1 combination therapy and the multiple lung metastases almost disappeared. To date, the patient has survived for >5 years while receiving continuous S-1 therapy, although some relapse has appeared (Fig. 4).

Univariate and multivariate analysis of factors associated with SADR. We investigated the prognostic significance of various clinicopathological factors in HCC patients with lung metastasis and only treatment with S-1 was found to be of prognostic significance for SADR in the univariate and multivariate analysis (P=0.018 and 0.0091, respectively). Child-Pugh score and venous invasion by the primary liver lesion exhibited marginal significance in both analyses (Table III).

Discussion

Pulmonary metastasis is the most common type of extrahepatic recurrence of HCC (20,21). We previously reported that ~9% of patients undergoing radical surgery for HCC developed

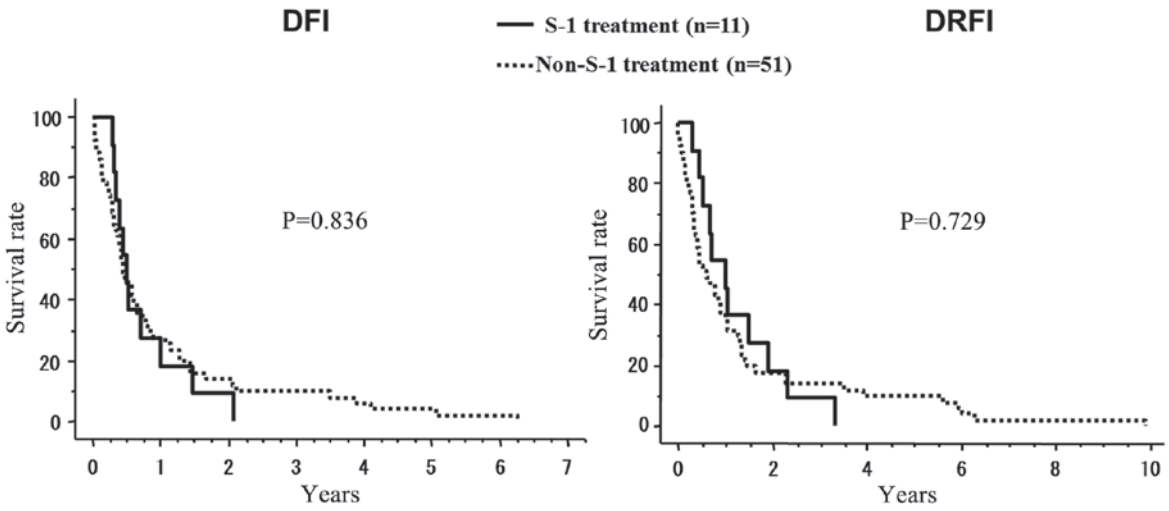

Figure 2. Kaplan-Meier method and log-rank test for disease-free interval (DFI) and distant recurrence-free interval (DRFI). There was no significant difference in DFI or DRFI between the S-1 and non-S-1 treatment groups.

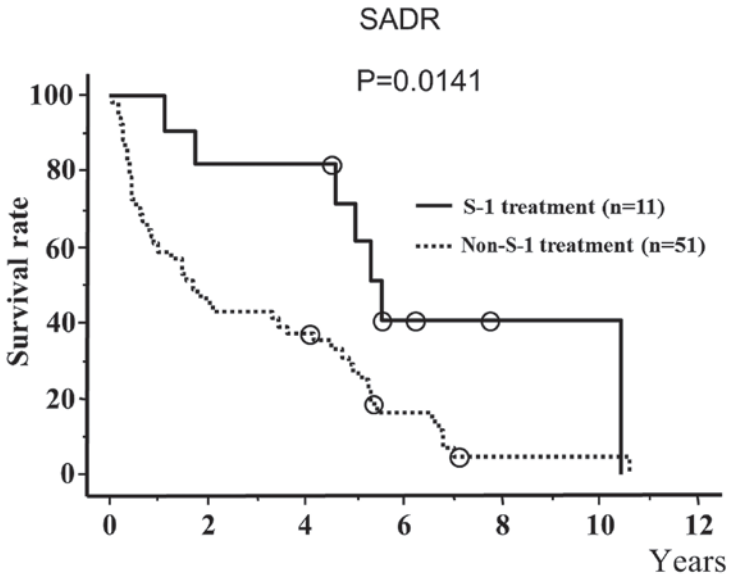

Figure 3. Kaplan-Meier method and log-rank test for survival after distant recurrence (SADR). SADR was higher among patients who received S-1 treatment compared to that in patients without S-1 treatment (P=0.0141).

pulmonary matastasis (6). While there have been several studies on the treatment of pulmonary metastasis, an effective therapeutic approach has not yet been established. The development of such methods is crucial for improving the prognosis of HCC patients with pulmonary metastasis.

Under certain conditions, resection appears to be one of the most effective options for controlling pulmonary lesions. Tomimaru *et al* (22) reported that patients undergoing pulmonary resection for lung metastasis exhibited significantly better prognosis compared to patients without pulmonary resection. The Metastatic Lung Tumor Study Group in Japan reported that the number of pulmonary metastatic lesions is associated with prognosis, with good survival expected in cases with <4 metastatic lesions (23). Additionally, Chen *et al* (24) reported that patients with a metastasis of >3 cm had a worse prognosis compared to those with metastasis of <3 cm. In the present study, 2 patients in the non-treatment group underwent pulmonary resection; of those patients, 1 remains alive without recurrence, whereas the other patient survived for >3 years. Considering the previous and present data, pulmonary resection may only be effective when the liver lesions are controllable, the number of pulmonary lesions is relatively small and the tumor size is small (<3 cm).

Due to these limitations regarding pulmonary resection, efforts have focused on developing effective systemic chemotherapy for pulmonary metastasis. Numerous agents, including 5-FU, CDDP and mitomycin, have been investigated for the treatment of advanced HCC, but have not produced good results (25,26). Gemcitabine is widely used for treating lung and pancreatic cancer and reportedly shows an 18% response rate when used as a single agent, although there have been some rebuttal studies (27-29). Several molecular-targeted agents have also been reported to be effective against advanced HCC (30,31). In 2008, the SHARP trial demonstrated that the multikinase

Table III. Univariate and multivariate analysis of factors associated with survival after distant recurrence.

	Univariate analysis			Multivariate analysis		
Characteristics	P-value	HR	95% CI	P-value	HR	95% CI
AFP (<400/≥400 ng/ml)	0.81	1.07	0.623-1.831	-	-	-
PIVKA II level (<1,000/≥1,000)	0.71	1.11	0.639-1.926	-	-	-
Child-Pugh score (A/non-A)	0.11	2.62	0.809-8.486	0.11	2.62	0.809-8.486
Histological differentiation (high + moderate/poor)	0.78	1.09	0.588-2.019	-	-	-
Primary Vp (+/-)	0.95	1.02	0.578-1.796	-	-	-
Primary Vv (+/-)	0.096	0.52	0.240-1.123	0.096	0.52	0.240-1.123
Disease-free interval	0.52	0.93	0.736-1.167	-	-	-
Distant recurrence-free interval	0.98	1.00	0.861-1.167	-	-	-
S-1 treatment (+/-)	0.018	0.38	0.171-0.847	0.0091	0.343	0.153-0.766

HR, hazard rario; CI, confidence interval; AFP, α-fetoprotein; PIVKA II, protein induced by vitamin K absence or antagonist-II; Vp, portal vein invasion; Vv, venous invasion.

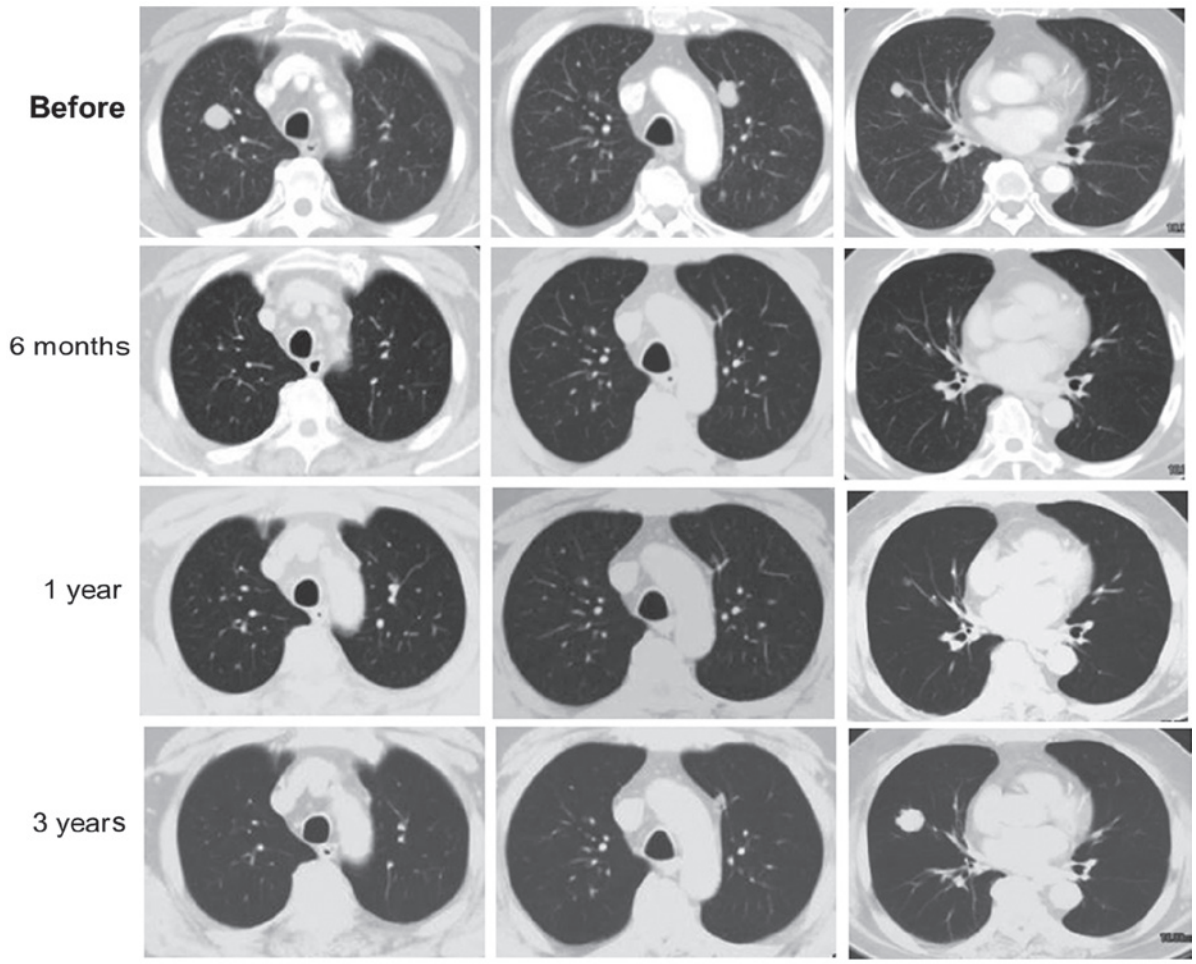

Figure 4. Time-course computed tomography of a patient who received S-1 treatment and exhibited a good response to S-1 combination therapy. The multiple lung metastases almost disappeared, although some relapse has appeared.

inhibitor sorafenib improves the prognosis in far-advanced HCC patients (8). Sorafenib is recommended as first-line chemotherapy for far-advanced HCC patients; however, Yau *et al* (9) reported that the presence of lung metastasis is associated with a poor response to sorafenib and, thus, the best treatment for patients with lung metastasis remains a matter of debate.

We previously reported that combination chemotherapy with intra-arterial infusion of 5-FU and subcutaneous IFN-α

injection was found to be clinically beneficial in patients with far-advanced HCC and PVTT (12,13). However, patients with extrahepatic metastasis are not expected to respond to this treatment. Therefore, we recently used combination therapy with IFN-α subcutaneous injection and S-1, rather than intra-arterial infusion of 5-FU, as systemic therapy for patients with extrahepatic metastasis (14).

In the present study, we selected HCC patients with lung metastasis as the first distant metastatic site, with the aim to achieve a clear study design and evaluate the clinical significance of this combination therapy for patients who are unlikely to benefit from sorafenib. We administered the combination therapy to 11 patients, all of whom survived for >1 year, while >40% of the 51 patients who did not receive this therapy succumbed to the disease within 1 year of lung metastasis detection. All the patients enrolled in this study had undergone surgery and had preserved liver function; therefore, it was difficult compare the present results with the results of sorafenib treatment in patients with lung metastasis. It was also difficult to determine whether this regimen would work as efficiently in patients with more severely compromised liver function. However, our results indicated that, at least in cases in which liver function is preserved to some extent, this combination therapy is a promising means of improving the outcomes of HCC patients with lung metastasis following radical surgery.

Advanced methods for treating extrahepatic metastasis are required to further improve the prognosis of HCC patients. In particular, an effective regimen is required for patients with lung metastasis who are unlikely to clinically benefit from sorafenib treatment. It is our opinion that the combination therapy with S-1 and IFN-α investigated in the present study may be a promising candidate treatment for such patients.

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