endothelial growth factor receptor-2/-3 (VEGFR-2/-3) and platelet-derived growth factor receptor beta (PDGFR-β), which is involved in peritumor neovascularization [5, 6]. In two pivotal international phase 3 trials of sorafenib vs. placebo, the so-called SHARP trial [7] and the Asia-Pacific trial [8], sorafenib demonstrated a prolonged overall survival and time-to-progression, compared with a placebo, in patients with advanced hepatocellular carcinoma (HCC). Therefore, sorafenib has been acknowledged as a standard therapy for advanced HCC.

In the therapeutic strategy of the Barcelona Clinic Liver Cancer Study Group [5], sorafenib was indicated for patients with extrahepatic metastasis and/or vascular invasion of Stage C disease (advanced stage), patients with a performance status (PS) of 1–2, and those with Stage B (intermediate stage) multifocal HCC refractory to TACE. In the 2010 updated version of the consensus-based clinical practice guidelines for the management of HCC proposed by the Japan Society of Hepatology [9, 10], patients with extrahepatic metastasis, with macrovascular invasion, and who were refractory to TACE are listed in the algorithm for treatment with sorafenib. The main indications for sorafenib are, therefore, considered to be patients who are refractory to TACE, those who have vascular invasion, or those who have extrahepatic metastasis. Subgroup analyses of the SHARP trial [7] and the Asia-Pacific trial [8] showed the treatment efficacies in patients with vascular invasion and extrahepatic metastasis. However, those in patients who are refractory to TACE have not been reported so far, although the outcome of patients with prior TACE has been reported [11, 12].

Before the introduction of sorafenib, hepatic arterial infusion chemotherapy was mainly performed in Japan for patients with advanced HCC [13–21], including those refractory to TACE [13, 14]. However, no consensus on a standard therapy has been achieved because large-scale prospective studies and randomized controlled studies have not been conducted and the survival benefit has not been clarified [10]. In this study, we clarified the efficacy of sorafenib in patients who were refractory to TACE (sorafenib group) and retrospectively compared the anti-tumor effect, time to progression, and overall survival between the sorafenib group and patients who were refractory to TACE and who were treated with hepatic arterial infusion chemotherapy using cisplatin (cisplatin group).

Patients and methods

Patients

Forty-eight consecutive chemotherapy-naive patients who were refractory to TACE without extrahepatic metastasis were extracted from 205 patients treated with sorafenib at the National Cancer Center Hospital East (East Hospital) between April 2009 and December 2011. Sixty-six of the 84 chemo-naive patients who were refractory to TACE and were treated with hepatic arterial infusion chemotherapy using cisplatin at the National Cancer Center Hospital and the East Hospital between July 2004 and September 2008, the period before the approval of sorafenib in Japan, were enrolled in the cisplatin group after excluding 18 patients with extrahepatic metastasis or the moderate retention of ascites. In this series, the total number of TACE sessions was 478, while the median number of TACE sessions was 4 (range 1–16). In previous TACE sessions, an emulsion containing an anticancer agent and lipiodol followed by gelatin sponge particles were used. In the present series, epirubicin was used for 394 sessions, adriamycin was used for 29 sessions, and mitomycin C was used for 12 sessions; the anticancer agent was unknown for 43 sessions. Patients who were refractory to TACE were defined as those showing progression or a tumor shrinkage rate of <25 % of the hypervascular lesions as visualized using dynamic computed tomography (CT) and/or magnetic resonance imaging (MRI) after 1–3 months of TACE [13]. The TACE-refractory status of individual patients was discussed at a weekly tumor board conference. HCC was diagnosed based on the presence of histopathological findings or imaging findings that were characteristic of HCC together with an increase in the serum α-fetoprotein level. The diameter of the tumor and the presence/absence of extrahepatic metastasis were confirmed using dynamic CT/MRI, ultrasound, or chest X-ray/CT prior to treatment. In our hospital, sorafenib is indicated for the treatment of patients with highly advanced HCC with a Child–Pugh score of either A or B. Informed consent for each treatment was obtained from all the patients before the initiation of treatment. This clinical study was conducted with the approval of the Ethics Committee of the National Cancer Center and was conducted in accordance with the ethical principals stated in the Japanese ethics guideline for epidemiological research.

Treatments

An oral dose of sorafenib at 400 mg was administered twice daily, after breakfast and dinner (800 mg/day). Treatment was continued as long as tolerability was observed without obvious disease progression. The dose was reduced or withdrawn and treatment was continued depending on the severity of adverse events. A dose increase up to 800 mg/day was permitted when the dose increase was judged possible in patients in whom the dose had been reduced.

For hepatic arterial infusion chemotherapy using cisplatin, intra-arterial cisplatin at a dose of 65 mg/m^2 was

administered over 20–40 min via a catheter inserted into the feeding arteries of the tumors. Treatment was repeated every 4–6 weeks for up to 6 courses until disease progression or unacceptable toxicities occurred. An infusion of 3,000 mL or more was administered on the day of treatment, and an infusion of 1,000 mL or more was continued for 3 days after administration to reduce renal toxicity caused by cisplatin; a diuretic (mannitol, furosemide, etc.) was administered as necessary to ensure an adequate urine volume.

Assessment and statistical analyses

Dynamic CT or MRI was used to confirm the anti-tumor effect every 1–2 months. The anti-tumor effect was evaluated using the Response Evaluation Criteria in Solid Tumors, version 1.0 (RECIST) [22], to judge the best overall response. The time to progression was defined as the period from the date of the start of treatment until the date of the confirmation of tumor progression by radiological evaluation or the day on which obvious tumor progression was judged to have occurred based on the clinical symptoms. Overall survival was defined as the period from the day of the start of treatment until the date of death or the final date of confirmed survival. A χ^2 test or Wilcoxon test was used to compare the patient characteristics and the anti-tumor effect between the sorafenib and the hepatic arterial infusion chemotherapy using cisplatin groups, and the Kaplan–Meier method was used to calculate the time to progression and the overall survival; the log-rank test was used to analyze differences between the groups. In a multivariate analysis, a Cox regression was used to analyze factors with $P < 0.10$ using a univariate analysis. $P < 0.05$ was judged to be statistically significant. JMP version 9.0 (SAS Institute Inc.) was used for the above statistical analyses.

Results

Patient characteristics

Table 1 shows the patient characteristics before each treatment. Age was significantly higher in the sorafenib group, although the medians were very similar (sorafenib group 71 years, cisplatin group 69 years). Although the Eastern Cooperative Oncology Group PS, the maximum tumor diameter, total bilirubin, AST, and ALT tended to be slightly worse in the cisplatin group, significant differences were not observed in the other parameters between the two groups. The median number of treatments in the cisplatin group was 2 (range 1–6 times). As a subsequent treatment, other systemic chemotherapy was performed in 14 patients, hepatic arterial infusion chemotherapy using cisplatin was performed in 7 patients, TACE was performed in 4 patients, and hepatic arterial infusion chemotherapy using 5-FU + interferon and radiotherapy was performed in one patient each in the sorafenib group; meanwhile, TACE was performed in 15 patients, hepatic arterial infusion chemotherapy using epirubicin was performed in 4 patients, other systemic chemotherapy was performed in 4 patients, hepatic arterial infusion chemotherapy using 5-FU + interferon was performed in 2 patients, and radiotherapy was performed in one patient in the cisplatin group. The median observation period was 9.4 months (range 2.1–31.6 months) in the sorafenib group and 7.5 months (range 0.8–43.1 months) in the cisplatin group; this difference was not statistically significant ($P = 0.44$).

Efficacy

The best overall response in the sorafenib group was evaluated as a complete response (CR) in one patient, a partial response (PR) in 2 patients, stable disease (SD) in 26 patients, progressive disease (PD) in 16 patients, and not evaluable (NE) in 3 patients. The response rate (CR + PR) was 6.3 % [95 % confidence interval (CI) 1.3–17.2 %], and the disease control rate (CD + PR + SD) was 60.4 % (95 % CI 45.3–74.2 %). The median time to progression and the progression-free rate at 6- and 12-months were 3.9 months, 32.6 %, and 12.1 %, respectively, while the median overall survival and the survival rate at 6-, 12-, and 24-months was 16.4 months, 88.9 %, 55.3 %, and 32.5 %, respectively, in the sorafenib group.

The best overall response in the cisplatin group was evaluated as a CR in 1 patient, PR in 0 patients, SD in 18 patients, PD in 39 patients, and NE in 8 patients. The response rate was 1.5 % (95 % CI 0.04–8.2 %), and a significant difference in the response rate, compared with the sorafenib group, was not observed ($P = 0.40$). The disease control rate was 28.8 % (95 % CI 18.3–41.3 %), which was significantly higher in the sorafenib group ($P = 0.001$). The median time to progression and the progression-free rate at 6- and 12-months in the cisplatin group was 2.0 months, 15.9 %, and 4.8 %, respectively, showing a significantly superior result in the sorafenib group (hazard ratio 0.44, $P < 0.01$) (Fig. 1). At the time of analysis, 21 patients had died because of tumor progression, and 1 patient had died because of hepatic failure in the sorafenib group. Additionally, 60 patients had died because of tumor progression, and 4 patients had died because of hepatic failure in the cisplatin group. The median survival time and the survival rate at 6-, 12-, and 24-months in the cisplatin group were 8.6 months, 62.0 %, 35.2 %, and 11.3 %, respectively, showing a significantly superior result in the sorafenib group (hazard ratio: 0.57,

Table 1 Patient characteristics

	Sorafenib		Cisplatin		*P* value
	n	(%)	*n*	(%)	
All patients	48	–	66	–	
Age (years)					
Median [range]	71	[53–83]	69	[40–82]	0.04
Sex					
Male	43	(90)	52	(79)	
Female	5	(10)	14	(21)	1.00
Performance status					
0	43	(90)	49	(74)	
1	5	(10)	17	(26)	0.07
HCVAb (positive)	32	(67)	45	(68)	1.00
HBsAg (positive)	7	(15)	8	(12)	0.92
Prior resection (present)	12	(25)	27	(41)	0.11
Prior ablation (present)	19	(40)	29	(44)	1.00
No. of prior TACE sessions					
Median [range]	4	[1–9]	4	[1–17]	0.86
Maximum tumor diameter (mm)					
Median [range]	30.5	[10–150]	40	[12–110]	0.07
Number of tumors					
1–3	8	(17)	13	(20)	0.32
≥4	40	(83)	53	(80)	0.64
Portal vein invasion (present)	9	(19)	16	(24)	0.64
Hepatic vein invasion (present)	3	(6)	4	(6)	0.99
Stage[a]					
II or III	38	(79)	49	(74)	
IVa	10	(21)	17	(26)	0.70
Ascites (present)	9	(19)	17	(26)	0.51
Child–Pugh class					
A	32	(67)	36	(55)	
B	16	(33)	30	(45)	0.27
Total bilirubin (mg/dL)					
Median [range]	0.9	[0.3–2.1]	1.1	[0.2–3.0]	0.02
Albumin (g/dL)					
Median [range]	3.5	[2.3–4.8]	3.3	[2.4–4.5]	0.21
AST (U/L)					
Median [range]	54	[20–165]	88	[35–287]	0.04
ALT (U/L)					
Median [range]	43	[10–139]	62	[22–187]	0.05
Prothrombin time (%)					
Median [range]	78	[40–107]	73	[48–104]	0.39
α-Fetoprotein (ng/mL)					
Median [range]	70.3	[1.3–218876]	324.3	[1.7–210200]	0.59
PIVKAII (mAU/mL)					
Median [range]	505.5	[11–291330]	438	[11–96390]	0.65
Subsequent treatments (present)	27	(56)	26	(39)	0.11

HCVAb hepatitis C viral antibody, *HBsAg* hepatitis B surface antigen, *TACE* transcatheter arterial chemoembolization, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *PIVKAII* protein induced by vitamin K absence or antagonists-II

[a] Japanese classification of primary liver cancer

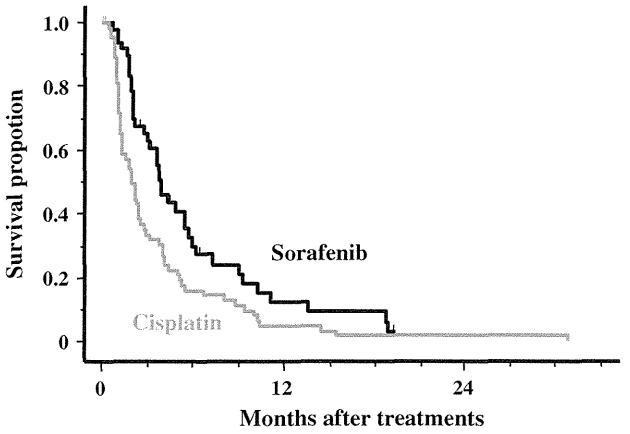

Fig. 1 Comparison of time to progression between sorafenib and hepatic arterial infusion chemotherapy using cisplatin in patients who were refractory to transcatheter arterial chemoembolization (TACE)

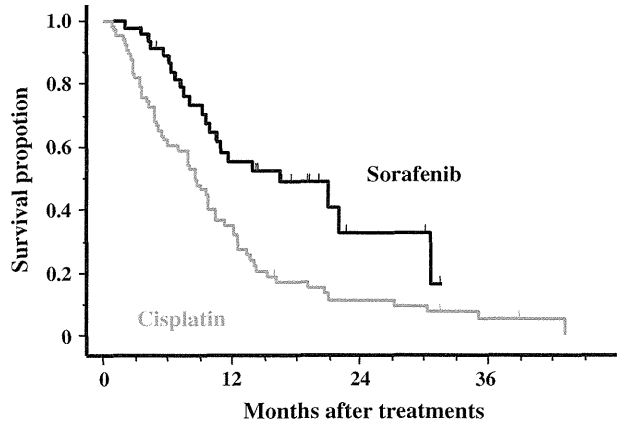

Fig. 2 Comparison of overall survival between sorafenib and hepatic arterial infusion chemotherapy using cisplatin in patients who were refractory to TACE

$P < 0.001$) (Fig. 2). The same analysis was performed for patients limited to Child–Pugh A, since sorafenib is widely recommended for the treatment of patients with Child–Pugh A. The results were similar, although the disease control rate and the time to progression were not statistically significant (data not shown).

Toxicity

Serious adverse events (SAE) occurred in two patients (1 patient, grade 4 hepatic encephalopathy; 1 patient, grade 3 erythema multiforme) in the sorafenib group, but none of the patients in the cisplatin group experienced an SAE. Thirty-eight patients (79 %) required a sorafenib dose reduction because of adverse events, such as liver dysfunction, hand-foot syndrome, or rashes, and treatment was discontinued in 7 patients (14 %) because of adverse events, such as liver dysfunction, hepatic encephalopathy, or erythema multiforme. On the other hand, none of the patients required a cisplatin dose reduction, and treatment was discontinued in 6 patients (9.1 %) because of adverse events, such as liver dysfunction, fatigue, or nausea/anorexia.

Predictive factors of time to progression and overall survival

Univariate analyses were performed to identify the factors that contributed to the prolongation of time to progression in patients who were refractory to TACE (Table 2). The univariate analyses showed that the significant factors that contributed to the prolongation of the time to progression ($P < 0.10$) were an age >65 years, a PS of 0, a maximum tumor diameter ≤3.0 cm, the absence of hepatic vein invasion, the absence of ascites, a bilirubin level ≤1.2 mg/dL, an α-fetoprotein level <1,000 ng/mL, and sorafenib treatment. A multivariate analysis was performed for the factors that showed a significant tendency ($P < 0.10$) in the univariate analysis, and the absence of hepatic vein invasion and sorafenib treatment were significant independent factors that contributed to the prolongation of the time to progression (Table 3). Univariate analyses were performed to identify the factors that contributed to survival prolongation in patients who were refractory to TACE (Table 2). The univariate analyses showed that the significant factors that contributed to the prolongation of survival ($P < 0.10$) were an age >65 years, a PS of 0, a maximum tumor diameter of ≤3.0 cm, 3 or fewer tumors, the absence of hepatic vein invasion, Child–Pugh class A, the absence of ascites, an albumin level >3.5 g/dL, a bilirubin level ≤1.2 mg/dL, an AST level <100 U/L, an α-fetoprotein level <1,000 ng/mL, a protein induced by vitamin K absence or antagonist-II (PIVKA-II) level <1,000 mAU/mL, and sorafenib treatment. A multivariate analysis was performed for the factors showing a significant tendency at $P < 0.10$, and the significant independent favorable prognosis factors were a PS of 0, 3 or fewer tumors, Child–Pugh A, an α-fetoprotein level <1,000 ng/mL, a PIVKA-II level <1,000 mAU/mL, and treatment with sorafenib (Table 3). Treatment with sorafenib had the smallest hazard ratio among these prognostic factors.

Discussion

Patients with vascular invasion, extrahepatic metastasis, and who are refractory to TACE are good candidates for sorafenib [5, 9, 10]. However, the efficacy of sorafenib in patients who are refractory to TACE has not been previously reported, although the outcome of patients with prior

Table 2 Univariate analysis of time to progression and overall survival time in patients refractory to transcatheter arterial chemoembolization treated with sorafenib or intra-arterial cisplatin

	n	Time to progression			Overall survival		
		Median (months)	Hazard ratio	*P* value	Median (months)	Hazard ratio	*P* value
Sex							
Female	19	2.9	1.01 (0.60–1.68)	0.98	10.5	0.92 (0.51–1.68)	0.79
Male	95	2.6			9.8		
Age (years)							
≤65	33	2.0	1.41 (0.92–2.14)	0.11	8.0	1.65 (1.03–2.66)	0.03
>65	81	3.0			11.4		
Performance status							
0	92	3.2	0.58 (0.35–0.95)	0.03	11.4	0.38 (0.22–0.66)	<0.001
1–2	22	1.6			4.8		
HCVAb							
Negative	37	2.8	0.82 (0.53–1.25)	0.35	9.9	0.72 (0.45–1.18)	0.19
Positive	77	2.5			9.8		
HBsAg							
Negative	99	3.0	0.86 (0.50–1.50)	0.60	9.9	1.09 (0.54–2.17)	0.82
Positive	15	2.1			9.8		
Maximum tumor diameter (cm)							
≤3.0	39	4.0	0.65 (0.43–0.99)	0.04	12.3	0.56 (0.34–0.83)	0.02
>3.0	75	2.2			8.7		
No. of tumors							
≤3	21	4.4	0.78 (0.48–1.29)	0.33	13.8	0.68 (0.39–1.19)	0.06
>3	93	2.4			8.0		
Portal vein invasion							
Present	25	3.2	0.89 (0.55–1.43)	0.62	5.4	1.34 (0.79–2.27)	0.23
Absent	89	2.6			8.7		
Hepatic vein invasion							
Present	7	2.5	2.12 (0.97–4.66)	0.05	4.8	2.17 (0.94–5.03)	0.13
Absent	107	2.8			9.2		
Stage[a]							
II or III	87	2.8	0.94 (0.59–1.48)	0.77	11.6	0.64 (0.39–1.07)	0.08
IV	27	2.5			6.2		
Child–Pugh class							
A	68	3.2	0.84 (0.56–1.26)	0.39	9.5	0.65 (0.41–1.01)	0.08
B	46	2.2			7.8		
Ascites							
Present	26	2.2	1.56 (0.98–2.47)	0.06	5.6	2.15 (1.32–3.53)	0.01
Absent	88	2.9			9.2		
Albumin (g/dL)							
≤3.5	76	2.4	1.17 (0.78–1.77)	0.44	7.8	1.90 (1.16–3.11)	0.02
>3.5	38	3.8			10.6		
Total bilirubin (mg/dL)							
≤1.2	81	3.2	0.66 (0.42–1.02)	0.06	11.6	0.42 (0.26–0.66)	<0.001
>1.2	33	1.6			4.8		
Prothrombin time (%)							
<70	42	2.9	0.95 (0.63–1.42)	0.79	10.5	0.93 (0.59–1.47)	0.77
≥70	72	2.5			9.9		

Table 2 continued

	n	Time to progression			Overall survival		
		Median (months)	Hazard ratio	*P* value	Median (months)	Hazard ratio	*P* value
AST (U/L)							
<100	82	3.0	0.86 (0.55–1.35)	0.50	12.3	0.44 (0.27–0.70)	<0.001
≥100	32	2.2			5.5		
ALT (U/L)							
<100	97	2.6	0.90 (0.52–1.56)	0.70	9.9	0.85 (0.44–1.57)	0.59
≥100	17	2.5			8.5		
α-Fetoprotein (ng/mL)							
<1,000	71	3.8	0.60 (0.40–0.91)	0.01	12.2	0.61 (0.39–0.96)	0.03
≥1,000	43	2.1			7.1		
PIVKA-II (mAU/mL)							
<1,000	67	3.1	0.78 (0.52–1.16)	0.22	10.6	0.62 (0.40–0.96)	0.03
≥1,000	45	2.1			9.5		
Treatments							
Sorafenib	48	3.9	0.57 (0.38–0.86)	0.01	16.4	0.44 (0.27–0.72)	<0.001
Cisplatin	66	2.0			8.6		

HCVAb hepatitis C viral antibody, *HBsAg* hepatitis B surface antigen, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *PIVKAII* protein induced by vitamin K absence or antagonists-II

[a] Japanese classification of primary liver cancer

Table 3 Multivariate analysis of overall survival and time to progression in patients refractory to TACE

	Hazard ratio	*P* value
Time to progression		
Hepatic vein invasion: present	0.41 (0.19–0.91)	0.03
Treatment: sorafenib	0.55 (0.37–0.83)	0.004
Overall survival		
Performance status: 0	0.46 (0.27–0.81)	0.006
No. of tumors: ≤3	0.51 (0.29–0.91)	0.02
Child–Pugh class: A	0.44 (0.27–0.71)	0.001
α-Fetoprotein: <1,000 ng/mL	0.52 (0.22–0.84)	0.008
PIVKA-II: <1,000 mAU/mL	0.47 (0.29–0.76)	0.002
Treatment: sorafenib	0.42 (0.25–0.77)	0.001

TACE has been reported [11, 12]. We retrospectively evaluated the efficacy of sorafenib in patients who were refractory to TACE. The following data were obtained: the response rate (CR + PR) was 6.3 %, the disease control rate (CD + PR + SD) was 60.4 %, and the median time to progression was 3.9 months; these results were comparable to those obtained for sorafenib to date [7, 8]. The median survival time of 16.4 months was regarded as favorable. The patients who were refractory to TACE have a lower frequency of vascular invasion, which is a significant predictor of a poor prognosis in patients with advanced HCC. In addition, most of the TACE refractory patients had an intermediate BCLC stage. The TACE refractory patients in this study (proportion of advanced stage 33 %) had a better BCLC stage than the patients in previous trials (proportion of advanced stage SHARP, 82 %; Asia-Pacific trial, 95.3 %). Favorable tendencies, therefore, might be shown for the overall survival of a subgroup of patients who are refractory to TACE among advanced HCC patients in whom sorafenib treatment is indicated.

A definition of "refractory to TACE" has not yet been established. In this study, the definition of "refractory to TACE" was regarded as progression or a tumor shrinkage rate of <25 % in hypervascular lesions as visualized using dynamic CT and/or MRI after 1–3 months of TACE. According to the consensus-based clinical practice guidelines proposed by the Japan Society of Hepatology 2010 [5], however, "refractory to TACE" is defined as two or over consecutive incomplete necrotic reactions or the appearance of a new lesion, vascular invasion, or extrahepatic metastases. Although a consensus has not been reached among clinicians, this is a critical issue when considering a conversion from TACE to sorafenib treatment in patients with unresectable HCC.

In the present study, sorafenib was compared with hepatic arterial infusion chemotherapy using cisplatin, which was used before the introduction of sorafenib. A consensus on a standard therapy has not been attained for hepatic arterial infusion chemotherapy, since its survival benefit has not been elucidated [10]. However, this regimen is still frequently used in Japan, because favorable antitumor effects and long-term survivals have been seen in a

few patients [15–21]. Nonetheless, hepatic arterial infusion chemotherapy has not been reported to have favorable results in patients who are refractory to TACE [13, 14]. Regarding hepatic arterial infusion chemotherapy using cisplatin in patients who were refractory to TACE ($n = 84$), the response rate at out-patient hospitals was 3.6 %, the median time to progression was 1.7 months, and the median overall survival period was 7.1 months [13], while the results of a phase II study of hepatic arterial infusion chemotherapy using cisplatin in patients with unresectable HCC ($n = 80$) were favorable, with a response rate of 33.8 % and a 1-year survival rate of 67.5 % [15]. One possible reason for the difference between these studies might be differences in the characteristics of the study populations. Most patients in the phase II trial of cisplatin were TACE-naïve, whereas only patients with TACE-refractory disease were included in the present study. Thus, hepatic arterial infusion chemotherapy may not be expected to show favorable therapeutic results when the patients are limited to those refractory to TACE, although the reason remains unknown. Therefore, the results were compared with those for patients who were refractory to TACE and were treated with sorafenib. Although the patient age was significantly higher in the sorafenib group and the PS and tumor size was slightly worse in the cisplatin group, no other significant differences in the patient characteristics were observed between the two groups. The response rate was comparable, but the sorafenib group showed significantly higher results for the disease control rate, time to progression, and overall survival. We also performed a multivariate analysis to examine the factors that contributed to the time to progression and overall survival in patients who were refractory to TACE, and treatment with sorafenib was one of the significant factors. These results suggest that sorafenib, rather than hepatic arterial infusion chemotherapy using cisplatin, might be the treatment of first choice in patients who are refractory to TACE. This outcome might not have much impact in overseas settings, where hepatic arterial infusion chemotherapy is less popular, but it is quite disappointing in Japan, since hepatic arterial infusion chemotherapy using cisplatin was expected to show a therapeutic effect comparable to that of sorafenib.

The present study has some limitations. First, the results for sorafenib treatment in patients who were refractory to TACE were obtained as part of a single-site, retrospective study. A prospective study enrolling only patients who are refractory to TACE should be performed in the future to verify the efficacy of sorafenib in patients who are refractory to TACE. Second, the periods of treatment differed between the sorafenib group and the cisplatin group. Third, the influence of subsequent treatment on the overall survival cannot be denied. Hepatic arterial infusion chemotherapy using cisplatin was administered as a subsequent treatment in 7 patients in the sorafenib group, whereas patients in the cisplatin group were not treated with sorafenib. Still, the anti-tumor effect of hepatic arterial infusion chemotherapy using cisplatin following sorafenib was PD in all the patients, and the impact would have been negligible. Finally, considering the possible selection bias in therapeutic policy after the introduction of sorafenib, we selected patients with different periods of treatment, but the results might also have been affected by the difference in periods. Also, no significant differences in the patient characteristics, except for age, total bilirubin, and AST, were seen between the sorafenib and the hepatic arterial infusion chemotherapy using cisplatin group, but subtle differences in the patient characteristics might have affected the favorable results for sorafenib, since this study was a retrospective comparison.

In conclusion, sorafenib showed a favorable efficacy in patients who were refractory to TACE, resulting in a significantly higher disease control rate, longer time to progression, and longer overall survival compared with hepatic arterial infusion chemotherapy using cisplatin. Thus, sorafenib, rather than hepatic arterial infusion chemotherapy, should be considered as the first-line therapy for patients who are refractory to TACE in the future.

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Conflict of interest The authors declare that they have no conflict of interest.

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CASE REPORT

Clinical and radiological feature of lymphoepithelial cyst of the pancreas

Hirofumi Terakawa, Isamu Makino, Hisatoshi Nakagawara, Tomoharu Miyashita, Hidehiro Tajima, Hirohisa Kitagawa, Takashi Fujimura, Dai Inoue, Kazuto Kozaka, Toshifumi Gabata, Tetsuo Ohta

Hirofumi Terakawa, Isamu Makino, Hisatoshi Nakagawara, Tomoharu Miyashita, Hidehiro Tajima, Hirohisa Kitagawa, Takashi Fujimura, Tetsuo Ohta, Department of Gastroenterologic surgery, Graduate School of Medical Science, Kanazawa University, Kanazawa 920-8641, Japan
Dai Inoue, Kazuto Kozaka, Toshifumi Gabata, Department of Radiology, Graduate School of Medical Science, Kanazawa University, Kanazawa 920-8641, Japan
Author contributions: Terakawa H and Makino I contributed equally to this work; Makino I, Nakagawara H, Miyashita T, Tajima H, Kitagawa H, Fujimura T and Ohta T performed surgery; Makino I, Nakagawara H and Kitagawa H managed postoperative treatment; Inoue D, Kozaka K and Gabata T diagnosed radiologically; Terakawa H and Makino I wrote the paper.
Correspondence to: Hirofumi Terakawa, MD, Department of Gastroenterologic Surgery, Graduate School of Medical Science, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan. hirofumi_terakawa@yahoo.co.jp
Telephone: +81-76-2652362 Fax: +81-76-2344260
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Abstract

A lymphoepithelial cyst (LEC) of the pancreas is a rare benign lesion. Because patients with LEC of the pancreas have a good prognosis, it is important that these lesions are accurately differentiated from other more aggressive pancreatic neoplasms for an appropriate treatment strategy. Previous studies have reported that a definitive diagnosis of LEC often cannot be obtained based solely on the findings of preoperative imaging (*e.g.*, Computed tomography or Magnetic resonance imaging). In this study, we reviewed four cases of pancreatic LECs to investigate the feature of LECs. We reviewed these cases with regard to symptoms, imaging findings, surgical procedures, and other clinical factors. We found that LEC was associated with unique characteristics on imaging findings. A preoperative diagnosis of LEC may be possible by comprehensively evaluating its clinical and imaging findings.

Key words: Lymphoepithelial cyst; Preoperative diagnosis; Magnetic resonance imaging

Core tip: A lymphoepithelial cyst of the pancreas is a rare benign lesion. In this study, we reviewed four cases of pancreatic lymphoepithelial cyst (LECs) to investigate the feature of LECs. We found that LEC was associated with unique characteristics on imaging findings. A preoperative diagnosis of LEC may be possible by comprehensively evaluating its clinical and imaging findings.

Terakawa H, Makino I, Nakagawara H, Miyashita T, Tajima H, Kitagawa H, Fujimura T, Inoue D, Kozaka K, Gabata T, Ohta T. Clinical and radiological feature of lymphoepithelial cyst of the pancreas. *World J Gastroenterol* 2014; 20(45): 17247-17253 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i45/17247.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i45.17247

INTRODUCTION

The differentiation and classification of cystic lesions of the pancreas are important for an appropriate treatment strategy. A lymphoepithelial cyst (LEC) of the pancreas is a rare benign cystic lesion[1,2]. It has been thought to be difficult to differentiate LEC from other pancreatic lesions such as serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) because the appearance on imaging of LEC varies from patient to patient and sometimes similar to other pancreatic lesions[3]. In many patients, the lesion is surgically resected because a neoplastic cyst cannot

Table 1 Patient demographics, clinical findings

	Year	Age	Gender	Size (mm)	Symptom	Location	CA19-9 (U/mL)
Case 1	2004	59	Male	90	Nonspecific	Body	4
Case 2	2009	49	Female	60	Nonspecific	Tail	298
Case 3	2012	56	Male	40	Nonspecific	Body	75
Case 4	2012	56	Male	60	Nonspecific	Head	96

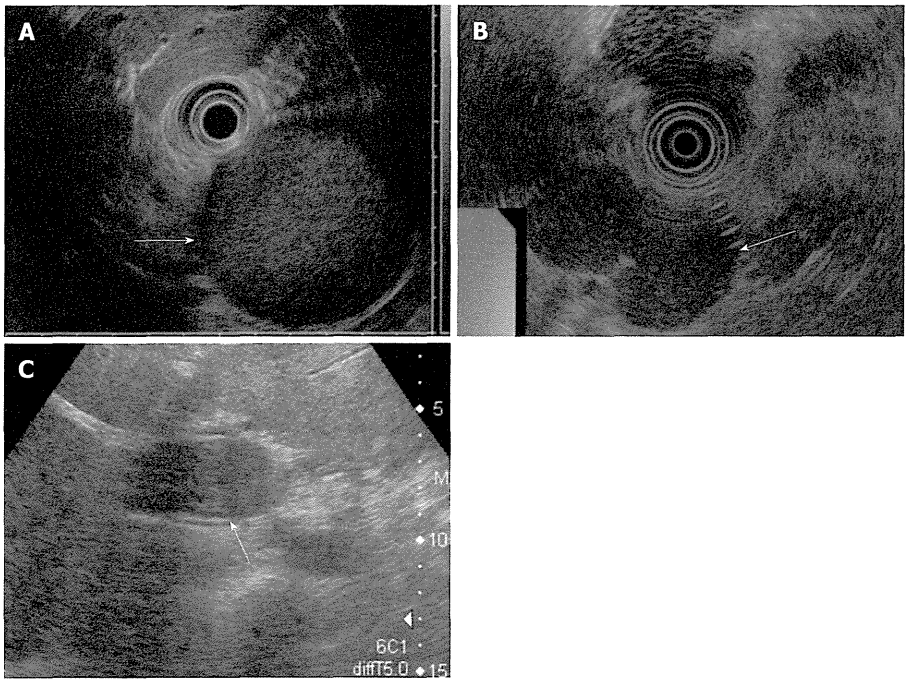

Figure 1 Ultrasonography and endoscopic ultrasonography findings. A: Findings of Patient #2, the cystic lesion had a hyperechoic appearance (arrow); B: Findings of Patient #3, the cystic lesion had a homogenous hypoechoic appearance (arrow); C: Findings of Patient #4, the cystic lesion displayed a mosaic pattern (arrow).

be ruled out[4-6]. If a LEC can be diagnosed preoperatively, many unnecessary surgeries may be avoided. In this paper, we present four patients with LEC who underwent surgical resection and were confined as LEC. We summarized clinical and radiological features of LECs.

CASE REPORT

A retrospective review of our institutional database revealed four cases of LEC of the pancreas in recent 10 years. We reviewed these cases with regard to symptoms, imaging findings, surgical procedures, and other clinical factors. Various imaging studies were performed during the preoperative evaluation of the lesions. Imaging studies included abdominal ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS) and endoscopic retrograde cholangiopancreatography (ERCP). All of the lesions were surgically resected and pathologically diagnosed as LEC.

Clinical findings

Table 1 summarized the patient demographics. Three patients were men and one patient was a woman. The average age was 55 years. All of the lesions were detected incidentally during a work-up for unrelated reasons. In Patient #1 and Patient #3, the cystic lesions were localized in the body of the pancreas; in Patient #2, in the tail of the pancreas; and in Patient #4, in the head of the pancreas. The mean cystic size was 62.5 mm (range, 40-90 mm). Three patients had a multilocular cystic appearance and one patient had a unilocular cystic appearance. Three patients had elevated serum CA19-9 levels.

US and EUS findings

The cystic lesion in Patient #2 had a slightly hyperechoic appearance. The cystic lesion had a homogenous hypoechoic appearance in Patient #3. The cystic lesion in Patient #4 displayed a mosaic pattern. None of the three patients had solid portions the cysts (Figure 1).

CT findings

All lesions were well-defined and were exophytic off the pancreatic parenchyma. The lesion in Patient #2 had a unilocular cystic appearance, whereas the lesions in

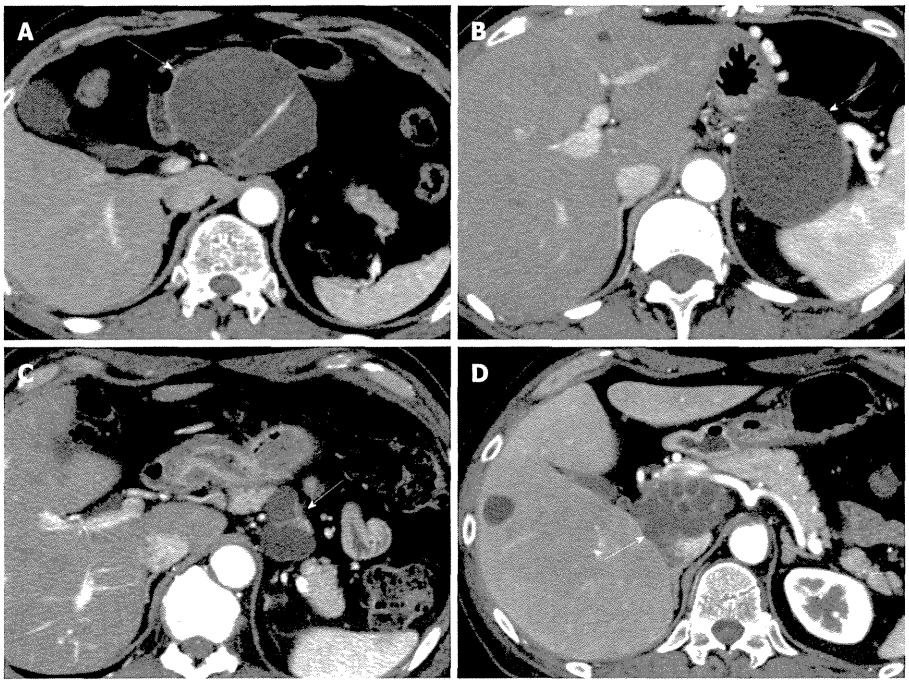

Figure 2 Computed tomography findings. All lesions were well-defined and were exophytic off the pancreatic parenchyma. The wall and septum of the cysts were enhanced. A: Findings of Patient #1, the lesion was localized in the body of the pancreas and had a multilocular cystic appearance (arrow); B: Findings of Patient #2, the lesion was localized in the tail of the pancreas and had a unilocular cystic appearance (arrow); C: Findings of Patient #3, the lesion was localized in the body of the pancreas and had a multilocular cystic appearance (arrow); D: Findings of Patient #4, the lesion was localized in the head of the pancreas and had a multilocular cystic appearance (arrow).

the other patients had a multilocular cystic appearance. The wall and septum of the cysts were enhanced. The contents of the cysts seemed homogeneous low density without enhancement. There were no solid portions within the cysts, calcification of the wall of the cyst, or dilatation of the main pancreatic duct, in any of the patients (Figure 2).

ERCP findings

All patients had normal pancreatic ducts. No patients had a communication between the pancreatic duct and the cystic lesion.

MRI findings

Figures 3-6 present the MRI findings of four patients. We presented MRI imaging of a case of SCN which had similar signal intensity with free water for comparing with the four cases (Figure 7). T1-weighted imaging of four patients showed a higher intensity than that of SCN. T2-weighted imaging and MRCP of four patients showed a lower intensity than those of SCN. Diffusion-weighted imaging (DWI) showed a higher intensity for cystic lesions than for the SCN. In particular, on DWI, the cystic lesions showed high intense signal in the central part and isointense in the periphery. Signal reduction in out-of phase and in-phase was not occurred in all patients.

DISCUSSION

A LEC is a rare benign lesion, which is lined with mature keratinizing squamous epithelium and surrounded by lymphoid tissue. It typically develops in middle-aged and elderly men, and it is localized to all parts of the pancreas with equal frequency. The mean size of these cysts is 47 mm. The cyst may be multilocular (60% of patients) or unilocular (40% of patients)[7]. Many patients with LEC have elevated serum levels of CA19-9[8-10]. The cyst contents may vary from serous to caseous-like, depending on the degree of keratin formation[2].

Because LEC is a benign lesion, it is often possible to select conservative treatment for ones without any significant symptoms if they can be diagnosed correctly[11]. However, surgical resection is still commonly performed because it is difficult to distinguish them from other cystic lesions that require surgical intervention on account of their malignant potential[4-6]. EUS-guided biopsy coupled with biochemical/tumor marker studies have recently helped to improve the diagnostic accuracy of pancreatic cysts[12,13]. However, EUS-guided biopsy for cystic lesions of the pancreas is not generally performed in Japan because of the risk of the dissemination of tumor cells or the development of pseudomyxoma. Therefore, a preoperative pathological diagnosis is difficult and imaging studies are very important for treating cystic lesions of pancreas in Japanese.

We summarized the characteristics of LEC obtained from our cases and previous reports in Table 2.

A LEC typically develops in middle-aged and elderly men[2]. Many patients with LEC have elevated serum CA19-9[8-10].

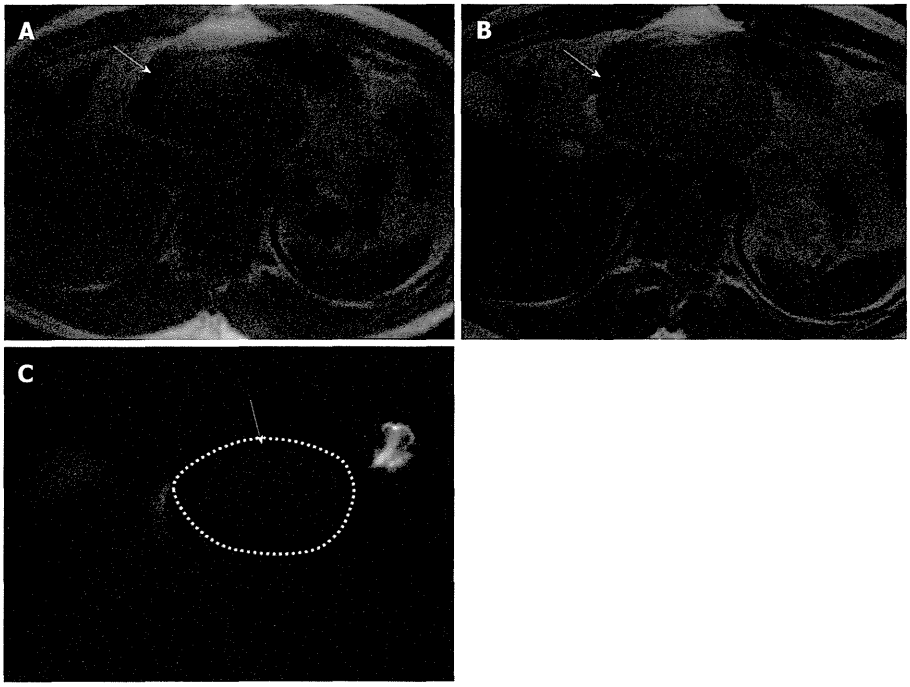

Figure 3 Findings of patient #1. A: Findings of T1-weighted imaging on magnetic resonance imaging (MRI). T1-weighted imaging of patient showed a higher intensity than free water (arrow), B: Findings of T2-weighted imaging on MRI. T2-weighted imaging of patient showed a lower intensity than free water (arrow); C: Findings of magnetic resonance cholangiopancreatography (MRCP). MRCP of patient showed a lower intensity than free water (arrow).

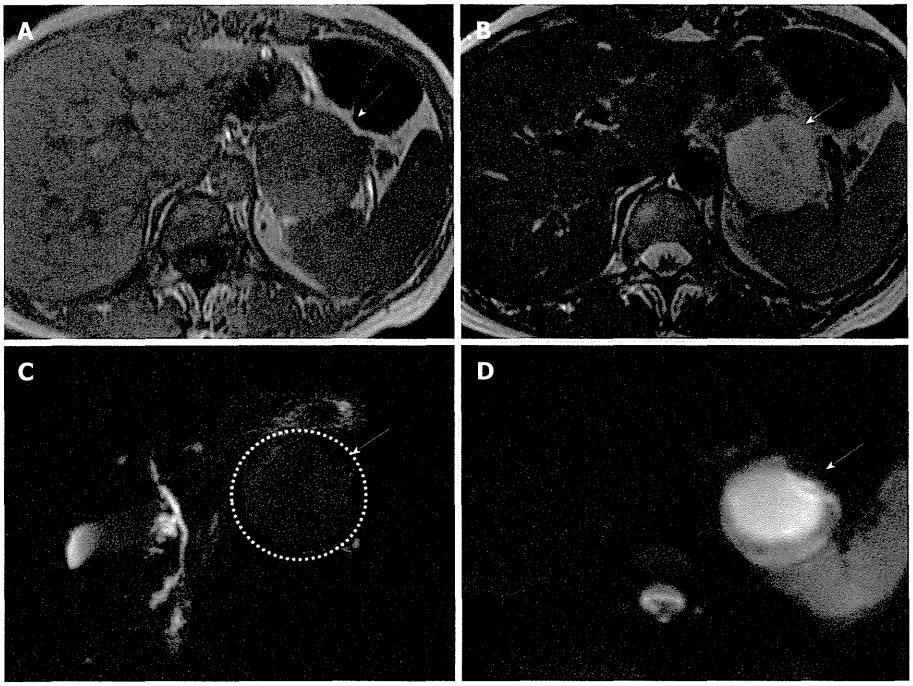

Figure 4 Findings of patient #2. A: Findings of T1-weighted imaging on magnetic resonance imaging (MRI). T1-weighted imaging of patient showed a higher intensity than free water (arrow); B: Findings of T2-weighted imaging on MRI. T2-weighted imaging of patient showed a lower intensity than free water (arrow); C: Findings of magnetic resonance cholangiopancreatography (MRCP). MRCP of patient showed a lower intensity than free water (arrow); D: Findings of diffusion-weighted imaging on MRI (arrow). Diffusion-weighted imaging of three patients showed a higher intensity than free water. The cystic lesions showed high intense signal in the central part and iso-intense in the periphery.

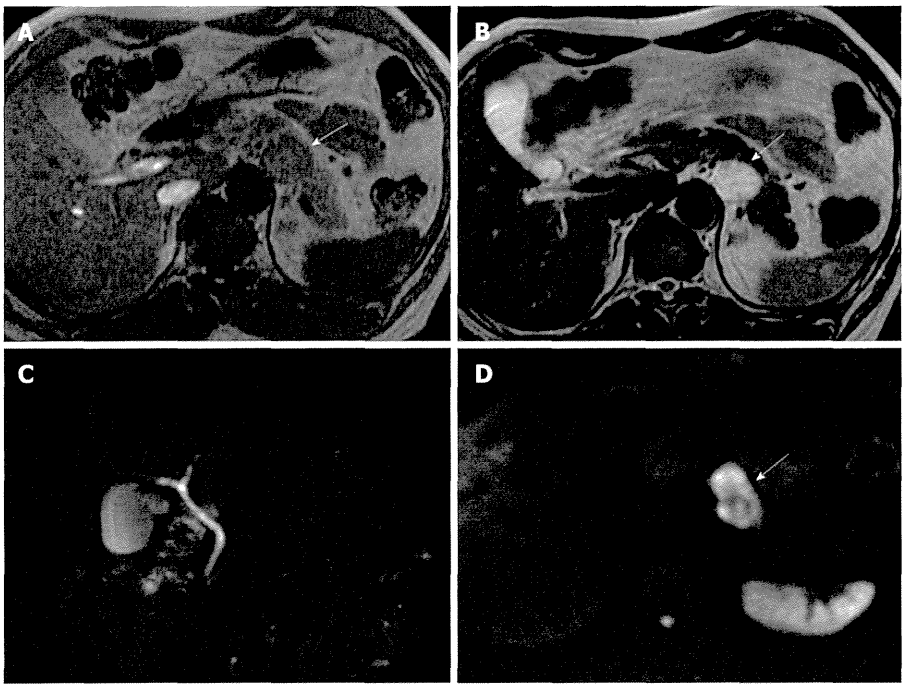

Figure 5 Findings of patient #3. A: Findings of T1-weighted imaging on magnetic resonance imaging (MRI). T1-weighted imaging of patient showed a higher intensity than free water (arrow); B: Findings of T2-weighted imaging on MRI. T2-weighted imaging of patient showed a lower intensity than free water (arrow); C: Findings of magnetic resonance cholangiopancreatography (MRCP). MRCP of patient showed a lower intensity than free water; D: Findings of diffusion-weighted imaging on MRI. Diffusion-weighted imaging of three patients showed a higher intensity than free water (arrow). The cystic lesions showed high intense signal in the central part and iso-intense in the periphery.

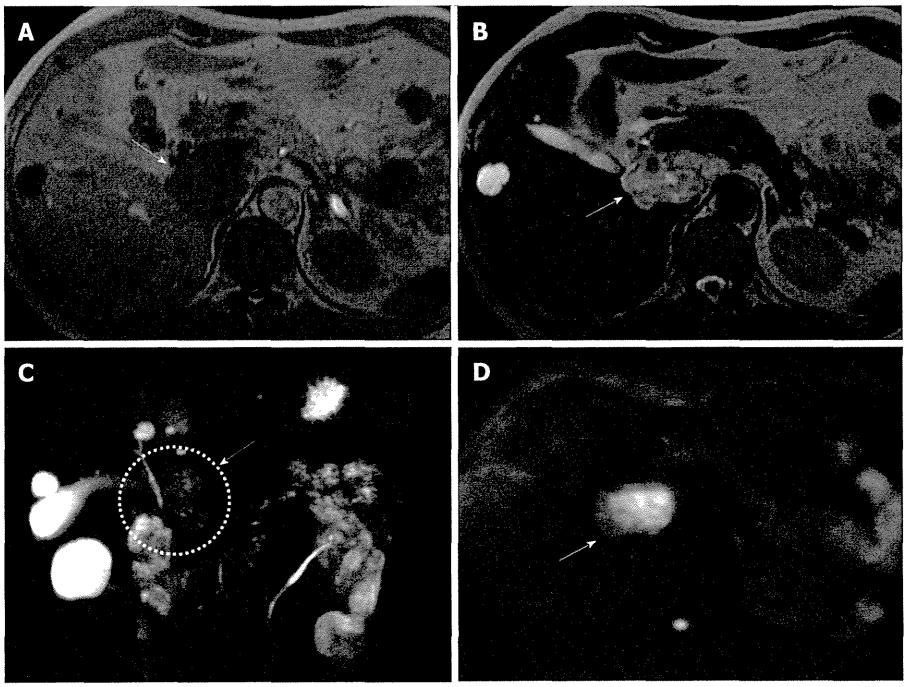

Figure 6 Findings of patient #4. A: Findings of T1-weighted imaging on magnetic resonance imaging (MRI). T1-weighted imaging of patient showed a higher intensity than free water (arrow); B: Findings of T2-weighted imaging on MRI. T2-weighted imaging of patient showed a lower intensity than free water (arrow); C: Findings of magnetic resonance cholangiopancreatography (MRCP). MRCP of patient showed a lower intensity than free water (arrow); D: Findings of diffusion-weighted imaging on MRI (arrow). Diffusion-weighted imaging of three patients showed a higher intensity than free water. The cystic lesions showed high intense signal in the central part and iso-intense in the periphery.

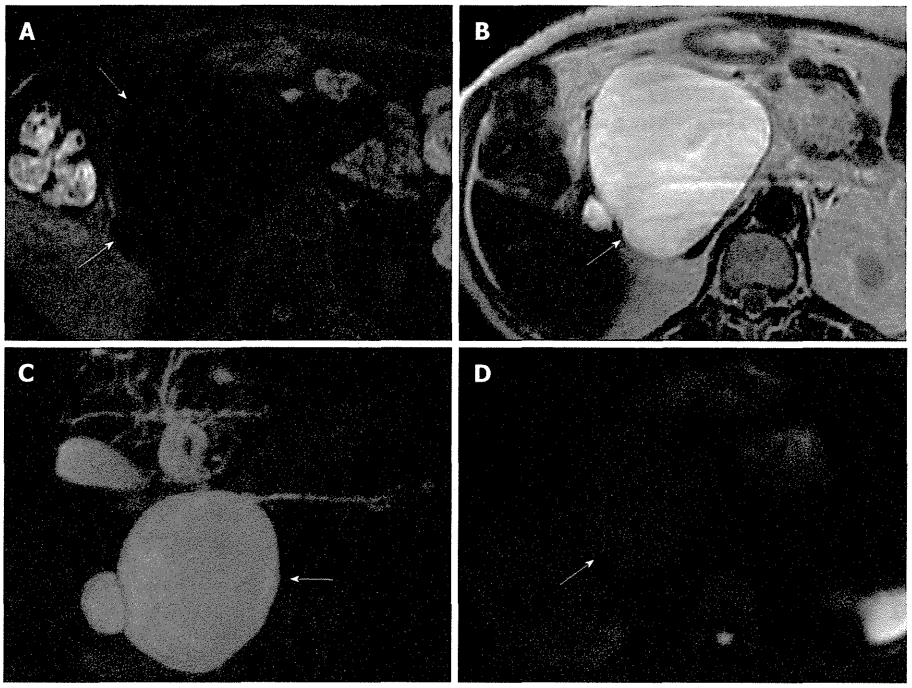

Figure 7 Findings of a case of serous cystic neoplasm. A: Findings of T1-weighted imaging on magnetic resonance imaging (MRI), the cystic lesion showed low intensity (arrow); B: Findings of T2-weighted imaging on MRI, the cystic lesion showed high intensity (arrow); C: Findings of magnetic resonance cholangiopancreatography, the cystic lesion showed high intensity (arrow); D: Findings of diffusion-weighted imaging on MRI, the cystic lesion showed high intensity (arrow).

Table 2 Feature of lymphoepithelial cyst of the pancreas

Characteristics	
Age, gender	Middle-aged and elderly men
Laboratory date	Elevation of serum CA19-9 level
The form	Well-defined
	Exophytic off the pancreatic parenchyma
	Multilocular (60%) or Unilocular (40%)
US findings	Mosaic pattern, depending on the degree of keratin formation
CT findings	Enhancement of the wall and septum of the cyst
	Low density cystic lesion without enhancement
	No pancreatic duct dilatation
MRI findings	
T1-weighted	Higher intensity than water
T2-weighted	Lower intensity than water
MRCP	Lower intensity than water
	No communication with the main pancreatic duct
Diffusion-weighted	Higher intensity than water

US: Ultrasonography; MRI: Magnetic resonance imaging; CT: Computed tomography; MRCP: Magnetic resonance cholangiopancreatography.

The form of a cystic lesion was well-defined and was exophytic off the pancreatic parenchyma. It might be multilocular or unilocular[12].

The US or EUS findings sometimes displayed a mosaic pattern, depending on the degree of keratin formation[5,13,14].

The CT findings demonstrated enhancement of the wall and septum of the cyst. The cyst itself showed uniform low density without enhancement[12]. The cyst contained no solid portions within it.

The MRI findings of the four patients we reviewed were characteristic of LEC, when comparing the intensity of the lesion with that of free water. Many cystic tumors have an intensity that is similar to that of free water on MRI. In contrast, T1-weighted imaging of LEC showed a higher intensity than that of free water because the content of LEC included keratin formation. T2-weighted imaging and MRCP showed lower intensity than that of free water[15]. Diffusion-weighted imaging showed higher intensity than that of free water[10]. In particular, on DWI, the cystic lesions showed high intense signal in the central part and iso-intense in the periphery. It seemed that the part showing high intense signal indicated keratin formation and iso-intense in periphery indicated the wall.

However, these findings should be cautiously interpreted, because MCN and IPMN can sometimes show similar signal intensity if bleeding into the cyst has occurred[16].

In summary, the clinical and radiological findings are sufficiently characteristic of LEC to establish a preoperative diagnosis for a majority of patients of LEC. It might be possible to select conservative treatment for asymptomatic patients with LEC.

COMMENTS

Case characteristics

Four cases were incidentally detected the pancreatic tumors and performed surgery.

Clinical diagnosis

Three patients had a multilocular cystic appearance and one patient had a unilocular cystic appearance.

Differential diagnosis

Serous cystic neoplasms, Mucinous cystic neoplasms, intraductal papillary mucinous neoplasms.

Laboratory diagnosis

Three patients had elevated serum CA19-9 levels.

Imaging diagnosis

All lesions were well-defined and were exophytic off the pancreatic parenchyma.

Pathological diagnosis

All of the lesions were pathologically diagnosed as the lymphoepithelial cyst.

Treatment

All of the lesions were surgically resected.

Related reports

A lymphoepithelial cyst of the pancreas has been thought to be difficult to differentiate from other pancreatic lesions.

Experiences and lessons

The authors found that the lymphoepithelial cyst was associated with unique characteristics on imaging findings. A preoperative diagnosis of the lymphoepithelial cyst may be possible by comprehensively evaluating its clinical and imaging findings.

Peer review

The discussion is simple. In this article, there were any findings about PET-CT and something else.

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Hepatic arterial infusion chemotherapy with gemcitabine and 5-fluorouracil or oral S-1 improves the prognosis of patients with postoperative liver metastases from pancreatic cancer

HIDEHIRO TAJIMA[1], HIROHISA KITAGAWA[1], TOMOYA TSUKADA[1], KOICHI OKAMOTO[1], SHIN-ICHI NAKANUMA[1], SEISHO SAKAI[1], ISAMU MAKINO[1], HIROYUKI FURUKAWA[1], HIRONORI HAYASHI[1], KATSUNOBU OYAMA[1], MASAFUMI INOKUCHI[1], HISATOSHI NAKAGAWARA[1], TOMOHARU MIYASHITA[1], HIROSHI ITOH[1], HIDETO FUJITA[1], HIROYUKI TAKAMURA[1], ITASU NINOMIYA[1], SACHIO FUSHIDA[1], TAKASHI FUJIMURA[1], TETSUO OHTA[1], WATARU KODA[2], TETSUYA MINAMI[2], YASUJI RYU[2], JUNICHIRO SANADA[2], TOSHIFUMI GABATA[2], OSAMU MATSUI[2] and YOSHIMICHI SAI[3]

Departments of [1]Gastroenterological Surgery and [2]Radiology, Division of Cancer Medicine, Graduate School of Medical Science, Kanazawa University; [3]Division of Pharmacy, Kanazawa University Hospital, Kanazawa, Ishikawa 920-8641, Japan

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Abstract. Hepatic metastasis is a common cause of treatment failure following resection of pancreatic cancer. In this study, we report our results of hepatic arterial infusion (HAI) chemotherapy with gemcitabine (GEM) plus 5-fluorouracil (5-FU) or oral S-1 treatment for postoperative liver metastases from pancreatic cancer. Seven patients with postoperative liver metastases from pancreatic cancer received HAI with GEM plus 5-FU or oral S-1 between October, 2008 and September, 2010 at Kanazawa University Hospital (Kanazawa, Japan). Three out of the 7 cases exhibited a partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) and stable disease (SD) was achieved in 3 out of the 7 cases (response rate, 85.7%). A decrease in serum tumor marker CA 19-9 levels was observed after 10 HAI treatment cycles in 5 out of the 7 cases. The median time to treatment failure was 8 months (range, 0-17 months). Adverse events included grade 3 leukocytopenia in 1 case and anemia in all 7 cases, although 5 out of the 7 patients were anemic prior to HAI therapy. Grade 2 thrombocytopenia was also observed in 2 cases. Non-hematological events, such as nausea, diarrhea, liver injury or neuropathy and life-threatening toxicities were not reported; however, 6 patients (85.7%) developed catheter-related complications and the HAI catheter and subcutaneous implantable port system had to be removed. These findings demonstrated that HAI may deliver high doses of chemotherapeutic agents directly into the tumor vessels, producing increased regional levels with greater effi acy and a lower incidence/severity of systemic side effects. In conclusion, HAI chemotherapy is a safe and effective treatment for liver metastases from pancreatic cancer.

Correspondence to: Dr Hidehiro Tajima, Department of Gastroenterological Surgery, Graduate School of Medical Science, Kanazawa University, 13-1 Takaramachi, Kanazawa, Ishikawa 920-8641, Japan
E-mail: hidetaji@staff.kanazawa-u.ac.jp

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Introduction

Pancreatic cancer is one of the major causes of cancer-related mortality worldwide, with a 5-year survival rate of <5% (1,2). For patients with localized disease, radical surgery may provide long-term benefits. However, even in patients who undergo resection, the reported 5-year survival rate remains low (7-24%) and the median survival is only ~1 year in most patient series, indicating that surgery alone is generally inadequate. Even following curative resection, patients with pancreatic cancer are likely to experience a 50-80% local recurrence rate and a 25-50% risk of developing distant metastases (3). Adjuvant chemotherapy with gemcitabine (GEM), the key drug used in the treatment of pancreatic cancer, improves the survival of patients with resectable pancreatic adenocarcinoma compared to resection alone (4), although to a limited extent.

However, 20-30% of patients are unable to receive the designated therapy due to postoperative complications, delayed surgical recovery and/or early disease recurrence (5,6). To improve the therapeutic results of resected pancreatic cancer, it is critical to optimize the postoperative management of liver metastases, which frequently constitute the major determining factor of prognosis.

An alternative treatment option that may be beneficial in pancreatic cancer patients with liver metastases is the hepatic arterial infusion (HAI) of chemotherapeutic agents. This treatment option has been applied to patients with primary or

metastatic hepatic malignancies that are confined to the liver and is soundly based on physiological and pharmacological factors. First, liver metastases that grow >2-3 mm depend on the hepatic artery for vascularization, whereas normal liver tissues are perfused by the portal vein (7,8). Second, HAI therapy allows drug delivery to hepatic metastases not achievable by systemic administration, particularly of drugs with a high systemic clearance rate (9). Third, first-pass hepatic extraction of certain drugs results in lower systemic concentrations and, thus, few systemic toxicities (10). Phase I studies of HAI chemotherapy with GEM in patients with liver malignancies have been previously published (8-10). Moreover, results from our recent pilot study suggest that HAI chemotherapy with GEM and 5-fluorouracil (5-FU) is safe and beneficial for the treatment of postoperative metastatic tumors confined to the liver, even in patients with poor general condition (11).

Over the past few years, we have expanded the number of cases treated with HAI chemotherapy with GEM at our institution to include cases with other metastases in addition to liver metastases, by the addition of oral S-1 in lieu of 5-FU. S-1 is an oral fluorinated pyrimidine compound developed by Taiho Pharmaceutical Co., Ltd., (Tokyo, Japan). The administration of oral S-1 is more convenient and simulates the effect of continuous infusion of 5-FU. The safety and effectiveness of the combination chemotherapy with GEM and S-1 for advanced pancreatic cancer were reported by previous studies (12-14) and a phase III (GEST) trial in Japanese patients demonstrated that S-1 was not inferior to GEM (15). In this study, we present the final results of the patients who were treated with HAI with GEM plus 5-FU or HAI with GEM and oral S-1.

Materials and methods

Patient eligibility. Seven patients with postoperative liver metastases from pancreatic cancer underwent HAI with GEM between October, 2008 and September, 2010 at Kanazawa University Hospital (Kanazawa, Japan). Patients with metastases confined to the liver following curative (R0) resection of the pancreatic primary adenocarcinoma underwent HAI with GEM plus 5-FU (GEM+5-FU group). However, patients with metastases confined to the liver following non-curative (R1 or R2) resection or cases that involved metastases to other organs along with liver metastases that may dictate prognosis, underwent HAI with GEM and oral S-1 administration (GEM+S-1 group). Written informed consent was obtained from each patient prior to enrollment in the study and the treatment was undertaken with the approval of the local Medical Ethics Committee.

The baseline characteristics of the patients are listed in Table I. Five out of the 7 patients received GEM plus 5-FU treatment and 2 received GEM plus S-1 treatment. The male:female ratio was 5:2. The median patient age was 64.9 years (range, 60-71 years). The Eastern Cooperative Oncology Group performance status score was 0 in all patients in this study. Four patients had received preoperative chemotherapy with GEM and oral S-1 and adjuvant chemotherapy with GEM had been administered to 5 out of the 7 patients prior to the appearance of liver metastases. The interval between surgery and the appearance of liver metastases was 7 months (range, 3-11 months). The median standard liver volume [SLV (ml) = 706.2 x body surface area (BSA) + 2.4] was 1.1 l (range, 9.0-1.3 l) (16).

Catheter placement and treatment regimen. An intrahepatic arterial catheter was percutaneously implanted following hepatic arteriography via a right femoral puncture to deliver chemotherapy. The catheter tip was placed in the hepatic artery proper by a radiologist. The catheter was then connected to a subcutaneous implantable port system, located in the lower right abdominal area. In the GEM+5-FU group, an 800-mg/SLV dose of GEM was dissolved in 50 ml of saline for administration over a 30-min period using a bedside pump. Following GEM infusion, a 250-mg/SLV dose of 5-FU dissolved in 50 ml of saline was infused continuously over 24 h on days 1-5, comprising 1 cycle of therapy. In case 1, only 400 mg of GEM was administered, due to the development of leukocytopenia (17). Each treatment cycle was continued biweekly on hospital days 1-6 (Fig. 1A). In the GEM+S-1 group, 60 mg/m^2/day of S-1 was administered for 7 consecutive days and an 800-mg/SLV dose of GEM was administered on day 8 as in the GEM+5-FU group. Each treatment cycle was continued biweekly in the outpatient clinic (Fig. 1B).

Assessment of response. Response to treatment was determined based on the following measures: results of physical examination, complete blood counts, biochemical tests and chest and abdominal radiography were obtained prior to the initiation of each cycle. Serum CA 19-9 was measured monthly and changes in this tumor marker were assessed prior to and following 10 HAI cycles. Follow-up contrast-enhanced computed tomography was performed upon completion of every 5 cycles, or more frequently for cases showing clinical deterioration. The response rate was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) (18). A complete response (CR) was defined as the disappearance of all evidence of disease and normalization of tumor markers persisting for at least 2 weeks. A partial response (PR) was defined as a >30% reduction on uni-dimensional tumor measurements, without the appearance of any new lesions or progression in any existing lesion. Progressive disease (PD) was defined as any of the following: i) a 20% increase in the sum of the products of all measurable lesions; ii) the appearance of any new lesion; or iii) the reappearance of any lesion that had previously disappeared. Stable disease (SD) was defined as a tumor response that did not fulfill the criteria for CR, PR or PD.

In the GEM+5-FU group, HAI of 5-FU was terminated after 10 cycles and administration of oral S-1 was initiated. Patients in the two groups received GEM HAI and administration of oral S-1 in the outpatient clinic for as long as possible, i.e., for as long as they exhibited no tumor regrowth or the appearance of any new lesions and were free of HAI catheter-related problems. The median survival time (MST) was calculated from the initiation of the study treatment until death and determined according to the Kaplan-Meier method.

Results

In 6 out of the 7 cases, >10 cycles of HAI chemotherapy were administered. In a single case (case 5), the HAI catheter and

Table I. Patient characteristics.

Case number	1	2	3	4	5	6	7
Age (years)	61	62	69	71	60	66	65
Gender	F	M	M	M	F	M	M
Performance status	0	0	0	0	0	0	1
Tumor location	H	H	BT	BT	BT	H	BT
Residual tumor	0	0	0	0	0	0	1
Preoperative chemotherapy	+	+	-	-	-	+	+
Postoperative chemotherapy	-	+	-	+	+	+	+
Interval between operation and liver metastases (months)	5	10	3	10	5	11	5
Body surface area (m^2)	1.6	1.7	1.8	1.5	1.3	1.7	1.5
Standard liver volume (l)	1.1	1.2	1.3	1.1	0.9	1.2	1.1
Other metastatic lesion prior to HAI	-	-	-	-	-	P	-
Group	GEM+5-FU	GEM+5-FU	GEM+5-FU	GEM+5-FU	GEM+5-FU	GEM+S-1	GEM+S-1

F, female; M, male; GEM, gemcitabine; 5-FU, 5-fluorouracil; H, head; BT, body and tail; P, peritoneal dissemination; HAI, hepatic arterial infusion.

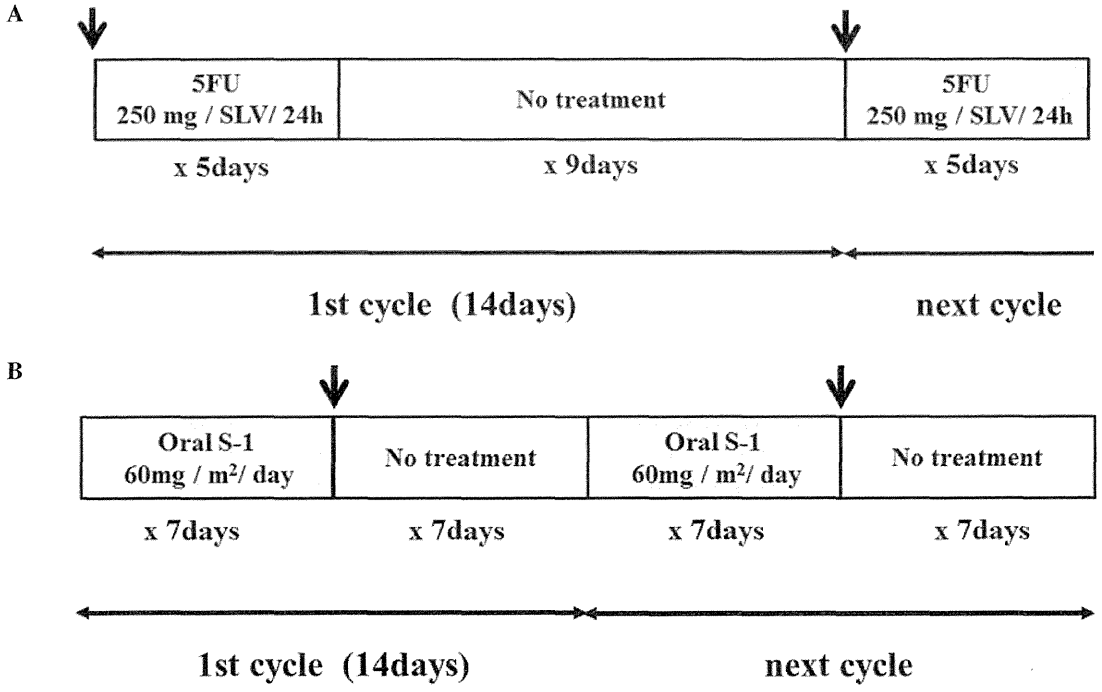

Figure 1. Treatment regimens of (A) gemcitabine (GEM) + 5-fluorouracil (5-FU) and (B) GEM+S-1 groups. (A) In the GEM+5-FU group, an 800-mg/SLV dose of GEM was administered over 30 min (arrow). Following GEM infusion, a 250-mg/SLV dose of 5-FU was administered continuously over 24 h on days 1-5, comprising 1 cycle of therapy. Each treatment cycle was continued biweekly on hospital days 1-6. (B) In the GEM+S-1 group, 60 mg/m^2/day S-1 was administered for 7 consecutive days and an 800-mg/SLV dose of GEM was administered on day 8 (arrow). Each treatment cycle was continued biweekly in the outpatient clinic.

subcutaneous implantable port system had to be removed after eight cycles due to a problem with the tube. Based on RECIST, PR was achieved in 2 out of the 7 cases and SD was achieved in 4 (response rate, 85.7%). CR was not achieved in any of the cases, whereas PD was observed in 1 case. In 5 out of the 7 cases, decreases in the serum tumor marker CA 19-9 levels were observed after 10 cycles of HAI treatment. The median time to treatment failure was 8 months (range, 0-17 months). The initial disease progression factor was nodal and lung metastasis in 3 cases and local recurrence plus peritoneal

Table II. Treatments and responses.

Case number	1	2	3	4	5	6	7
GEM administration (cycles)	13	40	23	10	8	15	12
5-FU administration (cycles)	10	10	10	10	6	0	0
S-1 administration (cycles)	3	30	13	0	2	15	12
Response	SD	PR	PR	PR	SD	SD	PD
TTF (months)	15	17	7	8	3	6	0
Other metastatic lesion	L, N	N, P	Lg	L, Lg	N	P	Lg
Other chemotherapy	Tx	Tx	Tx	Tx	Tx	Tx	Tx
Other therapy	RT	RT	-	-	-	-	-
Survival following HAI (months)	23	26	13	20	13	16	11
Catheter problems	+	+	-	+	+	+	+
CA19-9 prior to HAI (U/ml)	138	14	311	2,073	43,460	423	37
CA19-9 following 10 HAI cycles (U/ml)	33	65	221	811	32,200	34	1,060

GEM, gemcitabine; 5-FU, 5-fluorouracil; SD, stable disease; PR, partial response; PD, peritoneal dissemination; TTF, time to treatment failure; L, local recurrence; N, lymph node metastasis; Lg, lung metastasis; Tx, taxane; RT, radiation therapy; HAI, hepatic arterial infusion; CA 19-9, carbohydrate antigen 19-9.

dissemination in 2. The overall survival time from the initiation of the study treatment until death was 17.4 months (range, 11-26 months) (Table II).

Adverse events are listed in Table III. Grade 3 leukocytopenia was observed in case 1; this patient was not able to receive adjuvant systemic chemotherapy due to grade 2 leukocytopenia prior to HAI. Leukocytopenia was also observed in 1 of the remaining 6 cases. The patients were anemic; however, 5 out of the 7 patients had developed anemia prior to HAI therapy. Grade 2 thrombocytopenia was observed in 2 cases. Non-hematological events, such as nausea, diarrhea, liver injury (AST/ALT increase), or neuropathy were not observed. Of note, there were no life-threatening toxicities. However, catheter-related complications (arterial thrombosis or catheter dislocation) occurred in 6 cases (85.7%) and the HAI catheter and subcutaneous implantable port system had to be removed (Table II). All 7 patients eventually succumbed to the primary disease. The MST was 22.4 months (Fig. 2).

Table III. Treatment toxicities (NCI-CTC grade)

Case number	1	2	3	4	5	6	7
Anemia	2[a]	2[a]	1	1[a]	2[a]	2[a]	1
Leukocytopenia	3[b]	0	0	0	0	2[a]	0
Thrombocytopenia	2[a]	1	0	2	0	1[a]	0
Nausea	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	0	0	0
Liver injury	0	0	0	0	0	0	0
Neuropathy	0	0	0	0	0	0	0

[a]Grade 1 prior to hepatic arterial infusion (HAI) initiation, [b]grade 2 prior to HAI initiation. NCI-CTC, National Cancer Institute-Common Toxicity Criteria.

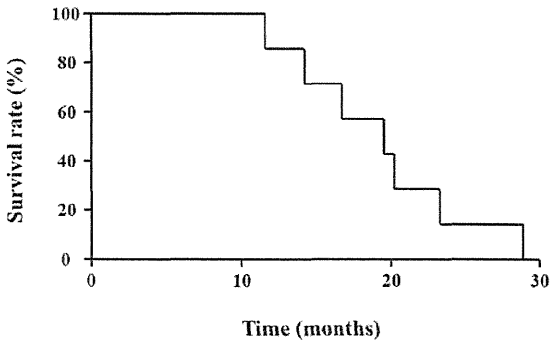

Figure 2. Overall survival curve for patients from the initiation of the hepatic arterial infusion (HAI) study treatment. All 7 patients eventually succumbed to the primary disease. The median survival time (MST) was 22.4 months.

Discussion

Pancreatic cancer is almost always fatal, with a 5-year survival rate of <5% (1,2). Surgery remains the only curative option and usually consists of radical pancreatic resection, including wide lymph node dissection and complete removal of the extra-pancreatic nerve plexus of the superior mesenteric artery or celiac axis (19,20). Adjuvant chemotherapy improves the survival of patients with resectable pancreatic adenocarcinoma compared to resection alone (4), although to a limited extent. However, 20-30% of patients are unable to receive the designated therapy due to postoperative complications, delayed surgical recovery and/or early disease recurrence (5,6). In particular, the appearance of liver metastases early in the postoperative period significantly contributes to a poor prognosis in postoperative patients. For these patients, HAI chemotherapy, which has less of an effect on the body as a whole, may provide an effective treatment alternative to standard adjuvant chemotherapy.

Arterial infusion chemotherapy with GEM and 5-FU has been reported as a treatment for locally advanced pancreatic cancer and liver metastases from pancreatic cancer (10,21,22).