Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.5449-20
Intern Med 60: 223-229, 2021
http://internmed.jp

【 CASE REPORT 】

Hepatic Arterial Infusion Chemotherapy for Liver Metastases Following Standard Chemotherapy for Pancreatic Cancer

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Abstract:
A 65-year-old man diagnosed with locally advanced pancreatic cancer underwent distal pancreatectomy and combined portal vein resection. One month after surgery, contrast-enhanced magnetic resonance imaging revealed multiple liver metastases. We administered two courses of gemcitabine plus nab-paclitaxel combination therapy followed by 17 modified FOLFIRINOX courses. However, the response was insufficient, and the patient thereafter developed grade 3 neutropenia, which made it difficult to continue the treatment regimen. As a result, we administered hepatic arterial infusion chemotherapy comprising gemcitabine plus 5-fluorouracil because the residual tumor was limited to liver metastases. The progression-free survival period was 7 months, and no drug-related adverse effects were noted during the treatment.

Key words: hepatic arterial infusion chemotherapy, liver metastases, recurrent pancreatic cancer

(Intern Med 60: 223-229, 2021)
(DOI: 10.2169/internalmedicine.5449-20)

Introduction

Pancreatic cancer is either the fourth or fifth most frequent cause of death from cancer in most developed countries. Despite developments in the detection and management of pancreatic cancer, only approximately 4% of patients are able to survive for 5 years after their diagnosis (1). In Japan, the median survival time (MST) of all patients with pancreatic cancer from 2001 to 2004 was 10.2 months, and the 3-year survival rate was 11.7%. The MST for all resected cases was 18.2 months, and the 3-year survival rate was 23.2% (2).

Recurrent pancreatic cancer (RPC) generally has a poor prognosis. Groot et al. (3) reported that the median overall survival of 662 patients with postoperative recurrence of pancreatic cancer was 21.1 months. Chemotherapy is the standard therapy for RPC but it has limited efficacy and it is also associated with serious adverse events.

Hepatic arterial infusion chemotherapy (HAIC) is a treatment strategy that involves local delivery of anticancer drugs into the nutrient vessel of a tumor directly via an implantable port to increase the concentration of drugs locally and reduce systemic adverse events. We herein report one patient who received HAIC for RPC that was limited to liver metastases following standard chemotherapy.

Case Report

A 65-year-old Japanese man was initially diagnosed with borderline resectable pancreatic cancer (solid tumor contacted with portal vein more than 180°, but allowing for safe and complete resection and vein reconstruction) (Fig. 1a, b). As no distant metastases and tumor progression were noted after neoadjuvant chemoradiation [30 Gy/10 fractions+oral tegafur/gimeracil/oteracil combination therapy (S-1) for 10 days], he underwent distal pancreatectomy and combined portal vein resection in September 2017. The tumor stage was found to be T3N1M0 (stage II b) according to the UICC TNM classification 8th edition (Fig. 1c, d). At 1 month after the surgery, contrast-enhanced magnetic resonance imaging revealed multiple liver metastases (Fig. 2).

Initially, we administered two courses of gemcitabine plus nab-paclitaxel (GnP); however, contrast-enhanced computed

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Received: May 26, 2020; Accepted: July 26, 2020; Advance Publication by J-STAGE: September 19, 2020
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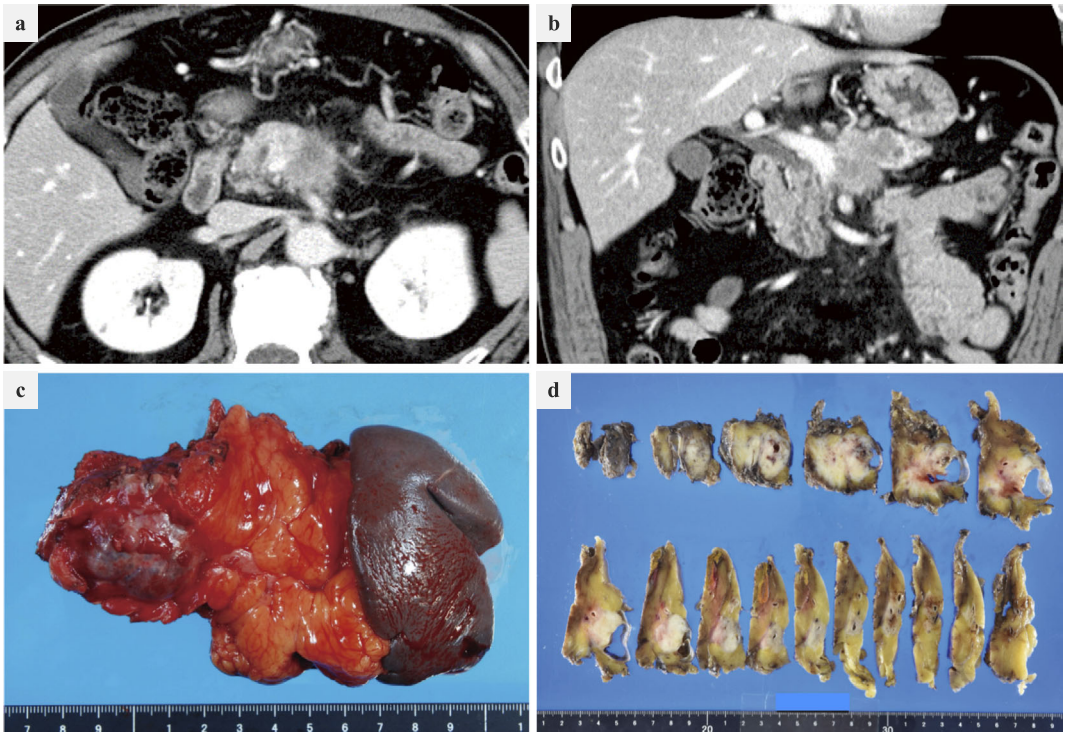

Figure 1. **(a, b) Abdominal contrast-enhanced computed tomography image showing a 45-mm ischemic mass in the pancreatic body. (c, d) Resected pancreatic cancer specimen. Pathological examination reveals invasive ductal carcinoma of the pancreas body with two metastatic regional lymph nodes. The tumor stage was found to be T3N1M0 (stage II b) according to the UICC TNM classification 8th edition.**

tomography after 2 months showed tumor growth, and we could not continue the treatment according to the standard regimen because the patient developed grade 3 neutropenia. Thereafter, we administered 17 courses of modified FOLFIRINOX. However, as grade 3 neutropenia in the patient recurred, we had to administer granulocyte colony-stimulating factor (G-CSF) concomitantly to continue the treatment according to the standard regimen. In addition, renal dysfunction, neuralgia, and dysgeusia (all grade 1) were all observed (Fig. 3). The treatment seemed to be effective, but nevertheless both the tumor and tumor markers increased again.

As the residual tumor was limited to liver metastases, we administered HAIC using gemcitabine (GEM) and 5-fluorouracil (5-FU) after obtaining approval from the relevant ethical review board in October 2018. We placed an anticoagulant-coated indwelling catheter (5-Fr W spiral catheter, Piolax Medical Devices, Yokohama, Japan) into the peripheral branch of the hepatic artery and positioned the handmade side hole at the common hepatic artery (Fig. 4). Then, we connected the catheter to a subcutaneous implantable port system located in the right thigh. GEM [800 mg/standard liver volume (SLV)] was administered over 30 min on the 1st day. Subsequently, 250 mg of 5-FU was administered continuously over 24 hours for days 1-6. Each treatment cycle was continued biweekly (Fig. 5). The SLV was calculated as follows: (706.2×body surface area+2.4)/1,000 (4).

We administered a total of 14 courses of the regimen. The progression-free-survival period was 7 months (Fig. 6), and no drug-related adverse events were noted during treatment (Fig. 7). The overall status of the patient was generally good. However, after the 14th cycle (7 months since the initial HAIC), peritoneal dissemination was detected. Thereafter, additional systemic chemotherapy comprising GEM plus S-1 was performed, but could not be continued owing to a jejunal passage disorder. The patient was able to eat after gastrojejunostomy, but his general condition did not improve sufficiently to continue additional chemotherapy. He died 2 years after the initial visit.

Discussion

After the radical resection of pancreatic cancer, approximately 80% of patients would develop recurrence (3). A meta-analysis showed that the weighted median rate of initial recurrence in the liver after resection of pancreatic cancer was 26.5% (5). Pancreatic cancer has a poor prognosis for postoperative recurrence, especially liver recurrence (3, 6). Therefore, the control of liver recurrence is important to improve the prognosis after surgery.

Chemotherapy is the standard therapy for RPC but has limited efficacy. In Japan, FOLFIRINOX and GnP are used as first-line therapies. However, the MST in phase-III studies has not been satisfactory (11.1 and 8.5 months for FOLFIRINOX and GnP, respectively) (7, 8). Furthermore, chemo-

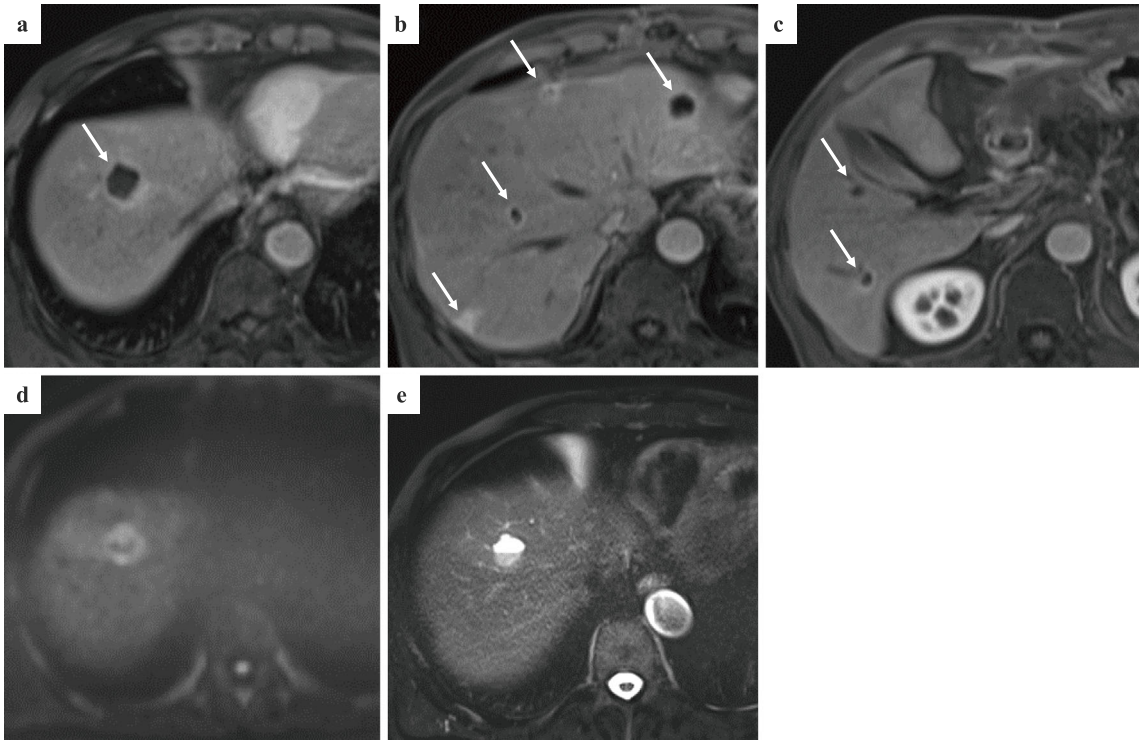

Figure 2. **(a-c) One month after the surgery, gadolinium ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging revealed new multiple tumors with perilesional ring enhancement in the arterial phase (arrows). (d) Diffusion-weighted image shows perilesional high signal that is not shown in the center. (e) T2-weighted HASTE image shows hyperintense lesions with a fluid-fluid level, which is considered to be an intratumoral hemorrhage. There were no symptoms or blood biochemical findings suggestive of infection; therefore, we ruled out abscesses from our differential, and considered the presence of multiple lesions to be metastases. HASTE: half-Fourier acquisition single-shot turbo spin echo**

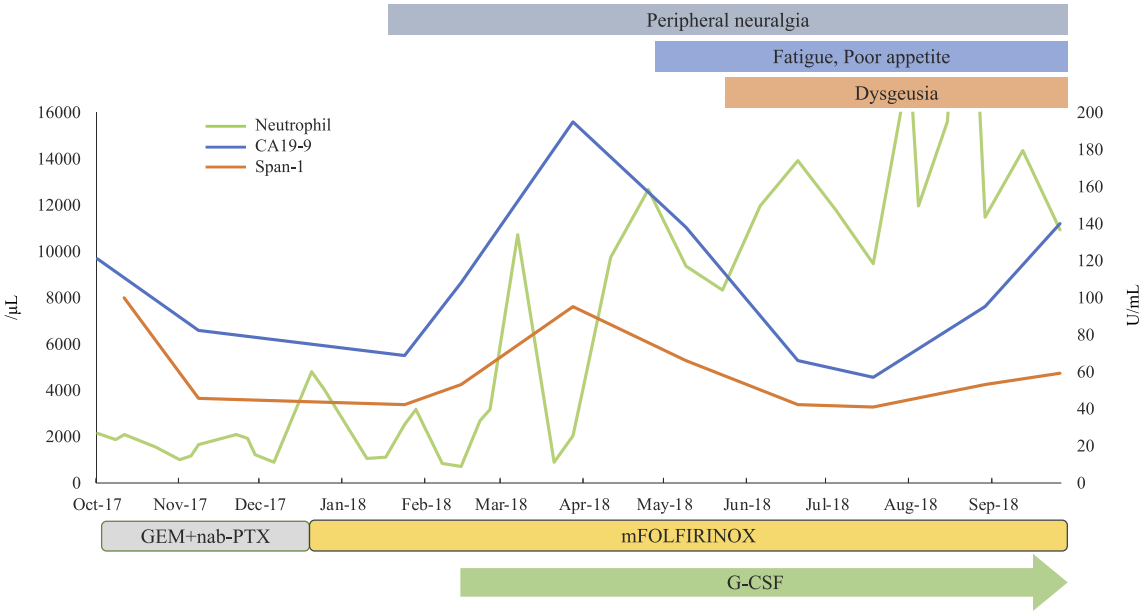

Figure 3. **The clinical course of the patient after surgery, along with the details of the course of chemotherapy and adverse events. G-CSF had to be administered to the patient for grade 3 neutropenia. G-CSF: granulocyte colony-stimulating factor**

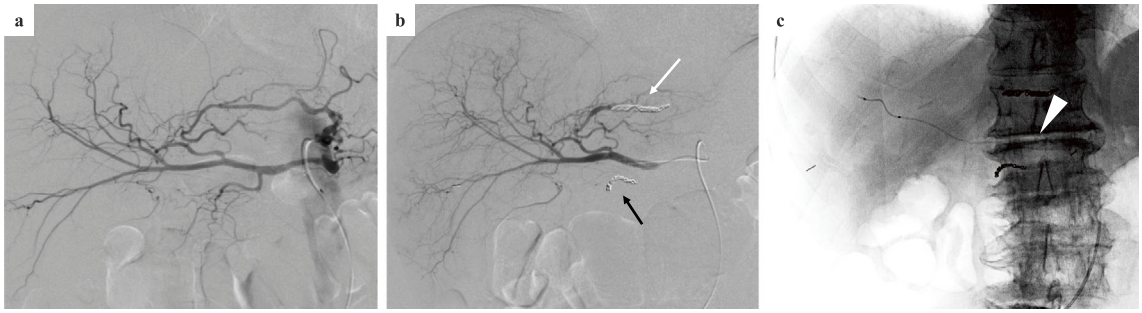

Figure 4. **(a) Abdominal angiogram revealing the replaced left hepatic artery. (b) It was embolized with microcoils to redistribute the entire hepatic arterial flow from multiple arteries into a single artery (white arrow). The gastroduodenal artery was also embolized to prevent chemotherapeutic agent distribution to the gastrointestinal tract (black arrow). (c) An anticoagulant-coated indwelling catheter (5-Fr W spiral catheter, Piolax Medical Devices, Yokohama, Japan) was placed. The catheter tip was inserted into the peripheral branch of the hepatic artery, and the handmade side hole (arrow head) was positioned at the common hepatic artery.**

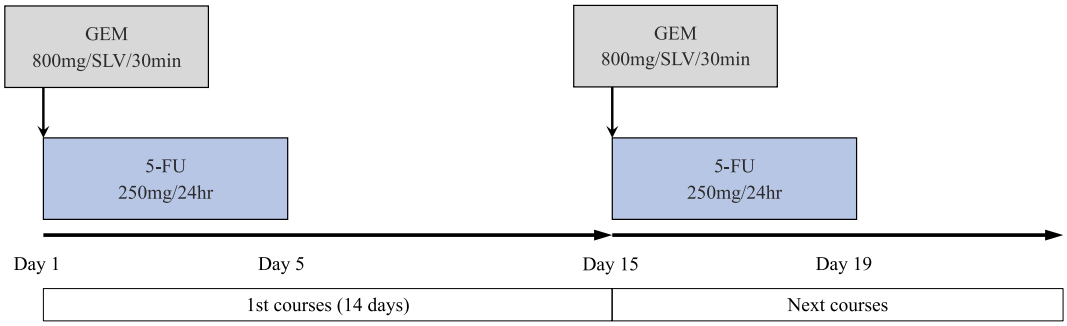

Figure 5. **The treatment regimen of hepatic arterial infusion chemotherapy (GEM plus 5-FU combination therapy). GEM (800 mg/SLV) was administered over 30 min on the 1st day. Subsequently, 250 mg of 5-FU was continuously administered over 24-h for days 1-6. Each treatment cycle was continued biweekly. The SLV was calculated as follows: (706.2×body surface area+2.4)/1,000 (4). GEM: gemcitabine, 5-FU: 5-fluorouracil, SLV: standard liver volume**

therapy is associated with serious adverse events. In phase-III studies, grade 3 or 4 neutropenia occurred in 45.7% and 37.8% of cases for FOLFIRINOX and GnP, respectively (7, 8). In the present case, the patient could not continue treatment with the standard drug volumes and needed concomitant G-CSF for severe neutropenia due to systemic chemotherapy. At present there is no strongly recommended second-line therapy (9). As such, we often experience a lack of chemotherapeutic methods and selectable drugs despite a patient's good general condition.

Arterial infusion is suggested to take advantage of the first pass effect of chemotherapeutic drugs by increasing their concentrations locally at the tumor cell membrane and enhancing cellular drug uptake (10). Previous reports, in which HAIC was used as an adjuvant chemotherapy or treatment for postoperative liver metastases for pancreatic cancer, are summarized in Table (11-18). There are many regimens using 5-FU and GEM. Adjuvant chemotherapy is common, and there are few reports where HAIC was used as a treatment for postoperative liver metastases. Hashimoto et al. (11) performed HAIC using 5-FU combined with systemic GEM for liver metastases after pancreatectomy in nine patients. In their report, the overall response and disease control rates were 44.4% and 88.9%, respectively. There were two cases of a complete response. The appropriate hepatic arterial infusion doses and flow rates for GEM and 5-FU have been reported previously (19-23). Tajima et al. (23) analyzed seven cases, in which the GEM concentration in the peripheral blood was measured after hepatic arterial infusion and concluded that 800 mg/SLV was the optimal dose. Tajima et al. (12) also adopted 250 mg of 5-FU as a dose with low adverse events based on peripheral blood concentrations when injected into the hepatic artery over a 24-h period. Their regimen was referred to in the present case.

HAIC seemed to be effective in the present case. A unique aspect of this case was the fact that the effect could be obtained by changing the drug administration method used in the preceding systemic chemotherapy to arterial injection. It was also noteworthy that the patient lived a normal life without any adverse events during the treatment course.

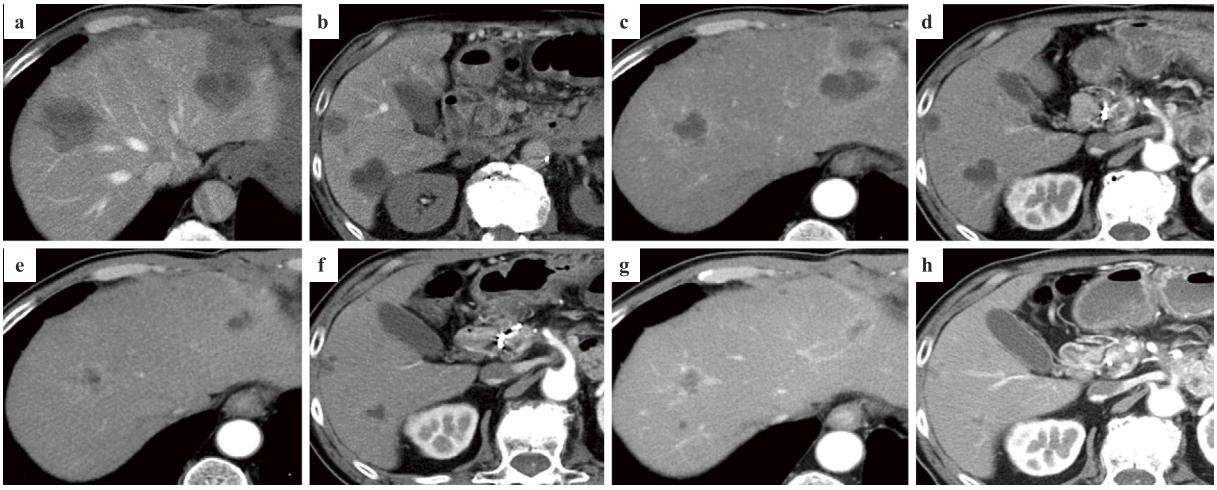

Figure 6. **Follow-up contrast-enhanced computed tomographic image revealing a decrease in the size of the liver metastases. There was no local recurrence or distant metastasis except for the liver. (a, b) Computed tomography findings during arterial portography before HAIC; (c, d) after the second treatment cycle; (e, f) after the sixth treatment cycle; (g, h) after the 10th treatment cycle. HAIC: hepatic arterial infusion chemotherapy**

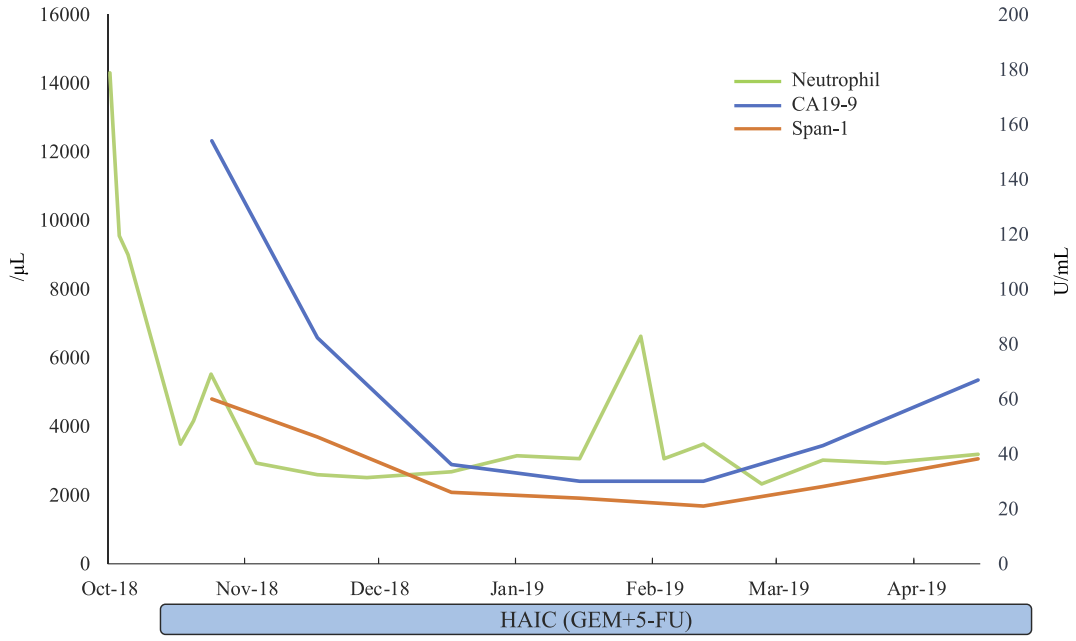

Figure 7. **The clinical course of the patient. Hepatic arterial infusion chemotherapy was continued up to the 14th cycle without any adverse events. The graph shows the reduction of tumor markers and stable neutrophil count.**

One of the disadvantages in the use of the regimen adopted in the present case was that it required the hospitalization of patients for 5-6 days every 2 weeks. It is important to devise a dosing regimen that allows outpatient chemotherapy to improve patient acceptance. It may also be possible to improve the therapeutic effect by changing the order of administration of chemotherapeutic drugs (e.g., administering 5-FU before GEM). 5-FU leads to an increase in the major mediator of the cellular uptake of GEM (24). In addition, it is unclear whether controlling liver metastases with HAIC improves the prognoses. In our case, peritoneal dissemination was finally deemed to be associated with the prognosis. Pancreatic cancer is a systemic disease and the application of local therapy alone presents critical limitations. Zheng et al. (13) in their randomized controlled trial reported that HAIC combined with systemic chemotherapy after pancreatectomy for pancreatic cancer significantly prevented liver metastases and improved the prognosis compared with systemic chemotherapy only. Their report does not adapt to chemotherapy for recurrent tumors, which was similar to that in our case, but it is important evidence that the combination of HAIC and systemic chemotherapy im-

Table. Previous Reports of Hepatic Arterial Infusion Chemotherapy as an Adjuvant Chemotherapy or Treatment for Postoperative Liver Metastases for Pancreatic Cancer (excluding Case Reports).

Reference	Study design	n	Aim	Treatment before HAIC	HAIC Regimen	Concurrent therapy or Monotherapy	Followed treatment	MST
14	prospective	15	ACT	NACRT 24Gy+5-FU	5-FU 125mg/d 28days	+LPC via portal vein 5-FU 125mg/d 28days	CRT 36Gy+SCT 5-FU 500mg/d 6days	62.0m
15	prospective phase2 study	27	ACT		5-FU 125mg/24h 21-28days	+LPC via portal vein 5-FU 125mg/24h 21-28days	SCT GEM 1,000mg/m2 /2w, at least 12c	27.5m
16	pilot study	5	chemotherapy for PLM	±NAC GEM+S-1, ±ACT GEM	GEM 800mg (d1)+5-FU 250mg (d1-5)/2w			22.4m
17	retrospective	31	ACT		5-FU 1,000mg/m2(d1, 8, 15)/4w, 3c	±SCT GEM 1,000mg/m2(d1, 8, 15)/4w, 3c	SCT GEM 1,000mg/m2 (d1, 8, 15)/4w, 3c	37.7m
11	retrospective	9*	chemotherapy for PLM	±NACRT 50-54Gy+GEM	5-FU 1,000mg/m2(d1,8,15)/4w, repeated	±SCT GEM 1,000mg/m2		14.1m†
		42*	ACT		5-FU 1,000mg/m2(d1,8,15)/4w, 3c	±SCT GEM 1,000mg/m2		36.8m
12	retrospective	5	chemotherapy for PLM	±NAC GEM+S-1, ±ACT GEM	GEM 800mg/SLV(d1)+5-FU 250mg/SLV/24h (d1-5)/2w			22.4m
		2			GEM 800mg/SLV(d8)/2w	+S-1 60mg/m2/d (d1-7)/2w		
13	RCT	52	ACT		GEM 800mg/m2 (d1,8)+5-FU 1,000mg/m2(d1), 2c		SCT GEM 800mg/m2 (d1, 8)+5-FU 1,000mg/m2(d1), 4c	30.0m‡
		54				SCT GEM 800mg/m2(d1,8)+5-FU 1,000mg/m2(d1), 6c		23.0m‡
18	retrospective	93	ACT	±NACRT 50-54Gy+GEM	5-FU 1,000mg/m2(d1, 8, 15)/4w, 3c	+SCT GEM 1,000mg/m2(d1, 8, 15)/4w	SCT GEM, 3c	44.0m

*: includes 2 periampullary cancer, †: median survival time from beginning of HAIC, ‡: inferred from Kaplan-Meier curve. ACT: adjuvant chemotherapy, PLM: postoperative liver metastases, HAIC: hepatic arterial infusion chemotherapy, NACRT: neoadjuvant chemoradiotherapy, NAC: neoadjuvant chemotherapy, LPC: liver perfusion chemotherapy, SCT: systemic chemotherapy, CRT: chemoradiotherapy, RCT: randomized controlled trial, 5-FU: 5-fluorouracil, GEM: gemcitabine, S-1: oral tegafur/gimeracil/oteracil combination therapy, SLV: standard liver volume, n: number of patients, MST: median survival time, c: cycles, h: hours, d: day, w: weeks, m: months

proved the prognosis of patients after surgery for pancreatic cancer. To perform effective treatments, it is therefore important to consider a combination of HAIC with systemic chemotherapy to control local recurrences and occult extrahepatic metastases.

To date, HAIC appears to be a useful method for local control in cases where effective chemotherapy cannot be administered in sufficient volume due to adverse events caused by systemic administration, and it plays a significant role in performing effective multidisciplinary treatment.

Conclusion

In the present case, HAIC caused no major adverse events and it may therefore be a useful technique for administering chemotherapy for the local control of RPC that is limited to liver metastases.

The authors state that they have no Conflict of Interest (COI).

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