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CASE REPORT

Transarterial Chemoembolization with Irinotecan-loaded Beads Followed by Arterial Infusion of 5-Fluorouracil for Metastatic Liver Tumors Refractory to Standard Systemic Chemotherapy

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Abstract:
We report two cases of liver metastases from colorectal and anal cancers after the failure of systemic chemotherapies that were successfully treated with a combination therapy of transarterial chemoembolization using irinotecan-loaded drug-eluting beads and hepatic arterial infusion chemotherapy. In both cases, hepatic arterial infusion chemotherapy was performed as maintenance therapy after irinotecan-loaded drug-eluting beads. Irinotecan at a dose of 120 mg was loaded on drug delivery beads for irinotecan-loaded drug-eluting bead-transarterial chemoembolization. A weekly high-dose 5-fluorouracil regimen (1000 mg/m^2/5 h) was used for hepatic arterial infusion chemotherapy. The liver metastases shrank remarkably in both cases, and progression-free survivals of 13 and 9 months, respectively, were obtained without any severe adverse events.

Keywords:
embolization, colorectal cancer, TACE

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Introduction

Previously published studies have reported that transarterial chemoembolization (TACE) using irinotecan-loaded drug-eluting beads (DEBIRI) might be effective for colorectal liver metastases, with a high response rate of 51.1%-75.0% [1]. However, in cases with the failure of systemic chemotherapy, tumors often increase rapidly, even after massive tumor necrosis obtained via DEBIRI. Conversely, performing repeated sessions of DEBIRI-TACE over a short time is impractical because of poor tolerance and a high risk of severe complications. At present, few treatment options are available for maintaining the efficacy of DEBIRI-TACE in such heavily pretreated patients.

Several researchers have previously demonstrated the efficacy of hepatic arterial infusion chemotherapy (HAIC) in patients with colorectal liver metastases refractory to standard systemic chemotherapy. Although the response rate of HAIC is not high, at only 12.4%-18.2%, the disease control rate of 64.0%-70.9% seems promising and adverse events (AEs) are tolerable [2-4].

Therefore, we considered that the combination therapy of DEBIRI-TACE followed by HAIC might be a promising therapy. Because a high tumor response greatly improves patient prognosis, DEBIRI-TACE with a higher response rate was performed first before the introduction of HAIC in our cases. Subsequent performance of HAIC might be expected to extend the interval of tumor growth suppression by DEBIRI. Here, we report two cases that responded to this combination therapy and discuss the possible advantages of this treatment approach.

We obtained our Institutional Review Board (IRB) approval for the use of DEBIRI in these patients. At our institution, case reports do not require IRB approval. Written informed consent was obtained from both patients for providing the treatments.

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Case Reports

Case 1

The patient was a 79-year-old woman who was diagnosed with colorectal cancer and liver metastases (cT4aN2M1a, Stage IVa) with Kras mutation. She underwent laparoscopic left hemicolectomy. After three courses of chemotherapy with S-1 and oxaliplatin (SOX) + bevacizumab (Bmab), partial hepatectomy was performed (Segments 2, 3, and 6 resection). Postoperatively, she was given chemotherapy with SOX + Bmab (one course), S-1 + Bmab (one course), and Bmab alone (three courses). Owing to AEs, such as fatigue, appetite loss, and numbness in the limbs, she refused further systemic chemotherapies. Eleven months after hepatectomy, multiple liver metastatic recurrences were detected. Although seven courses of capecitabine and Bmab were administered, the metastasis increased in size. She again refused further systemic chemotherapies. At that time, her Eastern Cooperative Oncology Group performance status (ECOG PS) was 0. A liver metastatic lesion with a diameter of 42 mm was found in the right lobe, along with three small metastases. There were no extrahepatic metastases.

DEBIRI-TACE was performed using 120-mg irinotecan loaded on 100-300-μm DC beads (Boston Scientific Co., Marlborough, MA, USA). First, saline was ejected from the vial using a filter needle. Next, 120-mg irinotecan solution (Nippon Kayaku Co., Ltd., Tokyo, Japan) was mixed with 100-300-μm DC beads. The syringe mixed with DC beads and irinotecan solution was inverted every 5 min for 30 min. After the loading of irinotecan was completed, the supernatant was ejected. Then, the irinotecan-loaded microspheres were mixed with 10 mL of contrast material (iopamidol 300 mg/mL). Before injection, diluted contrast material was mixed with the irinotecan-loaded microspheres for further dilution of the microspheres. The final dilution ratio was 30-60 times. The endpoint of the injection was the disappearance of the tumor staining. Intravenous dexmedetomidine (dexmedetomidine intravenous solution, Nipro Corp., Osaka, Japan) and fentanyl (fentanyl injection, Daiichi Sankyo, Tokyo, Japan) were used during the DEBIRI-TACE procedure and were continuously infused until the next morning to reduce intraoperative and postoperative pain. Contrast-enhanced CT (CE-CT) 1 week after the initial DEBIRI-TACE showed that most of the enhancement area in the tumor had disappeared. Next, HAIC was introduced as a maintenance therapy. An indwelling catheter-port system, Anthron PU catheter and Selsite Port (Toray Medical, Urayasu, Japan), was placed. The catheter tip was inserted into the gastroduodenal artery and fixed using metallic coils, and the side hole was placed in the common hepatic artery. A weekly high-dose 5-fluorouracil (WHF) regimen (1000 mg/m^2/5 h) was administered. DEBIRI-TACE was performed twice during the 12 courses of HAIC. The treatment period for this combination therapy was 3.5 months. AEs graded according to Common Terminology Criteria for Adverse Events version 5.0 included grade 1 abdominal pain and nausea. CE-CT at 4 months after the initial DEBIRI-TACE revealed complete response (CR) based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST) (**Fig. 1**). The CR was sustained for 9 months without any additional treatment until the recurrence of the liver metastases. She is still alive and receiving systemic chemotherapy. Consequently, the progression-free survival (PFS) was 13 months from the first DEBIRI-TACE.

Case 2

The patient was a 76-year-old man who had been diagnosed with anal cancer stage IIIb (cT2N3M0). The pathological phenotype was adenocarcinoma without a Kras mutation. In accordance with the treatment protocol for colorectal cancer, he had received seven courses of neoadjuvant chemotherapy with SOX + panitumumab (Pmab), followed by laparoscopic abdominoperineal resection. Despite 10 courses of adjuvant chemotherapy with irinotecan and S-1 (IRIS) with Bmab, multiple liver metastases were found, which increased in size despite SOX + Pmab therapy. At that time, his ECOG PS was 0. Owing to the failure of these two standard chemotherapy regimens and the absence of extrahepatic metastases, DEBIRI-TACE was planned.

The DEBIRI-TACE technique was the same as that in Case 1. A microcatheter was inserted into the tumor-feeding arteries in the subsegmental levels, and irinotecan-loaded 100-300-μm DC beads were injected. At the 1 month follow-up CE-CT, a large part of the tumor had a low density, suggesting a partial response (PR). However, because peritoneal lymph node metastases newly developed, radiotherapy (40 Gy/16fr) was performed along with S-1 therapy. During this chemoradiotherapy for 4 weeks, the liver metastases rapidly increased. Then, a second session of DEBIRI-TACE was performed, once again resulting in a PR. Owing to the rapid tumor growth, we considered that effective maintenance therapy was required, and hence, we planned to perform HAIC.

An indwelling catheter-port system, 2.7-Fr W-Spiral coaxial catheter (Piolax, Inc., Yokohama, Kanagawa, Japan), was placed, and a WHF regimen was administered. The patient received 13 courses of HAIC (**Fig. 2**). During the weekly HAIC, the third DEBIRI-TACE was performed from the inferior phrenic artery (IPA) for the tumor located in liver segment 7, which was growing because of the lack of distribution of 5-FU to this area. No complications were observed with DEBIRI-TACE from the IPA. The liver metastases were maintained in a state of PR for 9 months after the initial DEBIRI-TACE. AEs of grade 1 abdominal pain and nausea, grade 3 aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations, and grade 3 anemia were observed during the treatment period. The anemia appeared 3 weeks after the chemoradiotherapy for lymph node metastasis. The patient finally passed away 11 months after the initial DEBIRI-TACE because of infection caused by ileus.

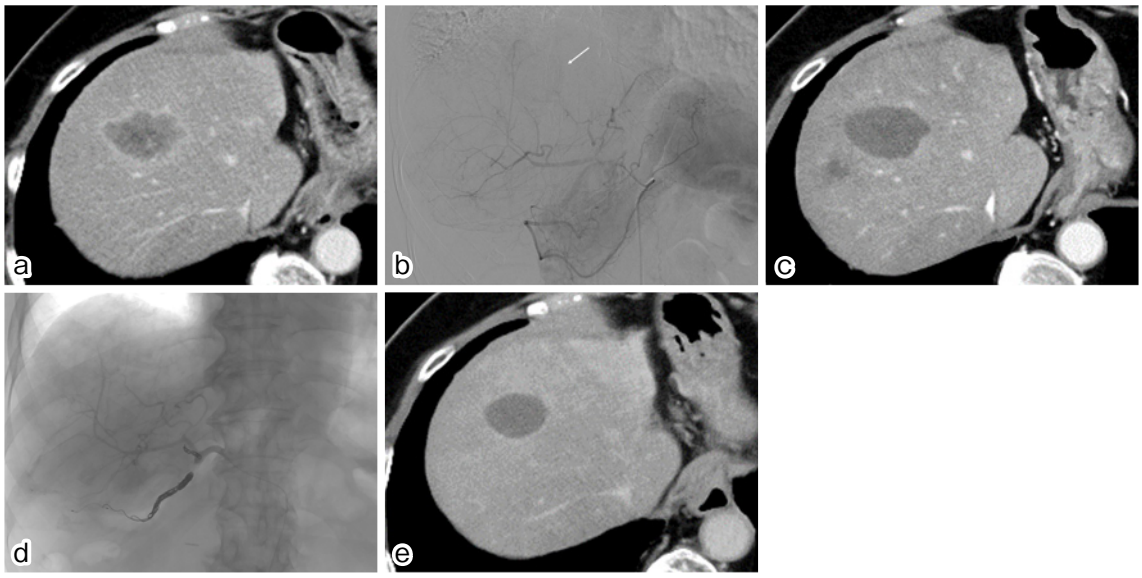

Figure 1. Case 1: A 79-year-old woman with liver metastases from colorectal cancer.
(a) CE-CT before DEBIRI-TACE showed liver metastasis in the liver segment 8. In addition to this lesion, multiple small metastases were found in the right lobe.
(b) Fine tumor stains were seen on digital subtraction angiography (DSA) (arrow).
(c) CE-CT 1 week after the initial DEBIRI-TACE showed that most of the enhancement area in the tumor had disappeared.
(d) An indwelling catheter is placed in the common hepatic artery. The right gastric artery was embolized with metallic coils. The catheter tip was inserted into the gastroduodenal artery and fixed by metallic coils.
(e) CE-CT at 4 months after the initial DEBIRI-TACE showed tumor shrinkage.

Discussion

The efficacy of DEBIRI-TACE for liver metastases of colorectal cancer after resistance to prior systemic chemotherapy has been previously reported [1]. After DEBIRI-TACE, a low-density area in the tumor on CE-CT was observed, and necrotic areas on pathological evaluation have been reported in this area [5]. Furthermore, DEBIRI-TACE has been reported to be effective regardless of prior irinotecan use or the number of chemotherapy lines [6]. Therefore, it is expected to be effective even in patients who do not respond to systemic administration of irinotecan. In our cases, despite systemic chemotherapy before DEBIRI-TACE and the inclusion of irinotecan in Case 2, CE-CT after DEBIRI-TACE in both cases showed hypodensity in most tumors.

Despite the efficacy of DEBIRI-TACE, PFS in patients after the failure of standard systemic chemotherapies is often unsatisfactory. In previous reports, the PFS of the patients treated with DEBIRI-TACE followed by capecitabine was only 4 months [7]. Generally, the tumor growing speed might be rapid after the failure of standard systemic chemotherapies. The PFS of third- or later-line therapy was ～2-3 months in regorafenib-treated patients and ～2 months in trifluridine/tipiracil (TAS 102)-treated patients [8]. Although DEBIRI-TACE should be repeated according to the rate of tumor growth, it is impractical to continue repeated DEBIRI-TACE in the short term because of the significant burden on the patient and occurrence of serious liver complications.

Conversely, the efficacy of HAIC with 5-FU has been reported for liver metastases of colorectal cancer refractory to standard systemic chemotherapy. The PFS of liver metastases was 4.6 months [2-4]. The rate of grades ≥3 AEs with HAIC has been reported to be only 5.5%. Therefore, HAIC might be effective as maintenance therapy after DEBIRI-TACE.

In our treatment, DEBIRI-TACE, which has a high response rate, was performed first because the failure of treatment would have had a major impact on prognosis. Previously, complete occlusion of tumor vessels by DEBIRI-TACE was reported in only 5 of 28 patients (17.9%) [9], and the effect of HAIC could be expected even after vascular embolization. In our cases, DEBIRI-TACE was repeated 2 and 4 times according to disease progression and tolerability. The resultant PFS was 13 and 9 months, respectively, which was better than that previously reported with DEBIRI-TACE alone. In Case 2, there were grade 3 AST and ALT elevations, both of which decreased to normal levels with conservative treatment. Both patients also had grade 1 postembolic syndrome, including abdominal pain and nausea. In a previous report, DEBIRI-TACE did not induce the dose-limiting toxicities usually associated with systemic administration of irinotecan, such as diarrhea and neutropenia, and 42% of the AEs were postembolic syndrome consisting of nausea, abdominal pain, and vomiting [10].

The following potential drawbacks and limitations of this combination therapy should be considered. First, extrahepatic metastases cannot be treated, as seen in Case 1. Sec-

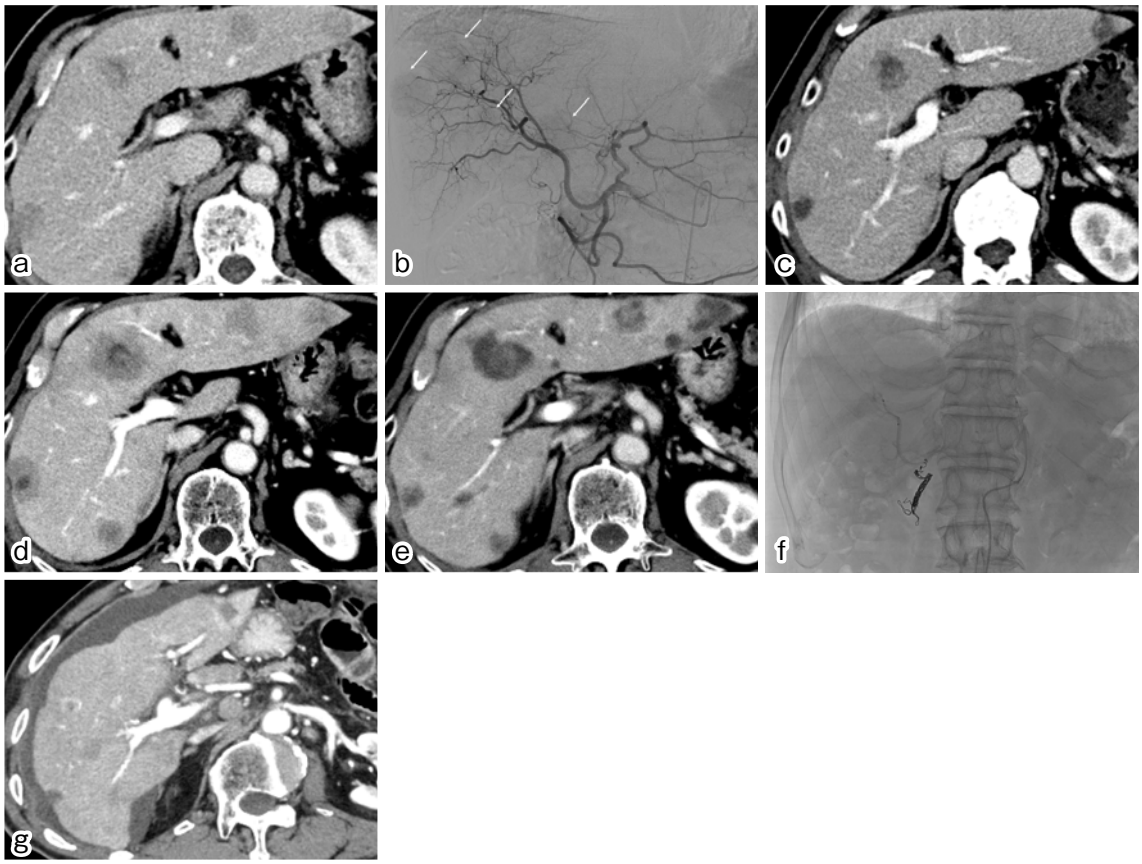

Figure 2. Case 2: A 76-year-old man with liver metastases from anal cancer.
(a) CE-CT before DEBIRI-TACE showed multiple liver metastases.
(b) Tumor stains were observed on DSA (arrows).
(c) At the 1 month follow-up CE-CT, a large part of the tumor had a low density.
(d) CE-CT after chemoradiotherapy for peritoneal lymph node metastasis showed rapid progression of liver metastases.
(e) CE-CT at 4 months after the initial DEBIRI-TACE again showed the disappearance of the tumor stains.
(f) An indwelling catheter-port system was placed in the common hepatic artery. The right gastric artery was embolized with metallic coils. The catheter tip was inserted into the gastroduodenal artery and fixed by metallic coils.
(g) CE-CT at 9 months after the initial DEBIRI-TACE showed tumor shrinkage.

ond, the procedure requires the implantation of a catheter-port system. Additionally, cases with anomalous hepatic artery anatomy, e.g., the replaced right hepatic artery, or with extrahepatic collaterals require multiple implantations.

In summary, our cases show that HAIC with 5-FU after DEBIRI-TACE in patients refractory to standard systemic chemotherapy is promising, achieving tumor response and prolonged PFS without severe AEs. Further clinical studies are needed to show the efficacy of this combination therapy.

Conflict of Interest: None
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