Case: Authentic multimodal therapy and liver resection for an initially unresectable intrahepatic cholangiocarcinoma

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A B S T R A C T

INTRODUCTION: Although curative resection is an outstanding prognostic factor of intrahepatic cholangiocarcinoma (ICC), certain segments remain unresectable. The standard therapy for initially unresectable ICC is uncertain. In this case report, we reported the feasibility of multimodal chemotherapy and curative resection.

CASE: A 59-year-old Asian woman with back pain was referred to the hospital by her family physician regarding liver mass visible on ultrasonography. At admission, the carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels were high, and images showed characteristic signs of ICC with intrahepatic metastases and invasions to the right Glisson's sheath. Multimodal therapy was applied to the ICC, which could not be resected at first. The therapy comprised hepatic arterial chemoembolization with drug-eluting beads (DEB-TACE), angiographic subsegmentectomy (AS), and systemic chemotherapy. Downstaging of the ICC, which results in curative resection, was planned due to non-normalization of the tumor markers, and pathological analysis revealed complete remission. At 34 months after the surgery, the patient was alive without relapse.

DISCUSSION: Recently, chemotherapy and/or an interventional approach were reported to be feasible, although unresectable advanced ICC has a poor prognosis. Some studies have reported that multimodal chemotherapy and R0 resection of initially unresectable ICC can prolong survival time. However, some reports have shown high morbidity and mortality associated with initially unresectable ICC treated with multimodal chemotherapy and R0 resection. Our study resulted in complete remission without complications.

CONCLUSION: Multimodal chemotherapy and hepatic curative resection on locally advanced ICC are feasible treatment approaches for initially unresectable ICC.

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1. Introduction

Curative resection is an important prognostic factor in intrahepatic cholangiocarcinoma (ICC); however, certain segments remain unresectable. Recently, the efficacy of combined therapy with systemic chemotherapy, interventional therapy, and hepatic curative resection for very advanced inoperable ICCs have been reported [1–4]. This paper reports the feasibility of multimodal chemotherapy including hepatic arterial chemoembolization with drug-eluting beads (DEB-TACE), angiographic subsegmentectomy (AS), systemic chemotherapy following radical surgery. This case report was in accordance with the SCARE criteria [5].

2. Case report

Here, we reported ICC in a 59-year-old Japanese woman with back pain, who had been referred to our hospital by her family physician. There were no special notes in her past medical, drug, and family history, or in her relevant physical examination and other significant clinical findings including no alcoholic habits. At admission, the CEA and CA19-9 levels were 910.5 ng/mL and 1965.3 U/mL, respectively. There were no evidences of hepatitis infection. (Table 1). Computed tomography (CT) findings revealed the presence of two low-density masses 68 mm in diameter in hepatic segments 2 and 3 and 72 mm in diameter in segment 8, with early enhancement of the peripheral area as the main loci. Magnetic resonance cholangiopancreatography revealed dilation of the distal intrahepatic bile duct from the tumors. Radiological findings as irregular masses of relatively low atten-
Table 1
Laboratory test results.

|    |       |       |       |      |
|----|-------|-------|-------|------|
| WBC| 9300  | 10^9/μl | PT(%) | 96.1 |
| RBC| 415   | 10^9/μl | PT(INR)| 1.02 |
| Hb | 12.2  | g/dl   | APTT  | 29.8 |
| Ht | 37.3  | %      |       | sec  |
| PLT| 27.3  | 10^9/μl | ICGR15| 6.8  |
| CRP| 0.77  | mg/dl  |       |      |
| Alb| 4.3   | g/dl   | CEA   | 910.5|
| T-bil| 0.71 | mg/dl  | CA19-9 | 1965.3|
| ALT| 25    | IU/l   | AFP   | 5    |
| AST| 31    | IU/l   | PIVKAII| 13   |
| ALP| 206   | IU/l   |       |      |
| γ-GTP| 101  | IU/l   | HCV Ab| (-)  |
| Cre| 0.67  | mg/dl  | HBV Ab| (-)  |
| Na | 141   | mEq/l  | HBV Ag| (-)  |
| K  | 4.2   | mEq/l  |       |      |
| Cl | 103   | mEq/l  |       |      |

ulation in the early phase that demonstrate minimal contrast enhancement at the periphery with focal intrahepatic bile duct dilatation showed peripheral cholangiocarcinoma. These tumors were clinically diagnosed as ICC and were suspected to invade the right Glisson’s sheath with multiple intrahepatic metastases classed as stage IVA according to the TMN classification, and were deemed initially unresectable (Figs. 1 and 2). After hepatic arterial chemoembolization therapy with drug-eluting beads (DEB-TACE), angiographic-subsegmentectomy (AS) and systemic chemotherapy with Gemcitabine and S1 were performed, tumor shrinkage was confirmed, and the tumor markers decreased to just above the normal range (Fig. 3). Thus, the patient was referred to our hospital for surgery. CT revealed that the tumor did not invade the right Glisson’s sheath and the intrahepatic metastases disappeared (Fig. 4). After the simulation of hepatic resection, left lateral segmentectomy and 8th subsegmentectomy were performed (Fig. 5). Blood loss was 600 mL, and the operative time was 470 min. Pathological examination after R0 resection revealed that no viable neoplastic cells remained in the specimen (Fig. 6). The patient was discharged on day 29 after surgery without complications, and no chemother-

Fig. 2. MRI images at admission. Peripheral dilation of the intrahepatic bile duct of the 8th branch can be seen, suggesting bile duct invasion.

apy was administered. Two years and 10 months after the surgery, the patient is alive without relapse (Fig. 7).

3. Discussion

Curative R0 resection resulted in improved survival and has been reported to be an extremely important prognostic variable of ICC [6,7]. However, a portion of the ICC that had been diagnosed as unresectable at admission remained. In ICC, larger tumor size, multifocal disease, lymph node metastasis, and vascular invasion

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Fig. 1. CT images at admission. Computed tomography (CT) showed two low-density masses of 68 mm in diameter in hepatic segments 2 and 3 and 72 mm in diameter in segment 8 as the main loci. These tumors were diagnosed as intrahepatic cholangiocarcinoma and were suspected to invade the right Glisson’s sheath (blue triangle) with multiple intrahepatic metastases (red triangles).
were considered as poor prognostic factors for survival [8]. In this case, MRI scans at admission revealed intrahepatic multifocal disease and vascular invasion. Thus, the surgical approach was not indicated.

Recently, chemotherapy and/or interventional approach, i.e., hepatic angiographic infusion of anticancer agents, transarterial chemoembolization (TACE), and transarterial radioembolization, revealed prolongation of survival [1–5]. According to the reported clinical outcomes of doxorubicin treatment for unresectable ICC, the ratio of partial response and stable disease was 15% and 80%, respectively. Furthermore, the availability of DEB-TACE has been mentioned in particular [9]. In this case report, DEB-TACE was introduced two times with epirubicin and AS. AS was associated with a high disease-free survival rate for hepatocellular carcinoma as hepatectomy [10]. In the present case, tumor size was reduced and tumor markers were decreased to 20% of the levels at admission.

The overall survival in the combined therapy of hepatic arterial infusion and systemic chemotherapy was longer than that in patients who received systemic chemotherapy alone [11]. Thus, systemic chemotherapy with gemcitabine and S1 was introduced. However, tumor markers did not decrease to within the normal range. Consequently, it was assumed that viable tumor cells remained. The patient was referred to our hospital for surgical indication of hepatectomy to reevaluate the possibility of R0 resection.

Table 2 shows the successful radical resection of the initially unresectable ICC [1,11–19]. In previous reports (Table 2), several effective anticancer agents for ICC were administered: mitomycin C, epirubicin; gemcitabine; cisplatin; 5-furulouracil, capecitabine, and S1. Epirubicin, gemcitabine, and S1 were selected for the present case. The successful downstaging and R0 resection rate increased from 7.7% to 36.4% using anticancer drugs, and the rate elevated from 17.7% up to 73.3% with radiation. In some reports,
Fig. 5. Operation images. The image illustrates a left lateral segmentectomy and 8th subsegmentectomy.

Fig. 6. Pathological examination. No viable neoplastic cells were present in the specimen.
Author contributions

Ethical approval

None

Funding sources

None

Conflict of interest statement

The patients’ data was approved by the ethical committee at the University of Tokyo and informed consent of all patients was obtained. The study was approved by the Research Ethics Committee of the University of Tokyo. The authors declare no conflict of interest.

Table 2

| Year | Number | Age (median/min-max) | Route | radiation dose (method) | Procedure | Operated rate (%) | Number (R, C) | Comments |
|------|--------|----------------------|-------|-------------------------|-----------|------------------|--------------|----------|
| 2007 | 1      | 75                   | TACE  | 59                      | Hepatectomy | 1                | (1/1)        | Asymptomatic |
| 2012 | 1      | 75                   | CDA   | 58                      | Hepatectomy | 1                | (1/1)        | Asymptomatic |
| 2014 | 1      | 75                   | CDA   | 58                      | Hepatectomy | 1                | (1/1)        | Asymptomatic |
| 2015 | 1      | 75                   | CDA   | 58                      | Hepatectomy | 1                | (1/1)        | Asymptomatic |
| 2016 | 1      | 75                   | CDA   | 58                      | Hepatectomy | 1                | (1/1)        | Asymptomatic |
| 2017 | 1      | 75                   | CDA   | 58                      | Hepatectomy | 1                | (1/1)        | Asymptomatic |
| 2018 | 1      | 75                   | CDA   | 58                      | Hepatectomy | 1                | (1/1)        | Asymptomatic |
| 2019 | 1      | 75                   | CDA   | 58                      | Hepatectomy | 1                | (1/1)        | Asymptomatic |
| 2020 | 1      | 75                   | CDA   | 58                      | Hepatectomy | 1                | (1/1)        | Asymptomatic |

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Registation of research studies
We have nothing to declare. This is a case report.

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