Pathologic complete response after gemcitabine and S-1 chemotherapy for far advanced intrahepatic cholangiocarcinoma

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Abstract

We report the case of a 72-year-old man who was initially diagnosed with far advanced intrahepatic cholangiocarcinoma, associated with bulky lymph node metastasis involving the common hepatic artery and moderate amount of ascites around the liver. After 10 cycles of systemic chemotherapy combining gemcitabine and S-1 with well-tolerated toxicities, a CT scan showed a marked shrinkage of the liver mass and lymph nodes (clinical partial response) with disappearance of ascites, which could permit a radical resection of the tumor. He underwent left lobectomy of the liver with lymph node dissection, and histopathological examination revealed pathologic complete response. Seven years after surgery, he is in a good overall condition.

Keywords Intrahepatic cholangiocarcinoma (ICC) · Pathologic complete response (pCR) · Gemcitabine (GEM) · S-1

Introduction

Intrahepatic cholangiocarcinoma (ICC), arising from the epithelial cells of the intrahepatic bile ducts, is the second most common, but relatively rare, primary hepatic tumor after hepatocellular carcinoma. The incidence and mortality of ICC has been rising worldwide recently [1, 2]. The only curative treatment is the complete surgical removal of the tumor, but the majority of patients are initially diagnosed with unresectable disease because of the lack of characteristic early symptoms. The prognosis for these patients is dismal, as chemotherapy and/or radiotherapy have only limited value in clinical practice. Even after curative resection, many patients subsequently experience tumor recurrence. Especially, lymph node metastases lead to extremely poor outcomes among patients undergoing radical surgery. We present the case of far advanced ICC receiving gemcitabine (GEM) plus S-1 (GS therapy) that permitted resection

with pathologic complete response (pCR) to the systemic chemotherapy.

Case report

A 72-year-old man with fever and appetite loss visited a local hospital. Laboratory data showed inflammation, anemia and liver dysfunction as follows: white blood cell (WBC) $21.3 \times 10^3/\mu\text{l}$, C-reactive protein (CRP) 17.1 mg/dl, hemoglobin 8.1 g/dl, albumin 2.1 g/dl, aspartate aminotransferase (AST) 119 U/l, alanine aminotransferase (ALT) 81 U/l, alkaline phosphatase (ALP) 1006 U/l, gamma-glutamyltranspeptidase (γ -GTP) 113 U/l, and total bilirubin (T. Bil) 0.9 mg/dl. Serum tumor markers including carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 were elevated at 228.5 ng/ml (normal range 0–5 ng/ml) and 301.9 U/ml (normal range 0–37 U/ml). Both serum HBs-antigen and HCV-antibody findings were negative.

An abdominal CT scan showed a 10-cm sized irregular hypovascular mass in the left hepatic lobe and moderate amount of ascites around the liver (Fig. 1a). The tumor was growing inferiorly to compress the stomach. Invasions of left portal vein and left hepatic vein were strongly suspected. Multiple lymph node enlargements were noted along the common hepatic artery, pancreatic body (Fig. 1b),

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Fig. 1 Enhanced CT scan prior to treatment showed (a) a 10 cm sized irregular hypovascular mass in the left hepatic lobe and bulky lymph nodes along (b) the pancreatic body and (c) common hepatic artery.

Especially, the common hepatic artery seemed to be involved by bulky lymph node (white arrow)

and para-aortic lesion. Especially, the common hepatic artery seemed to be involved by bulky lymph node (size: 4.7×2.5 cm) (Fig. 1c). Percutaneous needle biopsy from the liver tumor revealed that histopathological diagnosis of the specimen was adenocarcinoma (Fig. 2a). Neither bulky lymph node nor ascites around the liver were examined. Immunohistochemical examination showed that tumor cells were positive for cytokeratin (CK)-19 (Fig. 2b) and p53. Upper and lower gastrointestinal endoscopic examination did not show any other malignancy. Therefore, this patient was diagnosed with ICC (UICC stage IV, sixth classification). Since curative surgery of this far advanced ICC was not deemed feasible, systemic chemotherapy combining GEM and S-1 was started. GEM (1000 mg/day) was administered on day 1 and 8, every 3 weeks, and S-1 (80 mg/day) was orally done on day 1–14, every 3 weeks. One month after the onset of treatment, serum tumor markers (CEA and CA19-9) had dramatically declined to normal levels. After 10 cycles of GS therapy with only grade 3 neutropenia,

a CT scan showed a marked shrinkage of the liver mass (2.5 cm in diameter) (Fig. 3a) and lymph nodes with disappearance of ascites (Fig. 3b, c). Positron emission tomography with 18-fluorodeoxyglucose (FDG-PET)/CT fusion imaging confirmed no uptake in those. Finally judged to be eligible for a radical resection, he underwent left lobectomy of the liver with lymph node dissection along the common hepatic artery as well as in the hepatoduodenal ligament. Intraoperatively, induration in the liver was palpable but not exposed to serosa. The shrinking lymph node did not stand out. Hepatoduodenal ligament was edematous and firmly fixed, making difficult to separate. Cytological examination of ascites and histological examination of the swollen lymph nodes at para-aortic lesion showed no malignant cells. Gross examination of the resected specimen revealed a highly necrotic mass in the liver. The histopathological diagnosis revealed complete disappearance of cancer cells in the primary lesion of the liver (Fig. 4) as well as lymph nodes, confirming a pathologic complete response. This patient refused

Fig. 2 Histopathological and immunohistochemical examination of the percutaneous needle tumor biopsy prior to treatment. **a** Histopathological examination showed adenocarcinoma (H.E. staining, $\times 100$). **b** Immunohistochemical examination showed that tumor cells were positive for cytokeratin (CK)-19 ($\times 300$)

$\times 100$). **b** Immunohistochemical examination showed that tumor cells were positive for cytokeratin (CK)-19 ($\times 300$)

Fig. 3 Enhanced CT scan after chemotherapy showed (a) a marked shrinkage of the liver mass (2.5 cm in diameter) and (b, c) lymph nodes with disappearance of ascites

Fig. 4 Histopathological examination of the resected specimen showed the complete disappearance of cancer cells in the primary lesion of the liver (H.E. staining, $\times 100$)

to receive adjuvant chemotherapy. He is doing well 7 years after the operation without any sign of tumor recurrence.

Discussion

Radical surgical resection has been considered the only curative treatment for patients with ICC [3–5]. However, the prognosis for patients with ICC after resection remains unsatisfactory. The 5-year survival rate approaches 20–40% and median survival time is 11–37.4 months in cases with potentially curative resection [6–8]. Especially, lymph node metastases are associated with extremely poor outcomes even when aggressive surgery is performed [9, 10]. Uchiyama et al. [11] reported that the ICC patients with positive lymph nodes ($n = 139$) showed an actuarial 5-year survival rate of 7.0%. Inoue et al. [12] declared that the presence of lymph node metastasis means systemic disseminated and non-curable disease. The efficacy of lymph node dissection

is still unclear [13–15]. Yamamoto et al. [16] suggested that extended lymph node dissection does not improve outcome in cases of ICC with lymph node metastasis regardless of the sites of nodal metastasis. None of the ICC patients with positive lymph nodes, except the present case, survived > 5 years after radical surgical resection in our hospital. Therefore, multidisciplinary therapy, including chemotherapy, should be one of the treatment options for far advanced ICC patients [17].

Recently, GEM plus cisplatin (GC) therapy has become the golden standard regimen for the treatment of patients with advanced BTC based on the results of the phase 3 trial [18], which showed a significant advantage of GC therapy in the median overall survival, compared to GEM alone (11.7 vs. 8.1 months). Whereas, GS therapy was intensely investigated and reported as a promising therapy for advanced pancreatic ductal adenocarcinoma [19], which shares embryological and clinical features with BTC. GEM and S-1 were among the few effective agents approved for use with BTC in Japan, when our patient was diagnosed ICC. Also, multicenter phase II trial of GS therapy had been ongoing in Japan, with better response rate and overall survival [20]. These multidrug therapies occasionally convert locally advanced ICCs to operable group owing to an excellent response to “downstaging chemotherapy”. Downstaging chemotherapy for advanced ICC is uncertain with a limited number of reports, but could downsize tumor and improve the likelihood of achieving R0 resection, or avoid unnecessary surgery, which can contribute to better prognosis. Kato et al. [21] prospectively validated downsizing chemotherapy for initially unresectable BTC (24 cases in GEM alone and 39 cases in GC therapy), and reported that conversion-surgery could be performed in 10 of 39 patients (25.6%). In our case, GS therapy was selected, and a CT scan showed clinical partial response, which led to conversion-surgery.

Pathologic complete response to preoperative chemotherapy is extremely rare for ICC, with only three cases (Table 1). Slupski et al. [22] presented a case of a 33-year-old patient with pCR for disseminated ICC (focal changes

Table 1 Patient characteristics

Case	Age, sex	Diagnosis	Preoperative chemotherapy	Operation methods	Survival
1	33 male	ICC, metastases in lungs	Doxorubicin, cisplatin, 5-FU, IFN K (9 courses)	Right hemihepatectomy	> 30 months
2	67 male	ICC, tumor thrombosis into portal vein	GEM + oxaliplatin, GEM + cisplatin (4 courses, 5 courses)	Left trisectionectomy caudate lobectomy	> 6 months
3	–	Locally advanced ICC	GEM + cisplatin (not described)	Left trisectionectomy caudate lobectomy	Not described
Our case	72 male	ICC, lymph node metastasis, ascites	GEM + S-1 (10 courses)	Left lobectomy	> 7 years

ICC intrahepatic cholangiocarcinoma, IFN K interferon alpha Kinoid

in liver and metastases in lungs) following doxorubicin, cisplatin, 5-fluorouracil, and interferon combination chemotherapy. Tran et al. [23] also reported a 67-year-old man of locally advanced ICC with a satellite lesion and tumor thrombus into the portal vein who achieved pCR after GC and subsequent combination therapy of GEM and oxaliplatin. The third person was 1 of 10 patients who underwent conversion-surgery after downsizing GC therapy in the previous report [21]. All cases above were preoperatively diagnosed as ICC with biopsy, and first two cases were doing well with no evidence of local or distant recurrence (data of the third not shown). But our case is the first report of pCR for ICC involved by bulky lymph node, which associates with a quite inferior prognosis. There were not any specific characteristics in this case, including laboratory data, CT images, immunohistochemical findings of the tumor. Therefore, we cannot explain the reason why GS therapy was significantly effective in this case, while it has little effect for other most cases. There is an urgent need for new innovative biomarker that could predict the therapeutic effects of patients. In contrast, all 4 cases administered GEM or/and cisplatin, both of which are the key drugs for BTC [18]. In esophageal cancer, pancreas cancer, and rectal cancer, patients with pCR to neoadjuvant therapy are reported to be associated with better prognosis [24–26]. As for ICC, even though case of advanced ICC involved by bulky lymph node, down staging chemotherapy including GS therapy may be useful for long-term survival in selected patients.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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