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Gallbladder Cancer Showing a Great Response to Paclitaxel Plus Carboplatin Chemotherapy: A Case Report

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Currently, complete surgical resection is the most effective and the only potentially curative treatment for gallbladder carcinoma (GBC). However, GBC frequently presents various manifestations as it progresses, including liver invasion, bile duct invasion, hepatoduodenal invasion, venous invasion, and lymphatic invasion. Although there is a clear need for effective chemotherapeutic methods in the management of GBC, no standard chemotherapeutic regimen for advanced GBC has been established to date, and the prognosis remains poor. Herein, we report a case of successful treatment in a patient with advanced GBC who showed a great response to combination chemotherapy and who was subsequently able to undergo curative resection. A 38-year-old Japanese woman was first diagnosed with unknown primary cancer with bilateral ovarian, hepatic, and peritoneal metastases. Combination paclitaxel plus carboplatin chemotherapy was started at a dose of 653 mg of carboplatin and 248 mg of paclitaxel once a week for 3 weeks. After 6 cycles, the tumor had shrunk in size and was detected as only a slightly contrasted lesion in Couinaud's hepatic segments 4 and 5. One month after the final cycle of chemotherapy, we performed cholecystectomy and right lobectomy of the liver with D2 lymph node dissection. The patient exhibited an uneventful postoperative course. Five months have passed since the operation, with no signs of recurrent disease. Our findings suggest that combination chemotherapy with paclitaxel and carboplatin may be effective against advanced GBC.

Key words: Gallbladder cancer – Chemotherapy – Carboplatin – Paclitaxel

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The diagnosis and management of gallbladder carcinoma (GBC) patients has improved in recent years due to instrumental and technical advances. However, many cases are still not diagnosed until the advanced stage, and their prognoses are poor and need to be improved. GBC frequently presents various manifestations as it progresses, such as liver invasion, bile duct invasion, hepatoduodenal invasion, venous invasion, and lymphatic invasion. Such cases with distant metastases are not indicated for surgical resection, as no prognostic difference between surgical curative resection and nonresection has been reported.[1]

Although complete surgical resection offers the only chance for cure, only about 10% of patients with GBC present with early-stage disease and are thus candidates for such a procedure. On the other hand, patients with unresectable GBC have a poor prognosis, and show a low response rate to chemotherapy (18.9%–30.7%).[2–4] To date, no standard chemotherapeutic regimen for advanced GBC has been established. Recently, combined chemotherapeutic regimens, such as cisplatin plus gemcitabine, have been reported to improve the overall survival of patients with unresectable biliary tract cancer by 11.7 months.[5] However, the response rates to these regimens and the overall survival times are not sufficiently favorable. Therefore, the most appropriate chemotherapy regimen for GBC remains unclear and controversial.

In this report, we describe our successful treatment of a patient who presented with advanced GBC, including hepatic and peritoneal metastases, and who showed a great response to combination paclitaxel–platinum chemotherapy and was subsequently able to undergo curative resection.

Case Presentation

A 38-year-old Japanese woman was admitted to our hospital for a complaint of abdominal fullness. Her previous and family histories were unremarkable. Physical examination revealed cool moist skin, a pulse rate of 100 beats/min, and blood pressure of 106/86 mmHg. The laboratory findings were as follows: serologic examination was negative for hepatitis C virus antibody and hepatitis B surface antigen; hematocrit 32.5% (normal range, 34.5%–44.3%), platelets 251 $\times$ 10^3/μL (normal range, 162–329 $\times$ 10^3/μL), serum aspartate aminotransferase 21 IU/L (normal range, 10–35 IU/L), alanine aminotransferase 18 IU/L (normal range, 5–35 IU/L), bilirubin 0.5 mg/dL (normal range, 0.1–1.0 mg/dL),

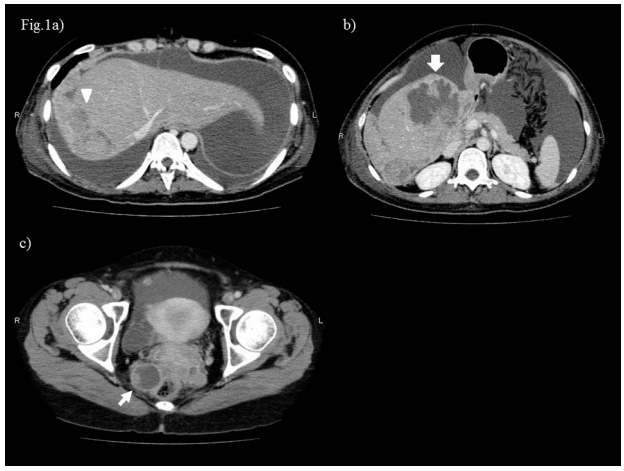

Fig. 1 Computed tomography images before chemotherapy. An unknown primary cancer was diagnosed, with (a) a liver tumor (arrowhead), (b) peritoneal metastases (arrow), and (c) ovarian tumors (arrow) and massive ascites observed.

total protein 8.8 g/dL (normal range, 6.3–8.0 g/dL), albumin 4.3 g/dL (normal range, 3.9–4.9 g/dL), and prothrombin time 65% (normal range, 90%–130%). The serum carcinoembryonic antigen (CEA) level was 12.9 ng/mL (normal range, <5.0 ng/mL), and the carbohydrate antigen (CA) 19-9 and CA125 levels were 314.2 U/mL (normal range, <37 U/mL) and 924.2 U/mL (normal range, <35 U/mL), respectively.

Abdominal computed tomography (CT) showed wall thickness of the gallbladder and a low density area with ring enhancement in the liver. Bilateral ovarian tumors and multiple subphrenic tumors were also observed on CT (Fig. 1). Abdominal ultrasound and magnetic resonance imaging showed similar findings. However, the primary lesion could not be diagnosed by biopsy of the liver and gallbladder, cytodiagnosis of the ascites, or laparoscopic laparotomy. Therefore, the patient was first diagnosed with an unknown primary cancer with bilateral ovarian, hepatic, and peritoneal metastases. This disease was judged to be inoperable due to the presence of distant metastases.

After obtaining the patient's informed consent, chemotherapy with carboplatin plus paclitaxel was started at a dose of 653 mg of cisplatin and 248 mg of paclitaxel once a week for 3 weeks, followed by 1 week of rest. The serum CA19-9 level gradually decreased, and a follow-up CT scan performed after 4 cycles showed that the main lesion had dramatically reduced in size, whereas the multiple peritoneal metastases and abdominal ascites had

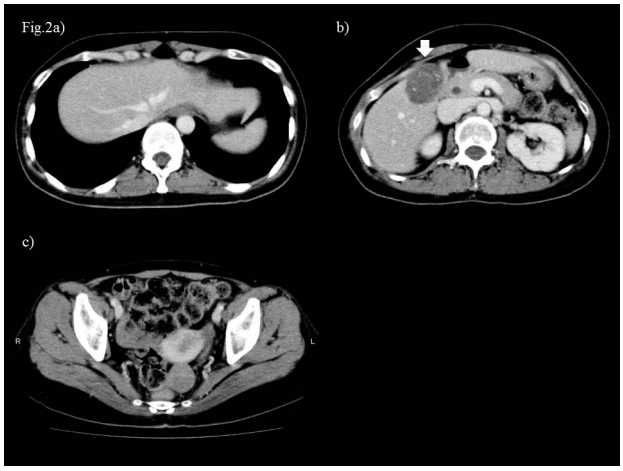

Fig. 2 Changes in CT images after 6 cycles of chemotherapy. (a–c) Abdominal enhanced CT showed that the gallbladder and liver tumor (arrow) had further shrunk in size. Peritoneal metastases, ovarian tumors, and ascites were not detected.

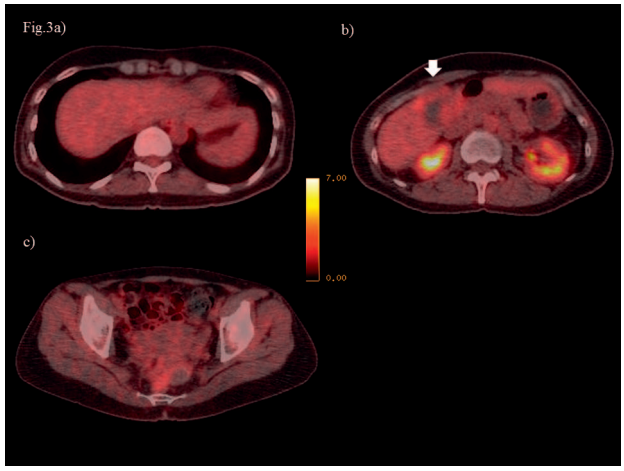

Fig. 3 Changes in FDG-PET images after 6 cycles of chemotherapy. (a–c) FDG-PET showed that the gallbladder and liver tumor (arrow) was detected as only a slightly contrasted lesion in the liver. Moreover, there was no uptake of FDG in the distant organ metastases. FDG-PET, 18F-fluorodeoxyglucose-positron emission tomography.

completely disappeared (Fig. 2). We performed bilateral salpingo-oophorectomy. Both the resected ovaries showed invasion of the metastatic adenocarcinoma. At that time, we considered the feasibility of surgical treatment and recommended an additional 2 cycles of chemotherapy, hoping to obtain a further effect and to confirm the absence of distant metastasis. After the 6 cycles, CT showed that the tumor had further shrunk in size and was detected as only a slightly contrasted lesion in Couinaud's hepatic segments 4 and 5.[6] Moreover, 18F-fluorodeoxyglucose-positron emission tomography showed no uptake of fluorodeoxyglucose in the main lesion or evidence of distant organ metastasis (Fig. 3). The serum CEA, CA19-9, and CA125 levels were 2.2 ng/mL, 101.5 U/mL, and 10.1 U/mL, respectively, at that time (Figure 4).

One month after the final cycle of chemotherapy, we performed right lobectomy of the liver and extrahepatic bile duct resection with D2 lymphadenectomy, which confirmed the absence of both peritoneal dissemination and liver metastasis, based on intraoperative macroscopic and ultrasound findings. However, a liver tumor was invading right hepatic artery and bile duct. Pathologic examination demonstrated viable cancer cells (well-differentiated adenocarcinoma) with rich fibrostic stroma in all the layers from the fundus to the neck of the gallbladder (Fig. 5). These cells were positive for cytokeratin (CD) 7 and 20 and negative for Wilms' tumor-1 (WT-1). The final diagnosis was hence advanced GBC. The cancer cells were found to have spread through the mucosal layer of the right hepatic duct and directly invaded to the liver. In addition, 2 lymph node metastases were noted around the bile duct of the hepatoduodenal ligament and on the posterior surface of the pancreatic head.

The patient exhibited an uneventful postoperative course. Administration of carboplatin plus paclitaxel was restarted as adjuvant chemotherapy,

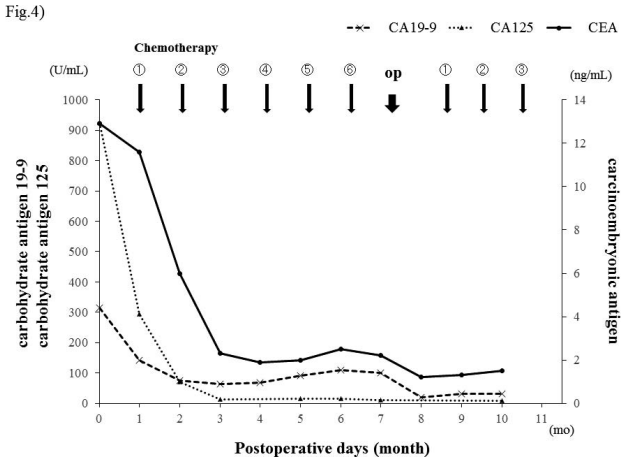

Fig. 4 Changes of the serum carcinoembryonic antigen and carbohydrate antigen 19-9 and 125 levels during treatment. The carcinoembryonic (CEA), carbohydrate antigen (CA)19-9, and CA125 levels decreased dramatically after paclitaxel plus carboplatin chemotherapy was started.

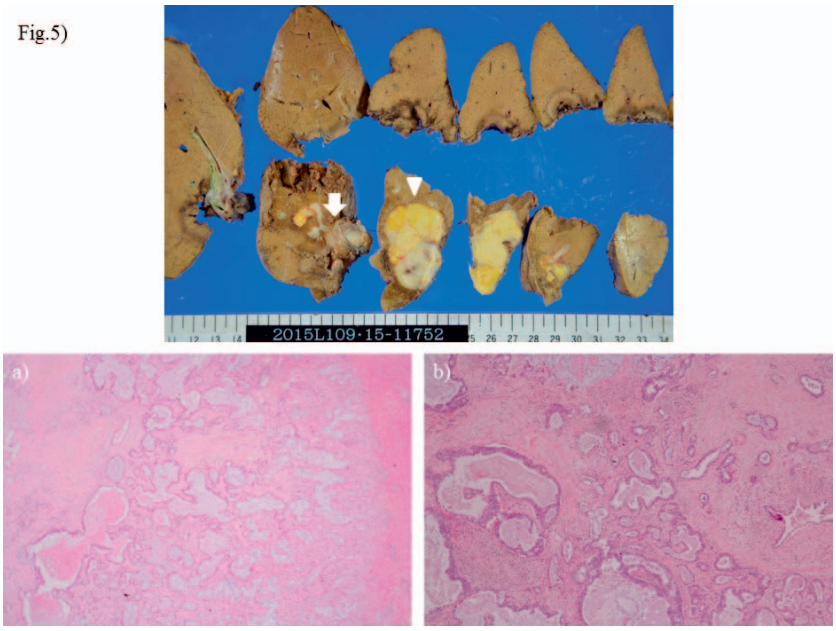

Fig. 5 Macroscopic and microscopic findings. Viable cancer cells with rich fibrostic stroma were found around the gallbladder tissues (arrow) and had invaded to the liver (arrowhead). (a) Hematoxylin and eosin stain, ×40; (b) hematoxylin and eosin stain, ×100.

and 3 cycles of the treatment were performed. Eight months have passed since the operation, with no signs of recurrent disease.

Discussion

Currently, complete surgical resection is the most effective and the only potentially curative treatment for GBC. However, GBC tends to be diagnosed at an advanced stage, resulting in a poor prognosis, owing to its anatomic characteristics and high malignancy. In patients with advanced-stage GBC who receive palliative therapy, the median survival time has been reported to be only about 6 months, indicating that the prognosis is not sufficiently favorable and needs to be improved. Accordingly, there is a clear need for effective chemotherapeutic methods in the management of GBC.

The present case was initially diagnosed with an unknown primary cancer due to the absence of a histologic diagnosis, although GBC was suspected at the time of discovery. Unknown primary cancers are defined as a group of metastatic tumors for which the site of origin cannot be detected at the time of diagnosis. According to the European Society of Medical Oncology, unknown primary cancers account for up to 5% of all malignancies. In Japan, paclitaxel plus carboplatin therapy has become the standard treatment for unknown primary cancer.[7]

Paclitaxel, classified as an antimicrotubule agent, is a novel chemotherapeutic agent that works by stopping the cancer cells from dividing, thereby blocking the growth of cancer. Paclitaxel has already been used extensively as one of the key drugs for the treatment of ovarian, breast, and gastric cancers. Ishigami *et al*[8] conducted a phase I/II study with a combination of S-1 and intravenous and intraperitoneal administration of paclitaxel to control peritoneal carcinomatosis from gastric cancer. The combination treatment was successful, with a 1-year survival rate of 78% and a median survival time of 23.6 months in previously untreated patients with extensive peritoneal metastases. Moreover, paclitaxel was found to be effective for the treatment of ascites after transvenous dosage.

Carboplatin is another common anticancer drug, classified as an alkylating agent. This drug works by damaging the DNA that tells the cell how to copy itself during division. Carboplatin is used to treat various cancers, including ovarian, esophageal, and breast cancers. It is known to have an additive or synergistic effect in combination with paclitaxel in ovarian cancer.

Although various randomized controlled studies for neoadjuvant therapy in unresectable GBC were performed, the response rates to these regimens and the median survival times are not sufficiently favorable (Table 1). To our knowledge, there has been no previous report of surgery of GBC with peritoneal dissemination and liver invasion after chemotherapy with carboplatin and paclitaxel. Therefore, the usefulness of such additional surgery was difficult to determine based on

Table 1 Neoadjuvant therapy in unresectable gallbladder cancer

Regimen	Response rate	MST (mo)	Year	Author
GEM + Mitomycin C	20%	6.7	2004	Kornek[9]
Capecitabine + MMC	31%	9.3		
5-FU	7%	5	2005	Ducreux[10]
5-FU + FA + CDDP	19%	8		
5-FU + FA + Etoposide	15%	12	2005	Rao[11]
5-FU + Epirubicin + CDDP	19%	9		
GEM	15%	-	2009	Valle[12]
GEM + CDDP	24%	-		
BSC	0%	4.5	2010	Sharma[13]
5-FU + FA	14%	4.6		
GEM + OX	31%	9.5		
GEM	16%	8.3	2010	Valle[14]
GEM + CDDP	26%	11.7		
GEM	12%	7.7	2010	Okusaka[15]
GEM + CDDP	20%	11.2		
GEM + OX	21%	9.5	2012	Lee[16]
GEM + OX + Erlotinib	40%	9.5		
S-1	17%	9	2013	Morizane[17]
GEM + S-1	36%	12.5		
GE	9%	9.2	2013	Sasaki[18]
GEM + S-1	20%	8.9		

BSC, best supportive care; CDDP, cisplatin; FA, folic acid; GEM, gemcitabine; MMC, mitomycin C; MST, median survival time; OX, oxaliplatin; S-1, tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate.

the available literature. Moreover, surgery after preoperative neoadjuvant chemotherapy for biliary tract cancers has seldom been reported. In the randomized controlled trial by Takada *et al*,[19] adjuvant chemotherapy with 5-fluorouracil plus mitomycin C showed a significant improvement in survival compared to surgery alone ($P = 0.037$). On the basis of these data, we selected adjuvant chemotherapy with paclitaxel and carboplatin for the present case, as the use of these agents preoperatively showed a good response. It is possible that the present result of a good prognosis with these agents might be incidental; however, chemotherapy for advanced GBC is likely to become more important along with future developments of chemotherapy. Although further investigation of a greater number of patients is needed to verify these results, our findings suggest that chemotherapy with paclitaxel and carboplatin may be effective against advanced GBC.

Conclusions

Today, no standard chemotherapeutic regimen for advanced GBC has been established. Our findings describe that our successful treatment of a patient who presented with advanced GBC and who showed a great response to combination paclitaxel-carboplatin chemotherapy and was subsequently able to undergo curative resection.

Acknowledgments

The authors declare that they have no conflict of interest or financial ties to disclose. The ethics approval and consent to participate was not applicable for this paper. The patient provided informed consent for the findings of this case to be published. The datasets supporting the conclusions of this article are available in the repository. Drs. Y. Inoue, M. Ota, K. Fujii, J. Matsuda, N. Kawaguchi, Y. Imai, T. Shimizu, M. Asakuma, F. Hirokawa, M. Hayashi, and K. Uchiyama have no conflicts of interest or financial ties to disclose. There was no funding for this paper. Regarding author contributions, YI conceived the study concept and design, was involved with patient care, and drafted the manuscript. MO, KF, JM, NK, YI, TS, FH, MH, and KU were involved in the formation of the study concept and design, patient care, and drafting of the manuscript. All authors have read and approved the final version of the manuscript.

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