Two Cases of Bile Duct Carcinoma which Showed Remarkable Response to a Combination of S-1 plus Cisplatinum (CDDP)

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ABSTRACT

In this paper we report two cases of bile duct cancer which showed remarkable response to therapy with S-1 plus cisplatinum (CDDP). The first patient was a 36-year-old male with cholangiocarcinoma described as multiple low density nodules in the liver by computed tomography. After two courses of S-1+CDDP all tumors almost disappeared. The time to progression and the survival period of this patient were 170 days and 371 days, respectively. The second patient was a 56-year-old male with cholangiocarcinoma in the left lobe of the liver with multiple lymph nodes metastasis around the hepatic hilus. Both the primary liver tumor and the swollen lymph nodes shrunk remarkably after two courses of S-1+CDDP treatment and he is still alive after 7 cycles of the treatment in 12 months. This combination chemotherapy may hold potential as an effective treatment for biliary tract cancer.

INTRODUCTION

Adenocarcinoma of the biliary tract remains a major challenge to surgical, medical, and radiation oncologists.[1,2] Because of the lack of characteristic early symptoms, approximately 70% of patients initially present with Stage III/IV disease.[3,4] Overall survival in patients with biliary tract carcinomas is poor. Only 15% of patients with untreated Stage II disease are alive 2 years after diagnosis, and among those diagnosed at Stage III/IV, 2-year survival drops to only 5%.[3-5] The role of non-surgical treatment remains a matter of debate, and has been thought to be largely ineffective, if not detrimental, in patients with advanced disease.

S-1 is a novel oral fluoropyrimidine derivative consisting of Tegafur (FT) and two modulators, 5-chloro-2, 4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo), in a molar ratio of 1:0.4:1.[6] Antitumor effect is provided by the 5-FU prodrug FT.[7] CDHP competitively inhibits the 5-FU degradative enzyme dihydropyrimidine dehydrogenase (DPD), resulting in the retention

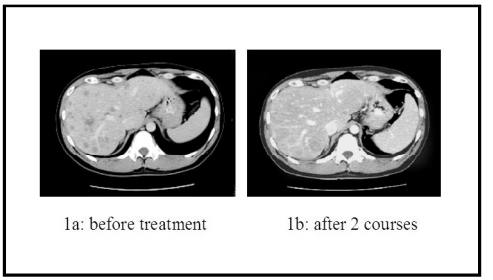

Figure 1. (A) Computed tomography (CT) scan of a 36-year-old male with cholangiocarcinoma revealed multiple low density nodules in the liver . (B) All tumors showed poorly defined borders after two courses of S-1+CDDP treatment.

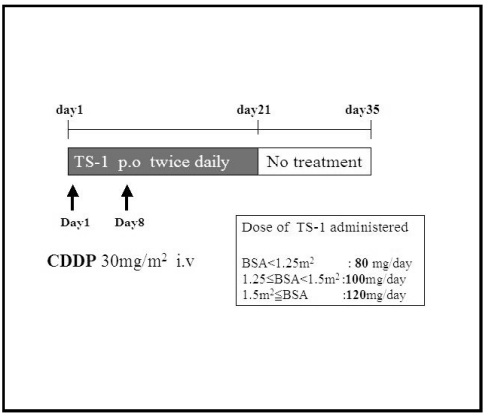

Figure 2. Treatment protocol of S-1+CDDP.

of a prolonged concentration of 5-FU in blood.[8] Oxo competitively inhibits orotate phosphoribosyl-transferase, which converts 5-FU to 5-fluorouridine 5'-monophosphate in vitro.[9] Because Oxo is mainly distributed in the gastrointestinal tract after oral administration, it acts to relieve the gastrointestinal toxicity induced by 5-FU.

Recent clinical trials using S-1 have shown promising results in various solid tumors. Response rates of 35-50% were reported for single agent S-1 use for gastric cancer,[10] colorectal cancer,[11] non-small-cell lung cancer, head and neck cancer, and breast cancer[12] in late phase II studies with a response rate of 44.6%, 35.5%, 22.0%, 28.8%, and 42.0%, respectively. As for biliary tract cancer, Ueno et al reported in a phase II study that S-1 as a single agent showed a response rate of 21.1% with 3.7 months of median time to progression (TTP) and 8.3 months of overall median survival time.[13] In Ueno's study, S-1 as a single agent seemed to be a feasible treatment modality with a high compliance rate, but its combination with other drugs is expected to improve results, as shown in studies treating patients with gastric tumors.

We previously reported that S-1 combined with cisplatinum (CDDP) significantly improved the response rate in pancreatic cancer with acceptable toxicity,[14] thus we considered it feasible to use this combination in patients with biliary tract cancer. In this paper we report two cases of bile duct cancer which showed complete response (CR) to therapy with S-1 and CDDP treatment.

CASE REPORTS

Case 1

The patient was a 36-year-old male with no symptoms at the time of diagnosis. During a routine screening medical evaluation, an abdominal ultrasound showed multiple hepatic nodules and the patient was referred to our hospital. Laboratory studies, including hemogram and liver and kidney function tests, were all within normal limits, but tumor markers were elevated: CEA was 25.5 (normal range: <5.0) and CA19-9 was 3099 (normal range: <37). There was no evidence of infectious hepatitis. Computed tomography (CT) showed multiple and irregular low density nodules distributed throughout the liver (Figure 1A). No tumors were detected in the stomach, colon, rectum, head and neck, lungs, testes, or other organs. Needle biopsy demonstrated poorly differentiated adenocarcinoma.

A diagnosis of cholangiocarcinoma was made and the patient was treated with S-1 plus weekly CDDP according to a protocol (Figure 2) consisting of S-1 60 mg twice daily for 21 days and CDDP 30 mg/m^2 on Day 1 and Day 8, followed

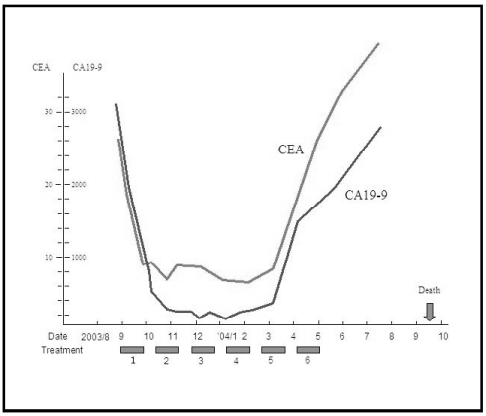

Figure 3. Tumor marker changes during the treatment period in case1.

by a 2-week period of no treatment.

After the first cycle of treatment the expression of tumor markers decreased markedly: CEA from 25.5 to 9.0 (65% decrease) and CA19-9 from 3099 to 540 (83% decrease). All tumors showed poorly defined borders on CT scan, representing partial response (Figure 1B). Appetite loss was observed during the second and third cycles. Unfortunately, however, the tumor increased in size after 4 courses of the treatment and the patient chose to terminate S-1+CDDP therapy at the sixth cycle. He continued to be treated only with supportive care until death 12 months after initiation of treatment (Figure 3). The time to progression and the survival period of this patient were 170 days and 371 days, respectively.

Case 2

The second patient was a 56-year-old male who complained of epigastralgia. Multiple liver tumors were seen on CT scan performed at a local clinic, and he was referred to our hospital. Laboratory studies, including hemogram and liver and kidney function tests, were all within normal limits, but tumor markers were elevated: CEA was 35.9 and CA19-9 was 2690. There was no evidence for infectious hepatitis. CT scans showed an irregular tumor 50 mm in diameter in the left lobe of the liver and multiple swollen lymph nodes around the hepatic hilus (Figure 4A). The patient had no evidence of other gastrointestinal tumors.

The patient was treated by the same protocol as was used in case 1 including S-1 plus weekly CDDP. After the second cycle, CT revealed remarkable tumor shrinkage (Figure 4B), which was categorized as partial response, and significant reductions in serum tumor marker expression: CEA went from 35.9 to 9.2 (74% decrease) and CA19-9, from 2690 to 1090 (59% decrease). At the present time this patient continues to have partial response status after 7 cycles of this treatment in 12 months (Figure 5). As for hematotoxicity, the patient experienced a grade-2 platelet reduction after 4 cycles. The patient has not manifested any other toxicities to date.

DISCUSSION

Biliary tract and gallbladder carcinomas are uncommon malignancies. The majority of patients with these cancers, however, initially present with metastases or invasion of the tumor directly into the liver or the hepatic artery and are, therefore, not candidates for surgical resection. For patients with either locally advanced biliary tract carcinoma not amenable to combined chemotherapy/radiation therapy or metastatic disease, chemotherapy is the primary form of therapy.

A large number of agents, including 5-fluorouracil (5-FU), mitomycin-C, cisplatin, methotrexate, etoposide, doxorubicin, nitrosoureas, paclitaxel, irinotecan, and gemcitabine have been tested as single-agent or combination therapy without appreciable efficacy.[15-19] Even partial responses, lasting from weeks to several months, have been observed in only 10-20% of cases.[20]

S-1 is a newly developed oral fluo-

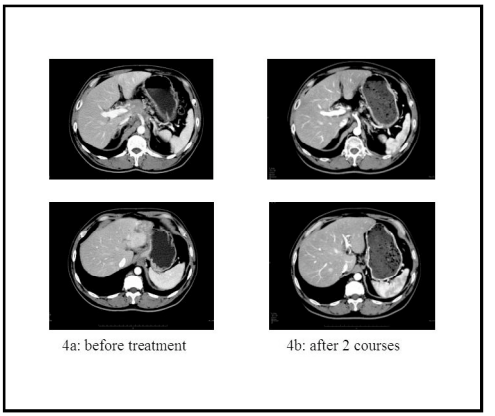

Figure 4. (A) CT scan of a 56-year-old male with cholangiocarcinoma revealed a bulky tumor in the left lobe of the liver and multiple swollen lymph nodes around the hepatic hilus. (B) The primary liver tumor and swollen lymph nodes decreased remarkably after two courses of S-1+CDDP treatment.

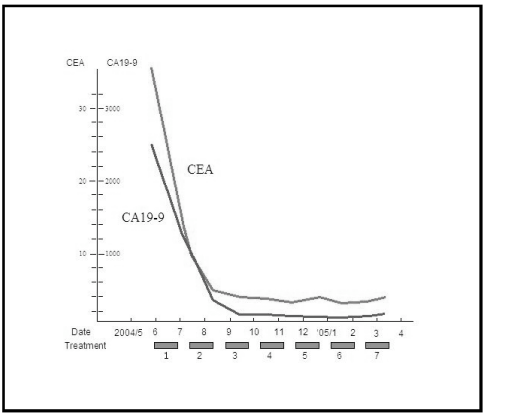

Figure 5 Tumor marker changes during the treatment period in case 2.

ropyrimidine derivative with demonstrated activity against several tumor types, and recently Ueno et al [13] reported in a phase II study that S-1 as a single agent showed a response rate of 21.1% with 3.7 months of median TTP and 8.3 months of overall median survival time. Based on our experience showing that S-1 plus CDDP improves the response rate in pancreatic cancer with acceptable toxicities, we elected to use this combination in two patients with biliary ductal cancer. S-1 was given orally after breakfast and dinner. Following previous phase II studies,[11,12] Body surface area (BSA) was used to determine the dose of S-1 administered as follows: for patients with BSA < 1.25 m^2, 40 mg was administered; for a BSA of 1.25-1.5 m^2, 50 mg was given; for BSA $\geq$1.5 m^2, 60 mg. We previously reported that the split infusion of CDDP 30 mg/m^2 had a comparable area under the curve (AUC) to that obtained by bolus administration of CDDP at 80 mg/m^2 every 4 weeks.[21] CDDP (30 mg/m^2) was dissolved in 500 mL saline and was given by slow drip infusion for 60 minutes.

In our previous pancreas study, CDDP was combined with S-1 according to the split protocol, and severe toxicities over grade 3 appeared in less than 20% of cases.[14] The present two cases of bile duct cancer showed only low-grade side effects, although they showed remarkable responses. Unfortunately, in the first case reported here, the TTP was just over 5 months, but in the second case, a tumor reduction of over 90% has been seen on CT evaluation for over 7 months and the patient is currently alive with no symptoms after 12 months from the start of S-1+CDDP treatment.

The success with our two bile duct cancer patients is encouraging, but our findings must be tested and substantiated in larger phase II/III studies. S-1+CDDP combination chemotherapy may hold potential as an effective treatment for biliary tract cancer.

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