

Treatment of Patients with Unresectable Advanced Carcinoma of Biliary Tract – Chemotherapy and Surgical Resection

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Abstract. *Background: The results of 12 consecutive patients with unresectable advanced biliary tract carcinoma treated with first line chemotherapy of S1/cisplatin, combined surgical resection and second line chemotherapy of gemcitabine are evaluated. Patients and Methods: Eight patients with intrahepatic cholangiocarcinoma, 1 with extrahepatic cholangiocarcinoma and 3 with gallbladder carcinoma were included in the study. All patients were treated with S1/cisplatin. Two of the patients underwent combined surgical resection before and 2 after therapy. Second line chemotherapy of gemcitabine was administered in 6 patients. Results: MST of the patients was 14.9 months. With S1/cisplatin therapy, 6 patients had PR and 4 had SD. Two patients with surgical resection after the therapy survived more than 3 years. Second line chemotherapy of gemcitabine with moderate effects and mild adverse effects was well tolerable. Conclusion: S1/cisplatin showed considerable anti-cancerous effects. Employing surgical resection for patients with good response may lead to the chance of long-term survival.*

Adenocarcinomas of biliary tract, which account for approximately 3-4% of all malignant neoplasms of the gastrointestinal tract (1), still remain a major challenge for surgeons and oncologists. Although complete surgical resection is thought to be the only cure, many patients with advanced diseases are not suitable for surgery, have no good treatment modalities and tend to subject to systemic chemotherapy with poor prognosis results (2). Recently, the strategy for the treatment of colorectal carcinoma, which is

also adenocarcinoma, has been changed dramatically with new anti-cancerous agents (3, 4). There are also reports which prove considerable anti-cancerous response for biliary tract carcinoma with new agents (5, 6).

The results of 12 consecutive patients treated with first line chemotherapy of S1 (tegafur/5-chloro-2,4-dihydropyridine/potassium oxonate)/cisplatin (CDDP), combined surgical resection and second line chemotherapy of gemcitabine are evaluated.

Patients and Methods

Eight intrahepatic cholangiocarcinoma (ICC), 1 extrahepatic cholangiocarcinoma (ECC), and 3 gallbladder carcinoma (GBC) patients with inoperable diseases were included in the study. The cohort included 4 males and 8 females, 48 to 78 (median: 69.5) years old and in good general condition (11 patients in Grade 0-1 and 1 in 2 of ECOG performance status) without uncontrollable cholangitis (1 with cholangitis controlled by percutaneous transhepatic biliary drainage). Four patients (3 with ICC and 1 with ECC) were not indicated for surgery (tentative curative resection) due to far-advanced local extension and 8 (5 with ICC and 3 with GBC) due to distant metastases (lymph node: 5 patients, lung: 3 patients, peritoneum: 2 patients, bone: 1 patient). Two patients with ICC enrolled with distant metastases after hepatectomy for the primary cancer. The follow-up periods were 20-46 (median 29) months (Table I).

First line chemotherapy with S1/CDDP. The protocol of the therapy was a 3 week-period of S-1 (80 mg/m²/day for inpatients and 70 mg/m²/day for outpatients) oral administration combined with 2 intravenous administrations of CDDP (35 mg/m²/6hrs for inpatients and 20 mg/m²/3hrs for outpatients) during the period. With two (or more) weeks of rest, the therapy was repeatedly performed 2-9 times (median 5) for each patient.

Combined surgical resection. Four patients underwent combined surgical resection, 2 after S1/CDDP chemotherapy and 2 before. Surgeries performed for the patients before chemotherapy were reduction surgeries, not tentative curative resections. A patient with ICC and peritoneal/lymph node metastases underwent surgical resection of primary site and reduction surgery for peritoneal metastases before the application of S1/CDDP. A patient with GBC

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Table I. Summary of the cases.

Case no.	Age/Gender	Origin	Factors out of surgical indication	Post-operative recurrence	Prognosis
1	60 F	ICC	Distant metastases (lung)	Yes	Alive, 46months
2	65 F	ICC	Distant metastases (lung, lymph-node)	No	Alive, 45months
3	70 M	ICC	Far-advanced local extension	No	Dead, 15months
4	53 F	ICC	Distant metastases (lymph-node, peritoneum)	No	Dead, 11months
5	54 F	ICC	Distant metastases (lung)	Yes	Alive, 23months
6	78 M	ICC	Far-advanced local extension	No	Dead, 14months
7	75 M	ICC	Far-advanced local extension	No	Dead, 21months
8	69 F	ICC	Distant metastases (bone)	No	Dead, 2months
9	74 M	ECC	Far-advanced local extension	No	Dead, 2months
10	75 F	GBC	Distant metastases (lymph-node)	No	Alive, 28months
11	73 F	GBC	Distant metastases (lymph-node)	No	Dead, 11months
12	48 F	GBC	Distant metastases (lymph-node, peritoneum)	No	Dead, 8months

Post-operative recurrence: case 1 and 5 both underwent hepatectomy twice for original lesions and intrahepatic recurrences.

and peritoneal/lymph node involvements underwent surgical resection of primary site before S1/CDDP. An ICC patient with lung and lymph node metastases underwent hepatectomy for the primary lesion after obtaining PR response with S1/CDDP. Another ICC patient with post-operative multiple lung metastases underwent pulmonary resection after obtaining SD response for the lesions.

Second line chemotherapy with gemcitabine. Second line chemotherapy of gemcitabine was employed for 6 patients without early death or combined surgery. Gemcitabine (1000 mg/m²) was given as a 30-minutes intravenous infusion weekly for 3 consecutive weeks, followed by a week of rest. The therapy was repeatedly performed 2-12 times (median 4.5 times) for each patient.

Evaluation of the effects and adverse events. The antitumor response was assessed with dynamic computed tomography (CT) and also tumor marker levels according to the RECIST guideline of 2000. The toxic effects were evaluated using the National Cancer Institute (USA) Common Terminology Criteria for Adverse Events v3.0 of December 2003.

Results

Median survival time of the patients was 14.9 months under the median follow-up time of 29 months (Table I).

With S1/CDDP therapy, 6 patients had PR (partial response in RECIST guideline) (response rate 50.0%) and 4 had SD (stable disease) (disease control rate 83.3%). Two PD (progressive disease) patients died within 3 months. The observed adverse events higher than grade 2 are leukocytopenia (5 patients), thrombocytopenia (2 patients) and anemia (1 patient) (Table II). Two patients with combined surgical resection after S1/CDDP survived more than 3 years. Two patients with combined surgical resection before S1/CDDP survived 9 and 11 months, respectively. Six patients with second line chemotherapy of gemcitabine were applied the therapy more than 6 months after S1/CDDP therapy. Five out of 6 patients underwent 3 or more cycles

of the gemcitabine therapy and survived more than 6 months. Another patient had early and rapid PD response with the therapy and died after 2 cycles/4 months. One patient had PR and 2 had SD responses. The adverse events higher than grade 2 were observed in 4 patients (leukopenia and thrombocytopenia in 3 patients, each) (Table III).

Discussion

There are various pilot trials and case reports of chemotherapies, including gemcitabine, S1 and other agents, for advanced biliary carcinomas, but only a few RCTs (randomized control trials) (7-10). One RCT described the patients with best supportive treatment had 2.5 months of median survival time and the patients with chemotherapy had 6.5 months (9). Major risk factors for the prognosis of patients with chemotherapy are poor general condition (PS) and uncontrollable cholangitis (7, 11). The patients in this study were in relatively good conditions (only one patient with Grade 2 of ECOG performance status and one with cholangitis, each). For this patient group, chemotherapy with good response rate is thought to be suitable, even though it has relatively higher risk of adverse events. Furthermore, since combined surgical resection could facilitate patients the chance of long term survival (6), the first line chemotherapy should be the regimen that has good response. S-1 is a fourth-generation oral fluoropyrimidine derivative consisting of tegafur and two modulators, 5-chloro-2,4-dihydropyridine and potassium oxonate (12). This combination yields high and sustained intracellular concentrations of 5FU and the limitation for toxic gastrointestinal effects. This agent has attracted considerable interest for the activity against gastric cancer and even up to 74% response rate has been reported for S-1/CDDP (13). In a previous study, S1/CDDP had a good response rate with acceptable adverse events for primary

Table II. Summary of S1/CDDP therapy.

Case no.	Performed duration of the therapy	Response	Adverse events (>grade2)	Combination therapy
1	3cycles (4Months)	SD	Leukopenia	Surgical resection
2	9cycles (14months)	PR	-	Surgical resection
3	8cycles (10months)	PR	-	-
4	3cycles (4months)	PR	Leukopenia	Surgical reduction before the therapy
5	4cycles (5months)	SD	-	-
6	6cycles (8months)	PR	Leukopenia	-
7	7cycles (9months)	PR	-	-
8	2cycles (2months)	PD	-	Intra-arterial chemo-embolization
9	2cycles (2months)	PD	Leukopenia, Thrombocytopenia	-
10	9cycles (11months)	PR	Anemia	-
11	6 cycles (7months)	SD	Leukopenia	-
12	2 cycles (6months)	SD	Thrombocytopenia	Surgical reduction before the therapy

Table III. Summary of gemcitabine therapy.

Case no.	Gemcitabine	Performed duration of the therapy	Response	Adverse events (>grade2)	Combination therapy
1	Not applied				
2	Not applied				
3	Yes	3cycles (7months)	PD	Thrombocytopenia	-
4	Not applied				
5	Yes	18cycles (18months)	SD	-	Cetuximab
6	Yes	3cycles (7months)	PD	Leukopenia and Thrombocytopenia	-
7	Yes	10cycles (12months)	SD	Leukopenia	-
8	Not applied				
9	Not applied				
10	Yes	7cycles (14months)	PR	-	-
11	Yes	2cycles (4months)	PD	Leukopenia and Thrombocytopenia	-
12	Not applied				

liver carcinomas, including ICC (14). Therefore, S1/CDDP was chosen for first line therapy in this study. Response rate and disease control rate with S1/CDDP in present study are considerable, compared to other regimens (7, 15).

After the failure of first line chemotherapy, the general condition of the patients was deteriorated with the progression of the disease and accumulated adverse effects. Second line chemotherapy with long survival and mild adverse effects could be ideal for those patients. Gemcitabine is thought to be the agent that has those characteristics. In this study, all 6 patients with gemcitabine had more than 6 months period of S1/CDDP treatment. However, five of 6 patients underwent 3 or more cycles of gemcitabine therapy and survived more than 6 months.

Leukopenia and thrombocytopenia are major adverse events for both S1/CDDP and gemcitabine. However, leukocytopenia was well-controlled with GCSF administration and there were no severe infectious complications observed. Also, no platelet transfusion was performed. Except for leukopenia and thrombocytopenia, there were no severe adverse events, such as toxic gastrointestinal effects or hand-foot syndrome.

Median survival time of the patients with this string of therapies is longer than other reported series with various regimens (7). The condition of the patients in the present study is better with lower PS and no chronic liver diseases, which have been recently associated with ICC development. Also many peripheral mass-forming-dominant ICC cases and cases with distant metastases have been included. They may be in the population with less invasive carcinoma to the bile duct. Less invasiveness to the bile duct leads to less cholangitis, which is a major risk factor for chemotherapy. There was only one patient who underwent biliary drainage for cholangitis and eventually developed PD response and early death. However, median survival time of 14.9 months with this string of therapies is quite considerable with good RR and disease control rate of S1/CDDP. Also two patients with surgical resection after good response of chemotherapy survived more than three years. In order to pursue long term survival of the patients, an attitude, in which there is awareness of the fact that this first line chemotherapy could be the induction chemotherapy for surgery is required and the operability during the therapy should be examined.

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