Twenty-six Cases of Advanced Ampullary Adenocarcinoma Treated with Systemic Chemotherapy

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Objective: Ampullary adenocarcinoma is a rare disease entity and little information regarding these tumors is available. The aim of the present study was to clarify the treatment outcome of systemic chemotherapy in patients with advanced ampullary adenocarcinoma.

Methods: This study consisted of a retrospective review of data obtained from patients diagnosed as having advanced ampullary adenocarcinoma who received non-surgical treatment at a single institution between 1997 and 2010.

Results: We identified 26 patients (15 men, 11 women; median age, 62.0 years) who received treatment for advanced ampullary adenocarcinoma. Twelve patients had Stage IV disease and 14 had recurrences. The chemotherapy regimens consisted of 5-fluorouracil-based regimens (5-fluorouracil + cisplatin, n = 3; tegafur-uracil + doxorubicin, n = 5 and tegafur, gimeracil and oteracil potassium, n = 3) and gemcitabine-based regimens (gemcitabine, n = 10 and gemcitabine + cisplatin, n = 5). The overall response rate was 7.7%. The median progression-free survival period was 3.2 months (2.5 months in the 5-fluorouracil group vs. 3.5 months in the gemcitabine group), and the median overall survival time was 9.1 months (8.0 months in the 5-fluorouracil group vs. 12.3 months in the gemcitabine group). The median overall survival was significantly longer in stage IV disease than in recurrent disease. The histological phenotype was determined in 10 of the 26 patients. Eight patients had intestinal-type adenocarcinomas and remaining two patients had pancreatobiliary-type adenocarcinomas.

Conclusions: The treatment outcome of patients with advanced ampullary adenocarcinoma was poor. Further development of novel treatments is necessary to improve the prognosis.

Key words: ampullary adenocarcinoma – chemotherapy – 5-fluorouracil – gemcitabine – histological phenotype

INTRODUCTION

Ampullary carcinoma is a particularly uncommon neoplasm. Between 1985 and 2005, the incidence of ampullary carcinoma in the USA was 0.7 cases per 10 000 males and 0.4 cases per 10 000 females (1), accounting for 0.5% of all gastrointestinal malignancies (2). The number of annual deaths because of ampullary carcinoma is only 100–200 in the USA and 800–900 in Japan (http://www.who.int/healthinfo/morttables/en/). This inconsistency in the number of annual deaths may be due to the different geographical regions.

Compared with other periampullary adenocarcinomas, ampullary adenocarcinomas is associated with a higher likelihood of resectability and a more favorable prognosis. Among patients who undergo radical resection, the overall 5-year survival rate ranges from 35 to 46%, which is better than that for patients with distal biliary adenocarcinomas (5-year survival...
We examined the chemotherapy regimens and the treatment outcome of systemic chemotherapy in patients with ampullary adenocarcinomas. The responses were evaluated according to the Response Evaluation Criteria in Solid Tumors 1.0. We classified the chemotherapy regimens into two types: 5-FU based and GEM based. The chemotherapy regimens were divided into two groups because GEM is a key drug for the current treatment of biliary adenocarcinomas, while 5-fluorouracil (5-FU) has been widely used as a key drug for gastrointestinal malignancies including biliary tract adenocarcinomas, colon adenocarcinomas and small bowel adenocarcinomas. In our hospital, 5-FU-based regimens were frequently used in clinical trials (10,11) for advanced biliary tract adenocarcinomas, including ampullary adenocarcinomas, or for clinical practical use before the recognition of GEM as a key agent for the treatment of biliary tract adenocarcinomas.

IMMUNOHISTOCHEMISTRY

Paraffin-embedded materials from a series of pancreaticoduodenectomy specimens (n = 9) and a biopsy specimen (n = 1) obtained at NCCH were used for the immunohistochemistry (IHC) analysis. Specimens from the other patients (n = 16) were not available for use at NCCH because the patients had been pathologically diagnosed as having advanced ampullary adenocarcinoma at another hospital.

For the IHC studies, the tissue sections were treated with hydrogen peroxide to inactivate endogenous peroxidases after deparaffinization in xylene and rehydration in ethanol. The slides were placed in 10 mmol/l of citrate buffer at pH 6.0, then autoclaved for antigen retrieval. The primary antibodies were incubated overnight, and a secondary antibody was used to detect protein expression using EnVision™ (Dako, Glostrup, Denmark). Diaminobenzidine was used as the chromogen, and the nuclei were counterstained with hematoxylin. The antibodies used in the analysis were as follows: MUC1 (Ma552, 1:100), MUC2 (Ccp58, 1:100), MUC5AC (CLH2, 1:100), MUC6 (CLH5, 1:100) and CD10 (56C6, 1:100) from Leica Biosystems (Newcastle Upon, Tyne, UK) and CDX2 (CDX2-88, 1:100) from Biocare medical (Concord, CA, USA).

Two independent observers without prior knowledge of the clinicopathological data scored the IHC findings; the presence of positive cancer cells at any staining intensity and accounting for >10% of the sample was considered a positive finding.

STATISTICAL ANALYSIS

The Fisher exact test was used to assess the hypothesis of independence between the categorical variables. For the quantitative data such as age, we used the Mann–Whiney test.

Treatment outcomes were estimated as the response rate, progression-free survival (PFS) and overall survival (OS). PFS was defined as the time from the initiation of chemotherapy to the confirmation of disease progression or death from any cause. Patients who were lost to follow-up were treated as censored observations. The OS period was defined as the time from chemotherapy until the date of death or the most recent death.
follow-up. Patients who were lost to follow-up were treated as censored cases. Both the PFS and the OS were estimated using the Kaplan–Meier method, and significance was determined using the log-rank test. All the statistical analyses were performed using StatView (Ver. 5.0; SAS, Inc., Tokyo, Japan).

RESULTS

PATIENT CHARACTERISTICS

We identified 28 patients with advanced ampullary adenocarcinoma who received non-surgical treatment between March 1997 and July 2010. The treatments consisted of chemotherapy \( (n = 26) \) and best-supportive care \( (n = 2) \). Among the 26 patients who received chemotherapy, the median age of the patients was 62.0 years \( (\text{range, 48–79 years}) \) and the ECOG performance statuses were as follows: 8 patients with PS 0, 5 patients with PS 1, and 0 patients with PS 2–4. All the patients also had metastatic lesion. None of the patients had metastasis of the liver \( (n = 17) \), lungs \( (n = 7) \), lymph nodes \( (n = 14) \), peritoneum \( (n = 1) \), and pleura \( (n = 1) \). None of the patients had locally advanced disease. The metastatic sites were as follows: 8 patients with PS 0 and 5 patients with PS 1. All the patients had metastatic lesion. None of the patients had metastases of the liver \( (n = 17) \), lungs \( (n = 7) \), lymph nodes \( (n = 14) \), peritoneum \( (n = 1) \), and pleura \( (n = 1) \). None of the patients had locally advanced disease. The metastatic sites were as follows: 8 patients with PS 0, 5 patients with PS 1, and 0 patients with PS 2–4. All the patients had metastatic lesion. None of the patients had metastasis of the liver \( (n = 17) \), lungs \( (n = 7) \), lymph nodes \( (n = 14) \), peritoneum \( (n = 1) \), and pleura \( (n = 1) \). None of the patients had locally advanced disease. The metastatic sites were the liver \( (n = 17) \), lungs \( (n = 7) \), lymph nodes \( (n = 14) \), peritoneum \( (n = 1) \), and pleura \( (n = 1) \). None of the patients had locally advanced disease. The metastatic sites were as follows: 8 patients with PS 0, 5 patients with PS 1, and 0 patients with PS 2–4. All the patients also had metastatic lesion. None of the patients had metastatic disease. The metastatic sites were the liver \( (n = 17) \), lungs \( (n = 7) \), lymph nodes \( (n = 14) \), peritoneum \( (n = 1) \), and pleura \( (n = 1) \). None of the patients had metastatic disease. The metastatic sites were the liver \( (n = 17) \), lungs \( (n = 7) \), lymph nodes \( (n = 14) \), peritoneum \( (n = 1) \), and pleura \( (n = 1) \). None of the patients had locally advanced disease. The metastatic sites were the liver \( (n = 17) \), lungs \( (n = 7) \), lymph nodes \( (n = 14) \), peritoneum \( (n = 1) \), and pleura \( (n = 1) \). None of the patients had metastatic disease. The metastatic sites were as follows: 18 patients with PS 0, 8 patients with PS 1, and 0 patients with PS 2–4. All the patients also had metastatic lesion. None of the patients had metastasis of the liver \( (n = 17) \), lungs \( (n = 7) \), lymph nodes \( (n = 14) \), peritoneum \( (n = 1) \), and pleura \( (n = 1) \). None of the patients had locally advanced disease. The metastatic sites were as follows: 8 patients with PS 0, 5 patients with PS 1, and 0 patients with PS 2–4. All the patients had metastatic lesion. None of the patients had metastasis of the liver \( (n = 17) \), lungs \( (n = 7) \), lymph nodes \( (n = 14) \), peritoneum \( (n = 1) \), and pleura \( (n = 1) \). None of the patients had locally advanced disease. The metastatic sites were as follows: 8 patients with PS 0, 5 patients with PS 1, and 0 patients with PS 2–4. All the patients had metastatic lesion. None of the patients had metastasis of the liver \( (n = 17) \), lungs \( (n = 7) \), lymph nodes \( (n = 14) \), peritoneum \( (n = 1) \), and pleura \( (n = 1) \). None of the patients had locally advanced disease.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>62.0 (48–79)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15 (58)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (42)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>18 (69)</td>
</tr>
<tr>
<td>1</td>
<td>8 (31)</td>
</tr>
<tr>
<td>2–4</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stage (UICC 7th edition)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>12 (46)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>14 (54)</td>
</tr>
<tr>
<td>Metastatic sites</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>17 (65)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>14 (54)</td>
</tr>
<tr>
<td>Lungs</td>
<td>7 (27)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Pleura</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group performance status; UICC, the Union for International Cancer Control TNM Classification of Malignant Tumors (7th edition).

### Table 2. Tumor response according to treatment groups

<table>
<thead>
<tr>
<th>Regimens</th>
<th>RR (%)</th>
<th>DCR (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU + CDDP ( (n = 3) )</td>
<td>33</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFT + doxorubicin ( (n = 5) )</td>
<td>0</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-1 ( (n = 3) )</td>
<td>33</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ( (n = 11) )</td>
<td>18</td>
<td>72.7</td>
<td>2.5</td>
<td>8.0</td>
</tr>
<tr>
<td>GEM group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEM ( (n = 10) )</td>
<td>0</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEM + CDDP ( (n = 5) )</td>
<td>0</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ( (n = 15) )</td>
<td>0</td>
<td>80</td>
<td>3.5</td>
<td>12.3</td>
</tr>
</tbody>
</table>

RR, response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival.
The response rate for the 5-FU group was 18.2% (95% CI = 2.3–51.8%), and the disease control rate was 72.7% (95% CI = 39.0–94.0%). In the GEM group, on the other hand, the response rate was 0% (95% CI = 0–21.8%) and the disease control rate was 80.0% (95% CI = 51.9–95.7%). The median PFS was 2.5 and 3.5 months for the 5-FU group and the GEM group, respectively ($P = 0.79$) (Fig. 2). The median OS was 8.0 and 12.3 months, respectively ($P = 0.29$) (Fig. 3).

Three patients (27%) in the 5-FU group received second-line chemotherapy. In the GEM group, 4 (27%) patients received second-line chemotherapy.

**Treatment Outcome According to Stage IV Disease or Recurrent Disease**

Stage IV disease was present at the time of diagnosis in 12 patients, while recurrent disease after resection was present in 14 patients. In stage IV disease, the median age of the patients was 65.0 years and the ECOG performance statuses were as follows: nine patients (75%) with PS 0 and three patients (25%) with PS 1. Five of the 12 patients with stage IV disease had received 5-FU-based regimens and the remaining 7 patients received GEM-based regimens. Meanwhile, in recurrent disease, the median age of the patients was 66.0 years and the ECOG performance statuses were as follows: 9 patients (64%) with PS 0 and 5 patients (36%) with PS 1. Six of the 14 patients with recurrent disease had received 5-FU-based regimens and the remaining 8 patients received GEM-based regimens.

The response rate for stage IV disease was 8.3% (95% CI = 0.2–38.5%), and the disease control rate was 75.0% (95% CI = 42.8–94.5%). In recurrent disease, on the other hand, the response rate was 7.1% (95% CI = 0.2–33.9%) and the disease control rate was 78.6% (95% CI = 49.2–95.3%).

The median PFS was 8.3 and 2.5 months for stage IV disease and recurrent disease, respectively ($P = 0.16$) (Fig. 4). The median OS was 23.8 and 7.9 months, respectively ($P = 0.02$) (Fig. 5).
Five patients (42%) in stage IV disease received second-line chemotherapy. In the recurrent disease, 2 (14%) patients received second-line chemotherapy.

**TREATMENT OUTCOME ACCORDING TO ADENOCARCINOMA PHENOTYPE**

We examined 10 of the 26 ampullary adenocarcinomas to determine their phenotypes. The treatment regimens and outcomes according to the phenotypes are shown in Table 3. Eight of the 10 patients with ampullary adenocarcinoma (80%) had intestinal-type adenocarcinomas, while the remaining 2 (20%) had pancreatobiliary-type adenocarcinomas. Both patients with pancreatobiliary-type adenocarcinoma had received a GEM-based regimen, while 3 of the 8 patients with intestinal-type received 5-FU-based regimens and the remaining 5 patients received GEM-based regimens. One patient with intestinal-type adenocarcinoma who received 5-FU + CDDP responded to the treatment (PR), and the best response of the nine other patients was stable disease. The median OS was 7.9 months for the intestinal-type adenocarcinoma patients. The OS periods of the two pancreatobiliary-type adenocarcinoma patients were 12.3 months (373 days) and 14.3 months (435 days), respectively.

**DISCUSSION**

Ampullary adenocarcinoma is a rare disease entity, and little information regarding these tumors is available. Patients with ampullary adenocarcinomas are typically diagnosed at a relatively early stage due to the early appearance of clinical symptoms such as jaundice, and the likelihood of resectability is therefore high (12,13). On the other hand, detailed reports on advanced ampullary adenocarcinomas are extremely rare, especially regarding the treatment outcome of systemic chemotherapy for advanced stage disease.

A previous report discussed the efficacy of CDDP-based chemotherapy (5-FU plus CDDP or GEM plus CDDP) in 29 patients with advanced ampullary carcinoma (7). The treatment outcomes resulted in a responses rate of 27.5%, a disease control rate of 72.4%, a median time to progression of 4.9 months and a median OS period of 12.5 months, with manageable toxicities. 5-FU, CDDP and GEM were the selected agents examined in their report similar to the present study. However, in their report, the differences in the response rate, time to progression and OS were not related to the chemotherapy regimens (5-FU plus CDDP or GEM plus CDDP). In our results, the differences in the DCR, the PFS and the OS between the 5-FU group and the GEM group were also not statistically significant. Both reports indicated a modest activity for these agents against advanced ampullary adenocarcinomas; however, the optimum regimen is unknown, and patient prognosis remains dismal.

The ampulla of Vater consists of the following three distinct epithelial elements: duodenal epithelium, pancreatic duct epithelium and biliary ductal epithelium. Because of the rarity of ampullary adenocarcinomas, they are usually regarded as biliary tract adenocarcinomas or small intestine adenocarcinomas when selecting a chemotherapeutic regimen. However, no consensus exists regarding which of these disease entities is most appropriate for the inclusion of ampullary adenocarcinomas.

In some previous reports, advanced ampullary adenocarcinomas have been included with advanced small bowel adenocarcinomas. Two prospective phase 2 studies have been performed for patients with small bowel adenocarcinoma, including ampullary adenocarcinoma. First, the combination of 5-FU, doxorubicin and mitomycin C (FAM) in 38 patients with advanced adenocarcinoma of the small bowel (n = 34) or ampulla of Vater (n = 4) resulted in a response rate of 18% and a median OS of 8 months for all the patients (14). In a subgroup analysis, the median OS of the advanced ampullary adenocarcinoma patients (n = 4) was 7 months, which was roughly similar to that of the small bowel adenocarcinoma patients (median OS: duodenum, 9 months; jejunum, 2 months; and ileum, 5 months). Secondly, the combination of capecitabine and oxaliplatin (CAPOX) in 30 patients with advanced adenocarcinoma of the small bowel (n = 18) or ampulla of Vater (n = 12) resulted in a response rate of 50% and a median OS of 20.4 months (15). However, in a subgroup analysis, the response rate for advanced ampullary adenocarcinoma was 33%, which was lower than the rate for small bowel adenocarcinoma (61%). This response rate was similar to that for the patients with biliary tract adenocarcinoma (16) treated with the CAPOX regimen (20%), rather than that for patients with small bowel adenocarcinoma. Although whether advanced ampullary adenocarcinomas should be treated as biliary tract adenocarcinomas or as small bowel adenocarcinomas remain uncertain, recent major recent clinical trials or retrospective studies examining the use of anticancer agents in patients with biliary tract adenocarcinoma have included ampullary adenocarcinoma as a subgroup of biliary tract
The largest randomized trial examining biliary tract adenocarcinomas was the ABC-02 trial, in which the efficacy and safety of GEM alone vs. the combination of GEM plus CDDP was evaluated by British research groups (Cancer Research UK and University College of London). That study also included 20 (4.9%) patients with advanced ampullary carcinoma (21). In a subgroup analysis of the ampullary adenocarcinomas, GEM plus CDDP tended to result in a longer survival period than GEM alone, although the difference was not significant (hazard ratio 0.62; 95% confidence interval, 0.21–1.81). Although our results do not indicate whether the treatment strategy for small bowel adenocarcinomas or for biliary tract adenocarcinomas is the most suitable, the latter strategy, which recommends GEM plus CDDP, is the only evidence supported by the ABC-02 trial at present.

Previous phase II studies in patients with biliary tract adenocarcinomas demonstrated that patients with primary tumors showed worse survival than patients without primary tumors (22,23). In our analysis, there was no subject with locally advanced disease. The patients with stage IV disease had significantly longer OS than those with recurrent disease, which was different from the result of previous reports. The possible explanations for this result were the difference in the number of patients who receiving the second-line chemotherapy and the limited number of patients in this study.

Recent studies have demonstrated the importance of classifying pathological phenotypes. Ampullary adenocarcinomas can be separated into two distinct groups with significantly different survival rates for patients with resectable disease (8,9): intestinal type (50–80% of all ampullary adenocarcinomas), which has a relatively favorable prognosis and pancreatobiliary type (15–20%), which has a poor prognosis. CDX2 and MUC2 expression may be useful for distinguishing intestinal type from pancreatobiliary type (24). In our study, 80% of the ampullary carcinomas were classified as intestinal type and 20% were classified as pancreatobiliary type using immunohistochemical examinations. These results were similar to those of previous reports. However, both of the patients with pancreatobiliary-type adenocarcinomas lived for >1 year, while the median OS for the patients with intestinal-type adenocarcinoma was only 7.9 months. This finding disagreed with existing reports on the resected ampullary adenocarcinoma (25). However, the target population of our study was advanced ampullary adenocarcinoma patients who received systemic chemotherapy; to our knowledge, this report is the first to investigate the correlation between histological phenotypes and treatment outcomes in such a population. Therefore, the reason for this discrepancy between our report and previous reports is uncertain. Possible reasons include the difference in disease stage (resectable disease vs. unresectable disease), the difference in treatment (resection vs. chemotherapy) and an insufficient sample size. The relationship between cancer phenotypes and suitable chemotherapeutic regimens is an unsolved topic of great interest. Further research such as multicenter study to investigate larger population is needed in order to obtain more detailed information.

In conclusion, advanced ampullary adenocarcinomas have an aggressive clinical course. Their sensitivity to chemotherapy is modest, and the outcomes of treatment are comparable to those of patients with other biliary tract carcinomas. GEM plus CDDP, which is the only evidence supported by the ABC-02 trial at present, is considered to be the standard therapy for advanced ampullary adenocarcinomas.

Conflicts of interest statement

None declared.
Chemotherapy in patients with ampullary carcinoma

References


