A Multi-center Retrospective Analysis of Survival Benefits of Chemotherapy for Unresectable Biliary Tract Cancer

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Background: This study examined the effect of five systemic chemotherapy regimens on survival in patients with unresectable biliary tract cancer (BTC) as compared with the best supportive care (BSC).

Methods: This study retrospectively reviewed data from 413 consecutive patients with BTC who were seen at any of nine central hospitals in Japan between April 2000 and March 2003. Patients were eligible if they had intra- or extrahepatic cholangiocarcinoma or gallbladder cancer with no prior chemotherapy. Hazard ratios of treatment regimens were estimated using the Cox proportional hazard model and the propensity score method.

Results: Three-hundred and four patients were enrolled: 125 (41.1%) received BSC and 179 (58.9%) took chemotherapy. Of those who received chemotherapy, 58 (19.1%) took gemcitabine (GEM), 45 (14.5%) took a cisplatin (CDDP)-based regimen, 30 (9.9%) took a 5-fluorouracil (5-FU)-based regimen, 27 (8.9%) took 5-FU + doxorubicin + mitomycin (FAM) and 20 (6.6%) took S-1. The response rate was 8.4% (n = 15). The CDDP-based regimen was associated with a high frequency of toxicity symptoms. The adjusted hazard ratio for GEM in the Cox regression was 0.53 (95% CI 0.34–0.82) and the hazard ratio for the CDDP-based regimen was 0.49 (95% CI 0.36–0.99).

Conclusion: Chemotherapy with GEM may benefit patients with BTC.

Key words: biliary tract cancer — chemotherapy — survival — retrospective study — clinical trial

INTRODUCTION

Biliary tract cancer (BTC) is a relatively rare disease in the United States and Western Europe (1), but a frequent and serious cancer in Japan. It is the sixth leading cause of cancer death in Japan, killing approximately 15,000 people every year (2), and the incidence is increasing. BTC have traditionally been divided into cancers of the gallbladder, the extrahepatic bile ducts and the ampulla of Vater, whereas intrahepatic bile-duct cancers have been classified as liver cancer (1). Lately, however, the term BTC has been used to include the gallbladder, the intrahepatic cholangiocarcinoma, the extrahepatic cholangiocarcinoma and the ampulla of Vater (1). Worldwide, incidence and mortality rates of intrahepatic cholangiocarcinoma are increasing, while incidence rates of extrahepatic cholangiocarcinoma and gallbladder cancer are slightly decreasing (3).

Surgical resection is the only curative treatment for BTC, but it is only feasible if the cancer is detected early. The 5-year survival rate for resectable patients is around 40% (1). Because of the lack of early symptoms, most patients are diagnosed at an advanced stage, by which time the cancer has often metastasized or invaded the adjacent liver or...
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who were treated with systemic chemotherapy or BSC. The objective of this study was to clarify the impact of systemic chemotherapy on BTC, particularly in the context of unresectable disease, using a multicenter observational study in Japan. We analyzed survival time in a group of patients with BTC or papilla of Vater cancer (because the number of patients was very small), arterial-injection chemotherapy, unclassified chemotherapy, radiotherapy, prior chemotherapy and missing clinical variables (serum carbohydrate antigen 19-9 (CA19-9) or carcinoembryonic antigen (CEA)) from the analysis (Fig. 1).

Classification of Chemotherapy Regimens

Chemotherapy regimens were classified into five types: 5 FU-based; 5-FU, doxorubicin and mitomycin C (FAM); and cisplatin (CDDP)-based regimens. Results of these studies in establishing a standard chemotherapeutic regimen to replace it have been disappointing. Although the efficacy of conventional systemic chemotherapy seems negligible, there is no agreement on the standard regimen. Many clinical trials of single- and multi-drug regimens have been conducted for BTC, but the reported response rates, toxicity and survival times have been variable. Most of the clinical trials conducted to date have been phase II trials.

PATIENTS AND METHOD

Study Design

We retrospectively reviewed 413 unresectable BTC patients seen between April 2000 and March 2003 at nine central hospitals in Japan. Patients were eligible if they had unresectable BTC (n = 126), extrahepatic cholangiocarcinoma (n = 97), gallbladder cancer (n = 169) or papilla of Vater cancer (n = 21). Two-hundred and seven patients were treated with systemic chemotherapy, seven with arterial injection chemotherapy, 45 with radiotherapy, 15 with chemoradiotherapy and 137 received BSC.

We excluded patients with cancer of the papilla (because the number of patients was very small), arterial-injection chemotherapy, unclassified chemotherapy, radiotherapy, prior chemotherapy and missing clinical variables (serum carbohydrate antigen 19-9 (CA19-9) or carcinoembryonic antigen (CEA)) from the analysis (Fig. 1).

Statistical Methods

Overall survival was measured from the first day of treatment (chemotherapy group) or from the day of diagnosis (BSC group) to the date of death or last visit. The study enrolled patients on March 31, 2003, and observations on those patients remaining at the end of the study were censored. Survival curves were calculated by the Kaplan–Meier...
method (40). Differences in survival among subgroups according to each factor were evaluated by logrank tests. Hazard ratios and 95% confidence intervals (CI) were estimated by the Cox regression (41). Multivariate Cox regression (41) and the Cox regression by modeling the propensity score were performed for adjustment of confounders (42,43). We used 16 covariates (tumor type, age, gender, PS, status of surgery, evidence for unresectability, biopsy, hepatic metastasis, peritoneal metastasis, distant lymph node metastasis, lung metastasis, ascites, biliary drainage, total bilirubin, CEA level and CA19-9 level) for adjustment. Statistical significance was defined as a two-sided P-value of 0.05 or less. The analyses were performed using the statistical software JMP 5.01.J and SAS version 8.01 (SAS Institute Inc., Cary, NC, USA).

RESULTS

PATIENT CHARACTERISTICS

The final analysis population comprised 304 patients (Table 1). Duration of follow-up time on the patients was median 4.57 months (range 0.10–52.57 months). Ninety-three patients (30.6%) had intrahepatic cholangiocarcinoma, 64 patients (21.1%) had extrahepatic cholangiocarcinoma and 147 patients (48.4%) had gallbladder cancer. Pathologic confirmation in cytological examination was 202 patients. Somewhat less than half (125 (41.1%)) of the patients received BSC and 179 (58.9%) took chemotherapy. Of the chemotherapy group, 30 patients (9.9%) were on 5-FU-based regimens, 20 patients (6.6%) took S-1, 58 patients (19.1%) took GEM, 27 patients (8.9%) took FAM and 44 patients (14.5%) were on CDDP-based regimens.

RESPONSE AND TOXICITY

Partial response was achieved in 15 of 179 chemotherapy patients (three with intrahepatic cholangiocarcinoma, two with extrahepatic cholangiocarcinoma and 10 with gallbladder cancer), but complete response was observed in no patients. Overall response rate was thus 8.4%. Stable disease was observed in 85 patients (47.5%) and progressive disease in 67 patients (37.4%). None (0%) of those on a 5-FU-based regimen showed a partial response, 11 (36.7%) remained
stable and 11 (36.7%) showed progressive disease. Three (15.0%) patients treated with S-1 showed a partial response, 10 (50.0%) remained stable and six (30.0%) showed progressive disease. Of those given GEM, four (6.9%) showed a partial response, 29 (50.0%) remained stable and 23 (39.7%) showed progressive disease. Three (11.1%) of the patients taking FAM showed a partial response, 11 (40.7%) remained stable and 13 (48.2%) showed progressive disease. Three (11.1%) of the patients taking CDDP showed a partial response, 24 (54.6%) remained stable and 11 (31.8%) showed progressive disease.

The data were also analyzed by tumor type. Three (6.0%) of the patients with intrahepatic cholangiocarcinoma showed a partial response, 24 (48.0%) remained stable, and 20 (40.0%) showed progressive disease. Two (5.7%) of the patients with extrahepatic cholangiocarcinoma showed a partial response, 17 (48.5%) remained stable and 12 (34.2%) showed progressive disease. Ten (10.6%) of the gallbladder cancer patients showed a partial response, 44 (46.8%) remained stable and 35 (37.2%) showed progressive disease.

As for toxicity, 40 (22.4%) had grade 3 nonhematological toxicities and 28 (15.6%) had grade 4 hematological toxicities. Among the patients taking 5-FU, five (16.7%) had grade 3 nonhematological toxicities. Of those taking S-1, 5 (25.0%) had grade 3 nonhematological toxicities. Of those taking GEM, 10 (17.2%) showed grade 3 nonhematological toxicities and two (3.5%) had grade 4 hematological toxicities. Two (7.4%) patients on the FAM regimen had grade 3 and six (22.2%) had grade 4 hematological toxicities. Among patients on a CDDP-based regimen, 18 (40.9%) had Grade 3 nonhematological toxicities and 20 (45.5%) had grade 4 hematological toxicities.

**Survival**

The number of deaths was 87 (69.6%) of the 125 BSC patients and 150 (83.8%) of the 179 chemotherapy patients. The median overall survival time was 3.12 months (95% CI 2.50–4.11) for BSC patients and 7.38 months (95% CI 6.25–8.77) for chemotherapy patients. Figure 2 shows the survival curves for the chemotherapy and the BSC groups. The difference in survival times was significant (logrank test $P$-value $< 0.0001$).

When the data for the chemotherapy group was analyzed by tumor type, the median overall survival time was 8.44 months (95% CI 5.15–11.2) for intrahepatic cholangiocarcinoma, 10.15 months (95% CI 5.38–13.7) for extrahepatic cholangiocarcinoma, and 6.50 months (95% CI 5.25–8.04) for gallbladder cancer. There was a statistically significant difference between extrahepatic cholangiocarcinoma and gallbladder cancer (logrank test $P$-value 0.029), but no difference between intrahepatic cholangiocarcinoma and gallbladder cancer (logrank test $P$-value 0.072). Gallbladder cancer patients died sooner than cholangiocarcinoma patients despite their better response to treatment.

Applying the Cox model yielded a hazard ratio for GEM of 0.50 (95% CI 0.35–0.72) and for CDDP-based regimens...
of 0.51 (95% CI 0.34–0.76; Table 2). Figure 3 shows the survival curves for patients on each regimen and receiving BSC. The median time to treatment failure was 2.76 months (95% CI 1.74–4.40) for GEM patients and 5.52 months (95% CI 2.07–6.77) for CDDP-based regimens.

The adjusted hazard ratio in the Cox regression model for GEM was 0.53 (95% CI 0.34–0.82) and for CDDP-based regimens was 0.49 (95% CI 0.36–0.99). The adjusted hazard ratio in the Cox regression by modeling the propensity scores for GEM was 0.54 (95% CI 0.36–0.80) and for CDDP-based regimens 0.60 (95% CI 0.36–0.99; Table 3). Hazard ratio estimates obtained using the Cox regression and the propensity score were similar.

**DISCUSSION**

There is no standard chemotherapy for advanced biliary tract cancer. This study reports the impact of five types of chemotherapy on BTC compared with BSC. GEM was the most effective treatment, with a reduction in mortality of about 50%. GEM has already been shown to be an effective therapy for BTC in phase II trials (16–21). Response rates in GEM ranged from 8 to 36% and overall survival times from 6.3 to 16 months (44). The treatment is remarkably well tolerated, with very few patients (5%) experiencing grade 4 hematologic toxicities. Hematologic adverse effects were infrequent and almost exclusively mild to moderate (44). A systematic review of the evidence on GEM from 13 single-arm phase II trials showed that GEM may be a reasonable option for treating BTC (45). Although GEM had been previously approved for solid tumors other than BTC (2), it was only approved for BTC in Japan in June of 2006.

CDDP-based regimens reduced mortality by 40%. However, we found a high frequency of grade 3 and 4 toxicities, making it unlikely that CDDP-based regimens can be used as standard therapy for BTC. Adverse events such as

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chemotherapy (n = 179)</th>
<th>BSC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-FU</td>
<td>S-1</td>
<td>GEM</td>
</tr>
<tr>
<td>n = 30 (9)</td>
<td>n = 20 (6)</td>
<td>n = 58 (19)</td>
<td>n = 27 (8)</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>17 (57)</td>
<td>7 (35)</td>
<td>28 (48)</td>
</tr>
<tr>
<td>Male</td>
<td>13 (43)</td>
<td>13 (65)</td>
<td>30 (52)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>60 and over</td>
<td>19 (39)</td>
<td>12 (40)</td>
<td>42 (28)</td>
</tr>
<tr>
<td>Less than 60</td>
<td>11 (61)</td>
<td>8 (60)</td>
<td>16 (62)</td>
</tr>
<tr>
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<td></td>
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<tr>
<td>0</td>
<td>13 (43)</td>
<td>9 (45)</td>
<td>27 (47)</td>
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<td>13 (43)</td>
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</tr>
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<td>4 (13)</td>
<td>2 (10)</td>
<td>2 (3)</td>
</tr>
<tr>
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<td>0 (0)</td>
<td>1 (2)</td>
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<tr>
<td>4</td>
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<tr>
<td>Tumor Type</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Intrahepatic</td>
<td>13 (43)</td>
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<td>8 (14)</td>
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<tr>
<td>Extrahepatic</td>
<td>7 (23)</td>
<td>2 (10)</td>
<td>16 (28)</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>10 (33)</td>
<td>18 (90)</td>
<td>34 (58)</td>
</tr>
<tr>
<td>CEA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 and over</td>
<td>7 (23)</td>
<td>9 (45)</td>
<td>22 (38)</td>
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<tr>
<td>Less than 10</td>
<td>23 (77)</td>
<td>11 (55)</td>
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<td>CA19-9</td>
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<td></td>
</tr>
<tr>
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<td>11 (37)</td>
<td>7 (35)</td>
<td>21 (36)</td>
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<tr>
<td>Less than 1000</td>
<td>19 (63)</td>
<td>13 (65)</td>
<td>37 (64)</td>
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<tr>
<td>Biliary drainage</td>
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<td></td>
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<tr>
<td>Liver</td>
<td>7 (23)</td>
<td>14 (70)</td>
<td>27 (47)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>4 (13)</td>
<td>2 (10)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>6 (20)</td>
<td>11 (55)</td>
<td>21 (36)</td>
</tr>
<tr>
<td>Lung</td>
<td>3 (10)</td>
<td>2 (10)</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

BSC, best supportive care; 5-FU, 5-fluorouracil-based regimen; GEM, gemcitabine; FAM, 5-FU + doxorubicin + mitomycin C; CDDP, cisplatin-based regimen; CEA, carcinoembryonic antigen; CA, serum carbohydrate antigen.

Table 1. Patient characteristics

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inflammation of the biliary duct and hematological toxicity have been reported in other trials (25,46).

The combination of GEM with CDDP or other new platinum products such as oxaliplatin or with other anticancer drugs (47) might be an attractive option. A pooled analysis of the evidence from 112 single-arm phase II trials showed that GEM combined with platinum may be promising drugs for treating BTC (48). Results of the pooled analysis in phase II trials and our study are similar. In the UK, ABC trial-01 evaluates the role of CDDP in combination with GEM compared with GEM alone (49). A similar trial is ongoing in Japan. In future randomized trials, we recommend comparing GEM with a combination regimen of GEM and new platinum products such as oxaliplatin (34–36).

Although the result of S-1 in this study was not good, S-1 trials for regulatory approval had finished yet in Japan. The result of the trial was good. The response rate was 35% and

**Table 2.** Median survival time and crude hazard ratio of treatment regimens and BSC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number (%)</th>
<th>MST (months) (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSC</td>
<td>125 (41)</td>
<td>3.12 (2.50–4.11)</td>
<td>Reference</td>
<td>—</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>179 (59)</td>
<td>7.38 (6.25–8.77)</td>
<td>0.55 (0.42–0.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-FU</td>
<td>30 (10)</td>
<td>7.23 (4.37–9.59)</td>
<td>0.65 (0.41–1.01)</td>
<td>0.058</td>
</tr>
<tr>
<td>S-1</td>
<td>20 (7)</td>
<td>5.95 (2.81–10.38)</td>
<td>0.71 (0.42–1.20)</td>
<td>0.209</td>
</tr>
<tr>
<td>GEM</td>
<td>58 (19)</td>
<td>8.05 (5.49–11.50)</td>
<td>0.50 (0.35–0.72)</td>
<td>0.0002</td>
</tr>
<tr>
<td>FAM</td>
<td>27 (9)</td>
<td>6.24 (4.93–7.66)</td>
<td>0.75 (0.48–1.18)</td>
<td>0.220</td>
</tr>
<tr>
<td>CDDP</td>
<td>44 (14)</td>
<td>8.51 (5.29–11.24)</td>
<td>0.51 (0.34–0.76)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

MST, median survival time; CI, confidence interval.

**Figure 3.** 5-FU: 5-fluorouracil-based regimen; GEM: gemcitabine; FAM: 5-FU + doxorubicin + mitomycin C; CDDP: cisplatin-based regimen. +: censored observations.
The median survival time was 9.4 months (50). The GEM + S-1 trial has not been done yet. In future, S-1 or GEM + S-1 combined chemotherapy will be tested.

The limitations of this study are its retrospective nature and its nonrandomized design. There were some unbalances of baseline information in patient characteristics between the chemotherapy group and the BSC group. There were some unbalances of baseline information in patient characteristics between the chemotherapy group and the BSC group. The proportion of patients with PS 2–3 or older age (over 60 years) in the BSC group was higher than in the chemotherapy group. We adjusted for known, measurable confounders through multivariate analysis and propensity score methods, but the study may still be limited by unmeasured confounders or information biases such as misclassification. We have no information for second- or third-line regimen each arm in this study. The second- or third-line treatment may affect the outcome of overall survival times. Our results should be supplemented by prospective trials using survival as the endpoint. The sample size was not large, and when the data was broken down by both disease and treatment regimen, some categories had few observations. For example, the S-1 treatment group included no patients with intrahepatic cholangiocarcinoma, and a much higher percentage of gallbladder cancer (90%) than the study group as a whole. This limits the interpretation of the results of the S-1 regimen. In the study, the low-dose CDDP regimen used a low dose under 10 mg. We thought that it should not classify within the class both this and another regimen with 80 mg/m² such as the CEA regimen.

In addition, we consulted chemotherapy experts in a nonresearch group. Through this process, we decided that the classification of chemotherapies in the study and these regimens were separate. We did not classify low dose 5-FU plus CDDP regimen within the CDDP regimen and excluded the patients from the study. This classification may be subject to other opinions. We reviewed all patients for 3 years from September to December 2004 more than a year and a half from starting the treatment. Most lost cases were patients who moved to other hospitals on their own decision. We could not follow them in the study. This is a limitation in the study.

Survival times for patients with BTC can be affected by factors such as PS and tumor type. Gallbladder cancer patients had shorter survival times than patients with intrahepatic or extrahepatic cholangiocarcinoma (15,21,23), possibly reflecting the more aggressive biology of gallbladder cancer (25). Alternatively, the pattern could result from differing sensitivities to chemotherapy due to biological differences between biliary tract and gallbladder cancers. Such differences in sensitivity could not clearly explain the difference in survival between patients with biliary tract and gallbladder cancer in this study. Future randomized trials should employ stratified randomization by strong prognostic factors such as type of cancer, PS and presence of metastases.

**Acknowledgment**

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**Conflict of interest statement**

None declared.

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