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ORIGINAL ARTICLE

# A phase II study of gemcitabine in combination with oxaliplatin as first-line chemotherapy in patients with inoperable biliary tract cancer

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**Abstract**
*Purpose* The aim of this study is to investigate the efficacy and safety of gemcitabine and oxaliplatin combination chemotherapy as first-line therapy in patients with inoperable biliary tract cancer (BTC).
*Methods* The treatment of this non-randomized phase II study consisted of gemcitabine 1,000 mg/m$^2$ intravenously (i.v.) on day 1 and oxaliplatin 85 mg/m$^2$ i.v. on day 2 every 2 weeks until disease progression, unaccep toxicity or patients' refusal.
*Results* From Sept 2006 to Oct 2007, 40 patients were enrolled. In the ITT analysis, the objective response rate was 15.0% and the disease control rate was 52.5%. The median overall survival (95% CI) was 8.5 months (6.4–10.7) and the time to progression was 4.2 months (0.5–7.9). For the 305 cycles, observed grade 3/4 toxicity was uncommon.
*Conclusions* Gemcitabine and dose adjusted oxaliplatin combination chemotherapy had moderate anti-tumor activity and was well tolerated as a first-line treatment for patients with inoperable BTC.

**Keywords** Biliary tract cancer · Gemcitabine · Oxaliplatin · Chemotherapy

## Introduction

Biliary tract cancer (BTC) is generally rare in Western countries but common in Korea where approximately 3,500 new patients are diagnosed annually [1]. The treatment of BTC is limited, although surgery provides the only curative treatment, most patients are not eligible for surgery because of the advanced stage of disease at diagnosis or combined impaired liver function [2]. Therefore, there is a need for palliative chemotherapy for inoperable BTC patients. However, BTC is generally resistant to systemic chemotherapy and no survival benefit of palliative chemotherapy has been demonstrated for

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advanced BTC. A single randomized trial suggested advantages of systemic chemotherapy in advanced BTC compared with best supportive care [3]. Finally, there is as yet no standard systemic palliative chemotherapy regimen for this disease.

5-Fluorouracil (5-FU) is the most extensively studied single agent used in the treatment of BTC; however, the efficacy of 5-FU-based regimens has been disappointing, with a response rate of <20% [4–7]. Several recent studies of new chemotherapeutic agents, such as gemcitabine, have indicated response rates higher than those reported previously [8, 9]. Clinical trials have examined combination therapy with gemcitabine and other drugs [10–13]. A phase II trial of cisplatin and gemcitabine for advanced BTC in Korea showed response rates of 7–34%, but relatively high toxicity [11, 12, 14]. A preclinical study demonstrated the synergistic effects of oxaliplatin and gemcitabine [15] and combination therapy with gemcitabine and oxaliplatin has been attempted in advanced BTC [16]. André et al. [16] reported that the response rate of the combination therapy with gemcitabine given as a fixed dose rate (FDR) infusion and oxaliplatin was about 30%. The dose intensities were 85–90% and 80% for gemcitabine and oxaliplatin administered at doses of 1,000 and 100 mg/m$^2$, respectively, every 2 weeks in several phase II trials, including studies of other solid tumors [16–18]. Adverse toxicities, such as grade III–IV neuropathy, were seen in 10–20% of cases. In addition, 10–20% of patients were withdrawn based on the cumulative oxaliplatin dose [16–19]. Therefore, there is a need to adjust the dose of oxaliplatin in a manner different from that used in the previous studies.

In summary, palliative chemotherapy may prolong survival and improve the quality of life in cases of advanced BTC; however, there is no standard regimen for systemic chemotherapy for the treatment of this disease. Therefore, this phase II trial was performed to investigate the efficacy and toxicity of combination chemotherapy with gemcitabine and dose adjusted oxaliplatin in patients with inoperable BTC in Korea.

## Patients and methods

### Eligibility criteria

The eligibility criteria for this study were as follows: (1) histologically or cytologically confirmed biliary tract adenocarcinoma; (2) inoperable disease as defined by: (i) localized disease that does not allow the possibility of complete surgical removal of the tumor with a clear resection margin; (ii) the presence of metastatic lesions; and (iii) an unresectable recurrent tumor after curative resection; (3) controlled biliary obstruction; (4) a minimum life expectancy of 12 weeks; (5) at least one measurable lesion according to the response evaluation criteria in solid tumors (RECIST) or an evaluable lesion present in an imaging study; (6) age over 18 years; (7) Eastern Cooperative Oncology Group (ECOG) performance status of ≤2; (8) adequate organ function as evidenced by; absolute neutrophil count (ANC) >1.5 × 10$^9$/l; platelets >100 × 10$^9$/l; total bilirubin ≤3 × upper limit of normal (UNL); aspirate aminotransferase (AST) or alanine aminotrasferase (ALT) <5 × UNL, creatinine <1.5 mg/dl or creatinine clearance >50 ml/min; and (9) a consent form signed and dated before the study. The study protocol and informed consent form were approved by the institutional ethics review board. Patients who had undergone prior systemic chemotherapy or had symptomatic or uncontrolled brain metastasis were excluded from the study.

### Pretreatment evaluation

Baseline laboratory analyses [blood cell count, serum creatinine, bilirubin, AST, ALT, alkaline phosphatase, lactic dehydrogenase, carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA 19–9)] were performed within 1 week, and tumor status was assessed using computed tomography (CT) scan or magnetic resonance imaging (MRI) within 4 weeks of starting the first cycle of therapy.

### Treatment

All patients were treated with gemcitabine at 1,000 mg/m$^2$/day intravenously (i.v.) on day 1 at a 10 mg/m$^2$/min followed by oxaliplatin at 85 mg/m$^2$/day i.v. 24 h later on day 2 as a 2-h infusion every 2 weeks. Treatment cycles were repeated for at least four cycles unless there was documented disease progression, unacceptable adverse events or withdrawal of consent. When grade 3 or 4 hematological toxicity occurred, the next chemotherapy cycle was started after recovery (ANC ≥ 1,500 × 10$^6$/l, platelet ≥ 75 × 10$^9$/l) with the dose of gemcitabine adjusted to 800 mg/m$^2$ unless there was confirmed disease progression or unacceptable toxicity. Once the dose was reduced, it could not be increased. When the delay interval exceeded 3 weeks, the chemotherapy schedule was ended. When neutropenic fever or combined infection occurred, granulocyte colony stimulating factor (G-CSF) was available for use, although the prophylactic use of G-CSF was not allowed. When grade 3 or 4 neurological toxicity occurred, the duration of oxaliplatin infusion was prolonged to more than 6 h beginning at the next cycle. With progression of neurological toxicity after infusion over more than 6 h, the administration of oxaliplatin was halted.

### Assessment of efficacy and toxicity

Tumor assessments using CT including the lesions, abdomen, pelvis, and/or chest were performed at baseline and

repeated every four cycles using the RECIST criteria. Tumor markers CA 19–9 and CEA was checked every four cycles. MRI was performed in patients whose response could not be assessed with CT. A physical examination including weight and toxicity assessment, ECOG performance status, complete blood count, and blood chemistry was performed before each cycle. Toxicity was graded according to the National Cancer Institute common toxicity criteria (NCI-CTC) version 3.0. The severity of any toxicity not defined in the NCI-CTC was graded as 1, mild; 2, moderate; 3, severe; or 4, very severe. All patients were included in the intention-to-treat analysis of efficacy. The response rate was calculated as the ratio of the number of patients who achieved complete or partial responses to the number of patients enrolled in the study. The disease control rate (DCR) was calculated as the ratio of the number of patients who achieved complete or partial responses or stable disease (SD) to the number of patients enrolled in the study.

### Statistical analysis

The primary end points were response rate and DCR. The secondary end points were safety, overall survival (OS), time to progression (TTP), and factors affecting the response rate or survival. Sample size was calculated to reject a 10% response rate in favor of a target response rate of 30%, with a significance level of 0.05 and a power of 90% using Simon's optimal two-stage design. In the initial stage, 18 evaluable patients were entered into the study and evaluated for response. If there were fewer than two responses, accrual was to be terminated. If more than three responses were observed in the first stage, then 18 additional patients were to be entered in the second stage to achieve a target sample size of 36 evaluable patients. Further assessment of the regimen was felt to be warranted if more than six responses were observed in the 36 patients. Considering a withdraw rate of 10%, the total target number was set to 40 patients. The relative dose intensity (DI) was calculated as the ratio of the DI actually delivered to the DI planned in the protocol.

TTP was calculated from the first day of treatment to the date on which progression of the disease was first observed or the date of last follow-up. OS was calculated from the first day of treatment to the date of death or last follow-up. OS and TTP were assessed using the Kaplan–Meier method, and the 95% confidence intervals (95% CI) for the median time to an event were calculated. Significant variables in the univariate analysis were considered as variables for the multivariate analysis performed using Cox's proportional hazard regression model.

## Results

### Patient characteristics

From Sept 2006 to Oct 2007, 40 patients were enrolled in this prospective study. The median age was 64 years (range 41–81) and seven of the patients were older than 70 years. The male:female ratio was 17:23. There were 9 (22.5%) cases of gallbladder (GB) cancer, 29 (72.5%) cases of cholangiocarcinoma, and 2 (5.0%) cases of cancer of the ampulla of vater. Of the patients, 32 (80%) had metastasis, while the remaining 8 (20%) had locally advanced disease. Half of the patients had elevated CEA levels, while 80% had elevated CA 19–9 levels.

In total, 305 cycles of therapy were administered with a median of 4.5 cycles (range 1–20) per patient. These clinical characteristics are summarized in Table 1.

**Table 1** Patient characteristics

| Characteristic | No. of patients ($n = 40$) | % |
|---|---|---|
| Age (years) | | |
| Median (range) | 64 (41–81) | |
| Gender | | |
| Male | 17 | 42.5 |
| Female | 23 | 57.5 |
| ECOG status, PS | | |
| 0 | 4 | 10.0 |
| 1 | 28 | 70.0 |
| 2 | 8 | 20.0 |
| Site of primary disease | | |
| Gallbladder cancer | 9 | 22.5 |
| Cholangiocarcinoma | 29 | 72.5 |
| Cancer of ampulla of vater | 2 | 5.0 |
| Disease status at presentation | | |
| Locally advanced | 8 | 20.0 |
| Metastatic | 32 | 80.0 |
| Organ involved (cases) | | |
| Liver | 23 | 57.5 |
| Peritoneum | 5 | 12.5 |
| Lung | 7 | 17.5 |
| Bone | 4 | 10.0 |
| Others[a] | 2 | 5.0 |
| Increased CEA level (>5 ng/ml) | 20 | 50.0 |
| Increased CA 19–9 level (>33 U/ml) | 32 | 80 |

*ECOG* Eastern Cooperative Oncology Group

[a] Adrenal gland and ureter

## Delivery of drugs

The average relative dose intensities of gemcitabine and oxaliplatin were 0.92 and 0.92, respectively. Dose reduction was required in three patients (12 cycles) due to myelosuppression (2 patients, 9 cycles) and fatigue (1 patient, 3 cycles).

## Tumor responses

Of the 40 patients enrolled in this study, 37 were evaluable in terms of treatment response. The remaining three patients could not be assessed, as two patients died (one from asphyxia after the first cycle and one from an unknown cause after the third cycle) and one patient refused further treatment because of a left femoral neck fracture after the third cycle. The intention-to-treat tumor response data for all patients enrolled in the study are summarized in Table 2.

The objective response rate (ORR) from the intention-to-treat analysis was 15.0% (95% CI, 3.4–26.6%) with no cases showing a complete response and six cases showing a partial response. The DCR was 52.5% (95% CI, 36.3–68.7%), including 15 patients with SD and 16 patients with progressive disease. In patients older than 70, the ORR was 14.3% and the DCR was 85.7%.

**Table 2** Tumor responses

| Response | No. of patients ($n = 40$) | % |
|---|---|---|
| Complete response | 0 | 0 |
| Partial response | 6 | 15.0 |
| Stable disease | 15 | 37.5 |
| Progressive disease | 16 | 40.0 |
| Not evaluated | 3 | 7.5 |
| Objective response rate | 6 | 15.0 |
| Disease control rate | 21 | 52.5 |

## Survival

All of the patients were evaluable in terms of survival analysis. With a median follow-up of 12.9 months (range 6.2–20.0), the median TTP was 4.2 months (95% CI 0.5–7.9) and the median OS was 8.5 months (95% CI 6.4–10.7). The Kaplan–Meier curves for TTP and OS are shown in Fig. 1.

## Factors affecting the outcomes

Elderly patients (>60 years) had better DCRs than younger patients (≤60 years) ($P = 0.044$). There were no other significant differences in the DCRs according to gender, performance status, primary site (GB cancer vs. cholangiocarcinoma vs. cancer of the ampulla of vater), disease status (locally advanced vs. metastatic), or increased CEA or CA 19–9 level (Table 3).

Responders had a significantly prolonged TTP compared with non-responders ($P = 0.009$) and there was tendency toward a survival benefit in responders compared with non-responders to chemotherapy ($P = 0.239$, median OS 8.3 vs. 11.6 months). In patients with disease controlled by chemotherapy ($P = 0.00002$), locally advanced disease ($P = 0.006$), or cholangiocarcinoma ($P = 0.013$), OS was prolonged significantly compared with patients with uncontrolled disease, metastatic disease, or GB cancer, respectively. In multivariate analysis, controlled disease was an independent factor favoring OS ($P = 0.00004$) (Fig. 2), while other factors such as age, gender, performance status, and increased CEA or CA 19–9 levels did not affect OS or TTP (Table 4).

## Toxicity

A total of 305 cycles were administrated, and all cycles were evaluable for toxicity. NCI-CTC grade 3/4 toxicities were uncommon, but included neutropenia (4.2% per cycle), thrombocytopenia (2.0% per cycle), nausea (2.7% per cycle), diarrhea (1.3% per cycle), fatigue (1.6% per

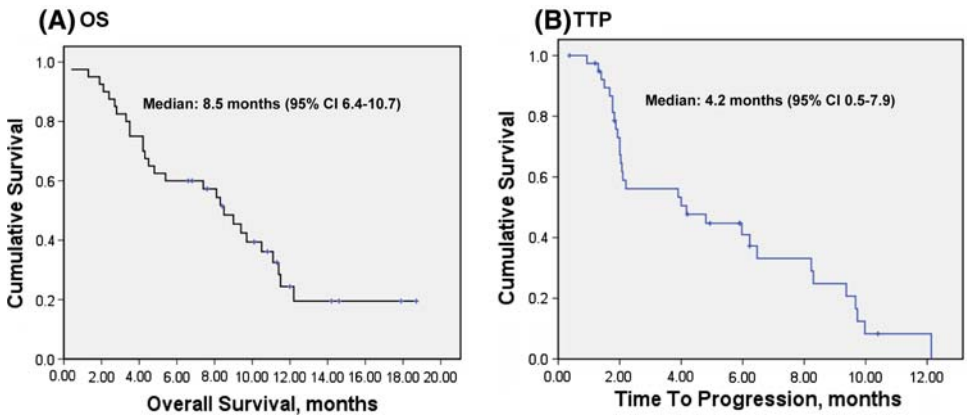


**Fig. 1** Kaplan–Meier survival curves of (**a**) overall survival (*OS*) and (**b**) time to progression (*TTP*) in 40 patients

**Table 3** Factors affecting the disease control rate

| Variables | Univariate analysis *P* value |
|---|---|
| Age (≤60 vs. >60) | 0.044 |
| Sex (male vs. female) | 0.519 |
| ECOG performance status (0 vs. 1 vs. 2) | 0.678 |
| Primary site (GB vs. cholangiocarcinoma vs. cancer of ampulla of Vater) | 0.682 |
| Disease status (locally advanced vs. metastatic) | 0.104 |
| CA 19–9 level (≤35 U/ml vs. >35 U/ml) | 0.517 |
| CEA level (≤3.5/ml vs. >3.5/ml) | 0.886 |

cycle), and peripheral neuropathy (10.0% per patient). Three grade 3/4 pulmonary thromboembolism events occurred in all cycles, but the relationship to chemotherapy was not clear. In the seven patients older than 70, a total of 56 cycles were administrated. NCI-CTC grade 3/4 toxicities were also uncommon, such as neutropenia (1.8% per cycle), thrombocytopenia (0% per cycle), nausea (0% per cycle), diarrhea (3.6% per cycle), fatigue (5.4% per cycle), and peripheral neuropathy (14.3% per patient). Toxicities seen during treatment are listed in Table 5.

## Discussion

Gemcitabine is one of the several new anticancer drugs under investigation for the treatment of advanced BTC. Gemcitabine and oxaliplatin are relatively safe in comparison to other cytotoxic drugs in patients with impaired liver function [20]. Combination therapy with gemcitabine and oxaliplatin is used mostly in pancreas cancer patients [18, 19]. The GERCOR and GISCAD phase III trials demonstrated the efficacy in terms of the response rate and PFS, but not in terms of OS, as well as the safety of gemcitabine and oxaliplatin combination therapy in comparison with gemcitabine single therapy in pancreatic cancer patients [19]. Pancreatic cancer and BTC are similar in terms of both tumor biology and the response to chemotherapeutic agents.

We used a different regimen from other phase II studies. Considering its neurotoxicity, we modified the dose of oxaliplatin to 85 mg/m$^2$ biweekly unlike other phase II studies [10, 16, 18]. In addition, we used a FDR method for gemcitabine infusion. The FDR schedule for gemcitabine resulted in increased gemcitabine triphosphate in peripheral blood mononuclear cells, although in is not clear whether this is also true of the target tumor tissue. The survival or response benefit of FDR was demonstrated in a randomized study of patients with pancreas cancer [21, 22], while no differences in the response rate or survival data were observed in non-small cell lung cancer or hepatocellular carcinoma [23, 24]. Finally, clinical data are mixed regarding the therapeutic benefit in terms of the response rate and survival advantage. The administration sequence of drugs did not affect the results significantly in pharmacokinetics studies [18, 25]. Therefore, we obtained similar results in terms of the response rate and survival, while obtaining a better outcome in the toxicity profiles as compared to previous trials using our modified method of administering gemcitabine and oxaliplatin. All of the patients tolerated the therapy remarkably well, and none of the patients withdrew from therapy due to treatment-related toxicity. With regard to neurotoxicity, two patients who received 20 cycles of treatment tolerated the treatment well. Thrombocytopenia was the most frequent toxicity reported in a German study [10]. In this previous study, frequent treatment delays (54% patients) were observed because of thrombocytopenia. In contrast, only one patient experienced NCI CTC grade 3 thrombocytopenia in the present study. Finally, the relative average dose intensities of gemcitabine and oxaliplatin were 91.7% and 92.3%, respectively, and most patients were treated with the planned dose and planned schedule. In this cohort of patients, 80% had a good performance status, which may have influenced the mild toxicity profile and

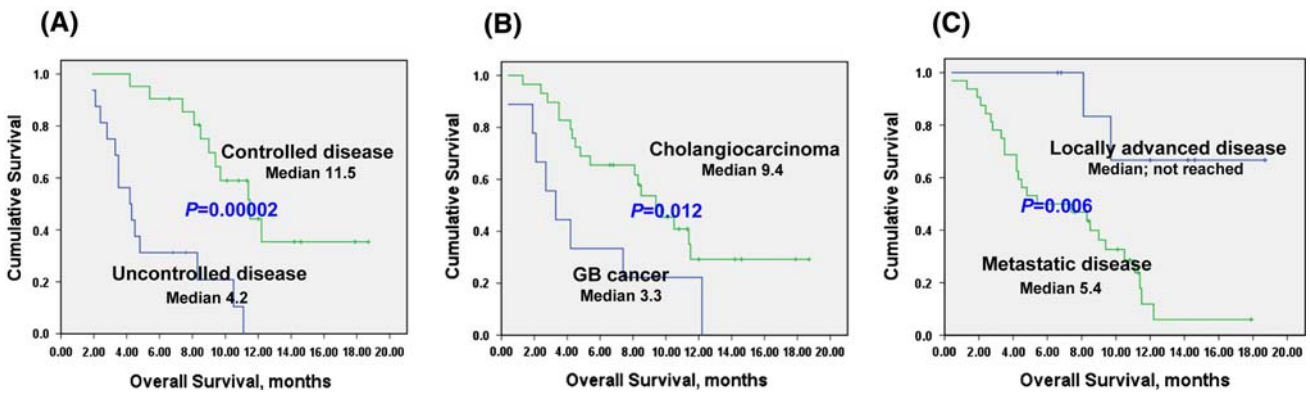


**Fig. 2** Kaplan–Meier survival curves of the overall survival according to **a** disease control status with chemotherapy, **b** primary site (GB cancer vs. cholangiocarcinoma), and **c** disease status at therapy (locally advanced disease vs. metastatic disease)

**Table 4** Factors affecting the survival

| | Univariate analysis, *P* value | |
|---|---|---|
| | TTP | OS |
| Responder | 0.009 | 0.239 |
| Controlled disease | 0.00000 | 0.00002[a] |
| Age (≤60 vs. >60) | 0.190 | 0.537 |
| CA 19–9 level (≤35 vs. >35 U/ml) | 0.225 | 0.760 |
| CEA level (≤3.5/ml vs. >3.5/ml) | 0.526 | 0.071 |
| Primary site (GB vs. cholangiocarcinoma vs. ampulla of vater) | 0.467 | 0.039[b] |
| Primary site (GB vs. cholangiocarcinoma) | 0.307 | 0.013 |
| ECOG performance status (0 vs. 1 vs. 2) | 0.830 | 0.990 |
| Sex (male vs. female) | 0.611 | 0.933 |
| Disease status (locally advanced vs. metastatic) | 0.469 | 0.006 |

[a] This value was confirmed as an independent significant factor for OS in multivariate analysis ($P = 0.00004$)

[b] This value was not significant when the Bonferroni factor was applied ($\times 3 = 0.117$)

**Table 5** Adverse events

| NCI-CTC Gr 3–4 toxicity | Per cycle, No (%) | Per patient, No (%) |
|---|---|---|
| Hematologic toxicity | | |
| Neutropenia | 13 (4.2%) | 7 (17.5%) |
| Thrombocytopenia | 6 (1.96%) | 1 (2.5%) |
| Nonhematologic toxicity | | |
| Nausea | 3 (2.7%) | 3 (7.5%) |
| Vomiting | 0 | 0 |
| Peripheral neuropathy | 10 (3.3%) | 4 (10%) |
| Diarrhea | 4 (1.3%) | 3 (7.5%) |
| Fatigue | 5 (1.6%) | 4 (10%) |
| Thrombosis | 3 (0.9%) | 3 (7.5%) |

the favorable activity, although the difference lacked statistical significance.

Responders to chemotherapy showed a slight survival benefit in comparison to non-responders ($P = 0.239$, median OS 8.3 vs. 11.6 months) and an additional survival benefit was demonstrated when including SD ($P = 0.00002$, median OS 4.2 vs. 11.5 months). This value was confirmed in the multivariate analysis. Therefore, we suggest that gemcitabine and oxaliplatin chemotherapy may be beneficial in patients with inoperable BTC, although this benefit must be confirmed in a phase III study. Nevertheless, the disease progressed in 40% of the patients despite chemotherapy. Therefore, a further large study is needed to identify the subgroup of patients that will benefit from this therapy. In our study, elderly patients (>60 years) had a better DCR, while there were no statistically significant differences in the DCR according to gender, performance status, primary site (GB cancer vs. cholangiocarcinoma vs. cancer of ampulla of vater), disease status (locally advanced disease vs. metastatic disease), and increased CEA or CA 19–9 level. Previous studies have indicated superior responses and tumor control rates but shorter OS for GB cancer as compared with cholangiocarcinoma [26, 27]. Although our data are limited by the small number of patients included in this study, we found that GB cancer had a poorer DCR than cholangiocarcinoma (42.9 vs. 60.7%, $P = 0.682$), although the difference was not significant, and a shorter OS (median OS 3.3 vs. 9.4 months, $P = 0.012$). Patients with locally advanced disease had a longer OS (median OS; not reached vs. 5.4 months, $P = 0.006$) than those with metastatic disease, although there was no significant difference in the DCR (87.5 vs. 48.2%, $P = 0.104$). Therefore, GB cancer may be more aggressive, as reported previously by other authors [28–30]. André et al. [30] reported that combination chemotherapy with gemcitabine and oxaliplatin had poorer activity in GB cancer than in non-GB cancer. Therefore, combination chemotherapy with gemcitabine and oxaliplatin may be more beneficial in patients with locally advanced disease or cholangiocarcinoma than in those with metastatic disease or GB cancer. A large, randomized study should be performed to investigate which patients would benefit from this therapy. In addition, it is necessary to identify molecular markers that can predict the outcome of combination gemcitabine and oxaliplatin chemotherapy in advanced BTC. Preclinical studies have suggested that resistance to cisplatin and oxaliplatin-based chemotherapy could be related to the loss of the mismatch repair (MMR) system [31]. The role of MMR has been explored in human GB cancer [32]. Altered expression of the excision repair cross-complementing gene 1 and 2 (ERCC1 and ERCC2), which are components of the DNA repair system, seems to be related to the resistance to cisplatin and oxaliplatin [33]. Ruiz van Haperen et al. described the first acquired gemcitabine-resistant cell line, and suggested that low deoxycytidine kinase activity plays an important role in the mechanism of resistance to gemcitabine [34].

In conclusion, gemcitabine and oxaliplatin chemotherapy using a modified dose in inoperable BTC is well tolerated and may be beneficial. Further trials using stratified randomization by clinical factors, such as type of cancer, presence of metastasis, and molecular marker, are required.

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