

## ORIGINAL ARTICLE

# Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

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## ABSTRACT

**BACKGROUND**

There is no established standard chemotherapy for patients with locally advanced or metastatic biliary tract cancer. We initially conducted a randomized, phase 2 study involving 86 patients to compare cisplatin plus gemcitabine with gemcitabine alone. After we found an improvement in progression-free survival, the trial was extended to the phase 3 trial reported here.

**METHODS**

We randomly assigned 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer to receive either cisplatin (25 mg per square meter of body-surface area) followed by gemcitabine (1000 mg per square meter), each administered on days 1 and 8, every 3 weeks for eight cycles, or gemcitabine alone (1000 mg per square meter on days 1, 8, and 15, every 4 weeks for six cycles) for up to 24 weeks. The primary end point was overall survival.

**RESULTS**

After a median follow-up of 8.2 months and 327 deaths, the median overall survival was 11.7 months among the 204 patients in the cisplatin–gemcitabine group and 8.1 months among the 206 patients in the gemcitabine group (hazard ratio, 0.64; 95% confidence interval, 0.52 to 0.80;  $P < 0.001$ ). The median progression-free survival was 8.0 months in the cisplatin–gemcitabine group and 5.0 months in the gemcitabine-only group ( $P < 0.001$ ). In addition, the rate of tumor control among patients in the cisplatin–gemcitabine group was significantly increased (81.4% vs. 71.8%,  $P = 0.049$ ). Adverse events were similar in the two groups, with the exception of more neutropenia in the cisplatin–gemcitabine group; the number of neutropenia-associated infections was similar in the two groups.

**CONCLUSIONS**

As compared with gemcitabine alone, cisplatin plus gemcitabine was associated with a significant survival advantage without the addition of substantial toxicity. Cisplatin plus gemcitabine is an appropriate option for the treatment of patients with advanced biliary cancer. (ClinicalTrials.gov number, NCT00262769.)

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\*The investigators in the Advanced Biliary Cancer (ABC)-02 Trial are listed in the Appendix. Drs. Valle, Wasan, and Bridgewater contributed equally to this article.

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**B**ILIARY TRACT CANCER IS AN UNCOMMON cancer in developed countries. There are approximately 1200 new cases in the United Kingdom<sup>1</sup> and 9000 new cases in the United States per year, although the incidence is increasing, perhaps related to gallstone disease.<sup>2</sup> Most patients have advanced disease at presentation and relapse despite surgery.<sup>3</sup> Although advanced biliary tract cancer can have a response to chemotherapy, there is no recognized standard palliative regimen because no single randomized study has ever been sufficiently robust to define a schedule; fluoropyrimidines,<sup>4,5</sup> cisplatin,<sup>6</sup> and gemcitabine<sup>7,8</sup> have shown activity.

Gemcitabine (Gemzar, Eli Lilly) treatment for biliary tract cancer has been increasingly prescribed by oncologists who specialize in hepatobiliary disease because of its use in pancreatic cancer. Cisplatin is known to have an additive or synergistic effect in combination with gemcitabine in a number of different tumor types (e.g., lung,<sup>9</sup> bladder,<sup>10</sup> and head and neck<sup>11</sup> cancers). We previously found an improvement in 6-month progression-free survival from 47.7% to 57.1% in a randomized, phase 2 trial (the Advanced Biliary Cancer [ABC]-01 trial) comparing cisplatin plus gemcitabine with gemcitabine alone; that trial involved 86 patients.<sup>12</sup> That study was extended to become a phase 3 trial (the ABC-02 trial) with a planned recruitment total of 400 patients and a primary end point of overall survival.

## METHODS

### STUDY DESIGN

This randomized, controlled, phase 3 trial was designed and developed by the ABC-02 Trial Management Group under the auspices of the Upper Gastrointestinal Cancer Clinical Studies Group of the United Kingdom National Cancer Research Institute. The study was conducted by investigators at 37 centers in the United Kingdom, and data were collected and analyzed at the Cancer Research United Kingdom and University College London Cancer Trials Centre, London. The trial was initially designed as a randomized, phase 2 study involving 86 patients (the ABC-01 trial), conducted between February 2002 and June 2004. The trial was extended into a phase 3 trial (the ABC-02 trial) because of an apparent benefit in progression-free survival; this extension used a similar approach to that described previously.<sup>13</sup>

The same treatment regimens and eligibility criteria were used in both phases. Investigators were unaware of the overall survival analysis in the ABC-01 trial, as mandated by the independent data and safety monitoring committee.

This trial was approved by a research ethics committee, and all necessary regulatory approvals were obtained. All patients were required to give written informed consent before random assignment, and the trial was conducted in accordance with the Declaration of Helsinki. An independent data and safety monitoring board regularly reviewed the data on safety.

Lilly Oncology provided the investigators with gemcitabine at no cost but was not involved in the accrual or analysis of the data, the interpretation of the results, or the preparation of the manuscript.

### PATIENTS

Patients were eligible for the study if they were 18 years of age or older and had received a histopathological or cytologic diagnosis of nonresectable, recurrent, or metastatic biliary tract carcinoma (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma); an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (on a scale ranging from 0 to 5, with lower scores indicating a higher level of functioning); and an estimated life expectancy of more than 3 months. Other eligibility criteria were adequate hematologic and biochemical function, in particular a total bilirubin level of 1.5 times the upper limit of the normal range or less, liver-enzyme levels that were five times the upper limit of the normal range or less, renal function with levels of serum urea and serum creatinine that were less than 1.5 times the upper limit of the normal range, and a calculated glomerular filtration rate of 45 ml per minute or higher.

### TREATMENT

Patients were randomly assigned to receive cisplatin plus gemcitabine or gemcitabine alone for up to 24 weeks. In the cisplatin-gemcitabine group, each cycle comprised cisplatin (25 mg per square meter of body-surface area) followed by gemcitabine (1000 mg per square meter), each administered on days 1 and 8 every 3 weeks, initially for four cycles. In the gemcitabine-only group, gemcitabine was administered at a dose of 1000 mg per square meter on days 1, 8, and 15 every 4 weeks,

initially for three cycles. Cisplatin plus gemcitabine was administered on an outpatient basis as a 2-hour infusion (1 liter of 0.9% saline including cisplatin, 20 mmol of potassium chloride, and 8 mmol of magnesium sulfate over 1 hour followed by 500 ml of 0.9% saline over 30 minutes before the administration of gemcitabine). All patients received gemcitabine as a 30-minute infusion.

If patients did not have disease progression at 12 weeks, they could continue with another 12 weeks of the same regimen. Dose modifications were defined per protocol, and modifications and delays were allowed for hematologic toxicity, abnormal renal function, nausea, vomiting, peripheral neuropathy, edema, or tinnitus. Treatment was discontinued at 24 weeks or because of disease progression, patient or clinician choice, or unacceptable toxic effects. Biliary obstruction per se was not considered to be disease progression in the absence of radiologically confirmed disease progression, and treatment could be recommenced after further biliary stenting and normalization of liver function.

#### ASSESSMENTS

Patients were seen at the start of every cycle for a physical examination, monitoring of symptoms and toxic effects, assessment of renal function, and a complete blood count. Tumor response, measured according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 criteria,<sup>14</sup> was assessed by means of computed tomography (CT) or magnetic resonance imaging (MRI) at week 12 and again at week 24 in patients who completed treatment (confirmatory scans were not required). Tumor control was defined as a complete response, a partial response, or stable disease. For the end point of progression-free survival, progressive disease was defined as either objective tumor progression based on RECIST 1.0 criteria or the confirmed emergence of local nonprimary, metastatic, or nodal disease. After the end of the study treatment, patients were seen in the clinic every 3 months. Follow-up visits consisted of clinical assessment and either CT or MRI to assess tumor progression. Once progressive disease was documented, patients underwent follow-up for survival only.

#### STATISTICAL ANALYSIS

The primary outcome was overall survival, and the secondary outcomes were progression-free sur-

vival, tumor response, and adverse events. The trial was designed to have 80% power to detect an increase in median survival from 8 months in patients receiving gemcitabine alone to 11 months in patients receiving cisplatin plus gemcitabine. A total of 354 patients would be required to reach 315 events, based on the use of the log-rank test with a two-sided significance level of 5% and assuming that the trial would recruit for 3 years with at least 6 months of follow-up for each patient. To allow for dropouts and to ensure that we had sufficient evidence to meet the trial objectives, we aimed to recruit 400 patients. Patients were randomly assigned by telephone by the Cancer Research United Kingdom and University College London Cancer Trials Centre, which coordinated the trial. Randomization was conducted with the use of a minimization algorithm stratified according to the primary tumor site, extent of disease (locally advanced vs. metastatic), performance status, previous therapy, and recruiting center.

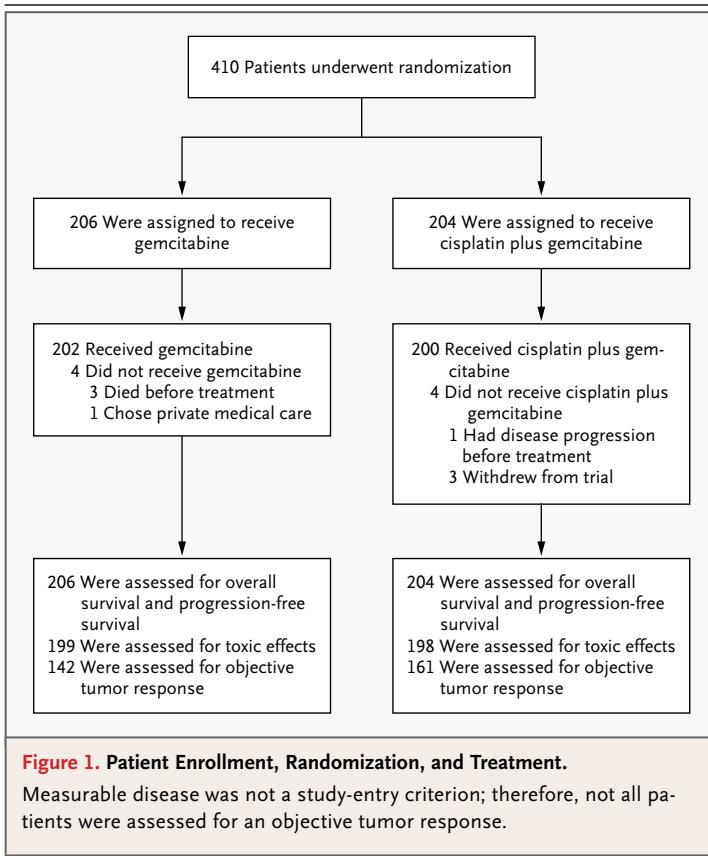
All analyses were performed on an intention-to-treat basis. Overall survival was calculated from the date of randomization until the date of death. Progression-free survival was measured from randomization until the date of disease progression or death. Patients who did not have disease progression and patients who died were excluded at the date of their last follow-up. Overall survival and progression-free survival were analyzed with the use of Kaplan–Meier curves and the log-rank test. A Cox proportional-hazards model was used to estimate the hazard ratios. Toxic effects were categorized according to the National Cancer Institute's Common Toxicity Criteria for Adverse Events, version 3. All analyses were performed with the use of Stata 10.1 software (Stata). The database was closed for analysis in June 2009.

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#### RESULTS

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We recruited 410 patients from 37 centers in the United Kingdom across the National Cancer Research Network between February 2002 and October 2008. A total of 204 patients received cisplatin plus gemcitabine, and 206 received gemcitabine alone (Fig. 1). The median follow-up time was 8.2 months. At the time of the final analysis, 327 deaths had occurred, and 362 patients (88.3%) had tumor progression. Baseline characteristics were well balanced between the two groups (Table 1).



There was an insignificant difference between the numbers of patients with locally advanced disease in the two groups (27.0% in the cisplatin–gemcitabine group vs. 23.8% in the gemcitabine-only group,  $P=0.46$ ). The majority of patients had either a histologic or a cytologic diagnosis of an adenocarcinoma or a carcinoma (99.0%). Two patients had an adenosquamous tumor; one was a squamous-cell carcinoma and one was a carcinosarcoma.

#### TREATMENT COMPLIANCE

At the end of the first 12 weeks, treatment compliance was similar in the two groups, with 66.5% receiving three cycles of gemcitabine alone and 73.5% receiving four cycles of cisplatin plus gemcitabine; however, in the treatment period overall, more patients in the gemcitabine-only group discontinued planned treatment prematurely, primarily because of disease progression (49 patients in the gemcitabine-only group vs. 26 patients in the cisplatin–gemcitabine group,  $P=0.004$ ). This discontinuation is reflected in the median duration of treatment (14 weeks in the gemcitabine-

only group vs. 21 weeks in the cisplatin–gemcitabine group,  $P=0.003$ ). Significantly more patients in the cisplatin–gemcitabine group than patients in the gemcitabine-only group went on to start the second 12 weeks of treatment (63% vs. 52%,  $P=0.02$ ). In the first 12 weeks of treatment, an average of 92% of the planned dose was delivered to patients in the gemcitabine-only group, as compared with 95% in the cisplatin–gemcitabine group ( $P=0.95$ ); however, in the second 12 weeks, the average was 69% in the gemcitabine-only group as compared with 88% in the cisplatin–gemcitabine group ( $P=0.046$ ). Among the 72 patients who went on to receive second-line therapy, 13 of 36 patients in the gemcitabine-only group (36%) received a platinum-based agent as compared with 10 of 36 patients in the cisplatin–gemcitabine group (28%) ( $P=0.45$ ). Four patients from each group received no treatment during the trial (Fig. 1). Tables 1 through 3 in the Supplementary Appendix, available with the full text of this article at NEJM.org, provide details of noncompliance and dose modifications.

#### TUMOR RESPONSE

Objective tumor response was measurable in 303 patients (patients were not required to have measurable disease at study entry). Tumor control (complete or partial response or stable disease) was achieved in 131 of 161 patients who received cisplatin plus gemcitabine (81.4%), as compared with 102 of 142 patients who received gemcitabine alone (71.8%) ( $P=0.049$ ). One patient from each group achieved a complete response. There were no differences in the rate of response between the gallbladder and cholangiocarcinoma subgroups (Table 4 in the Supplementary Appendix).

#### SURVIVAL AND DISEASE PROGRESSION

The final analysis was event-driven and performed 8 months after the last patient was enrolled in the trial, at which point 327 deaths had occurred (79.8%), including 10 noncancer deaths and 37 deaths for which the cause was unknown. A total of 362 patients had tumor progression (88.3%), of whom 278 died. There was one death from renal failure in the cisplatin–gemcitabine group; this death may have been related to cisplatin.

Figure 2A shows the Kaplan–Meier curves for overall survival. The median survival in the cisplatin–gemcitabine group was 11.7 months (95% confidence interval [CI], 9.5 to 14.3), as compared

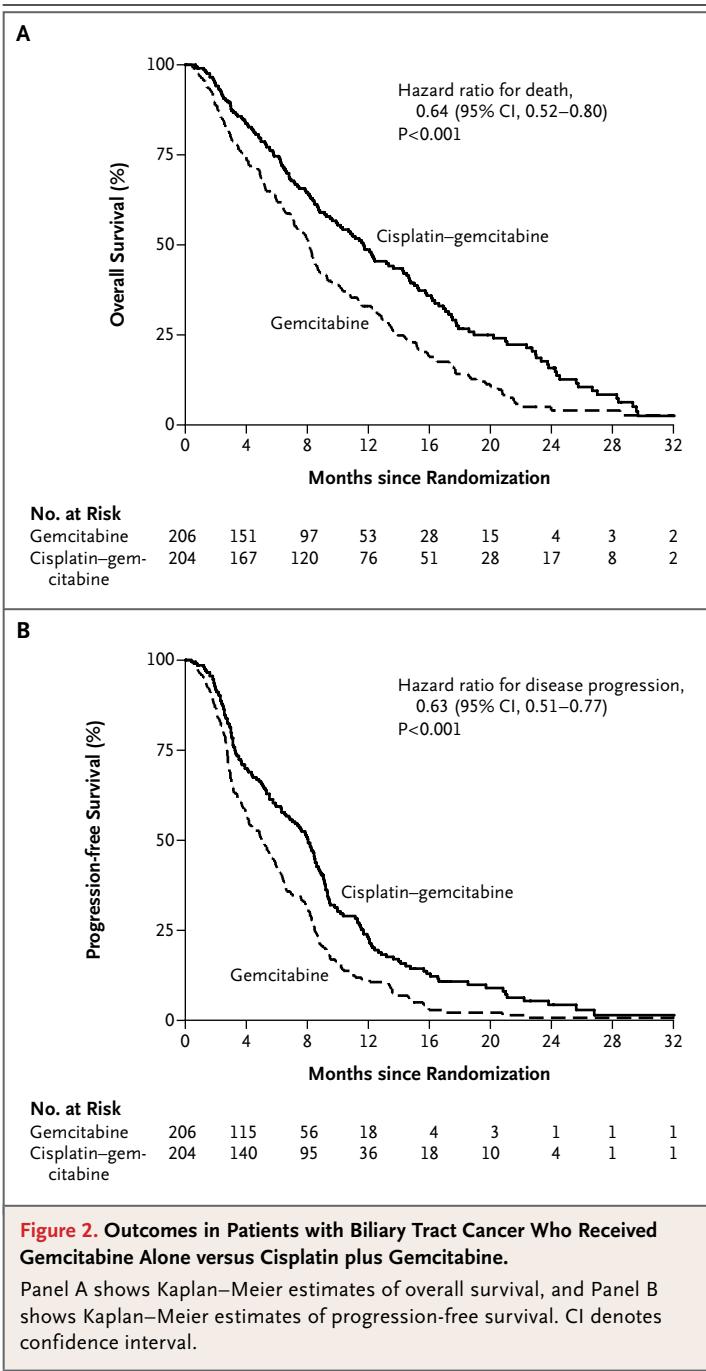
**Table 1. Baseline Characteristics of the Study Participants, According to Treatment Group.\***

Variable	Gemcitabine (N=206)	Cisplatin plus Gemcitabine (N=204)	P Value
Age — yr			
Median	63.2	63.9	0.88
Range	23.4–84.8	32.8–81.9	
Sex — no. (%)			
Female	108 (52.4)	108 (52.9)	0.92
Male	98 (47.6)	96 (47.1)	
Extent of disease — no. (%)			
Locally advanced	49 (23.8)	55 (27.0)	0.46
Metastatic	157 (76.2)	149 (73.0)	
Primary tumor site — no. (%)			
Gallbladder	76 (36.9)	73 (35.8)	0.87
Bile duct	119 (57.8)	122 (59.8)	
Ampulla	11 (5.3)	9 (4.4)	
Type of tumor — no. (%)			
Adenocarcinoma	191 (92.7)	186 (91.2)	0.27
Carcinoma, type not specified	12 (5.8)	17 (8.3)	
Adenosquamous carcinoma	2 (1.0)	0	
Squamous-cell carcinoma	1 (0.5)	0	
Carcinosarcoma	0	1 (0.5)	
ECOG performance-status score — no. (%)			
0	64 (31.1)	66 (32.4)	0.72
1	117 (56.8)	111 (54.4)	
2	24 (11.7)	27 (13.2)	
Unknown	1 (0.5)	0	
Previous therapy — no. (%)			
No	50 (24.3)	50 (24.5)	0.96
Yes	156 (75.7)	154 (75.5)	
Type of previous therapy — no. (%)			
Curative surgery	48 (23.3)	37 (18.1)	0.20
Palliative surgery	40 (19.4)	37 (18.1)	0.74
Laparotomy	49 (23.8)	48 (23.5)	0.95
Biliary stenting	92 (44.7)	93 (45.6)	0.85
Radiotherapy	5 (2.4)	3 (1.5)	0.48
Adjuvant chemotherapy	5 (2.4)	3 (1.5)	0.74
Photodynamic therapy	1 (0.5)	1 (0.5)	1.00
Other therapy	81 (39.3)	76 (37.3)	0.14

\* ECOG denotes Eastern Cooperative Oncology Group. ECOG scores range from 0 to 5, with lower scores indicating a higher level of functioning.

with 8.1 months (95% CI, 7.1 to 8.7) for the gemcitabine-only group ( $P<0.001$ ). Patients who received cisplatin plus gemcitabine were 36% less

likely to die at any time than those who received gemcitabine alone (hazard ratio, 0.64; 95% CI, 0.52 to 0.80). Adjustment for the randomization



stratification factors did not significantly alter this outcome (hazard ratio, 0.67; 95% CI, 0.54 to 0.84). Figure 2B shows the Kaplan–Meier curves for progression-free survival. Cisplatin plus gemcitabine significantly improved progression-free survival, with a median of 8.0 months (95% CI, 6.6 to 8.6) in the cisplatin–gemcitabine group as

compared with 5.0 months (95% CI, 4.0 to 5.9) in the gemcitabine-only group (P<0.001). The hazard ratio for disease progression was 0.63 (95% CI, 0.51 to 0.77). The 6-month progression-free survival rate was 59.3% in the cisplatin–gemcitabine group and 42.5% in the gemcitabine-only group.

Figure 3 shows the hazard ratios for death according to prespecified baseline factors. There was no evidence of a difference in treatment effect between the subgroups.

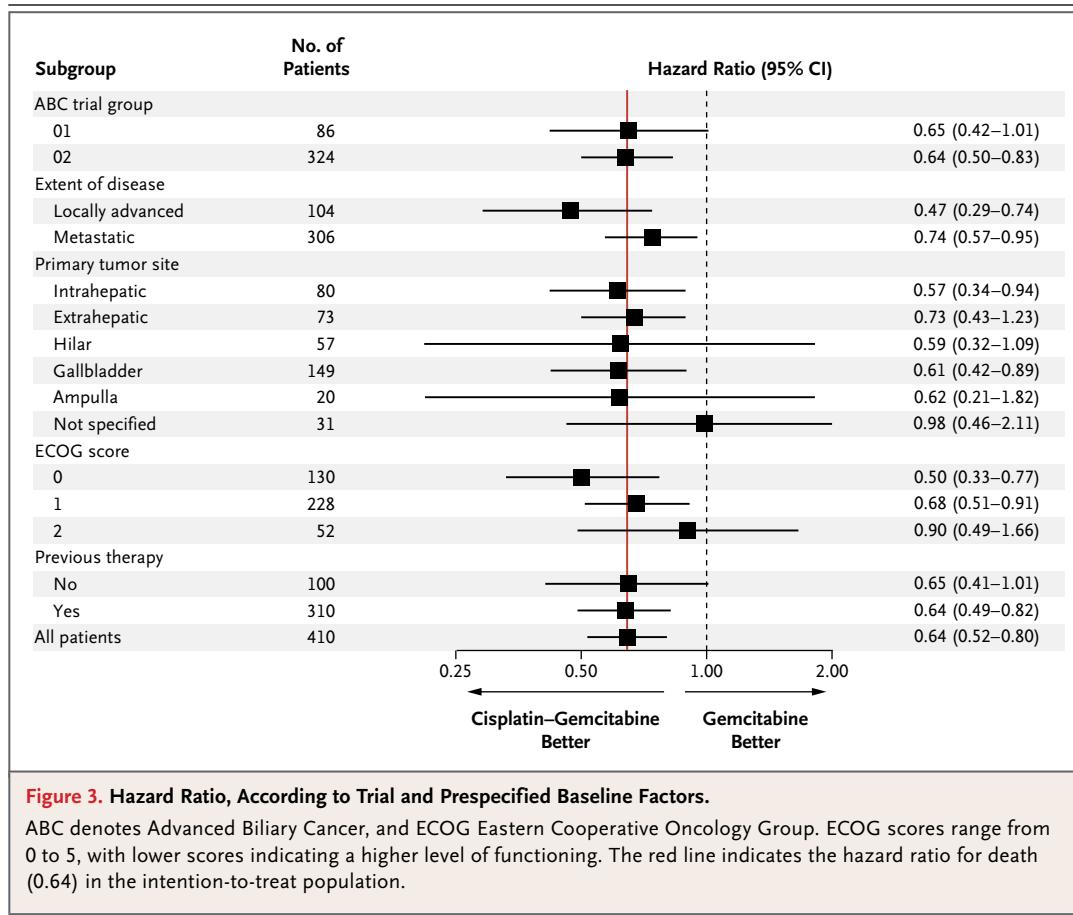
**ADVERSE EVENTS**

Table 2 summarizes the grades 3 and 4 adverse events reported during the trial. There was a non-significant excess of neutropenia in the cisplatin–gemcitabine group; infections were similar in the two groups. Liver function was significantly worse in the gemcitabine-only group (27.1%) than in the cisplatin–gemcitabine group (16.7%). We think this difference probably reflects better control of disease in the cisplatin–gemcitabine group. Otherwise, adverse events were similar between the two groups. Seven suspected, unexpected serious adverse reactions were reported during the trial, occurring in seven patients, all of whom were in the gemcitabine-only group.

**DISCUSSION**

These data provide evidence that cisplatin plus gemcitabine is an effective treatment option for locally advanced or metastatic biliary tract cancer. Patients treated with cisplatin plus gemcitabine lived an average of 3.6 months longer than those treated with gemcitabine alone. This benefit was achieved with the use of an outpatient schedule, and adverse events were similar between the two treatment regimens. These data are consistent with the known preclinical<sup>15</sup> and clinical<sup>9-11</sup> synergies of cisplatin and gemcitabine.

In the ABC-01 trial, there was an increase in grade 3 or 4 fatigue in patients who received cisplatin plus gemcitabine (28.6%, vs. 9.1% in the gemcitabine-only group<sup>12</sup>). However, this increase was not observed in the ABC-02 trial (18.7% vs. 16.6%). Patients who received gemcitabine had a significantly increased incidence of grade 3 or 4 abnormal liver-function tests (27.1%, vs. 16.7% for cisplatin–gemcitabine; P=0.01), possibly as a result of inferior disease control and biliary drainage.



**Figure 3. Hazard Ratio, According to Trial and Prespecified Baseline Factors.**

ABC denotes Advanced Biliary Cancer, and ECOG Eastern Cooperative Oncology Group. ECOG scores range from 0 to 5, with lower scores indicating a higher level of functioning. The red line indicates the hazard ratio for death (0.64) in the intention-to-treat population.

Until the results of the ABC-01 study<sup>12</sup> and now these data were reported, nonrandomized, phase 2 studies provided the best evidence base for the treatment of biliary tract cancer. A systematic review in 2005 identified 13 studies of the use of gemcitabine alone or in combination with other agents.<sup>16</sup> Three of these studies involved the use of a cisplatin–gemcitabine regimen and showed median survivals of 4.6, 6.5, and 10.4 months. A Japanese trial involving 83 patients conducted with the use of the same treatment regimens as those used in the ABC-02 trial<sup>17</sup> showed a median overall survival of 11.2 months in the cisplatin–gemcitabine group and 7.7 months in the gemcitabine-only group, consistent with our data. The French Biliary Cancers: EGFR Inhibitor, Gemcitabine and Oxaliplatin (BINGO) trial (ClinicalTrials.gov number, NCT00552149) randomly assigned 101 patients to receive gemcitabine plus oxaliplatin with or without cetuximab.<sup>18</sup> In the BINGO trial, investigators reported 4-month progression-free

survival rates of 50% in the gemcitabine–oxaliplatin group and 61% in the gemcitabine–oxaliplatin plus cetuximab group. These findings compare with a 4-month progression-free survival rate of approximately 70% in the cisplatin–gemcitabine group in the ABC-02 trial.

The management of biliary tract cancer has become multidisciplinary, with improvements in stenting, systemic chemotherapy,<sup>12</sup> and new methods such as photodynamic therapy.<sup>19</sup> Central to the case for active management is the possibility that small improvements in bile-duct lumen size will have a significant effect on biliary drainage, as determined by Poiseuille’s law,<sup>20</sup> which holds that, for a fixed-pressure difference, flow is related to tube diameter to the fourth power. Maintenance of biliary drainage is critical in patients with advanced biliary cancer because it enables systemic chemotherapy to continue without major delay for stent change and avoids potentially life-threatening biliary sepsis. A small response in tumor bulk

**Table 2. Grade 3 or 4 Toxic Effects during Treatment, According to Treatment Group.**

Variable	Gemcitabine (N=199)	Cisplatin plus Gemcitabine (N=198)	P Value
	number (percent)		
<b>Hematologic toxic effects</b>			
Decreased white-cell count	19 (9.5)	31 (15.7)	0.07
Decreased platelet count	13 (6.5)	17 (8.6)	0.44
Decreased hemoglobin level	6 (3.0)	15 (7.6)	0.04
Decreased neutrophil count	33 (16.6)	50 (25.3)	0.03
Any hematologic toxic effect	47 (23.6)	64 (32.3)	0.05
<b>Liver function</b>			
Increased alanine aminotransferase level	34 (17.1)	19 (9.6)	0.03
Other abnormal liver function	39 (19.6)	26 (13.1)	0.08
Any abnormal liver function	54 (27.1)	33 (16.7)	0.01
<b>Nonhematologic toxic effects</b>			
Alopecia	0	2 (1.0)	0.16
Anorexia	5 (2.5)	6 (3.0)	0.75
Fatigue	33 (16.6)	37 (18.7)	0.58
Nausea	7 (3.5)	8 (4.0)	0.78
Vomiting	11 (5.5)	10 (5.1)	0.65
Impaired renal function	2 (1.0)	3 (1.5)	0.83
<b>Infection</b>			
Without neutropenia	23 (11.6)	12 (6.1)	0.05
With neutropenia	14 (7.0)	20 (10.1)	0.28
Biliary sepsis	8 (4.0)	8 (4.0)	0.99
Any type	38 (19.1)	36 (18.2)	0.82
Deep-vein thrombosis	1 (0.5)	4 (2.0)	0.18
Thromboembolic event	3 (1.5)	7 (3.5)	0.20
Other	62 (31.2)	66 (33.3)	0.64
Any	100 (50.3)	108 (54.5)	0.39
<b>Any grade 3 or 4 toxic effect</b>	<b>137 (68.8)</b>	<b>140 (70.7)</b>	<b>0.69</b>

may therefore have a greater effect on survival than would be the case for other cancers.

Our data suggest that biliary tract cancers are sensitive to chemotherapy, a reality suggested but never proved by extant underpowered clinical data. Relatively little is known about the biology of biliary tract cancer, but it appears to lie in the spectrum of gastrointestinal epithelial cancers with similar oncogenic mutations.<sup>21,22</sup> Critical to the future rational treatment of biliary tract cancer is a molecular map with which targeted therapies may be directed, similar to that which is evolving for the common cancers.

In summary, this study shows a significant

survival advantage for cisplatin plus gemcitabine over gemcitabine alone in patients with advanced biliary cancer. Cisplatin plus gemcitabine is an appropriate option for the treatment of these patients.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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## APPENDIX

The recruiting sites and principal investigators in the ABC-02 study are as follows: *Aberdeen Royal Infirmary* — M. Nicholson; *Addenbrooke's Hospital* — P. Corrie; *Belfast City Hospital* — M. Eatock; *Bristol Royal Infirmary* — S. Falk; *Cheltenham General Hospital* — S. Elyan; *Christie Hospital* — J. Valle (co-chief investigator); *Cookridge Hospital* — A. Anthony; *Cumberland Infirmary* — J. Nicoll; *Derbyshire Royal Infirmary* — R. Kulkarni; *Dorset Cancer Centre* — R. Osbourne; *Glan Clwyd Hospital* — A. Garcia Alonso; *Hammersmith Hospital* — H. Wasan (co-chief investigator); *Maidstone Hospital* — J. Waters; *Mount Vernon Hospital* — M. Harrison; *Ninewells Hospital* — D. Adamson; *North Hampshire Hospital* — C. Rees; *North Middlesex Hospital* — J. Bridgewater (co-chief investigator); *Nottingham University Hospital* — S. Madhusudan; *Peterborough Hospital* — K. McAdam; *Princess Alexandra Hospital* — J. Bridgewater (co-chief investigator); *Princess Royal Hospital* — A. Maraveyas; *Queen Elizabeth Hospital Birmingham* — D. Palmer; *Royal Bournemouth Hospital* — T. Hickish; *Royal Free Hospital* — T. Meyer; *Royal Marsden Hospital* — D. Cunningham; *Royal South Hants Hospital* — T. Iveson; *Royal Surrey County Hospital* — G. Middleton; *St. Bartholomew's Hospital* — S. Slater; *St. George's Hospital* — F. Lofts; *St. Mary's Hospital Portsmouth* — C. Archer; *Salisbury Hospital* — T. Iveson; *Southampton General Hospital* — T. Iveson; *University College Hospital* — J. Bridgewater (co-chief investigator); *Velindre Cancer Centre* — S. Mukherjee; *Weston Park Hospital* — J. Wadsley; *Wrexham Maelor Hospital* — S. Gollins.

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