rate ranging from 24 to 27%) or pancreatic head adenocarcinomas (5-year survival rate around 15%) (2–6). However, for patients with advanced disease, an accurate prognosis cannot be made because of the lack of reliable data, with the exception of one retrospective study that examined the outcome of systemic chemotherapy in 29 patients with advanced ampullary adenocarcinoma (7). Because of the rarity of this disease, advanced adenocarcinomas are often treated using regimens designed for biliary tract adenocarcinomas or small bowel adenocarcinomas. The The National Comprehensive Cancer Network (NCCN) guidelines recommend that small bowel adenocarcinomas be treated with systemic chemotherapy according to the colon cancer guidelines which recommend folinic acid, 5-FU and oxaliplatin (FOLFOX) or folinic acid, 5-FU and irinotecan (FOLFIRI) ± bevacizumab as the initial therapy. Meanwhile, the NCCN guidelines recommend that biliary tract adenocarcinomas should be treated with gemcitabine (GEM) + cisplatin (CDDP) combination therapy. However, whether advanced ampullary adenocarcinomas should be treated as biliary tract adenocarcinomas or as small bowel adenocarcinomas remain uncertain. Additionally, ampullary adenocarcinomas can be separated into two histological phenotypes, intestinal type and pancreatobiliary type (8,9). However, no previous report has examined the outcome of systemic chemotherapy analyzed according to the histological phenotypes of advanced ampullary adenocarcinomas.

The objective of the present study was to clarify (i) the treatment outcome of systemic chemotherapy for advanced ampullary adenocarcinomas, (ii) the difference in outcomes according to the chemotherapeutic regimens, (iii) the difference in outcomes according to the disease status and (iv) the difference in outcomes according to the adenocarcinoma phenotype.

PATIENTS AND METHODS

Patients

We retrospectively reviewed the clinical data in our institution's database and extracted patients who were diagnosed as having advanced ampullary adenocarcinoma and who had received systemic chemotherapy between January 1997 and December 2010. Patients were eligible if they had a recurrent or unresectable adenocarcinoma arising from the ampulla of Vater. Written informed consent was obtained from all the patients before treatment. This study was approved by the institutional review board of the National Cancer Center Hospital (NCCH) of Japan and was performed in accordance with the Declaration of Helsinki in 1964.

The following clinical characteristics of all the patients with advanced ampullary adenocarcinoma were reviewed: age, Eastern Cooperative Oncology Group (ECOG) performance status, tumor histology and adenocarcinoma phenotype.

Classification of Chemotherapy Regimens

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

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 (range, 48–79 years) and the ECOG performance statuses were as follows: 18 patients with PS 0, 8 patients with PS 1, and 0 patients with PS 2–4. All 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 (Table 1). The chemotherapy regimens consisted of 5-FU + CDDP ($n = 3$), tegafur-uracil (UFT) + doxorubicin ($n = 5$), tegafur, gimeracil and oteracil potassium (S-1) ($n = 3$), GEM ($n = 10$) and GEM + CDDP ($n = 5$). The median number of cycles of first-line chemotherapy prescribed was 5-FU + CDDP in 5 (range 1–5), UFT +

doxorubicin in 3 (range 1–4), S-1 in 6 (range 2–11), GEM in 3 (range 1–11) and GEM + CDDP in 3 (range 1–9).

OUTCOME OF SYSTEMIC CHEMOTHERAPY FOR ADVANCED AMPULLARY ADENOCARCINOMAS

The response to systemic chemotherapy was evaluated in 26 patients, and these responses are listed in Table 2. None of the patients achieved a complete response. Two patients who received 5-FU + CDDP and S-1 exhibited partial responses and 18 patients achieved stable disease. The response rate (CR + PR) was 7.7% [95% confidence interval (CI) = 0.95–25.1%], and the disease control rate (CR + PR + SD) was 76.9% (95% CI = 56.4–91.0%).

As shown in Fig. 1, the median PFS and the OS from the initiation of chemotherapy were 3.2 and 9.1 months, respectively.

TREATMENT OUTCOME ACCORDING TO TREATMENT REGIMENS

The chemotherapy regimens were classified into two groups: the 5-FU group, consisting of 5-FU plus CDDP ($n = 3$), UFT plus doxorubicin ($n = 5$) and S-1 alone ($n = 3$) and the GEM group, consisting of GEM alone ($n = 10$) and GEM plus CDDP ($n = 5$). In the 5-FU group, the median age of the patients was 64.0 years and the ECOG performance statuses were as follows: 8 patients (73%) with PS 0 and 3 patients (27%) with PS 1. All the patients had metastatic lesion. In the GEM group, on the other hand, the median age of the patients was 66.0 years and the ECOG performance statuses were as follows: 10 patients (67%) with PS 0 and 5 patients (33%) with PS 1. All the patients also had metastatic lesion. None of the patient characteristics were significantly different between the two treatment groups.

The responses according to the treatment groups and regimens are listed in Table 2. In the 5-FU group, two patients (18%) achieved a partial response, six (55%) remained stable and three (27%) showed progressive disease. The response

Table 1. Patient characteristics

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

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

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

RR, response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival.

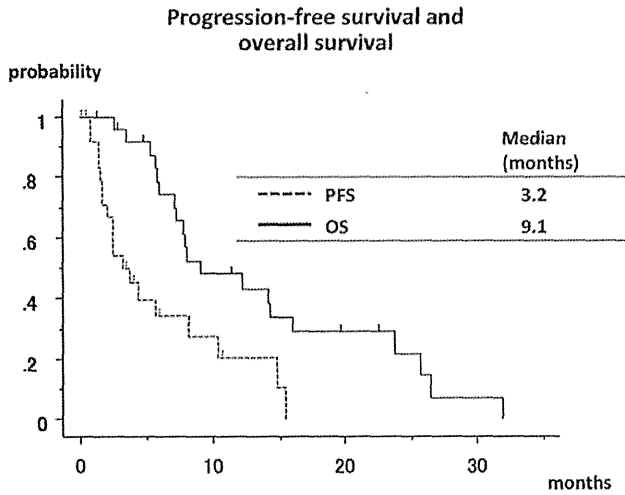## Progression-free survival and overall survival

Figure 1. Progression-free survival (PFS) curve and overall survival (OS) curve calculated using the Kaplan–Meier method for all adenocarcinoma patients.
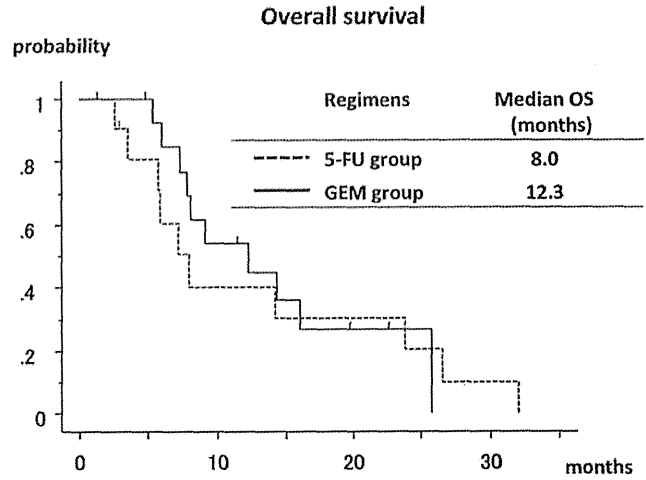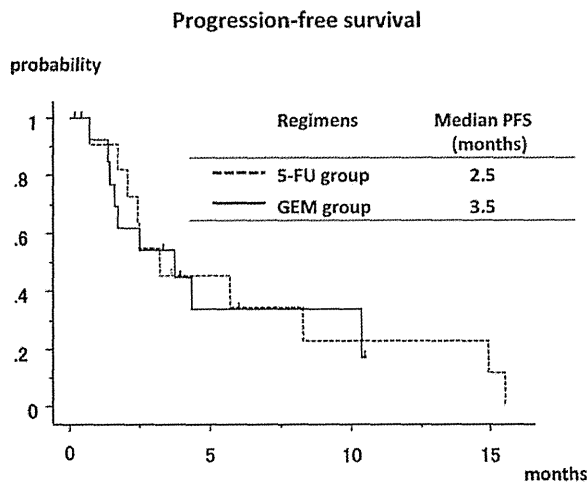
Progression-free survival

Figure 2. PFS calculated using the Kaplan–Meier method for groups classified according to the chemotherapy regimen.

Overall survival

Figure 3. OS curve calculated using the Kaplan–Meier method for groups classified according to chemotherapy regimen.

Progression-free survival

Figure 4. PFS calculated using the Kaplan–Meier method for groups classified according to stage IV disease or recurrent disease.

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
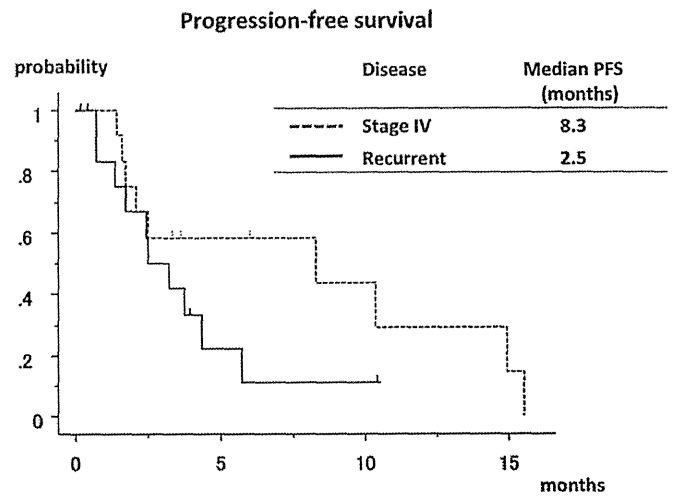
was 65.0 years and the ECOG performance statuses were as follows: nine patients (75%) with PS 0 and three patients (25%) with PS 1. Five of the 12 patient with stage IV disease had received 5-FU-based regimens and the remaining 7 patients received GEM-based regimens. Meanwhile, in recurrent disease, 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 patient 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.

Figure 5. OS curve calculated using the Kaplan–Meier method for groups classified according to stage IV disease or recurrent 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 ductal 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
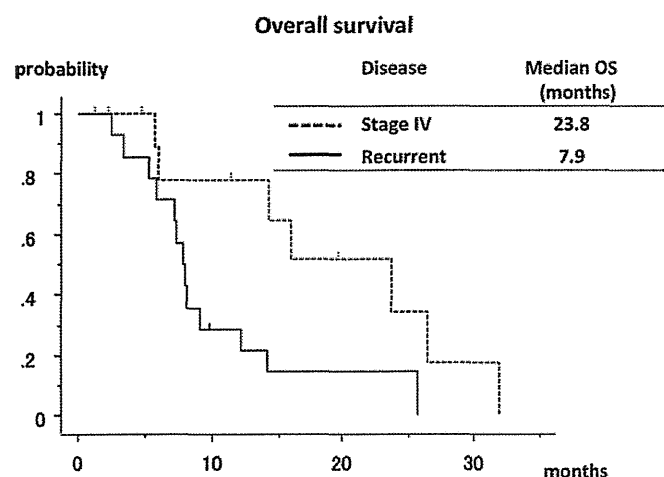
Table 3. Treatment regimens and outcomes according to phenotypes

Patient no.	Regimen	Phenotype	MUC2	CDX2	Best response	OS (months)	PFS (months)
1	S-1	Intestinal	f+	+	SD	2.6	2.1
2	UFT + Doxorubicin	Intestinal	+	−	SD	5.8	2.5
3	5-FU + CDDP	Intestinal	f+	−	PR	8.0	4.9
4	GEM + CDDP	Intestinal	−	+	SD	6.0	2.5
5	GEM + CDDP	Intestinal	−	+	NE	8.2	0.6 (c)[a]
6	GEM	Pancreatobiliary	−	−	NE	12.3	0.9 (c)[b]
7	GEM	Intestinal	f+	+	SD	7.9	1.4
8	GEM	Pancreatobiliary	−	−	SD	14.3	10.4
9	GEM	Intestinal	2+	2+	SD	7.3	4.1 (c)[b]
10	GEM	Intestinal	2+	+	SD	22.8 (c)	4.4

f+, focally positive; SD, stable disease; PR, partial response; NE, not evaluable; (c), censored case.
[a]Censored because of Grade 3 pneumonitis.
[b]Censored because of Grade 3 biliary tract infection.

cancer (17–20). 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 pancreaticobiliary 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.

References

1. Horner MJ, Ries LAG, Krapcho M, et al. *SEER Cancer Statistics Review, 1975–2006*. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2006/, based on November 2008 SEER data submission, posted to the SEER web site, 2009.
2. Chareton B, Coiffic J, Landen S, Bardaxoglou E, Campion JP, Launois B. Diagnosis and therapy for ampullary tumors: 63 cases. *World J Surg* 1996;20:707–12.
3. Miyakawa S, Ishihara S, Horiguchi A, Takada T, Miyazaki M, Nagakawa T. Biliary tract cancer treatment: 5,584 results from the biliary tract cancer statistics registry from 1998 to 2004 in Japan. *J Hepatobiliary Pancreat Surg* 2009;16:1–7.
4. Monson JR, Donohue JH, McEntee GP, et al. Radical resection for carcinoma of the ampulla of vater. *Arch Surg* 1991;126:353–7.
5. Roder JD, Schneider PM, Stein HJ, Siewert JR. Number of lymph node metastases is significantly associated with survival in patients with radically resected carcinoma of the ampulla of vater. *Br J Surg* 1995;82:1693–6.
6. Yeo CJ, Sohn TA, Cameron JL, Hruban RH, Lillemoe KD, Pitt HA. Periampullary adenocarcinoma: analysis of 5-year survivors. *Ann Surg* 1998;227:821–31.
7. Kim ST, Lee J, Lee KT, et al. The efficacy of frontline platinum-based combination chemotherapy in advanced adenocarcinoma of the ampulla of vater. *Med Oncol* 2010;27:1149–54.
8. Fischer HP, Zhou H. Pathogenesis and histomorphology of ampullary carcinomas and their precursor lesions. Review and individual findings. *Pathologe* 2003;24:196–203.
9. Kimura W, Futakawa N, Yamagata S, et al. Different clinicopathologic findings in two histologic types of carcinoma of papilla of vater. *Jpn J Cancer Res* 1994;85:161–6.
10. Ueno H, Okusaka T, Ikeda M, Takezako Y, Morizane C. Phase ii study of s-1 in patients with advanced biliary tract cancer. *Br J Cancer* 2004;91:1769–74.
11. Furuse J, Okusaka T, Funakoshi A, et al. Early phase ii study of uracil-tegafur plus doxorubicin in patients with unresectable advanced biliary tract cancer. *Jpn J Clin Oncol* 2006;36:552–6.
12. Bouvet M, Gamagami RA, Gilpin EA, et al. Factors influencing survival after resection for periampullary neoplasms. *Am J Surg* 2000;180:13–7.
13. Klempnauer J, Ridder GJ, Pichlmayr R. Prognostic factors after resection of ampullary carcinoma: multivariate survival analysis in comparison with ductal cancer of the pancreatic head. *Br J Surg* 1995;82:1686–91.
14. Gibson MK, Holcroft CA, Kvols LK, Haller D. Phase ii study of 5-fluorouracil, doxorubicin, and mitomycin c for metastatic small bowel adenocarcinoma. *Oncologist* 2005;10:132–7.
15. Overman MJ, Varadhachary GR, Kopetz S, et al. Phase ii study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of vater. *J Clin Oncol* 2009;27:2598–603.
16. Nehls O, Oettle H, Hartmann JT, et al. Capecitabine plus oxaliplatin as first-line treatment in patients with advanced biliary system adenocarcinoma: a prospective multicentre phase ii trial. *Br J Cancer* 2008;98:309–15.
17. Gruenberger B, Schueller J, Heubrandtner U, et al. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. *Lancet Oncol* 2010;11:1142–8.
18. Lee J, Park SH, Chang HM, et al. Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2012;13:181–8.
19. Iqbal S, Rankin C, Lenz HJ, et al. A phase ii trial of gemcitabine and capecitabine in patients with unresectable or metastatic gallbladder cancer or cholangiocarcinoma: Southwest Oncology Group Study s0202. *Cancer Chemother Pharmacol* 2011;68:1595–602.
20. Williams KJ, Picus J, Trinkhaus K, et al.. Gemcitabine with carboplatin for advanced biliary tract cancers: a phase ii single institution study. *HPB (Oxford)* 2010;12:418–26.
21. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010;362:1273–81.
22. Okusaka T, Nakachi K, Fukutomi A, et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. *Br J Cancer* 2010;103:469–74.
23. Morizane C, Okusaka T, Mizusawa J, et al. Randomized phase ii study of gemcitabine plus s-1 versus s-1 in advanced biliary tract cancer: a Japan clinical oncology group trial (jcog 0805). *Cancer Sci* 2013;104:1211–6.
24. Chu PG, Schwarz RE, Lau SK, Yen Y, Weiss LM. Immunohistochemical staining in the diagnosis of pancreatobiliary and ampulla of vater adenocarcinoma: application of cdx2, ck17, muc1, and muc2. *Am J Surg Pathol* 2005;29:359–67.
25. Roh YH, Kim YH, Lee HW, et al. The clinicopathologic and immunohistochemical characteristics of ampulla of vater carcinoma: the intestinal type is associated with a better prognosis. *Hepatogastroenterology* 2007;54:1641–4.

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disclosure

The authors have declared no conflicts of interest.

references

1. Dawood S, Merajver SD, Viens P et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011; 22: 515–523.
2. Hance KW, Anderson WF, Devesa SS et al. Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the National Cancer Institute. J Natl Cancer Inst 2005; 97: 966–975.
3. Schlichting JA, Soliman AS, Schairer C et al. Inflammatory and non-inflammatory breast cancer survival by socioeconomic position in the Surveillance, Epidemiology, and End Results database, 1990–2008. Breast Cancer Res Treat 2012; 134: 1257–1268.
4. Dawood S, Ueno NT, Valero V et al. Differences in survival among women with stage III inflammatory and noninflammatory locally advanced breast cancer appear early: a large population-based study. Cancer 2011; 117: 1819–1826.
5. Li J, Gonzalez-Angulo AM, Allen PK et al. Triple-negative subtype predicts poor overall survival and high locoregional relapse in inflammatory breast cancer. Oncologist 2011; 16: 1675–1683.
6. Gonzalez-Angulo AM, Hennessy BT, Broglio K et al. Trends for inflammatory breast cancer: is survival improving? Oncologist 2007; 12: 904–912.
7. Bear HD, Anderson S, Brown A et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2003; 21: 4165–4174.
8. Panades M, Olivotto IA, Speers CH et al. Evolving treatment strategies for inflammatory breast cancer: a population-based survival analysis. J Clin Oncol 2005; 23: 1941–1950.
9. Costa SD, Loibl S, Kaufmann M et al. Neoadjuvant chemotherapy shows similar response in patients with inflammatory or locally advanced breast cancer when compared with operable breast cancer: a secondary analysis of the GeparTrio trial data. J Clin Oncol 2010; 28: 83–91.
10. Parker JS, Mullins M, Cheang MC et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. J Clin Oncol 2009; 27: 1160–1167.
11. Carey LA, Dees EC, Sawyer L et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res 2007; 13: 2329–2334.
12. Knight WA, Livingston RB, Gregory EJ et al. Estrogen receptor as an independent prognostic factor for early recurrence in breast cancer. Cancer Res 1977; 37: 4669–4671.
13. Huber KE, Carey LA, Wazer DE. Breast cancer molecular subtypes in patients with locally advanced disease: impact on prognosis, patterns of recurrence, and response to therapy. Semin Radiat Oncol 2009; 19: 204–210.
14. Sorlie T, Perou CM, Tibshirani R et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 2001; 98: 10869–10874.
15. von Minckwitz G, Untch M, Blohmer JU et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30: 1796–1804.

Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials

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Background: Two recent studies (ABC-02 [UK] and BT22 [Japan]) have demonstrated the superiority of cisplatin and gemcitabine (CisGem) chemotherapy over gemcitabine (Gem) alone for patients with pathologically proven advanced biliary tract cancer (BTC: cholangiocarcinoma, gallbladder and ampullary cancers). This pre-planned analysis evaluates the efficacy of CisGem with increased statistical power.

Patients and methods: We carried out a meta-analysis of individual patient-level data of these studies to establish the effect of CisGem versus Gem on progression-free survival (PFS), overall survival (OS) and carried out exploratory sub-group analyses.

Results: CisGem demonstrates a significant improvement in PFS [hazard ratio (HR) = 0.64, 95% confidence interval (CI) 0.53–0.76, $P < 0.001$] and OS (HR = 0.65, 95% CI 0.54–0.78, $P < 0.001$) over Gem. This effect is most marked among

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patients with good performance status (PS 0–1): HR for PFS is 0.61 (95% CI 0.51–0.74), $P < 0.001$ and OS HR = 0.64 (95% CI 0.53–0.77), $P < 0.001$. CisGem resulted in improved PFS and OS for intra- and extra-hepatic cholangiocarcinomas and gallbladder cancer. The treatment effect between UK and Japanese patients was consistent with respect to OS (HR = 0.65, 95% CI 0.53–0.79 and 0.65, 95% CI 0.42–1.03, respectively); with similar OS in the combination arms (median 11.7 and 11.1 months, respectively). Subgroups least likely to benefit included patients with ampullary tumours and poor performance status (PS2).

Conclusions: CisGem is the standard of care for the first-line treatment of good-PS patients with advanced BTC regardless of ethnicity. Future studies should aim to enhance the effectiveness of this regimen in the first-line setting, establish the role of subsequent (second-line) therapy and assess the role of rationally developed molecular-targeted therapies.

Key words: biliary tract cancer, cholangiocarcinoma, gallbladder cancer, cisplatin, gemcitabine

introduction

Biliary tract cancer (BTC) is a collective term to include cancers arising from the gallbladder, bile ducts (intra-hepatic, hilar or extra-hepatic cholangiocarcinoma, depending on their site of origin) and ampulla of Vater adenocarcinomas. Although considered relatively rare in the US (with 5000 new cases diagnosed annually [1]) and European countries (e.g. UK incidence: 1200 cases per annum [UK National Statistics homepage at http ://www.statistics.gov.uk]), it has a much higher prevalence in Latin America [2] and East Asia. In Japan, the incidence is 10-fold that seen in the West with 17 311 deaths from BTC in 2007 making it the sixth leading cause of cancer death [3]. Moreover, the incidence, particularly of intra-hepatic cholangiocarcinoma, has been increasing in the US, Japan, UK and Australia since the 1970s, [4–6] increasing the need for effective cancer services.

Surgery remains the optimal modality of therapy leading to long-term survival for patients diagnosed with resectable disease. However, most patients have advanced (inoperable or metastatic) disease at presentation, often in the context of biliary obstruction and sepsis and age-related co-morbidities resulting in a 5-year survival of 5%–15% [7, 8].

Two phase III studies have demonstrated improved survival of chemotherapy over best supportive care (BSC) for patients with advanced (inoperable) disease. A Swedish study reported a median survival of 6 months in patients with mixed biliary and pancreatic cancers treated with 5-fluorouracil (5-FU), etoposide and leucovorin chemotherapy compared with 2.5 months with BSC [9]. A study from India in patients with gallbladder cancer demonstrated an improvement in median survival from 4.5 to 9.5 months using a gemcitabine and oxaliplatin regimen [10]. It can be concluded that the median survival in patients treated with

Table 1. Characteristics of the ABC-02 and BT22 trials

Characteristic	Study	
	ABC-02	BT22
Country	UK	Japan
Study design	Randomised phase III	Randomised phase II
Accrual period	February 2002 to October 2008	September 2006 to October 2008
Number of patients	410	84
Key eligibility criteria	Age $\geq$ 18 years	Age $\geq$ 20 years
	Confirmed histopathological or cytological diagnosis	Confirmed histopathological diagnosis
	Intra- or extra-hepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma	Intra- or extra-hepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma
	Non-resectable, recurrent or metastatic disease	Non-resectable, recurrent, or metastatic disease
	No prior chemotherapy for advanced disease	No prior chemotherapy for advanced disease
	Performance status of 0–2 (ECOG)	Performance status of 0-1 (ECOG)
	Life expectancy $\geq$ 3 months	Life expectancy $\geq$ 3 months
	Total bilirubin level of $\leq$1.5 × ULN	Total bilirubin level of $\leq$2 × ULN
	Liver-enzyme levels $\leq$ 5 × ULN	Liver-enzyme levels $\leq$ 3 × ULN
	Glomerular filtration rate $\geq$ 45 ml per minute	Creatinine clearance $\geq$ 45 ml per minute
Treatment schedule	"CisGem arm": cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2, each on days 1 and 8 of a 21-day regimen	"CisGem arm": cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2, each on days 1 and 8 of a 21-day regimen
	"Gem arm": gemcitabine 1000 mg/m^2 on days 1, 8 and 15 of a 28-day regimen	"Gem arm": gemcitabine 1000 mg/m^2 on days 1, 8 and 15 of a 28-day regimen
Duration of treatment	Up to 24 weeks	Until disease progression
Frequency of radiological assessment	Every 12 weeks	Every 8 weeks
Primary end point	Overall survival	1-year survival

BSC alone is ~2.5–4.5 months and palliative chemotherapy should be considered as a treatment option. A systematic review of chemotherapy studies for advanced BTC published in 2007 identified 104 studies since 1985. The largest study reported 65 patients; there was one phase III study (closed early due to poor recruitment) and two randomised phase II studies [11]. No standard regimen was identified although the most active regimens appeared to be those including gemcitabine alone, gemcitabine with a platinum agent or 5-FU with a platinum agent.

The Advanced biliary tract cancer (ABC)-02 study (Clinical Trials.gov number: NCT00262769) was a UK-wide phase III study, carried out under the auspices of the National Cancer Research Network, comparing doublet-chemotherapy (CisGem, cisplatin 25 mg/m² and gemcitabine 1000 mg/m², each on days 1 and 8 of a 21-day regimen) versus gemcitabine monotherapy (Gem, gemcitabine 1000 mg/m² on days 1, 8 and 15 of a 28-day regimen). It built on a randomised phase II study (ABC-01, at the time the largest global study with 86 patients) [12], which had demonstrated an improvement in 6-month progression-free survival from 47.7% to 57.1%. ABC-01 was then extended to the phase III ABC-02 study using an identical protocol but recruiting an additional 324 patients for a total of 410 patients. This extension would provide statistical power for an overall survival (OS) analysis. This study demonstrated a statistically improved OS in favour of the combination arm [median OS 11.7 versus 8.1 months, hazard ratio (HR) 0.64; 95% confidence interval (CI) 0.52–0.80, P < 0.001] with an improved progression-free survival [PFS, median 8.0 versus 5.0 months, HR = 0.63, 95% CI 0.51–0.77, P < 0.001) and an acceptable toxicity profile, [13] thus setting a reference regimen for patients with advanced BTC.

In parallel, the biliary tract (BT) 22 study (ClinicalTrials.gov number NCT00380588) was developed in Japan in order to replicate the ABC-01 data using an identical regimen to the ABC studies. Compared with Gem, patients who received CisGem had a better 1-year survival (the primary end point, 39.0% versus 31.0%); median OS (11.2 versus 7.7 months); median PFS (5.8 versus 3.7 months) and radiological response rate (19.5% versus 11.9%). The hazard ratio between the treatment arms was 0.69 (95% CI 0.42–1.13) for OS and 0.66 (95% CI 0.41–1.05) for PFS in favour of CisGem [14].

The meta-analysis reported here represents a pre-planned international collaboration between UK and Japanese investigators in order to achieve greater statistical power in the evaluation of the treatment effect.

patients and methods

The primary objective of this meta-analysis is to evaluate the effect of cisplatin and gemcitabine (CisGem) versus gemcitabine alone (Gem), with enhanced patient numbers by combining patient-level data from the ABC-01/ABC-02 and BT22 studies (Table 1). In addition, we sought to explore the relative treatment effect across both studies given the inherent differences between the study populations.

Each of the studies was carried out with Ethics Committee and other requisite approvals/notifications (governed by the country of each study sponsor); all patients were enrolled after giving informed consent to participate and the studies were conducted in accordance with the Declaration of Helsinki.

Gemcitabine was provided for the investigators in both studies by Lilly Oncology or Eli Lilly Japan, as appropriate. ABC-02 was carried out as an investigator-initiated academic study; Lilly Oncology was not involved in the accrual or analysis of the data, or the preparation of the manuscript. Data from ABC-02 were held by the study sponsor, University College London Clinical Trials Unit (UCL CTU). BT22 was originally a Lilly-sponsored trial although additional data collection for OS and PFS was made as an investigator-initiated study and supported by the Ministry of Health, Labour and Welfare (MHLW), Health Labour Sciences Research Grant; data were collected by the investigators and released following publication of BT22 to UCL CTU under a study-specific agreement for the sole purposes of this meta-analysis.

Cox proportional hazards model was used to estimate the effect of treatment on OS and PFS, providing a HR for CisGem versus Gem. The treatment effect was examined for each of the subgroups for pre-specified baseline factors, as well as age, sex and trial. A test for interaction with treatment was assessed for each set of subgroups.

OS was estimated from date of entry to the trial to date of death, or date last seen alive; PFS was estimated from date of entry to the trial until date of

Table 2. Baseline characteristics among ABC-02 and BT22 trial patients, by treatment

Baseline factor	No. (%)	
	Gemcitabine + cisplatin (N = 245)	Gemcitabine alone (N = 248)
Sex		
Female	131 (53)	129 (52)
Male	114 (47)	119 (48)
Age (years): median (range)	64 (32–81)	64 (23–84)
Disease status		
Locally advanced	60 (24)	57 (23)
Metastatic	174 (71)	181 (73)
Not stated	11 (4)	10 (4)
Primary tumour site[a]		
Intra-hepatic	51 (21)	57 (23)
Extra-hepatic	76 (31)	73 (29)
Gallbladder	88 (36)	93 (38)
Ampulla	13 (5)	11 (4)
Not stated	17 (7)	14 (6)
Histology		
Adenocarcinoma	225 (92)	232 (94)
Carcinoma unspecified	17 (7)	12 (5)
Adenosquamous carcinoma	2 (1)	3 (1)
Squamous-cell carcinoma	0 (0)	1 (<1)
Carcinosarcoma	1 (<1)	0 (0)
ECOG performance status		
0	100 (41)	92 (37)
1	118 (48)	131 (53)
2	27 (11)	25 (10)
Prior therapy		
No	80 (33)	78 (31)
Yes	165 (67)	170 (69)

[a]Hilar patients from ABC-02 are included in the extra-hepatic group.
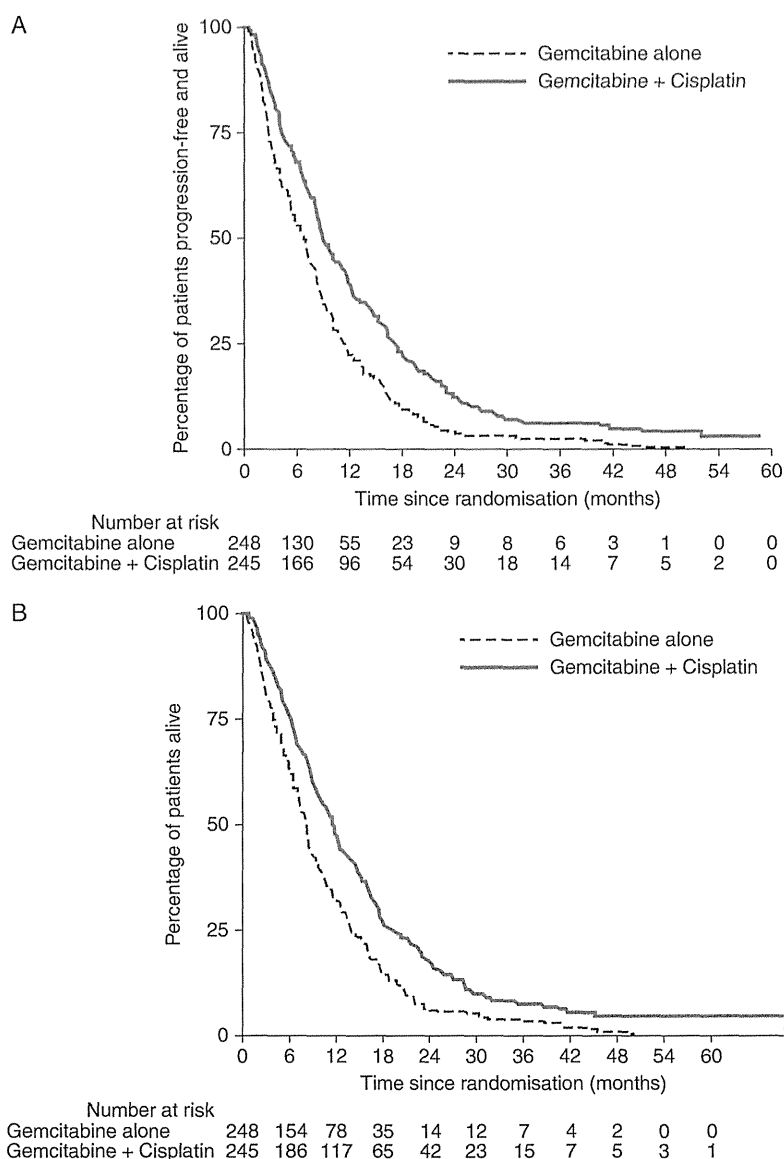
Figure 1. (A) Kaplan–Meier curve for progression-free survival, by treatment. Hazard ratio = 0.64 (95% CI 0.53–0.76), $P < 0.001$. (B) Kaplan–Meier curve for overall survival, by treatment. Hazard ratio = 0.65 (95% CI 0.54–0.78), $P < 0.001$.

progression or date of death, or date last seen alive for those patients without either event.

results

A total of 493 patients, median age 64 years (range 23–84 years) with approximately equal sex distribution, were randomised (ABC-02 study $n = 410$; BT22 study $n = 83$) to receive either CisGem [$N = 245$: ABC-02 ($n = 204$); BT22 ($n = 41$)] or Gem [$N = 248$: ABC-02 ($n = 206$); BT22 ($n = 42$)] (Table 2). Three-quarters of the patients had metastatic disease; 89% of patients had a good performance status (PS, 0-1) (patients with PS of 2 were eligible for ABC-02, but not BT22); and the histology was of adenocarcinoma type in 93% with a small number of patients with alternative histologies (Table 2). Sixty-eight percent of

patients had prior therapy, primarily in the form of biliary stenting; a total of 109 patients (22%) had undergone prior surgery with curative intent and subsequently relapsed; prior systemic chemotherapy for advanced disease was not allowed.

These data had slightly longer follow-up in both trials (median follow-up in ABC-02: 9.2 months; BT22: 9.0 months), compared with the published papers [13, 14]. When compared with gemcitabine monotherapy, the combination of cisplatin and gemcitabine was associated with an improved PFS (median 8.8 versus 6.7 months; HR = 0.64 (95% CI 0.53–0.76), $P < 0.001$) and OS (median 11.6 versus 8.0 months; HR = 0.65 (95% CI 0.54–0.78), $P < 0.001$), Figure 1a and b, respectively. Thus, the use of combination chemotherapy reduces the risk of progression or death (defined by PFS event) by 36%; and risk of death by 35%, compared with gemcitabine monotherapy.
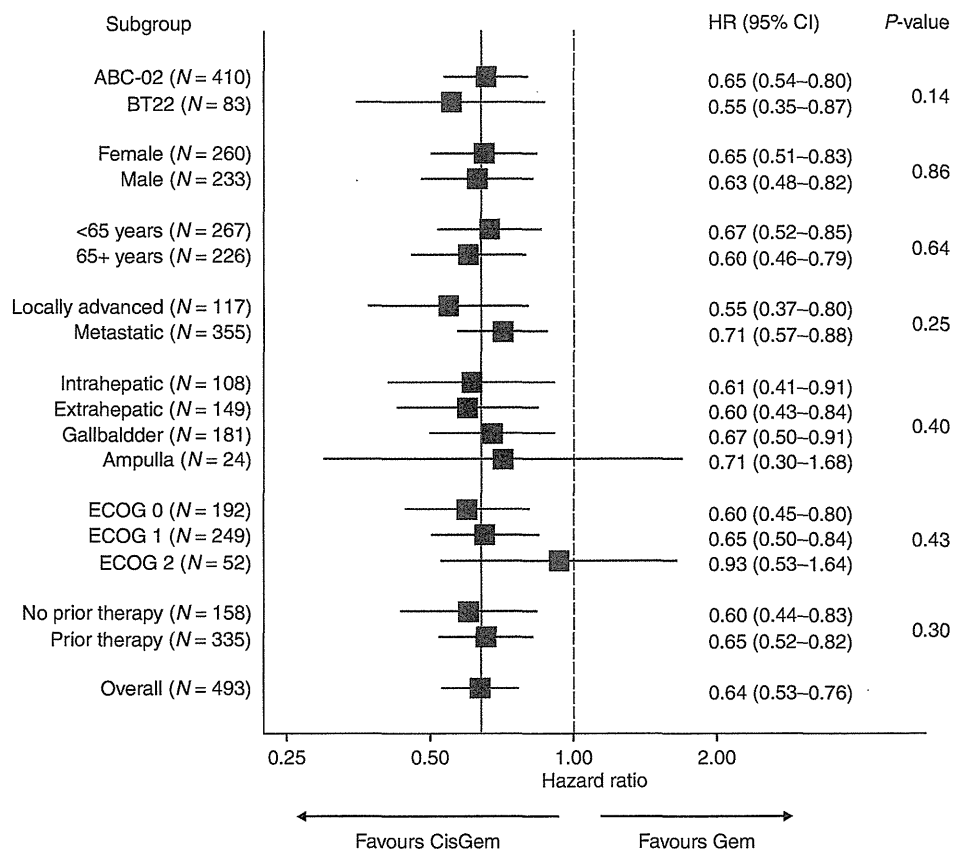
Figure 2. Progression-free survival, among ABC-02 and BT22 trials, by subgroups. The hazard ratio (95% confidence interval) for the treatment effect (CisGem versus Gem alone) is provided for each subgroup, per factor and the corresponding P-value for the test of interaction between treatment and factor. The forest plot excludes patients with unstated disease status and tumour site subgroup levels.

Exploratory subgroup analysis suggests that all patients benefit from CisGem versus Gem with respect to sex; age (<65 and ≥65 years), stage of disease (locally advanced and metastatic); site of primary tumour (intra-hepatic, extra-hepatic cholangiocarcinoma and gallbladder cancer); performance score (PS 0 and 1) and use of prior therapy (Figures 2 and 3). The widest confidence intervals are seen in patients with ampullary tumours and those with PS 2 due to the small size of each cohort ($n = 24$ and $n = 52$, respectively). When limited to patients with PS 0-1 only ($n = 441$), the HR for PFS is 0.61 (95% CI 0.51–0.74), $P < 0.001$ and for OS HR = 0.64 (95% CI 0.53–0.77), $P < 0.001$.

There is no evidence for a difference in treatment effects between any of the subgroups for PFS or OS (Figures 2 and 3). The treatment effect is remarkably similar between the two studies (BT22 versus ABC-02) with respect to OS (Figure 3; HR = 0.65 for both trials) and PFS (Figure 2) [test for heterogeneity for OS: $P = 0.90$; PFS: $P = 0.14$].

A total of 109 patients had surgery before trial entry; there is no evidence of an interaction between prior surgery status and treatment effect for OS and PFS ($P = 0.52$ and $P = 0.26$, respectively).

discussion

It was previously believed that the incidence of BTC was too low for prospective, adequately powered clinical studies to be carried

out. This meta-analysis, achieved by international collaboration, combines individual patient-level data from two prospective randomized, controlled trials in pathologically proven, advanced BTC using the same treatment comparisons [the UK ABC-02 phase III study ($n = 410$) and Japanese BT22 randomised phase II study ($n = 84$)] and thus represents the largest prospectively evaluated patient pool with close to 500 patients in total. This meta-analysis demonstrates a significant improvement in PFS and OS in favour of cisplatin and gemcitabine doublet chemotherapy over gemcitabine monotherapy, of the order of a 35% reduction in the risk of outcome.

There is a striking consistency between the treatment effect observed between the ABC-02 and BT22 studies (both HRs = 0.65) with respect to OS (Figure 3) with near-reproducible median survival in the combination arms (11.7 and 11.1 months, respectively). The similarity is less marked for PFS (HR 0.65 and 0.55), with median PFS of 9.7 and 6.5 months in each of the combination arms of ABC-02 and BT22, respectively. This is likely to be due to differences in protocol-driven assessments; specifically frequency of radiological tumour reassessment (6-weekly in BT22 and 12-weekly in ABC-02) [15].

This meta-analysis did not include an assessment of toxicity due to the different schedules for safety assessment between the protocols (specifically, BT22 included assessment of complete blood count and biochemistry on the rest week of treatment
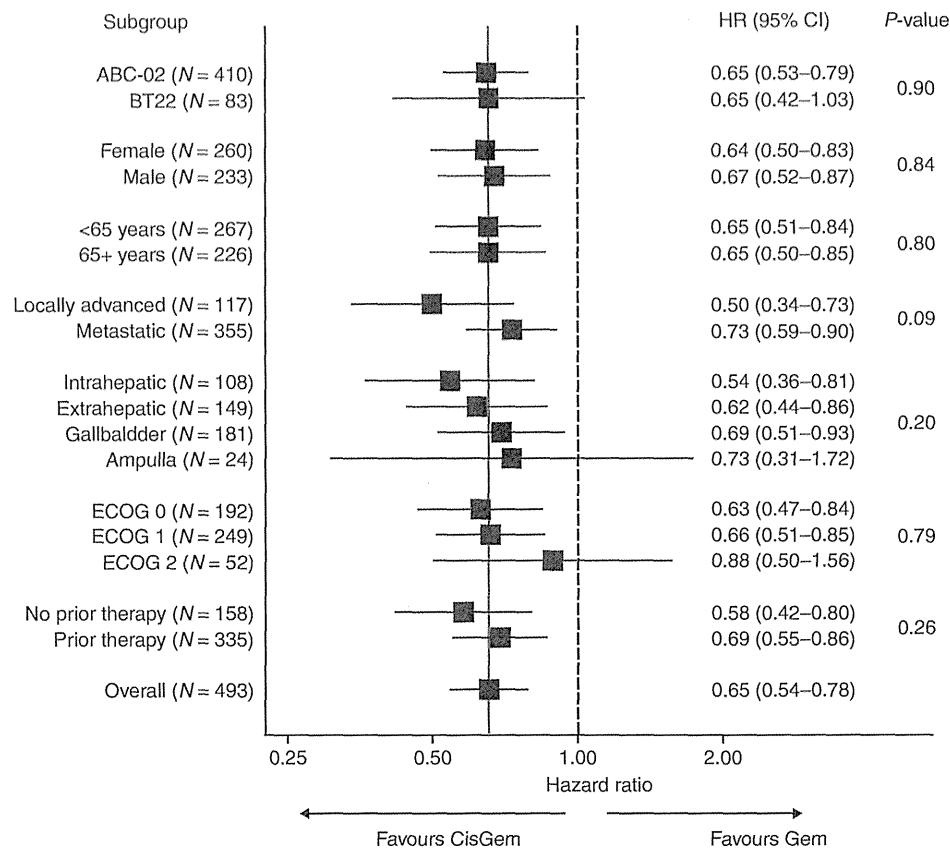
Figure 3. Overall survival, among ABC-02 and BT22 trials, by subgroups. The hazard ratio (95% CI) for the treatment effect (CisGem versus Gem alone) is provided for each subgroup, per factor and the corresponding P-value for the test of interaction between treatment and factor. The forest plot excludes the undefined disease status and tumour site subgroup levels.

(not required for ABC-02) which may explain the increased haematological toxicity reported in this study; [15] however, these regimens are well established and toxicities are detailed in the individual study publications [13, 14].

Patients with a good PS (0-1) appear to derive greater benefit from combination chemotherapy (HR for PFS and OS are 0.61 and 0.64, respectively). It is therefore appropriate for future studies using this combination chemotherapy to limit inclusion to PS 0-1 patients. PS2 patients were only included in the ABC-02 study and the HR for OS for this group was 0.88, 95% CI 0.50–1.56; thus, in the absence of studies specifically addressing therapy for PS2 patients, it may be preferable to consider gemcitabine monotherapy for this group given the very poor survival with BSC alone [9, 10].

With the exception of ampullary tumours combination chemotherapy resulted in statistically significantly favourable PFS and OS for all other tumour-location subgroups (intra-hepatic cholangiocarcinoma, extra-hepatic cholangiocarcinoma and gallbladder cancer). Although a reduced risk of 25%–30% was seen in the ampullary group, the small numbers did not permit a statistically meaningful result. As these cancers are uncommon, it may be necessary for another meta-analysis to provide the statistical power required for a robust assessment of this tumour subtype in future studies.

The remit of this meta-analysis is limited to the effect of first-line chemotherapy for patients with advanced BTC. The use of subsequent chemotherapy can confound the survival analysis. Only 18% of patients in the ABC-02 study went on to receive second-line chemotherapy, primarily due to there being no UK-recognised regimen in this setting. In contrast, 76% of patients in BT22 went on to receive second-line chemotherapy on disease progression in Japan where the oral fluoropyrimidine, S1, is a licensed treatment option for these patients. Despite this disparity, the survival in the combined arms was very similar as already discussed, accepting the inherent limitations of cross-study comparisons. There are no randomised phase III data that second-line chemotherapy improves survival for patients who have previously been treated with cisplatin and gemcitabine; specifically, no phase III studies have ever been carried out. A recent large retrospective single-centre series suggests that second-line chemotherapy (after a heterogeneous group of first-line regimens) is feasible in ~25% of patients; [16] moreover, after cisplatin and gemcitabine first-line chemotherapy, we have shown that patients who do go on to receive chemotherapy may derive additional benefit (median survival from start of second-line treatment: 8.1 months, median survival from start of first-line chemotherapy: 19.5 months) [17]. However, such analysis is highly subject to selection bias and prospective studies are

urgently needed to determine the benefit (if any) in terms of survival, impact on quality of life and cost-effectiveness of second-line chemotherapy.

This meta-analysis for efficacy, together with a recently published cost-effectiveness analysis [18] has strengthened the rationale for recommending cisplatin and gemcitabine as a reference regimen for development of further therapies across international patient populations with advanced BTC.

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references

1. Lazaridis KN, Gores GJ. Cholangiocarcinoma. Gastroenterology 2005; 128: 1655–1667.
2. Randi G, Malvezzi M, Levi F et al. Epidemiology of biliary tract cancers: an update. Ann Oncol 2009; 20: 146–159.
3. Matsuda T, Marugame T. International comparisons of cumulative risk of gallbladder cancer and other biliary tract cancer, from Cancer Incidence in Five Continents Vol. VIII. Jpn J Clin Oncol 2007; 37: 74–75.
4. Taylor-Robinson SD, Toledano MB, Arora S et al. Increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales 1968–1998. Gut 2001; 48: 816–820.
5. Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology 2001; 33: 1353–1357.
6. Khan SA, Taylor-Robinson SD, Toledano MB et al. Changing international trends in mortality rates for liver, biliary and pancreatic tumours. J Hepatol 2002; 37: 806–813.
7. Anderson CD, Pinson CW, Berlin J et al. Diagnosis and treatment of cholangiocarcinoma. Oncologist 2004; 9: 43–57.
8. DeOliveira ML, Cunningham SC, Cameron JL et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. Ann Surg 2007; 245: 755–762.
9. Glimelius B, Hoffman K, Sjoden PO et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. Ann Oncol 1996; 7: 593–600.
10. Sharma A, Dwary AD, Mohanti BK et al. Best supportive care compared with chemotherapy for unresectable gall bladder cancer: a randomized controlled study. J Clin Oncol 2010; 28: 4581–4586.
11. Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. Br J Cancer 2007; 96: 896–902.
12. Valle JW, Wasan H, Johnson P et al. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study—the UK ABC-01 Study. Br J Cancer 2009; 101: 621–627.

13. Valle J, Wasan H, Palmer DH et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010; 362: 1273–1281.
14. Okusaka T, Nakachi K, Fukutomi A et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br J Cancer 2010; 103: 469–474.
15. Furuse J, Okusaka T, Bridgewater J et al. Lessons from the comparison of two randomized clinical trials using gemcitabine and cisplatin for advanced biliary tract cancer. Crit Rev Oncol Hematol 2011; 80: 31–39.

16. Walter T, Horgan AM, McNamara M et al. Feasibility and benefits of second-line chemotherapy in advanced biliary tract cancer: a large retrospective study. Eur J Cancer 2012; 49: 329–35.
17. Bridgewater J, Palmer D, Cunningham D et al. Outcome of second-line chemotherapy for biliary tract cancer. Eur J Cancer 2012; 49: 1511.
18. Roth JA, Carlson JJ. Cost-effectiveness of gemcitabine + cisplatin vs. gemcitabine monotherapy in advanced biliary tract cancer. J Gastrointest Cancer 2012; 43: 215–223.

Pharmacogenetic predictors of severe peripheral neuropathy in colon cancer patients treated with oxaliplatin-based adjuvant chemotherapy: a GEMCAD group study

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Background: Oxaliplatin-based chemotherapy (CT), widely used as adjuvant therapy for stage III and selected high-risk stage II colon cancer (CC) patients, is often associated with cumulative peripheral neuropathy. Our aim is to identify single-nucleotide polymorphisms (SNPs) in genes involved in oxaliplatin metabolism, DNA repair mechanisms, cell cycle control, detoxification or excretion pathways to predict severe (grade 2–3) oxaliplatin-induced peripheral neuropathy (OXPN) among CC patients treated with oxaliplatin and fluoropyrimidine-based adjuvant CT.

Patients and methods: Genomic DNA was extracted from formalin-fixed-paraffin-embedded peritumoral samples from 206 high-risk stage II and stage III CC patients receiving oxaliplatin-based adjuvant CT from January 2004 to December 2009. Genotyping was carried out for 34 SNPs in 15 genes using MassARRAY (SEQUENOM) technology. A total of 181 stage II–III CC patients treated with the same CT regimens were enrolled as a validation set.

Results: The rs2230641 cyclin H (CCNH) rs2230641 C/C [odd ratio (OR) = 5.03, 95% confidence interval (CI) 1.061–2.41, P = 0.042] and the ATP-binding cassette subfamily G, member 2 (ABCG2) rs3114018 A/A genotypes (OR = 2.67; 95% CI 0.95–4.41; P = 0.059) were associated with a higher risk of severe OXPN. In addition, patients harboring the combination of CCNH C/C and/or the ABCG2 rs3114018 A/A genotypes had a higher risk of grade 2–3 OXPN than those with the CCNH any T and ABCG2 any C genotypes (37.73% versus 19.42%; OR = 2.46; 95% CI 1.19–5.07; P = 0.014) in the logistic regression analysis using age, gender, adjuvant CT regimen and cumulative dose of oxaliplatin as covariates. The ability to predict severe OXPN of this combined analysis was independently validated in the second cohort (58% versus 33.33%; OR = 2.99; 95% CI 1.45–6.13; P = 0.002).

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