

# Gemcitabine, alone or in combination with cisplatin, in patients with advanced or metastatic cholangiocarcinoma (CC) and other biliary tract tumours: a multicentre, randomised phase II (the UK ABC-01) study.

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## Abstract

**Background:** There is no established standard chemotherapy for patients (pts) with locally advanced (LA) or metastatic (M) (advanced) biliary cancers (ABC). We assessed the activity of gemcitabine (G) and, given the known synergistic effect of these agents, the cisplatin/gemcitabine (C/G) combination in patients with ABC. **Methods:** Pts, aged  $\geq 18$  years, with histologically/ cytologically-confirmed ABC, Karnofsky Performance (KP)  $\geq 60$ , with adequate haematological, hepatic and renal function were randomised to either G 1000 mg/m<sup>2</sup> on D1, 8, 15 q28d (Arm A) or C 25 mg/m<sup>2</sup> followed by G 1000 mg/m<sup>2</sup> D1, 8 q21d (Arm B) stratified by extent of disease (LA vs. M). The primary end-point was 6-month progression-free survival (6-mo PFS), disease progression. **Results:** From Feb 2002 to May 2004, 86 patients (A/B) 44/42 pts were randomised from 15 institutions. Median age (64/62.5 Treatment continued to a total of 6 months in the absence of radiological yrs), KP, primary tumour site (CC, gallbladder or ampullary cancer), prior surgery, indwelling biliary stent and disease stage (LA: 25%/38%) are comparable between treatment arms. Grade 3-4 toxicity included (A/B, % patients): anaemia (4.5/2.4), leucopenia (6.8/4.8), neutropenia (11.4/14.3), thrombocytopenia (9.1/11.9), lethargy (9.1/28.6), nausea/vomiting (0/4.8) and anorexia (2.3/4.8). Responses (WHO criteria, % of evaluable patients: A n=33 vs. B n=37): PR 15.2% vs. 24.3%, SD 42.4% vs. 51.4% for a tumour control rate (CR+PR+SD) of 57.6% vs. 75.7%. The TTP and 6-mo PFS were greater in the combination therapy arm (5.5 mo vs. 8.0 mo and 50.2% vs. 57.1% in arms A and B, respectively). **Conclusions:** Both regimens appear active in ABC. The C/G combination may be associated with an improved RR, tumour control rate, TTP and PFS (however, limited patient numbers preclude statistical comparison) and it is unclear whether these will translate into a survival benefit. The study has been extended (UK ABC-02 study) to determine the effect on survival and quality of life given the observed increase in toxicity (especially lethargy) in the C/G arm.

## Rationale

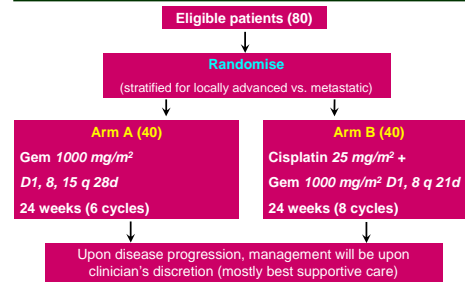
- Biliary tract tumours (cholangiocarcinomas, gallbladder (GB) cancer and ampullary tumours) account for <1% of cancers in adults (approx. 1200 new cases/ year in England and Wales) <sup>1</sup>.
- Both biliary obstruction and malignancy are potentially life-threatening; it is important that obstruction and infection should be prevented and dealt with wherever appropriate <sup>2</sup>.
- Surgical resection offers the only chance of cure; resectability rates are low and survival after surgical resection varies widely between centres (range 23% - 50% at 5-years) <sup>3</sup>.
- There is no "standard" therapy for patients with advanced (unresectable, metastatic or recurrent) disease.
- Small heterogeneous phase II studies suggest some activity for agents such as 5-FU and gemcitabine; there is a need for large multicentre studies assessing the role of chemotherapy in ABC.
- Cisplatin is known to enhance the activity of gemcitabine in a number of tumour types, with an expected increase in toxicity.

## Study end-points

**Primary:**  
6-month progression-free survival

**Secondary:**  
Response rate  
Overall survival  
Toxicity

## Study Design



## Patient Population

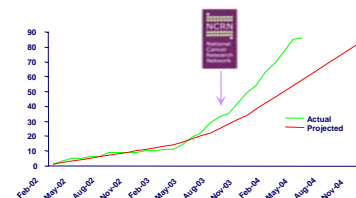
### Inclusion Criteria

- **Histologically or cytologically verified**, non-resectable, recurrent or metastatic CC, GB or ampullary carcinoma
- Measurable or evaluable disease on CT or MR scanning (WHO)
- KP  $\geq 60$ , Age  $\geq 18$  years, life expectancy > 3 months
- Adequate renal function (urea/creatinine < 1.5 x ULN, GFR  $\geq 60$  ml/min)
- Hb  $\geq 10g/dl$ , WBC  $\geq 3.0$ , ANC  $\geq 1.5$ , Plts  $\geq 100$
- Bilirubin < 30, ALT/AST/alk phos  $\leq 3$  x ULN ( $\leq 5$  if liver metastases)
- **Adequate biliary drainage**, with no evidence of ongoing infection.
- Previous XRT is allowed, as long as the measurable disease to be evaluated in this study does not fall within the previous field
- Patients must have given **written informed consent**

### Exclusion Criteria

- Incomplete recovery from previous surgery or unresolved biliary obstruction
- Any previous chemotherapy (except for radio-sensitising 5-FU or gemcitabine)
- Previous investigational agent in the last 12 weeks
- Clinical evidence of metastatic disease to brain
- Any pregnant or lactating woman

## Accrual



## Results

### Patient Characteristics

	Arm A (Gem) n (%)	Arm B (Cis/Gem) n (%)
Total	44 (51%)	42 (49%)
Age median (range) yrs.	64 (29 - 84)	62.5 (38 - 76)
Sex		
Male	19 (43%)	17 (41%)
Female	25 (57%)	25 (59%)
KP		
100	4 (9%)	5 (12%)
90	17 (39%)	16 (38%)
80	19 (43%)	14 (33%)
$\leq 70$	4 (9%)	7 (17%)
Disease site		
IH-CC	7 (16%)	12 (29%)
EH-CC	11 (25%)	9 (21%)
CC-NOS	10 (23%)	10 (24%)
GB Ca	12 (27%)	10 (24%)
Ampulla	4 (9%)	1 (2%)
Prior therapy		
Laparotomy	16 (37%)	12 (29%)
Palliative Surgery	10 (23%)	13 (31%)
Curative surgery	10 (23%)	3 (7%)
Stent insertion	23 (52%)	25 (60%)
Radiotherapy	3 (7%)	0
Extent of disease		
Locally Advanced	11 (25%)	16 (38%)
Metastatic	33 (75%)	26 (62%)

(CC=cholangiocarcinoma, IH=intrahepatic, EH=extrahepatic, NOS=not otherwise specified, GB=gallbladder)

### Treatment given

	Arm A (Gem) N=44	Arm B (Cis/Gem) N=42
Number of cycles given	158	239
Duration of cycle	4 weeks	3 weeks
Planned number of cycles	6 (=24 weeks)	8 (=24 weeks)
Mean duration of treatment (weeks)	15.0	23.1
Median number of cycles	3	7.5
Range	1-6	1-8

### Grade 3-4 toxicity by patient (%)

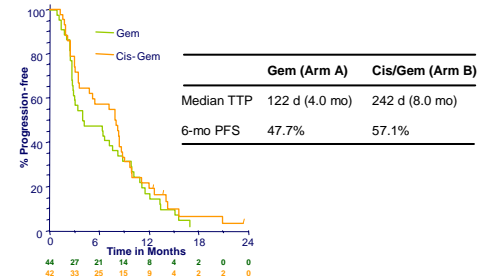
	Arm A Gem (n=44)	Arm B Cis/Gem (n=42)
Hb	4.5%	2.4%
WCC	6.8%	4.8%
Neut	11.4%	14.3%
Plts	9.1%	11.9%
Lethargy	9.1%	28.6%
Anorexia	2.3%	4.8%
Nausea	0	0
Vomiting	0	4.8%
Infection (Non-neutropenic)	18.2%	19.0%
Infection (Neutropenic)	0	2.4%
Transaminases	13.6%	9.5%
Bilirubin	20.4%	11.9%
Diarrhoea	0	4.8%
Stomatitis	0	2.4%
Renal	0	2.4%
Neurological	2.3%	0
Constipation	2.3%	2.4%
Oedema	2.3%	4.8%

### Response (WHO criteria)

	Arm A Gem (n=44)	Arm B Cis/Gem (n=42)
Not measurable *	11	5
Measurable	33	37
CR	0	0
PR	5 (15.2%)	9 (24.3%)
SD	14 (42.4%)	19 (51.4%)
<b>Tumour control (CR+PR+SD)</b>	<b>19 (57.6%)</b>	<b>28 (75.7%)</b>
PD	14 (42.4%)	9 (24.3%)

\* Patients were not required to have measurable disease at study entry, percentages given as a fraction of measurable patients.

## 6-month progression-free survival (PFS)



## Conclusions

Compared to gemcitabine alone, the cisplatin/gemcitabine combination results in:

- Improved 6-month PFS (57.1% vs. 47.7%) (Primary end-point)
- Improved RR in evaluable patients (21.4% vs. 11.4%)
- Improved tumour control rate (75.7% vs. 57.6%)
- Increased grade 3-4 toxicity (although both arms are well tolerated)
  - lethargy 28.6% vs. 9.1%
  - anorexia 4.8% vs. 2.3%
  - vomiting 4.8% vs. 0%

### Unanswered questions:

- Does this improvement in PFS translate into a survival advantage?
  - What is the effect on Quality of Life?
  - What is the correlation with serum CA19-9?
- To be answered by ABC-02 study

## References

1. Cancer Survival Trends in England and Wales 1971 - 1995, deprivation and NHS region
2. Ottow RT, August DA, Sugarbaker PH Treatment of proximal biliary tract carcinoma: an overview of techniques and results. Surgy 97:251-62, 1985
3. Klempnauer J, Ridder GJ, von Wasielewski R, et al. Resectional surgery of hilar cholangiocarcinoma: a multivariate analysis of prognostic factors. J Clin Oncol 15:947-54, 1997

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