When a rare cancer turns out not to so rare: Progress in biliary tract cancer

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UCL Cancer Institute
Epidemiology

BTC = cholangiocarcinoma, gallbladder cancer & ampullary cancer

3% of all GI cancers globally ¹

Rare tumours incidence:
- 1200 / year Eng & Wales ²
- 7500 / year USA

Incidence of IH-CCA is rising globally (USA, Japan, UK, Australia) ³

Second commonest primary hepatic tumour but more lethal than HCC ⁴

Patel, T. Hepatology 2001; 33:1353-1357
Survival in Biliary Tract Cancer

Surgery:
- only chance of cure
- most patients are inoperable
- disease progression following surgery is common

5YS (all patients):
- 5-10%
Obstacles to evaluation of treatments

Uncommon cancers
- Small statistically underpowered studies
- Prolonged accrual studies
- Heterogeneous populations
- Limited pharma interest

- Disease group
  - Unwell
  - Elderly population
  - Sepsis and biliary obstruction
- Histological / cytological confirmation difficult
- Disease often not measurable (unreliable response assessment)
Chemotherapy improves survival over BSC

Glimelius et al. [Ann Oncol 1996]
- Phase III: 5FU/etoposide/LV vs. BSC
- Pancreas (n=53) + BTC (n=37)
- Improved QoL
- Improved survival

<table>
<thead>
<tr>
<th></th>
<th>Glimelius et al</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSC</td>
<td></td>
<td>2.5</td>
</tr>
<tr>
<td>FELV</td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dwary et al [ASCO 2009]</th>
</tr>
</thead>
</table>
- Phase III: GemOx vs. 5FU/FA vs. BSC
- Gallbladder cancer only (n=81)
- Improved PFS
- Improved survival

<table>
<thead>
<tr>
<th></th>
<th>Dwary et al</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSC</td>
<td></td>
<td>4.5</td>
</tr>
<tr>
<td>5FU</td>
<td></td>
<td>5.4</td>
</tr>
<tr>
<td>GemOx</td>
<td></td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.038</td>
</tr>
</tbody>
</table>
Gemcitabine with or without cisplatin in patients with advanced or metastatic biliary tract cancer (ABC): final results of a multicentre, randomized phase III trial (the UK ABC-02 trial)

on behalf of NCRI Upper GI Clinical Studies Group and the ABC-02 investigators

ASCO: June 2009
ECCO/ESMO: Sep 2009
NEJM April 2010
Background: UK ABC-01 study

Randomised phase II study
First-line, patients with ABC
Primary endpoint: 6m PFS
Rationale:
  – Gemcitabine has documented activity
  – Cisplatin pre-clinical/clinical synergies with gemcitabine
N=86 patients

Valle Br J Cancer 2009
Background: ABC-01 - schema

Eligible patients (n=86)

Randomized 1:1
(stratified by centre, primary site, PS, prior therapy and locally advanced vs. metastatic)

Arm A
Gem 1000 mg/m² D1,8,15 q 28d
24 weeks (6 cycles)

Arm B
Cisplatin 25 mg/m² + Gem 1000 mg/m²
D1,8 q 21d
24 weeks (8 cycles)

6m PFS 45.5 vs 57.1%

Valle Br J Cancer 2009
Eligible patients (n=410)
Histologically / cytologically verified, 1st-line, ECOG PS 0-2, adequate biliary drainage, no uncontrolled infection

Randomized 1:1
stratified by: centre, primary site, PS, prior therapy and locally advanced vs. metastatic

Arm A
Gem 1000 mg/m² D1,8,15 q 28d
24 weeks (6 cycles)

Arm B
Cisplatin 25 mg/m² + Gem 1000 mg/m²
D1,8 q 21d
24 weeks (8 cycles)

Primary endpoint: Overall Survival

Final analysis: Aug 2009 (327 [79.8%] patients had died)
ABC-02 Primary Endpoint Results: Overall Survival (ITT)

- **Overall Survival (ITT)**
  - **Median Survival**:
    - Gem: 8.1 mo
    - CisGem: 11.7 mo
  - **HR (95% CI)**: 0.64 (0.52, 0.80)
  - **p-value**: <0.001

ECCO/ESMO: Sep 2009
ABC-02 Results: Progression-free survival (ITT)

Median: 5 → 8 mo

HR (95% CI): 0.63 (0.51, 0.77)
p<0.001

Number at risk
Gem 206 115 56 18 4 3 1 1 1 1
CisGem 204 140 95 36 18 10 4 1 1 1

ECCO/ESMO: Sep 2009
ABC-02 Overall Survival Stratified subgroup analysis

ECCO/ESMO: Sep 2009
# Haematological toxicity

<table>
<thead>
<tr>
<th></th>
<th>Gem</th>
<th>CisGem</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Platelets</td>
<td>13 (6.5)</td>
<td>17 (8.6)</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>6 (3.0)</td>
<td>15 (7.6)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>33 (16.6)</td>
<td>50 (23.3)</td>
</tr>
</tbody>
</table>

- Infection without neutropenia: 23 (11.6) / 12 (6.1)
- Infection with neutropenia: 14 (7.0) / 20 (10.1)
# Non-haematological toxicity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gem (N, %)</th>
<th>CisGem (N, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>34 (17.1)</td>
<td>19 (9.6)</td>
</tr>
<tr>
<td>Other liver function</td>
<td>39 (19.6)</td>
<td>26 (13.1)</td>
</tr>
<tr>
<td>Any liver function</td>
<td>54 (27.1)</td>
<td>33 (16.7)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>33 (16.6)</td>
<td>37 (18.7)</td>
</tr>
<tr>
<td>Renal function</td>
<td>2 (1.0)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>DVT/Thromboembolic disease</td>
<td>4 (2.0)</td>
<td>11 (5.5)</td>
</tr>
</tbody>
</table>
On average, the CisGem patients reported an overall quality of life that was 3% points greater than the Gem alone arm.

ECCO/ESMO: Sep 2009
Japanese BT-22 study: randomised phase II study

Advanced BTC (n=84)

Randomized 1:1
Primary endpoint: 1-year survival

N=42

Gem 1000 mg/m² D1,8,15 q 28d
48 weeks (12 cycles)

N=42

Cisplatin 25 mg/m² + Gem 1000 mg/m²
D1,8 q 21d
48 weeks (16 cycles)

Treatment until disease progression or unacceptable toxicity

Furuse et al, ASCO 2009 abstr 4579
## Survival

<table>
<thead>
<tr>
<th>Result</th>
<th>ABC-02 ¹</th>
<th>BT-22 ²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gem (%)</td>
<td>CisGem (%)</td>
</tr>
<tr>
<td>Median PFS (mo)</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>1-year survival (%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Median Overall survival</td>
<td>8.1</td>
<td>11.7</td>
</tr>
</tbody>
</table>

¹ ECCO/ESMO: Sep 2009  
² Furuse et al, ASCO 2009 abstr 4579
Poiseuille’s Law

Jean Louis Marie Poiseuille
1799 - 1869

Poiseuille’s Law

\[ F \propto r^4 \]

The \( r^4 \) factor

\[ \Delta P = 100 \text{ mmHg} \]

\[ \begin{align*}
  r=1 & \quad 1 \text{ ml/min} \\
  r=2 & \quad 16 \text{ ml/min} \\
  r=4 & \quad 256 \text{ ml/min}
\end{align*} \]
ABC studies in context (i)

Number of patients with ABC in prospective clinical trials of systemic therapies by study and year of publication to July 2009 (ABC-02 excluded)
ABC studies in context (ii)

Total number of patients with ABC within published prospective clinical trials of systemic therapy by year of publication to July 2009 (ABC-02 excluded)
## Current status of clinical trials with agents that target growth factor receptors and related signalling pathways for the treatment of biliary tract and gallbladder cancers

<table>
<thead>
<tr>
<th>Name</th>
<th>Target</th>
<th>Mechanism</th>
<th>Cotreatment</th>
<th>Status</th>
<th>Clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>VEGF-neutralizing antibody</td>
<td>Erlotinib</td>
<td>Phase II</td>
<td>NCT00350759[^7]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Erlotinib</td>
<td>Phase II</td>
<td>NCT00356889[^8]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Radiation</td>
<td>Phase I</td>
<td>NCT00426829[^21]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Floxuridine, dexamethasone</td>
<td>Phase II</td>
<td>NCT00410956[^9]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gemcitabine, oxaliplatin</td>
<td>Phase II</td>
<td>NCT00361231[^9]</td>
</tr>
<tr>
<td>Cediranib (AZD2171)</td>
<td>PAN-VEGFR, PDGFR, c-KIT</td>
<td>Tyrosine kinase inhibitor</td>
<td>AZD-0530</td>
<td>Phase I</td>
<td>NCT00475956</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>EGFR</td>
<td>Monoclonal antibody</td>
<td>Gemcitabine, oxaliplatin</td>
<td>Phase II</td>
<td>NCT00552149 (BINGO)[^22]</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>EGFR</td>
<td>Tyrosine kinase inhibitor</td>
<td>Gemcitabine, oxaliplatin</td>
<td>Phase II</td>
<td>NCT0033462[^12]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oxaliplatin, gemcitabine, radiation</td>
<td>Phase I b</td>
<td>NCT00266097[^16]</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>EGFR, erbB2</td>
<td>Tyrosine kinase inhibitor</td>
<td>Oxaliplatin, Capcitabine</td>
<td>Phase II</td>
<td>NCT00107536[^14]</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>VEGFR, PDGFR, c-Raf, B-Raf</td>
<td>Tyrosine kinase inhibitor</td>
<td>Capcitabine, Gemcitabine</td>
<td>Phase I / II</td>
<td>NCT0064751[^23]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase I / II</td>
<td>NCT00661830 (GEMSO)[^24]</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Proteasome</td>
<td>Proteasome inhibitor</td>
<td>Docetaxel</td>
<td>Phase II</td>
<td>NCT00085410[^13]</td>
</tr>
</tbody>
</table>

Emerging EGFR data

ABC (1st line) Stratification
- Stage (LA vs. M+)
- Type (gallbladder vs. other)
- Center
- Previous treatments *(Y/N)

**BINGO study**

<table>
<thead>
<tr>
<th>Malka et al</th>
<th>4-mo PFS</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GemOx</td>
<td>50%</td>
<td>5.0</td>
</tr>
<tr>
<td>GemOx / CTX</td>
<td>61%</td>
<td>7.0</td>
</tr>
</tbody>
</table>

Until disease progression or limiting toxicity

K-ras mutation present in 3/25 patients (12%)
K-ras wt expression does not seem to correlate with RR, PFS or OS

Study extended to N=150 pts

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1 Malka et al, ASCO 2009, 2 Gruenberger et al. ASCO 2009
AZD2171 - Cediranib

Cediranib is a highly potent and selective VEGF signalling inhibitor.

VEGF is a key driver of angiogenesis – the formation of new blood vessels.

By inhibiting all three VEGF receptors\(^1\), cediranib hinders angiogenesis and so prevents the blood supply that tumours need to grow and spread.

\(^1\) Wedge et al - Cancer Research 2005
Histologically / cytologically confirmed advanced biliary tract cancer
Measurable disease
ECOG PS 0-2
No prior systemic therapy for advanced disease
Resolved biliary obstruction / sepsis

Randomise

Chemotherapy + AZD 2171
Chemotherapy + Placebo

AZD 2171
Placebo

Randomised phase II study

No disease progression = 24 weeks chemotherapy
No disease progression @ 24 weeks AZD 2171 / placebo continues until disease progression or death

Chemotherapy is Cisplatin + Gemcitabine, on days 1 and 8 of a 21-day regimen (1 cycle)
Histologically / cytologically confirmed advanced biliary tract cancer
- Measurable disease
- ECOG PS 0-2
- No prior systemic therapy for advanced disease
- Resolved biliary obstruction / sepsis

**Primary Endpoint**
- Progression-free survival

**Secondary endpoints**
- Response Rate (RECIST)
- Toxicity
- Survival
- Biomarker evaluation (inc. circulating tumour cells, VEGF, sVEGFR-2, bFGF, LDH and CA 19-9)
- Quality of Life
- Cost effectiveness analysis

Chemotherapy is Cisplatin + Gemcitabine, on days 1 and 8 of a 21-day regimen (1 cycle)
Advanced biliary cancer (ABC) studies

**ABC-01**
- R-Phase II (n=86)
- $1^0$ endpoint: PFS
- Grant: industry
- Adopted by NCRN
- NCRI-UGI CSG: BTC working party formed
- BJC 2009

**ABC-02**
- Phase III (n=400 inc ABC-01)
- $1^0$ endpoint: OS
- Grant: CRUK (UCL)
- 43 centres open (37 centres recruited)
- Completed accrual 13/10/08 (n=410)
- Defining “standard care”
- NEJM April 2010

**ABC-03**
- Study in design
- Phase III
- Chemo + AZD2171/placebo
- (AZ/NCRN initiative)
- $1^0$ endpoint: OS
- Grant: CRUK (UCL)
- Biomarker sub-study
- Imaging sub-study

**Context**
- 104 studies since 1985 (5-65 patients per study)
- One Phase III RCT (n=56), two R-phase II
- No widespread UK collaboration
Advanced biliary cancer (ABC) studies

**ABC-04**
- Phase I/II
- AZD 6244 + CisGem followed by R-phase II
- select best phase II for next phase III
- CTAAC endorsed
- AZ funded

**ABC-05**
- 2nd-line study
- 5FU +/- oxaliplatin
- CTU: UCL
- CTAAC funding
- In development

**ABC-06**
- Phase I/II
- AZD 2891 + 5FU followed by R-phase II
- select best phase II for next phase III
- In development

Collaborations:
- Australia (D Goldberg, J Zalcberg)
- Japan (J Furuse)
- France (M Dureux, D Malka)
- Canada (J Knox, C O’Callaghan)
Conclusion

Biliary tract cancers are chemo-responsive

Most commonly used regimens include gemcitabine, fluoropyrimidines and platinum

Efficacy of CisGem from the ABC-02 study has provided a point of reference in first-line therapy

No standard second-line, adjuvant, neo-adjuvant regimen(s)

Many clinical trials underway investigating novel therapies

Key to improving survival: Collaboration
  ➢ Timely accrual and reporting of studies
  ➢ Adequately-powered studies