Biliary tract neoplasm
Medical treatment

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Biliary tract cancer

- Rare tumor
- Different entities
- Diagnosis sometimes problematic
- Elderly patients with comorbidities
- Cholestasis
- Therapeutic options limited (mostly phase II trials; potentially curative surgery possible in < 20%)

Different Entities

<table>
<thead>
<tr>
<th>Incidence/10^5</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallbladder (f &gt; m)</td>
<td>1.2</td>
</tr>
<tr>
<td>Biliary tree</td>
<td></td>
</tr>
<tr>
<td>intrahepatic (m &gt; f)</td>
<td>0.9</td>
</tr>
<tr>
<td>extrahepatic (m &gt; f)</td>
<td>1.6</td>
</tr>
<tr>
<td>perihilar</td>
<td></td>
</tr>
<tr>
<td>distal</td>
<td>25%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>11</td>
</tr>
<tr>
<td>Esophagus</td>
<td>5</td>
</tr>
<tr>
<td>Colon</td>
<td>54</td>
</tr>
</tbody>
</table>

Epidemiology and carcinogenesis

- Rising incidence of cholangiocarcinoma over the past 30 years documented on 3 continents
- Unknown cause
  - Hypothesis: rise in one or several genotoxic environmental agents, causing cholangiocyte DNA damage
  - Khan et al.
    - levels of DNA adducts significantly higher in DNA from 12 patients with intrahepatic cholangiocarcinoma compared with non-cancer patient DNA (n=7); 2.9; p = 0.03
  - Hedgehog signalling pathway: role in mature tissue homeostasis

Subtypes

France: Malka 2007
Gallbladder carcinoma: a specificity

- Gallstone disease (0.5%-20%)  
- Genetics (ethnicity, gender)  
- Anatomy (APBDJ) (15%)  
- Gallbladder adenoma  
- Salmonella typhi (+ other)  
- Chemicals

Very high (>9/105)  
High (4-9/105)

Wistuba and Gazdar. Nature Reviews Cancer 2004

Sequential histological and molecular changes in GBC

Age: ~30-40  
~45  
~55  
~60

- Gallstones and chronic inflammation  
- p53 mutations  
- TP53 inactivation  
- Methylation of TP53 promoters

Loss of heterozygosity at SSCP  
Loss of heterozygosity at Cts 6q32 and 6p21

Wistuba and Gazdar. Nature Reviews/Cancer 2004

Two pathways to GBC

Risk factors for intra-hepatic cholangiocarcinoma

Shaib, 2005

- Intra-hepatic cholangiocarcinoma
  - SEER between 1993 and 1999
  - 625 cases, 90 834 controls
  - Multivariate analysis
  - Several risk factors
    - Liver cirrhosis 27.2
    - Hepatitis C virus infection 6.1
    - HIV infection 5.9
    - Diabetes 2.3

Risk factors for bile duct carcinoma

- Primary sclerosing cholangitis
  - Progressive liver disease, associated with IBD
  - AP and GGT elevated, ERCP or MRCP for Dx
  - Cumulative risk for CCC 10-15%
  - Up to 36% CCC in explants before LTx
- Biliary malformation/Caroli Disease (5%-20%)
- Parasites: Clonorchis and Opisthorchis
- Secondary cholangitis/intraductal stones
- ?? Chronic inflammation
- ?? Transactivation of the EGF-R by bile

Growth Pattern

- Mass-forming
- Periductular-infiltrating
- Intraductal

Mass Forming - intrahepatic


Periductal-infiltrating


Intraductal papillary


Prognosis

- Ahmed et al, ASCO GI 2008 #135
  - OS longer in EHCC (6.0 vs. 3.7 months)
  - OS with surgery similar (13.6 vs. 13.6 months)
  - Surgery more likely in EHCC (26%) vs IHCC (9%)

- Beg et al, ASCO 2008 #15518
  - SEER database 1973-2004
  - OS for EHCC: 6 months vs. IHCC: 5 months

Survival of intraductal tumors much longer
  - > 2 years

Different patterns of recurrence

Jarnagin, 2003

- 177 patients potentially curative resection: 97 gallbladder, 80 hilar cholangiocarcinoma
  - Different median time to disease recurrence:
    - Gallbladder: 11.5 versus 20.3 months
    - Different type of recurrence:

<table>
<thead>
<tr>
<th>Local</th>
<th>Metastatic</th>
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<tbody>
<tr>
<td>Gallbladder</td>
<td>15%</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>59%</td>
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</table>

Carcinologic treatments
Gallbladder carcinoma

- Surgery with resection of segment IV of the liver
- Natural venous access from the gallbladder to the liver
- In case of incidental diagnosis of gallbladder a complementary resection of the liver + lymph node dissection is recommended

Adjuvant chemotherapy ???

- Takada, 2002
  - 508 patients: 139 bile duct, 140 gallbladder, 56 ampullomas
  - 5FU + MMC followed by oral 5FU versus control
  - 112 gallbladder eligible: 5-year survival 26% versus 14% (p = 0.0367)
  - Subgroup analysis… A lot of non eligible patients…

Intrahepatic bile duct cancer

Overall outcome intrahepatic CCC

- Resection

Survival (n=71)

Otto et al, 2007

Disease free survival

Otto et al, 2007
**Disease free survival**

Otto et al, 2007

**Central bile duct cancer (Klatskin Tumor)**

**Surgery of Klatskin tumor**

Otto, 2008

**Extrahepatic CCC – Surgery**

Miyazaki M 1999

- Resection Treatment of choice for ‘normal’
  - Klatskin tumors:
    - En Bloc resection
    - + portal vein resection
    - + lymph node dissection
  - Extrahepatic tumors:
    - + Pancreatoduodenectomy
- Resection yields dismal results in PSC
  - often multifocal CCC
  - 10% of pts with CCC have PSC

**Liver Transplantation**
Liver transplantation – Two periods

<table>
<thead>
<tr>
<th>Institution</th>
<th>Year</th>
<th>1y</th>
<th>3y</th>
<th>5y</th>
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<tbody>
<tr>
<td>European Transplant Registry</td>
<td>1997</td>
<td>80</td>
<td>60</td>
<td>50</td>
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<tr>
<td>King’s College, London, UK</td>
<td>1995</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Institute Hospital, Germany</td>
<td>1996</td>
<td>25</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>University of Pittsburgh, USA</td>
<td>1998</td>
<td>15</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Medical Center, Hamburg, Germany</td>
<td>1999</td>
<td>15</td>
<td>35</td>
<td>35</td>
</tr>
</tbody>
</table>

- 49 liver transplantations, 3 liver resections; 109 patients (109 LTX + LT with partial pancreatectomy).

Liver transplantation and adjuvant treatment

**Mayo Clinic experience**

- Rea, 2005
- 71 patients selected for transplantation
  - 38 underwent LT
    - Neoadjuvant therapy: RT 45 Gy, 5FU IV CI + brachytherapy 20–30 Gy, followed by 5FU or capecitabine
  - 26 resections
  - 28 unresectable disease

Liver transplant : 2nd period

**Criteria for LTx**

- Unresectable, perihilar
- Mass, radial diameter <3 cm, no cut off for longitudinal diameter
- If PSC, any ductal tumor <3 cm

Cholangiocarcinoma Treatment Protocol

- Results – September 2007
  - 148 patients
  - Irradiation + 5-FU
  - 123 staging operation
  - 90 liver transplantation
  - 12 receiving neoadjuvant Rx
    - 25 (20%) positive
    - 3 awaiting transplantation
    - 2 deaths
    - 3 transplant elsewhere
    - 63 deceased donor
    - 26 living donor
    - 1 domino donor

**Results – September 2007**

- 12 deaths, debilitation, or disease progression
  - 2 transplant elsewhere
  - 12 receiving neoadjuvant Rx
  - 25 (20%) positive
  - 3 awaiting transplantation
  - 2 deaths
  - 3 transplant elsewhere
  - 63 deceased donor
  - 26 living donor
  - 1 domino donor

Patient Survival After Transplantation

CCA Versus Other Diagnoses

- CCA (28)
- HCC (70)
- HCV (147)
- PSC (131)

**Patient Survival After Transplantation**

- CCA (28)
- HCC (70)
- HCV (147)
- PSC (131)
One problem of the medical treatment:
- Palliation of biliary obstruction

Palliative treatments

Methods = Plastic Stents
- Plastic stents => stent occlusion develops after 3-5 months
  - biliary obstruction and cholangitis
  - requires stent exchange

Due to a multifactorial process = deposition of a material containing bacterial biofilm, calcium bilirubinate and calcium palmitate crystals

Metal Stents
- Composed of either stainless steel or nitinol
- Delivered into bile duct while constrained by a sheath allowing insertion as a small circumference delivery system (7.5-10 French).
  - When the sheath is retracted, the wire mesh stent expand to a diameter up to 10 mm

Plastic vs Metal Stents?
5 comparative trials
- Longer patency of metal vs plastic stents 273 vs 126 days (Davids Lancet 1992;340:1488)
- 28 % reduction in ERC
- Survival duration did not differ
- Cost-effectiveness analysis = placement of a metal stent more economical than plastic stent only in patients with a survival > 4-6 months
- Identification of factors that reliably predict patient survival : multivariate analysis
  - Prat, Gut 1998 = tumor size > 3 cm (3.2 vs 6.6 months)
  - Kaassis, GIE 2003 = liver metastases (2.7 vs 5.7)

Malignant Hilar Obstruction
Bismuth-Corlette Classification

7/13/2009
Hilar Cholangiocarcinoma

Endoscopic management of malignant hilar obstruction of stage II to IV is controversial with respect to optimal types of stents and extent of drainage.

Drainage of 25% of the liver volume can achieve adequate palliation (Dowsett Gastroenterology 1989;96:1180).


2 Stents for Stage II

A = 1 lobe opacified same lobe drained

B = 2 lobes opacified and drained

C = 2 lobes opacified, 1 lobe drained

Partial drainage?

Guidelines for the Endoscopic Drainage

Distal cholangiocarcinomas
  - Plastic stents in patients with poor prognosis (large tumor, metastasis, poor general status)
  - Metal stents in the others

Hilar tumors
  - Evaluation with MRCP
  - Planning of optimal drainage
  - Limited opacification during ERC and insertion of the guidewire in preselected bile ducts

Photodynamic therapy

- Ablative Treatment for malignant/premalignant lesions
- Application of photosensitizing drug
- Irradiation with laser light (630 nm)
- Intracellular activation of photosensitizer
- Cellular injury
- additional effects: peritumoral thrombosis, immune resp.
Photodynamic therapy

- Clearly successful in several trials
- Excellent option for advanced unresectable ca.
- Available in few centers only
- Complex, time consuming procedure
- Suboptimal photosensitizer
- Suboptimal fibers
- Comparison with CT or RCT?

Glimelius, 1995
93 patients with pancreatic or biliary metastatic cancer
Improvement of survival and quality of life in the treated group (global analysis)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n patients</th>
<th>Survival</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>BSC</td>
<td>19</td>
<td>2.5 months</td>
<td></td>
</tr>
<tr>
<td>5FU-LV or ELF</td>
<td>18</td>
<td>6 months</td>
<td>NS</td>
</tr>
</tbody>
</table>

BSC vs FUFOL vs GEMOX in gallbladder

- Randomised monocentric study
- Main endpoint: overall survival
- Non resectable or metastatic gallbladder cancer
- ECOG 0-2, age 18-70 years (median age: 50)

<table>
<thead>
<tr>
<th></th>
<th>BSC</th>
<th>FUFOL</th>
<th>GEMOX</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>27</td>
<td>28</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>PFS (months)</td>
<td>2.8</td>
<td>3.5</td>
<td>8.5</td>
<td>0.001</td>
</tr>
<tr>
<td>SG (months)</td>
<td>4.5</td>
<td>4.6</td>
<td>9.3</td>
<td>0.019</td>
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</table>

Methodological problems?
Confirm efficacy of combination treatment

Metastatic biliary tract cancer

Monochemotherapy with old drugs: not very active!

<table>
<thead>
<tr>
<th>Drug</th>
<th>n patients</th>
<th>OR</th>
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<tbody>
<tr>
<td>5FU</td>
<td>70</td>
<td>14 %</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>49</td>
<td>20 %</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>13</td>
<td>8 %</td>
</tr>
<tr>
<td>Methyl-CCNU</td>
<td>17</td>
<td>6 %</td>
</tr>
<tr>
<td>Amsacrine</td>
<td>23</td>
<td>9 %</td>
</tr>
<tr>
<td>Streptozotocin</td>
<td>14</td>
<td>17 %</td>
</tr>
</tbody>
</table>

Metastatic biliary tract cancer: New drugs

- Irinotecan: Alberts 2002
  - 39 patients with gallbladder carcinoma
  - 125 mg/m² weekly for 4 weeks, two weeks of rest
  - ORR: 8%
- Tegafur: 16 patients: 0 response
- S1: 19 patients: ORR = 21%, OS = 8.3 months
- Paclitaxel: Jones, 1996
  - 15 patients: no response
- Docetaxel: Souglakos, 2001
  - 25 patients: ORR = 20%
Classical Combination – EORTC 40955
not very active

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>5FU</th>
<th>5FU + FA + P</th>
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<tbody>
<tr>
<td>n = 27</td>
<td>n = 26</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>PR</td>
<td>7%</td>
<td>15%</td>
</tr>
<tr>
<td>ORR [CI]</td>
<td>7.1% [1 - 30]</td>
<td>18.5% [8 - 35]</td>
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<tr>
<td>Early toxic death</td>
<td>0</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Median survival</td>
<td>Overall (months)</td>
<td>5.0 [4.0 - 7.4]</td>
</tr>
<tr>
<td>Progression free</td>
<td>3.3 [1.7 - 4.7]</td>
<td>3.3 [2.3 - 6.7]</td>
</tr>
</tbody>
</table>

Gemcitabine monotherapy

<table>
<thead>
<tr>
<th>Trial Schedule</th>
<th>Patients</th>
<th>ORR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
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<tbody>
<tr>
<td>Jacobsen, 2003 (A)</td>
<td>Gem, 5FU</td>
<td>27</td>
<td>33</td>
<td>4.4</td>
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<tr>
<td>Hsu, 2004</td>
<td>Gem, 5FU, LV</td>
<td>30</td>
<td>21</td>
<td>4.7</td>
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<tr>
<td>Alberts, 2005</td>
<td>Gem, 5FU</td>
<td>42</td>
<td>8.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Gellibert, 2005</td>
<td>Gem, FDR</td>
<td>11</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Jacobson, 2003 (A)</td>
<td>Gem, 5FU, LV</td>
<td>48</td>
<td>9.5</td>
<td>9.6</td>
</tr>
<tr>
<td>Knox, 2005</td>
<td>Gem, Cap</td>
<td>45</td>
<td>31</td>
<td>7.0</td>
</tr>
<tr>
<td>Cho, 2005</td>
<td>Gem, Cap</td>
<td>44</td>
<td>32</td>
<td>6.0</td>
</tr>
<tr>
<td>Bhargava, 2003</td>
<td>Gem, irinotecan</td>
<td>14</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>Korni, 2004 (Hi)</td>
<td>Gem, MMC</td>
<td>25</td>
<td>20</td>
<td>4.2</td>
</tr>
<tr>
<td>Kuhn, 2002</td>
<td>Gem, docetaxel</td>
<td>43</td>
<td>9</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Combination chemotherapy with Gemcitabine (excluding platinum analogs)

<table>
<thead>
<tr>
<th>Trial Schedule</th>
<th>Patients</th>
<th>ORR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knox, 2004</td>
<td>Gem, 5FU</td>
<td>27</td>
<td>33</td>
<td>5.3</td>
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<td>Munsel, 2003</td>
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<td>31</td>
<td>9.0</td>
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<td>Hsu, 2004</td>
<td>Gem, 5FU, LV</td>
<td>30</td>
<td>21</td>
<td>4.7</td>
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<td>Jacobsen, 2003 (A)</td>
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<td>Alberts, 2005</td>
<td>Gem, 5FU, LV</td>
<td>42</td>
<td>8.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Gellibert, 2005</td>
<td>Gem, FDR, Cap</td>
<td>52</td>
<td>10</td>
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<td>7.0</td>
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<tr>
<td>Cho, 2005</td>
<td>Gem, Cap</td>
<td>44</td>
<td>32</td>
<td>6.0</td>
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<tr>
<td>Bhargava, 2003</td>
<td>Gem, irinotecan</td>
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<td>14</td>
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<tr>
<td>Korni, 2004 (Hi)</td>
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<tr>
<td>Kuhn, 2002</td>
<td>Gem, docetaxel</td>
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Gemcitabine + platinum analogs

<table>
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<tr>
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<th>PFS (months)</th>
<th>OS (months)</th>
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<td>Knox, 2004</td>
<td>Gem, cisplatine</td>
<td>30</td>
<td>37</td>
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<tr>
<td>Hsu, 2004</td>
<td>Gem, cisplatine</td>
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<td>31</td>
<td>4.8</td>
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<tr>
<td>Jacobson, 2003 (A)</td>
<td>Gem, cisplatine</td>
<td>48</td>
<td>9.5</td>
<td>6.8</td>
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<td>Cho, 2005</td>
<td>Gem, Cap</td>
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<td>32</td>
<td>6.0</td>
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<td>Bhargava, 2003</td>
<td>Gem, irinotecan</td>
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<td>Gem, MMC</td>
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<td>20</td>
<td>4.2</td>
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<td>Gem, docetaxel</td>
<td>43</td>
<td>9</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Palliative chemotherapy:

Systematic review (1985-2005):

<table>
<thead>
<tr>
<th>TRIALS</th>
<th>Patients</th>
<th>ORR (%)</th>
<th>IC50 (%)</th>
<th>Range (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
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<tbody>
<tr>
<td>1</td>
<td>2137</td>
<td>23.3</td>
<td>21.5-25.2</td>
<td>0-89</td>
<td>4.1</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Taxanes, irinotecan : negative impact on ORR
Gemcitabine : ∗ (non significant) OR with 5FU (or CAP) (22% vs 17%) Platinum analogues : significant ∗ OR with 5FU (27% vs 17%) or GEM (42% vs 22%)

Promising results should be evaluated in randomized trials
Good option for standard care

Multicentric Gemox gallbladder : to be or not to be?

André, 2006
70 patients
− Cholangiocarinoma + gallbladder tumours
− Locally advanced and metastatic disease

Location | Gallbladder | Non gallb. | %RO | PFS | OS |
<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
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<tr>
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<td>25</td>
<td>35</td>
<td>4</td>
<td>1.8</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>35</td>
<td>3.8</td>
<td>11.2</td>
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</tr>
</tbody>
</table>
The same for Gem-Cap
Knox, 2006
- 23 Cholangiocarcinoma + 22 gallbladder tumours
- Locally advanced and metastatic disease

<table>
<thead>
<tr>
<th>Location</th>
<th>n</th>
<th>%RO</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallbladder</td>
<td>22</td>
<td>28%</td>
<td>4.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Non gallb.</td>
<td>23</td>
<td>34%</td>
<td>9.0</td>
<td>19</td>
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</table>

Completely different with Xelox
Nehls, ASCO 2006
- Xelox
  - 65 patients, median number of cycles = 5
  - Good tolerance

<table>
<thead>
<tr>
<th>Location</th>
<th>CR / PR</th>
<th>SD</th>
<th>Median OS</th>
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</thead>
<tbody>
<tr>
<td>Gallbladder (n=27)</td>
<td>4 / 23%</td>
<td>45%</td>
<td>12.8 m</td>
</tr>
<tr>
<td>Intra-hepatic CC (n=18)</td>
<td>0 / 0%</td>
<td>28%</td>
<td>5.8 m</td>
</tr>
<tr>
<td>Extra-hepatic CC (n=20)</td>
<td>5 / 20%</td>
<td>45%</td>
<td>12.8 m</td>
</tr>
</tbody>
</table>

**ABC-02 study schema**

**Results: activity**

**GEM vs GEMCIS - UK-ABC 02 trial**

**GEM vs GEMCIS UK-ABC 02**

Intermediate analysis of ABC 01 and 02
- 410 patients, median age 64 (23-85)
- LAD 25% / M+ 75%
- ECOG 0-1 87% / 2 13%
- Gallbladder 36%/ Biliary tree 59% / Ampulloma 5%

Comparable toxicity (Gr 3-4: 65.5 vs 64.2%)

<table>
<thead>
<tr>
<th></th>
<th>GEM</th>
<th>GEMCIS</th>
<th>HR (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>206</td>
<td>204</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS (months)</td>
<td>11.7</td>
<td>8.3</td>
<td>0.70 (0.54-0.89)</td>
<td>0.002</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>8.4</td>
<td>6.5</td>
<td>0.72 (0.57-0.90)</td>
<td>0.003</td>
</tr>
</tbody>
</table>
GEM vs GEMCIS UK-ABC 02

Overall survival

Gemmabine + cisplatin: new standard of care

Targeted therapies

Anti-angiogenic?

- Bevacizumab
  - Clark, ASCO 2007
    - Gemcitabine + oxaliplatin + bevacizumab
    - 19 patients, 10 biliary tract, 9 gallbladder
    - 3 PR, 5 stable disease
    - Low toxicity profile
    - No survival results

- Sorafenib ???, Elkhoueiry ASCO 2007
  - 36 patients
  - 400 mg x 2 / day
  - Leucoencephalitis 1 pt, perforation 1 pt, haemorrhag 1 pt
  - Median PFS: 2 months
  - Overall survival: 6 months
  - Non encouraging results

Targeted therapies

Anti-EGFR

Phase II study of Erlotinib in Patients With Advanced Biliary Cancers

<table>
<thead>
<tr>
<th>Phase II Study of Erlotinib in Patients With Advanced Biliary Cancers</th>
</tr>
</thead>
</table>
| Philip A. Pippin, Michelle R. McNeilly, Calvina Adams, Jarnen Flandre, Henry C. Pink, George Kim, 
  Ben C. Bonventre, Ron Pink, Joel Pluse, and Charles Elliott |
BINGO: international, multicenter, open-label, randomized phase 2 trial

- Gemcitabine 1000 mg/m² in 100 min (10 mg/m²/min) IV – D1
- Oxaliplatin 100 mg/m² in 120 min IV – D2 Every 2 weeks
- Gemcitabine 1000 mg/m² in 100 min (10 mg/m²/min) IV – D1
- Cetuximab 500 mg/m² in 150 min IV – D1 or D2 Every 2 weeks

Endpoints
- Primary: 4-month PFS rate (RECIST)
- Secondary:
  - Toxicity
  - ORR, DCR, resectability rate
  - PFS, OS
- Exploratory: identification of predictive biomarkers for efficacy
- Biological study (blood, tumor): EGFR pathway analyses
- Functional imaging study (PET)

Grade 3/4 toxicity

<table>
<thead>
<tr>
<th>Severe toxicity (% patients)</th>
<th>GEMOX (n=17)</th>
<th>GEMOX + cetuximab (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>76</td>
<td>67</td>
</tr>
<tr>
<td>Hematologic</td>
<td>43</td>
<td>39</td>
</tr>
<tr>
<td>Anemia</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia (febrile)</td>
<td>25 (0)</td>
<td>28 (6)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>31</td>
<td>6</td>
</tr>
<tr>
<td>Peripheral neuropathy b</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Rash / hypersensitivity</td>
<td>0</td>
<td>17</td>
</tr>
</tbody>
</table>

* NCIC-CTC v3.0, grade 3-4
* Modified Levits, grade 2-3

Efficacy

- 4-month PFS:
  - GEMOX (n=18): 44%
  - GEMOX + Cetuximab (n=18): 61%

Median follow-up: 5 months

Conclusion

- Medical treatment of biliary tract carcinoma remains difficult
- Jaundice should be treated and photodynamic therapy seems to be an improvement
- Gallbladder carcinoma and other cholangiocarcinomas are very different tumours
- Gemcitabine + cisplatin in a new CT standard
- Gemox + cetuximab: next step???
- Specific evaluation of new molecules should be done with stratification factors