Chemotherapy for pancreatic cancer
Is there a role for neoadjuvant therapy in resectable disease?

Dr Roopinder Gillmore
July 2017
Simple answer

No

Should there be?
## Pancreas cancer at presentation

<table>
<thead>
<tr>
<th>Status</th>
<th>Survival Rate</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>15–20%</td>
<td>22–28 months</td>
</tr>
<tr>
<td>Borderline / locally advanced</td>
<td>15–20%</td>
<td>9–15 months</td>
</tr>
<tr>
<td>Metastatic</td>
<td>60–70%</td>
<td>6–12 months</td>
</tr>
</tbody>
</table>
Pancreas management

- Does the patient have resectable disease?
  - Definitely not
  - Definitely
  - Borderline resectable
  - Locally advanced

MDT
Surgeons
Resectable disease

Three options:

Surgery followed by adjuvant treatment****

Neo–adjuvant treatment followed by surgery

Neo–adjuvant treatment, surgery followed by adjuvant treatment
### Results to date with adjuvant treatment

<table>
<thead>
<tr>
<th>Trial name</th>
<th>No. of patients</th>
<th>Treatment</th>
<th>5 year survival</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONKO 01</td>
<td>368</td>
<td>Observation</td>
<td>10.4%</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemcitabine</td>
<td>20.7%</td>
<td></td>
</tr>
<tr>
<td>ESPAC 3</td>
<td>1088</td>
<td>5-FU</td>
<td>16%</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemcitabine</td>
<td>17.5%</td>
<td></td>
</tr>
<tr>
<td>JASPAC-01</td>
<td>378</td>
<td>S-1</td>
<td>44%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemcitabine</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>ESPAC 4</td>
<td>722</td>
<td>GEMCAP</td>
<td>28.8%</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemcitabine</td>
<td>16.3%</td>
<td></td>
</tr>
</tbody>
</table>
Is it all about adjuvant treatment?

50% of patients recurred

25% of patients died within the first year

Data from Oettle et al (CONKO-1)
JAMA 2007 and 2013
## Ongoing adjuvant trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Estimated numbers</th>
<th>Experimental arm</th>
<th>Comparator</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITALIAN</td>
<td>310</td>
<td>FOLFOXIRI</td>
<td>Gem</td>
<td>DFS</td>
</tr>
<tr>
<td>PRODIGE 24</td>
<td>490</td>
<td>mFOLFIRINOX</td>
<td>Gem</td>
<td>DFS</td>
</tr>
<tr>
<td>APACT</td>
<td>800</td>
<td>Nab–P/Gem</td>
<td>Gem</td>
<td>DFS</td>
</tr>
<tr>
<td>RTOG 0848</td>
<td>950</td>
<td>GEM+Erl</td>
<td>GEM</td>
<td>OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GEM+/- Erl</td>
<td>GEM +/– Erl +/- CRT</td>
<td></td>
</tr>
</tbody>
</table>
Management of resectable cancers

- 2015 ESMO guidelines
  - A multi-disciplinary team is required
  - Patients who stand a good chance of having an R0 resection should have upfront surgery
  - Adjuvant treatment should be with Gem or 5–FU
  - No routine use of CRT outside of clinical trials
  - No mention of neoadjuvant treatment
Management of resectable cancers

- 2017 NCCN guidelines
  - A multi-disciplinary at a high volume centre
  - Patients who stand a good chance of having an R0 resection should have upfront surgery
  - Adjuvant treatment – clinical trials / chemotherapy alone / chemotherapy followed by CRT
  - For patients with tumours that are clearly resectable neo-adjuvant therapy is only recommended in the context of a clinical trial
Management of resectable cancers

- 2016 ASCO guidelines “potentially curable”
  - Pre-op treatment could be given as an alternative treatment for patients
    - Patients whose PS currently preclude surgery
    - Those with a Ca19–9 suggestive of disseminated disease
    - Locally advanced disease
  - Evidence quality low
    - Multiple single arm phase II trials
  - No particular treatment recommended
What might be the advantages of a neo–adjuvant approach?

- Tumour shrinkage and ? better chance of R0 resection
- Target micro–metastases
- Identify patients with rapid progression and poor “biology” who can be spared ineffective surgery
- Potentially start treatment earlier
Questions about which neoadjuvant treatment?

- Which treatment algorithm?
  - chemotherapy,
  - chemoradiotherapy,
  - chemotherapy followed by chemoradiotherapy?

- Which chemotherapy?
  - FOLFIRINOX
  - Nab–P/Gem

- Which duration?

- What are the endpoints?
  - Overall survival,
  - R0 resection rate
  - RECIST response
  - Pathologic response
Problems with previous trials

- Lack of control arm
- Small numbers of patients
- Often included borderline resectable patients
- Resectability criteria varied between institutes
- Retrospective studies
Current clinical trials

Different local treatment options
- Nab–P/Gem + Hypofractionated Image–Guided Intensity Modulated Radiotherapy (n=25 in < 3 years)
- FOLFIRINOX (6) and GEM–based IMRT pre–op
- CAP–based SBRT pre–op
- GEM–based CRT pre–op

Systemic treatments
- FOLFIRINOX (4) pre–op and then FOLFIRINOX (2)

Immunotherapy
- Cancer vaccine+low dose cyclophosphamide +/− Nivolumab pre op followed by adjuvant CRT and then cancer vaccine/ low dose cyclophosphamide +/− Nivolumab (n=50)
- Pembrolizumb + Paricalcitol+/− Nab–P/Gem pre–op(n=30)
- RO7009789(anti CD40) +/− Nab–P/Gem followed by surgery followed by Nab–P/Gem and RO7009789 (n=10)
Current standard is surgery when an R0 resection is thought to likely and then adjuvant treatment

- Japan S1 is the standard
- GEMCAP is probably the new standard elsewhere
- CRT in adjuvant setting is not standard
Take home messages

- Neo–adjuvant treatment is not routine practice

- ASCO guidelines
  - Poor PS / Very high Ca19–9 suggesting disseminated disease / Vascular contact

- Ongoing clinical trials – will there be a role for CRT / immunotherapy
Locally advanced pancreas cancer

- SCALOP 1 trial
  - activity, safety, and feasibility of both gemcitabine-based and capecitabine-based chemoradiotherapy after induction chemotherapy for patients with locally advanced pancreatic cancer
  - GEMCAP chemotherapy initially
  - 50.4Gy with either CAP or GEM
Primary objective
- 39 week PFS

Secondary objectives
- Toxicity, during and after treatment
- Quality of life questionnaires
- Overall survival
- Disease response
- Progression free survival
- Radiotherapy quality assurance
- Change over time of CA19–9
216 assessed for eligibility

102 excluded
  79 did not meet inclusion criteria
  19 declined to participate
  4 other reasons

114 registered

40 excluded
  15 progressed
  10 excluded by clinician (because of intolerance, surgery needed for complications, or weight loss)
  9 opted out
  5 died
  1 should not have been registered

74 randomly allocated

36 allocated to capecitabine group
38 allocated to gemcitabine group
Objective disease response 26 weeks post registration

<table>
<thead>
<tr>
<th></th>
<th>Cap group (n=35)</th>
<th>GEM group (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>6 (17%)</td>
<td>7 (19%)</td>
</tr>
<tr>
<td>SD</td>
<td>22 (63%)</td>
<td>24 (67%)</td>
</tr>
<tr>
<td>PD</td>
<td>5 (14%)</td>
<td>5 (14%)</td>
</tr>
</tbody>
</table>

Five patients (capecitabine group (n=2) and gemcitabine group (n=3) went on to have surgery. Histology were reported as ypT1N0 (n=1), ypT2N0 (n=1), and ypT3N0 (n=3); all had pathologically clear margins.
Patients who proceeded to be randomised to chemoradiotherapy (n=74) had a median overall survival of **14·6 months** (95% CI 13·0–15·8)

Patients who did not proceed to randomisation (n=40) had a median overall survival of **8·1 months** (95% CI 4·1–10·5)

Median overall survival was **15·2 months** (95% CI 13·9–19·2) in the capecitabine group

Median overall survival was **13·4 months** (95% CI 11·0–15·7) in the gemcitabine group
SCALOP 2 – stage 1

All patients get 3 cycles of GEM/Abx

Screened for CRT

Up to 6 patients treated with 1000mg bd nelfinavir + Cap CRT 830mg/m2 50.4Gy/28#

Depending on tolerability will increase to 1250mg bd nelfinavir or decrease to 750mg bd
All patients get 3 cycles of GEM/Abx

Screened for CRT / Cycle 4 GEM ABx

Arms A–D Treatment Break

Arm A nef 1250mg bd
50.4 Gy +cap+ nef

Arm C nef 1250mg bd
50.4 Gy +cap

60 Gy +cap+ nef

60 Gy +cap

Arm E – 2 more cycles GEM ABx
SCALOP 2 – primary objectives

- Does increasing the radiotherapy dosing schedule from 50.4 to 60Gy improve 12 month overall survival rate?

- Does the addition of nelfinavir to CRT improve the progression free survival in LAPC?
SCALOP 2 – secondary objectives

- To evaluate safety, OS and resection rates by adding nelfinavir to CRT

- To study the effect of increasing RT dose to PFS, resection rates and safety

- To assess resection rates and QoL with addition of CRT

- Objective disease response in each arm
ESPAC 5 f trial – Borderline

Randomisation

Arm A (n=40) Straight to surgery

Arm B (n=20) GEMCAP X 2 cycles

Arm C (n=20) FOLFIRINOX X 4 cycles

Arm D (n=20) CRT Cap 50.4Gy in 28#

rescan

And then surgery
ESPAC 5 – Primary objectives

- Recruitment rate
  - Number of centres that successfully engage in the study
  - Overall recruitment rate (aiming for 100 in 2 years)

- Resection rates
  - R1 and R0
  - Numbers explored
Acknowledgements

- HPB team
  - Surgeons
  - Oncology colleagues – Dr Grant Stewart
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  - Palliative care team
  - Dietician support – Andrea Davis

- Patients and families