Chemotherapy for Pancreatic Ductal Adenocarcinoma: How we got to now.

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Leeds Regional Pancreatic Cancer Study Day
Precision Chemotherapy

Neoadjuvant chemotherapy

Adjuvant chemotherapy

Palliative chemotherapy
Palliative chemotherapy in pancreatic cancer

Does it help?
Meta-analysis of 29 trials
(3,458 pts)

Median OS (months):
Chemotherapy – 6.3
BSC – 3.8

• Gemcitabine
• 10% objective response
• 30% Clinical benefit
• mOS – 6 months
FOLFIRINOX / IrOxMdG

FOLFIRINOX
Irinotecan / Oxaliplatin / 5FU

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<th>F</th>
<th>G</th>
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<tbody>
<tr>
<td>RR</td>
<td>27.6%</td>
<td>11%</td>
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<tr>
<td>mPFS</td>
<td>6.4</td>
<td>4.3</td>
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<td>mOS</td>
<td>11.1</td>
<td>7</td>
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Greater toxicity.
Patients ECOG 0/1 and < 76 years
60% required G-CSF
Dose reductions / interruptions
Gemcitabine / Nab-Paclitaxel

m-PACT
Gem v’s Gem/Nab-Paclitaxel
ECOG 0-2 (only 7% good PS-2)
No upper age limit

mOS – 6.7 v’s 8.5 months
Increased neurotoxicity
Increased lethargy

Nab-Paclitaxel as stromal modifier or gemcitabine enhancer? SEIGE trial

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<th>Time point</th>
<th>Survival rate, %</th>
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<tr>
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<td>nab-P + Gem (n = 431)</td>
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<tr>
<td>6 months</td>
<td>66</td>
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<tr>
<td>12 months</td>
<td>35</td>
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<td>24 months</td>
<td>10</td>
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<td>36 months</td>
<td>4</td>
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<td>40 months</td>
<td>3</td>
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<td>42 months</td>
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*Gem = gemcitabine; nab-P = nab-paclitaxel.
2nd line chemotherapy?

Oxaliplatin (after Gemcitabine)

CONKO-03 & PANCREOX trials
5FU/FA +/- Oxaliplatin after failure of 1st line Gemcitabine

CONKO-03 – 2.6 month improvement mOS but no change PFS
PANCREOX – no difference mPFS and detriment mOS

Liposomal Irinotecan (after Gemcitabine)

NAPOLI-1- Liposomal Irinotecan +/- 5FU/FA
1.9 month improvement in mOS. 20 – 25% 12 month survival but little difference between arms.
2\textsuperscript{nd} – line chemotherapy

- Gem-Abraxane post Folfirinox
- Single institute series
- Winnipeg – 4 wk improved PFS
- Pittsburg – mPFS 3m but 5.5m if at least SD to FOLFIRINOX

- Gemcitabine post Folfirinox
- Single institute series
- Marseilles – 11\% ORR
- 5\% ORR in patients progressing 1\textsuperscript{st} line
- Brazil – 10\% ORR.
- mPFS 1 - 2 months
Adjuvant chemotherapy

ESPAC-1 (5FU): Trend towards improved DFS/OS
CONKO-01 (Gem): Improved DFS & OS
ESPAC-3 (5FU vs Gem): Equivalence in DFS/OS
CONKO-05 (GemErlotinib vs Gem): no improvement in experimental arm

JASPAC-1: Gem vs S1 (oral fluoropyrimididine)
385 patients. DFS and OS significantly improved in S1 arm (44% vs 24% 5yr survival). ? applicable to UK/European population
Does adjuvant chemotherapy improve survival?

Disease-Free Survival

- Log-Rank $P < .001$

Overall Survival

- Log-Rank $P = .06$

**No. at Risk**

- No chemotherapy: 142, 89, 41, 18, 11, 7
- Chemotherapy: 147, 99, 56, 38, 22, 11
Which drug & combination best?

**ESPAC-3**

Overall survival

- Fluorouracil + folinic acid
- Gemcitabine

Log-rank $\chi^2 = 0.74; P = .39$; HR, 0.94 (95% CI; 0.81-1.08)

**ESPAC-4**

Overall survival

- Gemcitabine
- Gemcitabine plus capcitabine

Hazard ratio for death: 0.82 (95% CI, 0.68-0.98); stratified log-rank $p=0.012$

### Progression-free survival

Log-rank $\chi^2 = 0.40; P = .53$; HR, 0.96 (95% CI; 0.84-1.10)

### Number at risk

- Gemcitabine: 166
- Gemcitabine plus capcitabine: 164

### Median survival time

- Gemcitabine: 25.5 months
- Gemcitabine plus capcitabine: 28.0 months

### Overall survival

- Gemcitabine-positive: Median S(T) = 23.0 months
- Gemcitabine-negative: Median S(T) = 27.9 months
- Gemcitabine plus capcitabine-positive: Median S(T) = 22.7 months
- Gemcitabine plus capcitabine-negative: Median S(T) = 33.5 months

### Number at risk

- Gemcitabine-positive: 219
- Gemcitabine-negative: 167
- Gemcitabine plus capcitabine-positive: 221
- Gemcitabine plus capcitabine-negative: 143

### Time from randomisation (months)

- Median S(T) trend = 14.83, $p=0.0001$
PRODIGE 24 trial

- 493 patients randomized
- mFOLFIRINOX – v’s Gemcitabine: 24 weeks treatment
- Median 2.5 years follow up
- mDFS Gem 12.8m v’s mFOLFIRINOX 21.6m
- mOS Gem 35m v’s mFOLFIRINOX 54.4m
- Greater toxicity

- Manuscript not published so significant unanswered questions as yet.
Neo-adjuvant Chemotherapy

• No agreed definition of borderline resectable disease. No large clinical trials.
• Studies retrospective and small
• Neoadjuvant chemotherapy / CRT – feasible and tolerable
• ? Best results in operable but likely R1 disease rather than borderline operable?
• ESPAC-5 trial, NEPOFOX, NEONAX etc.
Other Issues

- Pre-surgical imaging: PET-PANC: Up front PET/CT changed management in 45% of cases over CT scan. MRI of liver

- Agreed pathological assessment criteria: Definitions of R0/R1 resection

- Neo-adjuvant LMWH FRAGEM, CONKO-04 – prophylactic anti-coagulation reduces incidence of VTE significantly

- Adjuvant chemotherapy after neoadjuvant chemotherapy / chemorad?
Precision medicine in PDAC

- POLO trial – olaparib in PDAC patients with BRCA mutation