Modern Oncological Management of Pancreatic Cancer

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Overview

- Things to consider at MDT
- Role of adjuvant chemotherapy in pancreatic cancer
- Management of locally advanced disease
- Management of metastatic disease
- Current clinical trials
Why is pancreatic cancer difficult to manage?

• Advanced disease at presentation
• Difficult surgical site
• Complicated by biliary obstruction and effects on nutrition
• Poor response to chemotherapy agents
Things to consider at MDT

- Performance status
- Patient wishes
- Liver function
- Comorbidities
- Clinical trials

Is there metastatic disease?

- No
  - Is the tumour surgically resectable?
    - Yes
      - Surgery
    - No
      - Chemotherapy/chemoradiotherapy
  - Yes
    - Palliative Chemotherapy vs best supportive care
Management of resectable disease
Management of resectable disease

- Surgery currently only curative treatment option
- Adjuvant chemotherapy increases progression free survival and reduces risk of recurrence
- Offered to all patients
- There has been some exciting progress in adjuvant treatment in recent years
Historically.....

Single agent chemotherapy

Gemcitabine has been standard of care

- CONKO-001 study (2007, 2013)
- 6 months vs observation
- 5 year overall survival 20.7% vs 10.4%
- 10 year overall survival 12.2% vs 7.7%
- Median overall survival 22.8 months
Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial

Prof John P Neoptolemos, MD, Prof Daniel H Palmer, PhD, Prof Paula Ghaneh, MD, Eftychia E Psarelli, MSc, Juan W Valle, MD, Christopher M Halloran, MD, Olusola Faluyi, MD, Derek A O'Reilly, MD, Prof David Cunningham, MD, Prof Jonathan Wadsley, MD, Suzanne Darby, MD, Prof Tim Meyer, MD, Roopinder Gillmore, MD, Alan Anthoney, MD, Pehr Lind, MD, Bengt Glimelius, MD, Stephen Falk, MD, Prof Jakob R Izbicki, MD, Gary William Middleton, MD, Sebastian

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ESPAC 4 trial

• Doublet chemotherapy
• Gemcitabine vs Gemcitabine + Capecitabine
• Median overall survival 25.5m vs 28m
  • HR 0.82 P=0.032
• Increase in grade 3-4 toxicity
  • Diarrhoea
  • Neutropenia
  • Hand and foot syndrome
Recommendations for adjuvant treatment

• Give people time to recover from surgery before starting adjuvant therapy and ensure they are well enough to tolerate all 6 cycles

• Offer adjuvant gemcitabine plus capecitabine to people who have had sufficient time to recover after pancreatic cancer resection

• Consider adjuvant gemcitabine for people who are not well enough to tolerate combination chemotherapy
Hot off the press!
Unicancer GI PRODIGE 24/CCTG PA.6 trial: A multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas.
PRODIGE 24/CCTG PA.6

• Triplet chemotherapy!
• Phase III randomised trial
• Comparing single agent gemcitabine vs FOLFIRINOX
  • 5-FU (leucovorin), Oxaliplatin, Irinotecan
  • 2 weekly for 6 months
• Median overall survival 54.4m vs 34.8m
• However associated with increased toxicity
  • Grade 3-4 toxicity 51.1% vs 75.5%
Management of Locally advanced disease
What are the aims of treatment in locally advanced disease?

• Can include chemotherapy and chemoradiotherapy
• Borderline resectable disease
  → To improve the chance of clear margins at resection
• Unresectable locally advanced disease
  → To provide local disease control
  • May achieve conversion to surgical resectability
    • Large meta-analysis = 33% (Gillen et al PLoS Med 2010)
  • Overall survival comparable to primary resection
• Control micrometastatic disease?
Recommendations for Neo-adjuvant treatment

• Only consider neoadjuvant therapy for people with borderline resectable pancreatic cancer as part of a clinical trial
• Only consider neoadjuvant therapy for people with resectable pancreatic cancer as part of a clinical trial
Neoadjuvant treatment of borderline resectable and non-resectable pancreatic cancer
Heinemann V, Haas M, Boeck S. Annals of Oncology 0: 1–8, 2013
Neoadjuvant Chemotherapy options

Gemcitabine
- Response Rate 5-12%

Gemcitabine + Capecitabine
  (Cunningham et al JCO 2009)
- Response Rate 19%

Gemcitabine + Abraxane (nab-paclitaxel)
  (Van Hoff et al NEJM 2013)
- Response Rate 23%

FOLFIRINOX
- 5-fu, irinotecan, oxaliplatin
  (Conroy et al NEJM 2011)
- Response rate 32%
Chemoradiotherapy
Chemoradiotherapy

Previously

- Simple fields with infusional 5-FU
- Over 6 weeks (2 week break)
Radiotherapy now
- Conformal or IMRT – Image modulated radiotherapy
- IGRT – Image guided radiotherapy
- 50.4-60Gy in 28-30# treating 5 days per week
- Concurrently with gemcitabine or capecitabine
Recommendations for locally advanced disease

• Offer combination chemotherapy to people with locally advanced disease who are well enough to tolerate it
• Consider Gemcitabine alone for people not well enough to tolerate combination chemotherapy
• When using chemoradiotherapy, consider capecitabine as the radiosensitiser
Current Clinical trials
ESPAC-5F

Phase 2 feasibility study

Borderline resectable

4 arm randomised study

• Arm A = Surgery alone
• Arm B = Gem Cap (8 weeks)
• Arm C = FOLFIRINOX (8 weeks)
• Arm D = ChemoRt
  ◦ 50.4Gy in 28# + Capecitabine
SCALOP2

Non-resectable disease

Gemcitabine + Abraxane induction chemotherapy (12 weeks)

If response/stable disease on CT randomised to:

- Continue chemotherapy
- ChemoRT
  - 2x2 design
  - 50.4Gy vs 60Gy
  - Capecitabine vs Capecitabine + Nelfinavir
- Surgery if resectable on completion
Nelfinavir

Started as an anti-retroviral drug

Will it improve tumour response to radiotherapy?
- Improves perfusion and normalises tissue vasculature
- Increases vascular flow
- Increases tumour cell line sensitivity to chemotherapy induced apoptosis
- Radio sensitisation
- Reduces hypoxia
Management of Metastatic Disease
## Chemotherapy options

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<th>2&lt;sup&gt;ND&lt;/sup&gt; LINE</th>
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<tbody>
<tr>
<td>Gemcitabine</td>
<td>FOLFOX</td>
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<td>Gemcitabine + Abraxane</td>
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<tr>
<td></td>
<td>FOLFIRINOX</td>
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<td>Gemcitabine</td>
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Palliative chemotherapy

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<tr>
<th>FOLFIRINOX</th>
<th>GEMCITABINE</th>
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<tr>
<td>5 FU, oxaliplatin, irinotecan</td>
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<tr>
<td>Performance Status 0-1</td>
<td>Performance Status 2</td>
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<tr>
<td>Need bilirubin &lt; 1.5 x ULN</td>
<td>Need bilirubin &lt; 2-3 x ULN</td>
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<tr>
<td>Response rate 30%</td>
<td>Response rate 7-9%</td>
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<tr>
<td>Median overall survival 11m</td>
<td>Median overall survival 7m</td>
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# Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine

Daniel D. Von Hoff, M.D., Thomas Ervin, M.D., Francis P. Arena, M.D., E. Gabriela Chiorean, M.D., Jeffrey Infante, M.D., Malcolm Moore, M.D., Thomas Seay, M.D., Sergei A. Tjulandin, M.D., Wen Wee Ma, M.D., Mansoor N. Saleh, M.D., Marion Harris, M.D., Michele Reni, M.D., et al.

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<td>1370 Citing Articles</td>
<td>October 31, 2013</td>
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DOI: 10.1056/NEJMoa1304369
Gemcitabine + Abraxane (Nab-Paclitaxel)

- Nab - Nanoparticle albumin bound
- Response rate 23%
- Median overall survival 8.5 months

- Associated with increased toxicity compared with single agent gemcitabine
  - Peripheral neuropathy
  - Neutropenia and infections
  - Diarrhoea
- Some long term responders with survival longer than 3 years
A. Overall Survival

Hazard ratio for death, 0.72 (95% CI, 0.62–0.83)
P<0.001 by stratified log-rank test

No. at Risk
- nab-Paclitaxel–Gemcitabine: 431, 357, 269, 169, 108, 67, 40, 27, 16, 9, 4, 1, 1, 1, 0
- Gemcitabine: 430, 340, 220, 124, 69, 40, 26, 15, 7, 3, 1, 0, 0, 0
Recommendations for Metastatic disease

1st line treatment

• Offer FOLFIRINOX if ETOG performance status PS 0-1
• Consider Gemcitabine combination therapy for patients not well enough to tolerate FOLFIRINOX
• Nab-paclitaxel (abraxane) is recommended in combination with Gemcitabine in untreated pancreatic cancer if they are unsuitable for other combination chemotherapies and would otherwise be offered single agent gemcitabine
Recommendations for Metastatic disease

2\textsuperscript{nd} line treatment

• Consider \textbf{oxaliplatin} based chemotherapy in patients who have not had in the 1\textsuperscript{st} line setting

• Consider \textbf{gemcitabine} for patients who have progressed on 1\textsuperscript{st} line FOLFIRINOX

• Pegylated liposomal irinotecan alongside 5-FU is not recommended for treatment of patients who have progressed after 1\textsuperscript{st} line gemcitabine based chemotherapy
Current Clinical trials
Halo 301

Double blind Phase 3 trial for patients with metastatic disease

Combining PEGPH20 with Gemcitabine and Abraxane
- Vs Gemcitabine and Abraxane + placebo
- Randomised on 2:1 basis

PEGPH20
- PEGylated Recombinant Human Hyaluronidase

Patients must be proven to be ‘Hyaluronan High Pancreatic Ductal Adenocarcinoma’ on biopsy
- ‘HA-High’

Aim of the drug is to break down the hyaluronan found within the tumour to enable chemotherapy to reach tumour cells more effectively
Take home messages

There is some exciting progress in adjuvant treatment of pancreatic cancer

Even in the setting of locally advanced or metastatic disease some patients have a good and durable response to treatment leading to an improvement in quality of life and overall survival

There are a number of clinical trials currently recruiting in local centres
Thankyou

Any questions?
References


10. SCOLAP 2 - https://www.clinicaltrials.gov/ct2/show/NCT02024009

... HALO 301 - http://halo301.com/