Clinical case discussion:
Locally advanced and metastatic pancreatic cancer

Thomas Seufferlein
Department of Internal Medicine I
and Comprehensive Cancer Center Ulm
Ulm University, Germany
Locally advanced PDAC

1) Therapeutic options
2) Biomarkers for the efficacy of gemcitabine
3) Role of chemoradiation in LA-PDAC
4) Markers for the efficacy of chemoradiation?
Clinical case discussion: Locally advanced and metastatic pancreatic cancer

- Two interesting cases with LA-PDAC
  - First case: Prolonged survival on gemcitabine
  - Second case: Chemoradiation -> no residual tumor -> peritoneal carcinosis
Clinical case discussion:
Locally advanced and metastatic pancreatic cancer

Which chemotherapeutic regimen would you have used in the first case?

1) Gemcitabine
2) FOLFIRINOX
3) Gemcitabine plus nab-paclitaxel
4) Gemcitabine plus other agent (capecitabine, cisplatin, oxaliplatin)
5) Chemoradiation, e.g. with gemcitabine
Clinical case discussion: Locally advanced and metastatic pancreatic cancer

• Goals in LA-PDAC

1) Prolong survival
2) Achieve secondary resectability
   possible in ≈ 15-30% of patients with LA-PDAC

ESMO Guideline: In case of larger tumors and/or tumors with vessel encasement that are borderline resectable or technically non resectable, *patients may benefit from neoadjuvant chemotherapy or chemoradiotherapy to achieve downsizing of the tumor and may convert the tumor to become resectable.*

Seufferlein , ... Van Cutsem et al., Annals Oncol 2012
ESMO guideline:
In the case of borderline resectable patients, a neoadjuvant chemotherapy approach may be able to identify a subgroup of patients *unlikely to benefit from surgical resection*. Patients who develop metastases during neoadjuvant chemotherapy or who progress locally are not candidates for secondary surgery.
What treatment?
Significance of pathologic response to preoperative therapy in pancreatic cancer

Chun et al., Ann Surg Oncol 2011
## Comparison of various chemotherapy regimens

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine</th>
<th>Gem + Erlotinib</th>
<th>Gem + Cape</th>
<th>Gem + Cisplatin</th>
<th>Gem + Oxaliplatin</th>
<th>Gem + nab Paclitaxel</th>
<th>FOLFIRINOX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RR %</strong></td>
<td>7-17.3</td>
<td>8.6</td>
<td><strong>19.1</strong></td>
<td>12.9</td>
<td><strong>26.8</strong></td>
<td>23</td>
<td>31.6</td>
</tr>
<tr>
<td><strong>mPFS, mo</strong></td>
<td>2.33-3.9</td>
<td>3.75 HR 0.77</td>
<td>5.3 HR 0.78</td>
<td>3.8 HR 0.97</td>
<td>5.8 HR 1.287</td>
<td>5.5 HR 0.69</td>
<td>6.4 HR 0.47</td>
</tr>
<tr>
<td><strong>mOS, mo</strong></td>
<td>5.65-10**</td>
<td>6.37 (10.5*) HR 0.86</td>
<td>7.1 HR 1.10</td>
<td>7.2 HR 1.18</td>
<td>8.8 HR 1.18</td>
<td>8.5 HR 0.72</td>
<td>11.1 HR 0.57</td>
</tr>
</tbody>
</table>

**ESMO guideline:**
In patients with unresectable tumors, GEM treatment in conventional dosing (1000 mg/m^2 over 30 min) is recommended.

*in case of grade 2 rash
**locally advanced tumors

Burris 1997; Louvet 2005; Moore 2007; Colucci 2010; Cunningham, 2009; Conroy 2011; von Hoff 2013
Intensified chemotherapy: Triple drug combination FOLFIRINOX

Prodige 4 - ACCORD 11 trial design

Randomize:
- Metastatic pancreatic cancer
  - Folfirinox
  - Gemcitabine

Inclusion Criteria

- Histologically/cytologically confirmed pancreatic adenocarcinoma
- ECOG performance status of 0 or 1
- Measurable metastases
- No prior cytotoxic chemotherapy
- No prior abdominal radiotherapy
- Age 18-75 years
- Adequate hematopoietic, hepatic and renal function
- Bilirubin < 1.5 UNL
- No unstable angina or myocardial infarction within 12 months before entry
- Written informed consent

<table>
<thead>
<tr>
<th>Folfirinox</th>
<th>Gemcitabine</th>
<th>p</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=171</td>
<td>N=171</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.1 mo.</td>
<td>6.8 mo.</td>
<td>&lt;0.0001</td>
<td>0.57</td>
</tr>
<tr>
<td>[CI 95%]</td>
<td>[5.5 - 7.6]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-yr. survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48.4%</td>
<td>20.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-mo. survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.6%</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conroy et al., NEJM 2011
Pilot trial: Neoadjuvant FOLFIRINOX in locally advanced PDAC

Hosein, ASCO GI 2011
MPACT: Nab-paclitaxel plus Gemcitabine in metastatic PDAC; Von Hoff et al., ASCO 2013, #4005

- Patients with KPS 70% and >75y included!
- Normal bilirubin!
Neoadjuvant nab-paclitaxel plus gemcitabine in locally advanced PDAC; MacKenzie, ASCO 2013

In 30% of the patients substantial tumor regression

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N = 21&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0 resection, n (%)</td>
<td>20 (95)</td>
</tr>
<tr>
<td>R1 resection, n (%)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Pancreaticoduodenectomy, n (%)</td>
<td>13 (62)</td>
</tr>
<tr>
<td>Distal pancreatectomy, n (%)</td>
<td>8 (38)</td>
</tr>
<tr>
<td>Tumor destruction, n (%)</td>
<td></td>
</tr>
<tr>
<td>Grade 1 (1% - 9%)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Grade 2 (10% - 90%)</td>
<td>10 (48)</td>
</tr>
<tr>
<td>Grade 3 (&gt; 90%)</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Grade 4 (absence of viable tumor cells)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Twenty-one of 25 patients underwent surgical resection. In 4 patients, surgery was not performed: metastasis at preoperation staging (n = 1), metastasis at surgery (n = 1), preoperative death (n = 1), patient declined surgery (n = 1).
SPARC – a matricellular protein and survival after resection of PDAC

No. at risk
Tumor-/Stroma  49  37  21  10  7
Tumor-/+Stroma  50  35  15  9  7
Tumor+/-Stroma  156  74  17  7  3
Tumor+/+Stroma  44  24  9  5  4
LA-PDAC: Therapeutic options

- Gemcitabine: still standard
- FOLFIRINOX and gemcitabine plus nab-paclitaxel: interesting options
  - Higher toxicity
  - Higher chance of tumor regression
  - Higher chance of secondary resectability?
  - Who is eligible for this treatment?
  - > prospective trials warranted – and under way!
Locally advanced PDAC

In the first case presented, the patient benefitted from Gemcitabine treatment.

Advantage: Low toxicity

Do we have predictive biomarkers for the efficacy of gemcitabine?
hENT1 and Gemcitabine efficacy
hENT1 expression and efficacy of Gemcitabine and 5-FU

- RTOG9704
- hENT1 is the major gemcitabine transporter in PDAC
- hENT1 protein expression is associated with increased overall survival in PDAC patients receiving gemcitabine, but not in those receiving 5-FU

Farrell Gastroenterology 2009
hENT1 and Gemcitabine in the adjuvant treatment of PDAC – Neoptolemos ASCO 2013; #4006

- Retrospective analysis of data from the ESPAC1 and -3 trial.
Phase II: CO-101 vs. Gemcitabine in metastatic PDAC – prospective evaluation of hENT1 expression and clinical outcome
Poplin, ASCO 2013, #4007;

- N=232
- CO-101: Lipid conjugated gemcitabine
- Crosses plasma membrane independently of hENTs

Anti-hENT1 SP120 antibody/ Ventana
CO-101 vs. Gemcitabine in mPDAC overall survival

OS whole group

OS in hENT low

OS high hENT1 (>80% of tumor cells)
hENT1 and Gemcitabine

- Adjuvant: Significant correlation between hENT1 expression in IHC and use of Gemcitabine (p<0.0002) using a novel anti-hENT1 antibody
- Metastatic setting: No difference between CO 101 and gemcitabine
- Efficacy of CO 101?
- Comparison of both antibodies?!
Clinical case discussion:
Locally advanced and metastatic pancreatic cancer

- In the second case chemoradiotherapy was used.
- Should we use a local treatment for a systemic disease?
- If so, how?
PDAC is in many cases a metastatic disease at the time of diagnosis

- PDAC grows exponentially
- Cells with high metastatic potential are generated during tumor expansion (1 per 1 million tumor cells)
- Also small tumors can exhibit metastases prior to surgery

How can we define who has a more local disease?
Chemotherapy, radiotherapy or radiochemotherapy in locally advanced PDAC?

Huguet et al., JCO 2009

<table>
<thead>
<tr>
<th>Study</th>
<th>Database</th>
<th>Included Data</th>
<th>Main End Point</th>
<th>Secondary End Points</th>
<th>Included Trials</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemoradiotherapy vs radiotherapy</td>
<td>MEDLINE</td>
<td>Published data</td>
<td>Overall survival</td>
<td>Time to progression, survival duration, overall response rate, toxicities</td>
<td>2 randomized trials</td>
<td>HR = 0.69; 95% CI, 0.51 to 0.94</td>
</tr>
<tr>
<td>Sultana et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yip et al.</td>
<td>MEDLINE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT vs. RT: HR 0.69 (95% CI: 0.51-0.94)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Database</th>
<th>Included Data</th>
<th>Main End Point</th>
<th>Secondary End Points</th>
<th>Included Trials</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemoradiotherapy vs chemotherapy</td>
<td>MEDLINE</td>
<td>Published data</td>
<td>Overall survival</td>
<td>Time to progression; survival duration; overall response trials</td>
<td>4 randomized trials</td>
<td>HR = 0.79; 95% CI, 0.32 to 1.95</td>
</tr>
<tr>
<td>Sultana et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yip et al.</td>
<td>MEDLINE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT vs. CT: HR 0.79 (95% CI: 0.32-1.95)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: HR, hazard ratio.
Phase III: Gemcitabine vs. Gemcitabine + RT in LA-PDAC

Recruitment stopped after 74/316 patients (poor recruitment)

Gem 1000 mg/m^2/w
50.4 Gy + Gem 600 mg/m^2/w -> Gem x 5 cycles

- Grade 4 toxicity from 5.7 to 41.2%
- No difference in QoL
- Distant metastases:
  - 14% (G) vs. 23% (G+RT)

mOS 11.1 vs. 9.2 months

Loehrer et al., JCO 2011
Radiochemotherapy (RCT) in LA PDAC

Retrospective analysis

181 patients with LA pancreatic adenocarcinoma

- Evaluation after 3 months of initial chemotherapy
  - 53 patients (29.3%) with disease progression
  - 128 patients (70.3%) without disease progression

72 patients treated with CRT (group A)
56 patients treated with CT alone (group B)

RCT may be beneficial in patients with LA PDAC and at least stable disease under initial chemotherapy

Huguet JCO 2007
LA-PDAC:
Gemcitabine-> CRT – LAP07 trial

Quality assurance of radiotherapy!

Hammel ; ASCO 2013, LBA 4003
LA PDAC:
Gemcitabine-> RCT – LAP07 trial

Hammel ; ASCO 2013, LBA 4003
Locally advanced PDAC: Gemcitabine-> CRT – LAP07 trial

• RCT was not superior to CT in this setting (4 months CT prior to RCT)
• RCT was well controlled in the trial
• Was capecitabine the right choice for RCT? Gemcitabine better?
If RCT – which regimen?

- RCT with Cape less toxic
- Comparable effectiveness to Gem

Mukherjee, ASCO GI 2013
ESMO Guidelines

• Trials comparing chemoradiation with chemotherapy alone reported contradictory results.
• The optimal neoadjuvant strategy is still under investigation and there is so far no standard protocol for neoadjuvant chemoradiotherapy in Europe.

Seufferlein, ... Van Cutsem et al., Annals Oncology 2012
Clinical case discussion:
Locally advanced and metastatic pancreatic cancer

• „Neoadjuvant treatment“ will allow downsizing and secondary resection in up to 30% of patients with „boderline resectable“ LA-PDAC.
• The best chemotherapeutic regimen has still to be established.
• Novel combinations such as FOLFIRINOX and nab-paclitaxel plus gemcitabine are promising in early phases.
• Gemcitabine remains an option in patients with LA-PDAC
• The role of radiochemotherapy in LA-PDAC is still unclear and subject to further clinical trials. Some patients benefit, but currently we cannot predict who.