Strategies to improve the outcome of locally advanced pancreatic cancer patients

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Disclosures C. Louvet

Celgene
Roche
Nucana
Role of radiation therapy in locally advanced pancreatic cancer highly debated

- **Local control** remains an important issue
  - → chemoradiation (CRT)

- High rate of **distant metastasis**
  - → chemotherapy
Frontline CRT versus chemotherapy in LAPC

→ **Contradictory** results
Induction CT followed by CRT in LAPC

CRT after 3 months of induction chemotherapy

Huguet F et al, J Clin Oncol 2007

→ Promising strategy
<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>N pts</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>1-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huguet</td>
<td>CT</td>
<td>181</td>
<td>7.4</td>
<td>11.7</td>
<td>47.5</td>
</tr>
<tr>
<td>(retrosp)</td>
<td>CT then CRT</td>
<td></td>
<td>10.8</td>
<td>15</td>
<td>65.3</td>
</tr>
<tr>
<td>Krishnan</td>
<td>CRT</td>
<td>323</td>
<td>4.2</td>
<td>8.5</td>
<td>-</td>
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<tr>
<td>(retrosp)</td>
<td>CT then CRT</td>
<td></td>
<td>6.4</td>
<td>11.9</td>
<td></td>
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<tr>
<td>Brunner</td>
<td>CRT</td>
<td>172</td>
<td>-</td>
<td>7.6</td>
<td>21</td>
</tr>
<tr>
<td>(retrosp)</td>
<td>CRT then CT</td>
<td></td>
<td></td>
<td>13.5</td>
<td>65</td>
</tr>
<tr>
<td>Ko</td>
<td>CT then CRT</td>
<td>25</td>
<td>10.5</td>
<td>13.5</td>
<td>62</td>
</tr>
<tr>
<td>(phase 2)</td>
<td>(32% PD after CT)</td>
<td></td>
<td>(12.7)</td>
<td>(17)</td>
<td></td>
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<tr>
<td>Schneider</td>
<td>CT - CRT - CT</td>
<td>18</td>
<td>-</td>
<td>12.8</td>
<td>-</td>
</tr>
<tr>
<td>(phase 2)</td>
<td></td>
<td></td>
<td></td>
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</table>
SCALOP (phase 2)

74 pts

R

CRT 50.4 Gy with capecitabine

15.2 months

p = 0.01

CRT 50.4 Gy with gemcitabine

13.4 months

Concurrent chemotherapy?

Mukherjee S et al. Lancet Oncol 2013
1 month = Gemcitabine (1000 mg/m²)/wkX3

Erlotinib : 100 mg/d with gem 150 mg/d as single agent

Secondary surgery allowed at any time
Objectives of LAP07 study

• **Primary objective:** to assess whether administering CRT increases overall survival in patients whose tumor is controlled after 4 months of induction chemotherapy

• **Secondary objectives:**
  - Role of erlotinib
  - Progression free survival (PFS)
  - Tolerance
  - Impact of Radiation Therapy Quality Assessment (RTQA)
  - Predictive molecular markers, circulating tumor cells

Assessed for eligibility (n= 449)

1st Randomization Intent-to-treat principle (n= 442)

Gemcitabine (n= 223)

Gemcitabine + erlotinib (n= 219)

Excluded (n= 7)

Excluded (39.1%) (n= 173)
111 progressive disease
15 toxicity
11 delay
11 patients' will
16 investigator decision
6 intercurrent disease
3 surgery

2nd Randomization Intent-to-treat principle (n= 269)

Chemotherapy (n= 136)

Chemoradiotherapy (n= 133)
Overall Survival

Chemotherapy: n=136  n.events=112  median time=16.5
Chemoradiotherapy: n=133  n.events=109  median time=15.2
Log-rank p=0.829
HR - 95%CI: 1.03 [0.79-1.34]
Site of progression

- **R2 patients:**
  
  236/269 patients (88%) with tumor progression
  93 with local progression only (39.4%)
  122 with metastatic (± local) progression (51.7%)
  21 unknown (8.9%)
Progression Free Survival

- Chemotherapy: n=136, n.events=125, median time=8.4 months
- Chemoradiotherapy: n=133, n.events=122, median time=9.9 months
- Log-rank p=0.055
- HR - 95%CI: 0.78 [0.61-1.01]
Treatment Free Survival

Chemotherapy:  n=136  n.events=121  median time=3.7
Chemoradiotherapy:  n=133  n.events=112  median time=6.1
Log-rank p=0.017

<table>
<thead>
<tr>
<th>Time since the last LAP protocol treatment (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
<td>1.0</td>
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N at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>75</th>
<th>37</th>
<th>27</th>
<th>17</th>
<th>10</th>
<th>6</th>
<th>6</th>
<th>2</th>
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<tbody>
<tr>
<td>Chemotherapy</td>
<td>136</td>
<td>75</td>
<td>37</td>
<td>27</td>
<td>17</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Chemoradiotherapy</td>
<td>133</td>
<td>89</td>
<td>60</td>
<td>37</td>
<td>24</td>
<td>11</td>
<td>8</td>
<td>6</td>
<td>5</td>
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</tbody>
</table>
LAP07 Conclusions

• LAP07 prospectively confirmed the value of frontline chemotherapy in LAPC patients

• Overall survival in CRT arm is not superior to chemotherapy arm in LAPC patients with tumor controlled after 4 months of chemotherapy

• However, trend for PFS in favor of CRT

• In the CRT arm, patients had a significantly less local tumor progression and a longer period without chemotherapy
Strategies to improve the outcome of LAPC patients

1– Improvement of systemic chemotherapy
FOLFIRINOX  Overall Survival

Stratified Log-rank test, p<0.0001
HR=0.57 : 95%CI [0.45-0.73]

Number at risk
- Gemcitabine: 171 134 89 48 28 14 7 6 3 3 2 2 2
- Folfirinox: 171 146 116 81 62 34 20 13 9 5 3 2 2

Months

- Folfirinox
- Gemcitabine

Probability
171 146 116 81 62 34 20 13 9 5 3 2 2
Nab-P + Gem  Overall Survival

OS, months

<table>
<thead>
<tr>
<th>Events/N (%)</th>
<th>Median (95% CI)</th>
<th>75th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>333/431 (77)</td>
<td>8.5 (7.89–9.53)</td>
<td>14.8</td>
</tr>
<tr>
<td>359/430 (83)</td>
<td>6.7 (6.01–7.23)</td>
<td>11.4</td>
</tr>
</tbody>
</table>

HR = 0.72  
95% CI (0.617–0.835)  
P = 0.000015

Pts at Risk

\[\begin{array}{cccccccccccc}
\text{nab-P + Gem:} & 431 & 357 & 269 & 169 & 108 & 67 & 40 & 27 & 16 & 9 & 4 & 1 & 1 & 0 \\
\text{Gem:} & 430 & 340 & 220 & 124 & 69 & 40 & 26 & 15 & 7 & 3 & 1 & 0 & 0 & 0 \\
\end{array}\]

Von Hoff et al., ASCO GI 2013 LBA148
Nab-Paclitacel + FOLFOX

Phase I study (Saffran, ASCO 2014)
Very promising results
Strategies to improve the outcome of LAPC patients

1– Improvement of systemic chemotherapy

2- Personalized medicine
Strategies to improve the outcome of LAPC patients

1– Improvement of systemic chemotherapy

2- Personalized medicine
   
   Prognostic factor analysis from LAP07
   
   Biomarkers and targeted drugs
SPARC
Gemcitabine: mechanisms of action

- Intracellular uptake
  - hENT1
  - hCNT 3

- Activation
  - dCK
    - Nucleoside Phosphate Kinase

- Inactivation
  - CDA
  - DCTD
  - 5’-NT

- Action
  - Inhibition DNA synthesis
hENT1

« Positive » trials

- RTOG (adjuvant, retrospective)
- French-Belgium series (adjuvant, retrospective)
- ESPAC 1&3 (adjuvant, retrospective)

Negative trials

- Clovis C01-101 (metastatic, prospective)
- ECOG (metastatic, retrospective)
- CONKO-01 (adjuvant, retrospective)
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Prognostic</th>
<th>Predictive</th>
<th>Current clinical impact</th>
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<tr>
<td>CA 19.9</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CTC / cDNA</td>
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<td>No</td>
<td>No</td>
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<tr>
<td>miRNAs</td>
<td>Yes</td>
<td>No</td>
<td>? (Anti-sens)</td>
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<tr>
<td>Proteomic / LAMC</td>
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<td>No</td>
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<td>Genomic profiles</td>
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<td>No</td>
<td>No</td>
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<tr>
<td>hENT1</td>
<td>No</td>
<td>Yes (Gem)</td>
<td>Likely (Gem)</td>
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<tr>
<td>dCK</td>
<td>No</td>
<td>Yes (Gem)</td>
<td>Likely (Gem)</td>
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<tr>
<td>CDA</td>
<td>No</td>
<td>Yes (Gem toxicity)</td>
<td>Likely (Gem)</td>
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<tr>
<td>SPARC</td>
<td>Yes</td>
<td>?</td>
<td>? (Abraxane)</td>
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<td>Histone modifications</td>
<td>Yes</td>
<td>?</td>
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<td>Hedgehog</td>
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<td>?</td>
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<tr>
<td>CXCR4</td>
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<td>?</td>
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<td>HER2</td>
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<tr>
<td>IGFR</td>
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</table>
Strategies to improve the outcome of LAPC patients

1– Improvement of systemic chemotherapy

2- Personalized medicine

3- Improvement of chemoradiation
Strategies to improve the outcome of LAPC patients

1– Improvement of systemic chemotherapy

2- Personalized medicine

3- Improvement of chemoradiation
   - Dose radiation
   - Target volume
   - IMRT, gating
   - Concurrent radiosensitizer
Strategies to improve the outcome of LAPC patients

1- Improvement of systemic chemotherapy

2- Personalized medicine

3- Improvement of chemoradiation

4- Improvement in strategy and techniques
Strategies to improve the outcome of LAPC patients

1- Improvement of systemic chemotherapy

2- Personalized medicine

3- Improvement of chemoradiation

4- Improvement in strategy and techniques
   
   Increased time of systemic CT before CTRT ?
   Place of secondary surgery after systemic CT and CTRT ?
   Place of HIFU ?
RTOG 1201 will help address the question of whether more effective chemotherapy impacts the role of radiation in locally advanced disease.

Locally advanced PDAC

Stratify:
SMAD4 status (predicts patterns of local vs distant disease progression)

Gemcitabine/nab-paclitaxel x 3 months

3D-CRT + cape 50.4 Gy
IMRT + cape 63 Gy
Continue chemotherapy

(P.I.: Christopher Crane, MD Anderson)
**Phase III SCALOP 2 design**

LAPC patients, PS 0-1
255 pts

Randomise if eligible for CRT (65%) 1:1:1:1:1 between arms A-E
Then GEM/Nab-Paclitaxel x 1 cycle whilst RT is planned

<table>
<thead>
<tr>
<th>Arm</th>
<th>- Nelfinavir</th>
<th>+ Nelfinavir</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n=66</td>
<td>n=66</td>
</tr>
<tr>
<td>50.4 Gy</td>
<td>Arm B n=33</td>
<td>Arm C n=33</td>
</tr>
<tr>
<td>n=66</td>
<td>CAPE 50.4Gy/28F</td>
<td>CAPE 50.4Gy/28F +Nelfinavir</td>
</tr>
<tr>
<td>60 Gy</td>
<td>Arm D n=33</td>
<td>Arm E n=33</td>
</tr>
<tr>
<td>n=66</td>
<td>CAPE 60Gy/30F</td>
<td>CAPE 60Gy/30F + Nelfinavir</td>
</tr>
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</table>
Methodological and medico-economic issues

Systematic QoL studies?

Composite endpoints?

Amount of requested material for genomic issues?

Place of « liquid biopsies »?

Cost of new drugs and of CTRT?
Strategies to improve the outcome of LAPC patients

1- Improvement of systemic chemotherapy

2- Personalized medicine

3- Improvement of chemoradiation

4- Improvement in strategy and techniques

5- Methodological and medico-economic issues