Organ preservation: Role of induction chemotherapy

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Head and neck squamous cell carcinoma (HNSCC)
Meta-Analysis of chemotherapy in HNC (MACH-NC)

- 63 randomized trials (1965-1993)
- N=10,717 pts with SCC of the oropharynx, oral cavity, larynx or hypopharynx
- Comparison of locoregional treatment with and without chemotherapy
- Median follow-up: 6 years
- Overall benefit of chemotherapy: 4% at 5 years (32% vs 36%)

<table>
<thead>
<tr>
<th>Trials</th>
<th>N</th>
<th>RR</th>
<th>P value</th>
<th>Absolute benefit (5 years), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>8</td>
<td>1854</td>
<td>0.98</td>
<td>NS</td>
</tr>
<tr>
<td>Induction</td>
<td>31</td>
<td>5245</td>
<td>0.95</td>
<td>NS</td>
</tr>
<tr>
<td>Concomitant</td>
<td>26</td>
<td>3727</td>
<td>0.81</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Pignon JP, Lancet 2000
Update of MACH-NC

- 24 added trials—87 studies, 16,485 patients

- MACH-HN I: 8% absolute benefit Concurrent-no significant effect of IC

- No significant difference ($p = 0.19$) was seen between mono-chemotherapy (HR 0.84) and poly-chemotherapy (HR 0.78)

- Mono-chemotherapy group:
  - the effect of chemotherapy was significantly higher ($p = 0.006$) with PLATIN than with other types of mono-chemotherapies

Pignon JP, Radiotherapy Oncol 2009
Platin + radiotherapy is the standard for locally advanced HNSCC
### MACH-NC: neo-adjuvant chemo and local control for laryngeal tumors

<table>
<thead>
<tr>
<th></th>
<th>Induction CT+ RT if good response (n=305)</th>
<th>Total laryngectomy (n=297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>42%</td>
<td>34%</td>
</tr>
<tr>
<td>Local</td>
<td>25%</td>
<td>12%</td>
</tr>
<tr>
<td>Metastatic</td>
<td>14%</td>
<td>19%</td>
</tr>
<tr>
<td>Both</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Second primary</td>
<td>9%</td>
<td>12%</td>
</tr>
<tr>
<td>Death/other cause</td>
<td>19%</td>
<td>16%</td>
</tr>
<tr>
<td>Alive w/o disease</td>
<td>30%</td>
<td>38%</td>
</tr>
</tbody>
</table>

Pignon, Lancet 2000
Larynx preservation trials at 5 years: survival differences = NS

Meta-Analysis of Chemotherapy in Head & Neck Cancer

Initial total laryngectomy

Induction chemotherapy

J. Bourhis courtesy
Induction PF followed by RT was a viable alternative to up-front total laryngectomy in good responders
The ways to optimise the chemo-selection approach

- Better patients selection (comorbidities, exclude T4 with cartilage invasion …)
- Optimise the induction regimen
- Optimise radiotherapy
- Combine RT with the best drug(s)
Optimise the induction regimen: Randomized trials of induction PF+/- taxane

<table>
<thead>
<tr>
<th>Eligibility</th>
<th>N</th>
<th>T+PF CR+PR (%)</th>
<th>PF CR+PR (%)</th>
<th>TPF/PF PFS mos</th>
<th>TPF/PF OS mos</th>
<th>P value (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hitt</strong> JCO 2005</td>
<td>Stage III-IV</td>
<td>382</td>
<td>80%</td>
<td>68%</td>
<td>20 vs 12</td>
<td>43 vs 37</td>
</tr>
<tr>
<td><strong>TAX 323</strong> NEJM 2007</td>
<td>Unresectable</td>
<td>358</td>
<td>68%</td>
<td>54%</td>
<td>11 vs 8</td>
<td>18.6 vs 14.2</td>
</tr>
<tr>
<td><strong>TAX 324</strong> NEJM 2007</td>
<td>III-IV</td>
<td>538</td>
<td>72%</td>
<td>64%</td>
<td>2y PFS 53% vs 42%</td>
<td>70 vs 30</td>
</tr>
</tbody>
</table>
TPF vs PF for larynx preservation

- GORTEC
- Larynx/hypopharynx
- Stage II to IV
- N=213

Pointreau et al JNCI 2009
TPF vs PF: laryngeal preservation

Pointreau et al JNCI 2009
Updated meta-analysis:
6 randomised trials taxan-PF vs PF

Survival (%)

Time from randomisation (Years)

TPF improves OS

Absolute difference at 5 years:
7.4 ± 2.59, p = 0.0002
TPF is the recommended regimen for induction chemotherapy of locally advanced HNSCC, especially for laryngeal preservation.
Does induction TPF followed by RT+/-CT do better than upfront RTCT?
## Randomized trials of sequential therapy: definitive chemo RT +/- induction

<table>
<thead>
<tr>
<th>Trial</th>
<th>Eligibility</th>
<th>Target N</th>
<th>Actually enrolled</th>
<th>Control</th>
<th>Experimental arm</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeCIDE</td>
<td>N2-3</td>
<td>400</td>
<td>285</td>
<td>DHFX</td>
<td>TPFx2 DHFX</td>
<td>NS</td>
</tr>
<tr>
<td>Paradigm</td>
<td>Stage III-IV</td>
<td>300</td>
<td>145</td>
<td>Cisplatin CB-RT</td>
<td>TPFx3 Carbo-RT or D-CB-RT</td>
<td>NS</td>
</tr>
<tr>
<td>SWOG</td>
<td>Oropharynx</td>
<td>400</td>
<td></td>
<td>Cisplatin RT</td>
<td>TPFx1-3 Surgery or cisplatin-RT</td>
<td></td>
</tr>
<tr>
<td>Hitt</td>
<td>Stage III-IV</td>
<td>439</td>
<td>439</td>
<td>Cisplatinx3-RT</td>
<td>PF or TPF CRT</td>
<td>NS</td>
</tr>
<tr>
<td>Ghi</td>
<td>Unresectable</td>
<td>361</td>
<td>361</td>
<td>Cisplatinx2-RT</td>
<td>TPFx3 Cisplatin*2 or cetux</td>
<td>P=0.02</td>
</tr>
</tbody>
</table>

CB, concomitant boost; DHFX, docetaxel, fluorouracil, and hydroxyurea
GORTEC 2007-02
phase III randomised trial

**Carboplatin**
- \(70 \text{ mg/m}^2/\text{j} + 5\text{-FU}\) 600 mg/m\(^2\)/d J1–J4, week 1, 4 and 7
- RT 70 Gy, 35 fractions, 5 fractions/semaine
- No induction

**Cetuximab**
- 400 mg/m\(^2\) J-8, puis 250 mg/m\(^2\)/s x 7 weeks

**Docetaxel**
- 75 mg/m\(^2\) D1 (T)
- + **cisplatine** 75 mg/m\(^2\) D1 (P)
- + **5-FU** 750 mg/m\(^2\) D1–5 (F)
- x 3 cycles
  - if RC, RP ou S

**RT**
- 70 Gy, 35 fractions, 5 fractions/week

L. Geoffrois, et al., ASCO 2016, OS 6000
GORTEC 2007-02
Recurrence free survival (RFS)

Patients at risk

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>TPF-cetux-RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>179</td>
<td>181</td>
</tr>
<tr>
<td>1</td>
<td>89</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

HR (95%CI) : 0.93 (0.73 à 1.20)

$p = 0.58$

L. Geoffrois, et al., ASCO 2016, OS 6000
GORTEC 2007-02
Overall survival (OS)

HR (95%CI) 1.12 (0.86 à 1.46)
$p = 0.39$

Temps (années)

Survie globale (%)
GORTEC 2007-02
Metastasis free survival (MFS)

HR : 0.62 (95% CI 0.40 to 0.95 )

$p = 0.03$

Patients at risk

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>TPF + cetux-RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPF</td>
<td>179</td>
<td>111</td>
</tr>
<tr>
<td>Patients</td>
<td>109</td>
<td>72</td>
</tr>
<tr>
<td>at risk</td>
<td>73</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
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L. Geoffrois, et al., ASCO 2016, OS 6000
GORTEC 2007-02

- No benefit of induction followed by Cetux-RT
  - In terms of RFS, OS, local control

- Significant decrease of distance metastasis associated with induction

- Standard treatment remains RCT

- Induction is an option that provides equivalent results when compared with RCT
What is the best concomitant chemo after induction phase III randomised trial

**Stade III/IV**
- T1–4, N0-3
- Not resectable
- Oral cavity, oropharynx, larynx, hypopharynx
- PS 0–1

**Primary endpoint:**
- Non-inferiority of cetuximab-RT vs CRT in terms of OS

**TPF†**
- Cetuximab 400mg/m² then 250mg/m² weekly + RT
- Cisplatine 100mg/m² D 1,22,43 + RT

**After 2 or 3 cycles**
- N=407
- N=530

R. Hitt et al., ASCO 2016, OS 6001
- PFS: NS
- Local control: NS
It seems that RT+ cetux or RT+cisplatine provide equivalent results after TPF induction.

In both arms, the 3 year local control rate is excellent (>50%).

42% of patients did not receive the 3 cycles of high dose cisplatine with RT.
Conclusion

- **Induction TPF**
  - is not a Standard of Care in LA HNSCC
  - is an important option for Larynx preservation
  - reference treatment, but has to be carefully handle if co-morbidities
Thanks