Induction Chemotherapy with Cisplatin-Docetaxel followed by Concurrent Chemoradiation for Locally Advanced Head and Neck Cancer

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Head and neck malignancies accounts for 52,160 newly diagnosed cancers in US each year

12,000 deaths per year

5 year survival rates are low

Treatment strategies have moved away from single modality therapy and now encompasses a multimodality approach:

- Surgery
- Chemotherapy
- Radiation
- Targeted molecular therapies
MACH-NC Meta-analysis results:

- **Absolute benefit of chemotherapy:**
  - 4.5% increased 5 year survival

- **Subgroup analysis showed IC:**
  - 2.4% overall survival benefit vs CRT
  - 26 of 31 trials used combination of 5FU and platinum-based (not TPF)

- **Rationale for induction chemo:**
  - Shrinkage of tumor
  - Reducing metastatic disease
  - Assessment of tumor responsiveness
  - Organ preservation (larynx)

- But does the benefit of achieving tumor control locally and distally offset the potential harm of delaying definitive therapy?
Background:

VA Larynx trial:
- IC with PF $\rightarrow$ RT versus Laryngectomy $\rightarrow$ RT alone
- Result: similar survival in both arms
- 64% organ preservation with IC

French study- *Domenge et al*:
- Induction PF $\rightarrow$ Locoregional trt versus Locoregional trt alone
- For resectable and unresectable oropharyngeal carcinomas
- Found significantly higher survival with IC
- Median survival 5.1 years verses 3.3 years p=0.03
RTOG 91-11: Organ preservation:

- 3 arms:
  1. Induction with PF → RT
  2. Concurrent chemoRT - bolus cisplatin
  3. RT alone

- Results: intact larynx higher at 2 years in IC and CRT groups
- Similar survival in all groups

5 year update:

- CRT and IC better laryngectomy free survival versus RT alone
- Larynx preservation rate better with CRT versus Induction with PF arm and RT alone arm
- Surprisingly, trend towards survival with PF versus other two arms.
Background:

- In the last 10 years, taxane therapy inspired a resurgence of interest in IC
- In 1998, a trial from the Eastern Cooperative Oncology Group- 30 patients with recurrent, metastatic or locally advanced H&N ca. found high dose paclitaxel has a 40% response in patients.
- Sparked induction chemotherapy studies- phase I and II using docetaxel, cisplatin and 5FU (TPF)
Background:

- **TAX-323: Vermorken et al**
  - Stage III and IV unresectable, no evidence of distant mets
  - Randomized to TPF versus PF for 4 cycles $\rightarrow$ RT
  - Median follow up of 32.5 months

Results:
- Longer PFS in TPF 11 months versus 8.2 months
- Lower risk of death of 27%
- OS time of 18.8 months versus 14.5 months
- TPF had fewer pts with nausea, mucositis, vomiting, grade 3 hearing loss
- But had higher incidence of neutropenia 76.9% vs 52.5%
- Febrile neutropenia was also higher: 5.2% vs 2.8%
- Updated 5 yr PFS was 22.9% with TPF versus 13.5% with PF
TAX-324: Posner et al

- Resectable and unresectable, stage III and IV, no distant mets, and candidates for organ preservation
- Induction TPF versus Induction PF → CRT in both arms
- At minimum 2 year follow-up, median survival improved with TPF versus PF (71 versus 30 months)
- More neutropenia/neutropenic fever like TAX-323
- GORTEC 200-001 trial for larynx preservation showed TPF > PF induction chemo
Induction chemotherapy regimens with docetaxel, cisplatin and 5-flourouracil (TPF) have shown an overall survival benefit when compared with Cisplatin and 5-flourouracil (PF).

TAX 323 and TAX 324 studies comparing TPF verses PF:
- Median progression free survival:
  - 11 versus 8 months (TAX 323)
  - 36 versus 13 months (TAX 324)
- Limited data on outcomes for induction Cisplatin and Taxotere (TP)
- TPF induction chemotherapy has shown an increased incidence of grade 3-4 neutropenia
  - 83% neutropenia in TAX 323
Purpose:

- Patients treated IC with Taxotere-Cisplatin → concurrent CRT

Endpoints:
- Progression-free survival
- Overall survival
- Recurrence rate
- Toxicities
Materials and Methods

- 203 patients with stage III or IV HNSCC were identified
- 19 (9.3%) patients determined to be too frail to receive full course TPF received induction chemo with TP alone and were included for this analysis.
  - All went on to receive chemo (weekly cisplatin or carboplatin) concurrently with EBRT of at least 70 Gy.
  - 2 of the 19 patients (10.5%) were unable to receive or complete radiation course due to progression of disease.
Materials and Methods

- Patients received between 1 and 4 cycles of induction chemotherapy.
- Overall survival and progression free survival functions were generated using the Kaplan-Meier method.
PET/CT before and after Induction Chemo:

Before chemotherapy:

After chemotherapy:
Results:

- The primary indication for induction chemotherapy:
  - “large burden” of disease (94.7%)

- Follow up was 2.8 - 45.6 months

- Median follow up of 11.9 months
Table 1: Outcomes with Induction Cisplatin and Taxotere (TP)

<table>
<thead>
<tr>
<th>End point</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>65.6%</td>
</tr>
<tr>
<td>Loco regional failure</td>
<td>42.1%</td>
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<tr>
<td>Median Progression Free Survival (PFS)</td>
<td>19.8 months</td>
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<tr>
<td>One year PFS</td>
<td>57.9%</td>
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</table>
Results: Toxicity

- Grade 3 or higher mucositis in 15.8%
- Grade 3 or higher dysphagia in 57.9%
- Grade 3 or higher anemia in 31.5%
- Grade 3 or higher neutropenia in 21%
- Long term toxicities were rare
  - Mainly xerostomia
Conclusions:

- PFS with induction TP was 19.8 months which is consistent with results from large randomized studies of TAX 323 and TAX 324.

- However, grade 3 or higher neutropenia was less with TP (31.5% with TP versus 76.9-83% with TPF).

- While this is a small study of induction TP in a frail population, the results are promising and may warrant further study.
Evidence in favor of TP Induction Chemo:

A phase II trial by Barone et al in 2008 investigated induction regimen of cisplatin, paclitaxel (TP) followed by RT for stage III/IV pts

- 70% with unresectable or bulky disease
- Results: median time to progression 10.7 months
- Median survival 17 months
- 2 year survival 30%, 3 year survival 25%
- Locoregional control in 51%
- Grade 3-4 neutropenia in 14%
- Grade 3 mucositis in 23%
Evidence in favor of TP Induction Chemo:

- Pergolizzi et al, Italian study, 2011:
- Induction chemotherapy with cisplatin and paclitaxel (TP) followed by CRT with weekly paclitaxel for locally advanced, stage IV (Mo)

Results:

- Prospective study found 74% of patients had response after induction and 97.7% after CRT
- Median time to treatment failure was 20 months
- Disease progression rate: 3 years: 33%, 5 yr was 23%
Evidence in favor of TP Induction Chemo:

Abstract in IJROBP 2013, Herman et al:

- Retrospective study at University of Illinois: TPF versus TP induction chemotherapy in locally advanced H&N cancers
- Median follow up 18.9 months
- Results: Improved 2 year LRC (78.9% with TP versus 46.1% with TPF)
- Improved 2 year PFS: 61% versus 36%
- Trend towards improved distant mets with TP vs TPF
- Worse renal toxicity with TPF vs TP
Recent trials on Induction Chemotherapy:

- Recently two randomized clinical trials were presented:
  - 1. PARADIGM
  - 2. Docetaxel Based Chemotherapy Plus Induction chemotherapy to Decrease Events in Head and Neck Cancer trial (DeCIDE)
- These trials showed no benefit of Induction chemotherapy (IC) followed by CRT
- But did show a lower rate of distant metastatic disease
  - suggesting that patients who are high risk for metastatic disease may benefit from IC
The DeCIDE and PARADIGM trials were designed to settle the debated questions around IC. The DeCIDE trial did show IC decreases distant disease suggesting it can eradicate micrometastatic disease. Why didn’t it translate to overall survival?

- It could be due to poor accrual
- Many oropharynx patients in these trials- don’t know how many were HPV positive- we know these do better
- Maybe more stage III, early stage IV and not late stage IV
Future of Induction Chemotherapy:

- Further studies are needed to identify the exact role of induction chemotherapy in H&N cancer
- Induction chemotherapy remains as an option for locally advanced H&N cancer - especially in those with high risk of distant failure
- Possible reasons to recommend Induction Chemo for patients with:
  - N2b, N2c, and N3 disease
  - Low neck disease
  - Dermal metastasis
  - Advanced disease and possible distant mets on CT/PET that cannot be pathologically confirmed

- For frail patients undergoing induction chemotherapy, consider TP instead of TPF
- A phase III randomized study comparing TPF verses TP with longer follow up is needed


