De-Escalate Trial for the Head and neck NSSG

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HPV+ H&N – A distinct disease entity

The molecular biology of head and neck cancer

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<table>
<thead>
<tr>
<th>Feature</th>
<th>HPV-negative HNSCC</th>
<th>HPV-positive HNSCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Decreasing</td>
<td>Increasing</td>
</tr>
<tr>
<td>Aetiology</td>
<td>Smoking, excessive alcohol use</td>
<td>Oral sex</td>
</tr>
<tr>
<td>Age</td>
<td>Above 60 years</td>
<td>Under 60 years</td>
</tr>
<tr>
<td>Field cancerization</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>TP53 mutations</td>
<td>Frequent</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Predilection site</td>
<td>None</td>
<td>Oropharynx</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Poor</td>
<td>Favourable</td>
</tr>
</tbody>
</table>

HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus.

Leemans et al., Nature Reviews, 2011
Good news...

Improved response to CRT

Meta-analysis: HPV +ve 28% reduced risk of dying
49% reduced risk of local recurrence

2 yr OS: 95% vs 62%

CRT toxicity in oropharyngeal patients

Higher survival rates in younger patients = living longer with morbidity

**Acute toxicity**

- Grade 3-5 toxicity
  - Severe, life threatening

CRT: 202 events in 109 living pts = 185%

Double those treated with RT alone

Calais, *JNCI*, 1999

**Late toxicity (5 yrs)**

- Grade 3-5 toxicity
  - Severe, life threatening

66 % of 27 living pts with CRT

- 56% swallowing problems
- 56% xerostomia

Denis, *JCO*, 2004
Treatment paradigms in the new age

3 risk categories (not simply HPV +/-):

- **Low risk**: HPV + / no or low smokers (50% patients)
  
  OS 3 yr 93%

- **Intermediate**: HPV + / smokers / N2b-N3 or HPV - / no or low smokers / T2-3
  
  OS 3 yr 70.8%

- **High risk**: HPV - / high smokers or low smokers w/ T4
  
  OS 3 yr 46.3%

Ang, *NEJM*, 2010
EGFR inhibitors – biological rationale

Epidermal Growth Factor Receptors (EGFR) expressed in normal epithelial tissues

EGFR overexpressed in human cancers, including colon, rectum and head & neck

Cetuximab inhibits growth and survival of tumour cells that overexpress EGFR as shown in vitro assays and in vivo animal studies

KEY:
- EGF receptor
- TGF alpha
- EGF
- Cetuximab

Cell growth
Apoptosis

Cell growth
Apoptosis

Inhibits growth & induction of apoptosis by blocking phosphorylation and activation of receptor-associated kinases
EGFR inhibitors – biological rationale

Mechanism of action of Epidermal Growth Factor (EGF) Receptor blockers

- Anti-tumour effects of blocking EGFR
- Radiosensitizer by blocking the radio-resistance effect induced by RT through EGF and TGF-alpha

Song, *Oncology*, 2004
EGFR inhibitors – clinical rationale

- Significant survival difference in favour of cetuximab + RT compared to RT alone.
  
  HR death = 0.74 (p = 0.03)

  Bonner, *NEJM*, 2006

- OPSCC were only tumour subset in Bonner trial to show significant survival difference at 5 years

  HR death = 0.68

EGFR inhibitors – clinical rationale

Toxicity: Cetuximab compared to RT in short or long term
  ❖ No increased toxicity or QOL effects
  ❖ Apart from skin toxicity

Curran, 2007

Severe late toxicity:

Chemoradiation  43%  (Machtay, 2008)
Cetuximab + RT  20%  (Bonner, 2006)
Most recent data on EGFR and HPV

108 patients, 18 HPV +
Median F/U = 35 months

P16+ve
- Cetuximab better OS and DFS than cisplatin
  - OS 88% vs 60% (p=0.01)
  - DFS 75% vs 47% (p=0.01)

P16-ve
- No difference in survival or DFS
Why De-ESCALaTE?

Cetuximab has been shown to be effective in the management of SCCHN and is potentially less toxic.

Head and neck is the 6th most common cancer.

HPV+OPSCC appears to be a distinct disease entity.

Primary aim of decreasing toxicity and increasing quality of life.

Affects younger patients who can live with side effects for decades.

Increasing incidence of OPSCC attributed to rise in HPV related OPSCC.

Standard platin-based chemoradiotherapy causes acute toxicity and long-term sequelae.
OVERVIEW

• Phase III, randomised, international, multi-centre, open-label clinical trial

• Cisplatin + RT versus cetuximab + RT

• Patients with Human Papillomavirus-positive oropharyngeal squamous cell carcinoma (HPV+OPSCC)

• Registration Cohort Study (HPV-)

• Translational research: Blood, oral fluid & tissue collection
TRIAL SCHEMA

SCREENING:
T3-T4NO – T1N1-T4N3
OPSCC

Eligible for De-ESCALaTE HPV & written informed consent?

HPV+ tumour by p16 immunohistochemistry [via central laboratory]

Registration Cohort Study

YES

Arm A
Concomitant cisplatin + radiotherapy
[100mg/m² at days 1, 22 and 43 from start of radiotherapy]

Randomise 304 Patients

152

152

Follow up: 2 years

Primary endpoint:
- Overall severe toxicity (Grade 3-5)

Secondary endpoints:
- Acute severe toxicity
- Late severe toxicity
- Quality of Life
- Dysphagia
- Cost-effectiveness
- Overall survival
- Locoregional recurrence

NO

Arm B
Concomitant cetuximab + radiotherapy
[400mg/m² 1 week before start of radiotherapy, followed by weekly dose of 250mg/m²]
STUDY DESIGN: Objectives

**Primary Objective:**

To compare the severe (acute and late) toxicity (Grade 3-5) caused by cetuximab and RT to that caused by cisplatin and RT in patients with low-risk HPV+OPSCC.

**Secondary Objectives:**

- Compare overall number of events of acute severe toxicity between treatment arms (defined as occurring during treatment or within 90 days of end of treatment) and compare overall number of events of late severe toxicity between treatment arms (defined as occurring more than 90 days up to two years from end of treatment).

- Compare the quality of life outcomes assessed by EORTC C30 and HN35 between the two treatment arms.

- Compare the effect on swallowing of the two treatment arms (assessed by MDADI and by PEG or RIG utilisation rate at 1 and 2 years).

- Compare the cost-effectiveness of the two treatment arms (assessed by EuroQoL-5D).

- Compare overall survival, recurrence and metastasis between the two arms.
Patient Eligibility

Inclusion criteria

✓ American Joint Committee on Cancer (AJCC) TNM Stage III-IVa (T3N0-T4N0, and T1N1-T4N3) oropharyngeal squamous cell carcinoma (SCC) tumours

✓ Clinical multidisciplinary team decision to treat with primary curative cisplatin chemoradiotherapy

✓ No previous treatment for the primary tumour, including surgery, neck dissection or tracheostomy [except node biopsies or diagnostic tonsillectomy]

✓ Medically fit (ECOG 0, 1 or 2)

✓ Adequate cardiovascular, haematological, renal and hepatic function

✓ Age ≥ 18 years

✓ Written informed consent given

✓ Using adequate contraception [male and female participants]. Must take contraceptive measures during, and for at least three months after treatment.
Patient Eligibility (cont.)

Exclusion Criteria

- Distant metastasis (i.e. AJCC TNM stage IVc disease)
- AJCC TNM Stage T1-2N0 disease
- Treated with primary radical surgery to the primary site (e.g. resection)
- Concurrent use of CYP3A4 inducers or inhibitors
- Serious cardiac illness or other medical conditions precluding the use of cisplatin or cetuximab
- Patients who have p16+ tumours who also have N2b, N2c or N3 nodal disease and whose lifetime smoking history is also more than 10 pack years (i.e. have both risk factors)
- Pregnant or lactating
- Previous treatment for any other cancer with cytotoxics, radiotherapy or anti-EGFR therapies
- Inadequate renal, haematological or liver functions
- Patients with clinically significant hearing impairment
- Life expectancy less than 3 months
- Other malignancy within the past 3 years except basal cell skin cancer or pre-invasive carcinoma of the cervix
Patient selection schema-smokers

- Is tumour oropharyngeal squamous cell carcinoma?
  - YES
  - Is nodal status N0-N2A?
    - YES
      - Eligible for consent to De-ESCALaTE
    - NO
      - Is lifetime smoking history less than or equal to 10 pack years?
        - YES
          - Eligible for consent to De-ESCALaTE
        - NO
          - Not Eligible
STUDY DRUGS*

CISPLATIN (ARM A)
• 100 mg/m$^2$ administered intravenously on Days 1, 22 & 43 of radiotherapy
• Cisplatin given within 24 hrs of required day is acceptable

CETUXIMAB (ARM B)
• Initial dose must occur 1 week prior to radiotherapy, 400 mg/m$^2$ administered intravenously over 120 minutes
• Weeks 2-8 (concurrent with RT): 250 mg/m$^2$ administered intravenously over 60 mins. prior to radiation therapy
• Radiation therapy should be given within 24 hrs of starting cetuximab infusion

*For more detailed information, please always refer to the Summary of Product Characteristics and current protocol
RADIOTHERAPY (RT)

- Dose: 70GY in 35 fractions
- RT given over 7 weeks
- Modality:
  - Bilateral RT: IMRT
  - Unilateral RT: IMRT or 3D-conformal radiotherapy
  - Two outlining protocols: anatomical or volumetric
TRANSLATIONAL RESEARCH

• Blood, oral fluid, and tissue collection

• Choice of collection (Registration Form)

• Optional on a per-patient basis

• Separate consent form (De-ESCALaTE HPV Collect)

• Translational Research SOPs provided
JCUH experience

- Opened August 2013
- 4 patients so far, 3/4 had cetuximab
- Example:
  - 59 F never smoked, PS0
  - Lump in left neck and abnormal tonsil
  - T4 N2b M0 squamous cell carcinoma of the left tonsil, left level II nodes involved
PET MIP $Volumetric$ for PET-CT
- 70 Gy in 35 fractions to CTV1 the primary tumour and left levels Ib and II
- 56 Gy in 35 fractions to the right level Ib and II and bilateral III-V
Dose volume histogram

![Dose Volume Histogram](image-url)
Any questions?