Treatment De-Escalation for HPV+ Oropharynx Cancer (OPX)

Steven Seyedin, md (PGY-5)
Faculty Advisor: C Arryn Anderson, MD
University of Iowa hospital and clinics
Case

- 58 yo male with dysphagia who noticed a right tonsillar mass

- Referred to ENT
  - Right tonsillar mass confined to the tonsillar fossa
  - Biopsy of mass = +p16 squamous cell carcinoma

- CT Larynx with contrast
  - 2.5 x 1.3 cm right tonsillar soft tissue mass
  - Subcentimeter hypodense/necrotic lymph node level 2A concerning for metastasis

- PET-CT positive tonsil and right 2a node, negative for metastatic disease
Case

• Standard treatment options for locoregionally advanced OPX include
  – Surgery + adjuvant RT (60 Gy) +/- concurrent cisplatin
  – Chemoradiation (70 Gy + cisplatin)

• For more details on work-up and standard of care treatment, refer to Oropharynx ARRO Case by Drs. Thaker, Haque, and Garden

• Our patient enrolled in ECOG 3311:
  – Transoral Surgery (TORS) for HPV+ OPX followed by risk-stratified adjuvant therapy (more to follow)

• Several methods to treatment de-escalation have been proposed since the release of the sub-analysis of OPX patients from RTOG 0129 (next slide)
Rationale for HPV+ OPX Treatment De-Escalation

• Analysis of OPX patients on RTOG 0129 noted differences in outcomes comparing patients with HPV+ vs HPV- tumors

• Low, intermediate, and high risk stratification created based on variables shown to determine overall survival on recursive-partitioning index analysis (figure on the right)

• All HPV+ OPX cancers are either low or intermediate risk

Ang et al NEJM 2010
Rationale for HPV+ OPX Treatment
De-Escalation

• OS at 3 years:
  – Low-risk: 93%
  – Intermediate-risk: 70.8%
  – High risk: 46.2%

• HPV+ OPX patients demonstrated improved outcomes with radiation compared to HPV- population

• Hypothesis: De-escalating therapy to reduce side effects could be achieved without compromising control outcomes in HPV+ OPX

• Many methods to de-escalate treatment have been proposed

Ang et al NEJM 2010
Proposed Ways to De-Escalate Treatment

• 1) Induction chemotherapy (IC) and response dependent RT de-escalation
  – E1308
  – OPTIMA
  – UCLA/UC Davis

• 2) Concurrent chemoRT with reduced RT dose

• 3) Change Cisplatin to Cetuximab

• 4) Surgery + Adjuvant RT+/- Chemo
E1308: Phase II trial

- Pts: Stage III-IV (T1-3N0-N2b)
- Intervention
  - IC
    - Cisplatin 75 mg/m² day 1, paclitaxel 90 mg/m² days 1, 8 and 15, cetuximab 400 mg/m² day 1 followed by weekly 250 mg/m²
    - Repeat every 21 days x 3
  - Assess clinical response within 2 weeks of completing induction chemotherapy
    - Complete response (CR) = no residual disease
    - Partial response (PR) = 30% or more reduction in the sum of the longest diameter
    - Progressed disease (PD) = 20% or more increase in the sum of the longest diameter
    - Stable disease (SD) = between PR and PD

Marur et al JCO 2016
E1308: Phase II trial

– Radiation dose stratification to primary site and nodes determined by response
  • If cCR: 54 Gy/27 fx at primary site
  • If not cCR: 69.3 Gy/33 fx at primary
  • Uninvolved cervical nodes treated to 51.3 Gy in 27 fx
  • 1 cm margin was required for all involved lymph nodes
  • Both arms continued cetuximab until the end of radiotherapy

– Endpoints
  • Progression free survival (PFS) and OS @ 2-years, clinical and radiologic responses
  • Common Terminology Criteria for Adverse Events vs 4.0
  • Vanderbilt H&N Survey: 50-item survey
E1308

• Characteristics
  – 80 analysis-eligible patients with T1-3 (89%), N0-2b (69%), non-current smokers (84%)
  – 96.2% completed IC
    • 56 pts (70%) with primary CR
      – 51/56 completed 54 Gy (other 5 underwent 69.3 Gy, protocol deviation)
    • 8 of 18 pts with less than CR received only 54 Gy (protocol deviation)
    • 46 pts (58%) with nodal CR

Marur et al JCO 2016
• Toxicity
  – CTCAE Grade 3/4 toxicity during
    • IC: acneiform rash (28%), lymphopenia (6%), neutropenia (12%)
    • 54 Gy: mucositis (30%), dysphagia (15%), acneiform rash (12%), RT dermatitis (7%)
    • 69.3 Gy: mucositis (47%), dysphagia (29%) acneiform rash (24%), RT dermatitis (12%)
  – Vanderbilt H&N Score @ 12 months
    • Less difficulty swallowing solids in 54 Gy arm (40% vs 89%, p = 0.011)
    • Less impaired nutrition (10% vs 44%. P = 0.025)
Patients treated to 54 Gy to the primary site
- 2-yr PFS: 80%
- 2-yrs OS: 94%
- Subgroup analysis
  - T1-3, N1-2b disease < 10 pack-year history (PYH) of smoking: 2-yr PFS and OFS 96%
- Pattern failures
  - 4 at primary site
  - 2 at nodal site
  - 2 at nodal and primary site
  - 1 distant failure

Marur et al JCO 2016
E1308

- With short follow-up, dose de-escalation appears to be safe especially in low-volume, low-risk patients (T1-3, N1-2b disease < 10 PYH)
  - Less dysphagia, mucositis, and dermatitis compared to traditional 69.3
- Interestingly: Small number of patients with < CR at primary site (n = 11) also received 54 Gy (off protocol) had similar disease control to those with cCR
OPTIMA Trial: Phase II

- Stratified patients:
  - Low risk: T1-3, N0-2b (except nodal disease ≥ 6 cm), ≤ 10 PYH
  - High risk: T4, N2c and bulky N2b, > 10 PYH

- Treatment:
  - 3 cycles of carboplatin (AUC = 1) and nab-paclitaxel (100 mg/m² days 1, 8, and 15) – every 21 days
  - RT (VMAT or IMRT) dose stratified by primary and nodal response using RECIST v1.1 criteria
    - Low risk patients with ≥ 50% response: 50 Gy RT alone in 25 fractions
    - Low risk patients with 30-50% or high-risk with ≥ 50% response: 45 Gy (1.5 Gy BID) + TFHX (below)
    - Low risk < 30% response, high risk < 50% response: 75 Gy (1.5 Gy BID) + TFHX x 5 (14-day cycles)
  - TFHX: 5-FU 600 mg/m² infusion days 0-5, paclitaxel 100 mg/m² day 1, hydroxyurea 500 mg PO BID (11 doses /cycle)

Seiwert et al Annals of Oncology 2018
OPTIMA

• Treatment ctd
  – Unique RT volumes
    • PTV1 = pre-induction chemotherapy gross disease + 1.5 cm expansion
    • PTV2 = next echelon of uninvolved at-risk lymph nodes
• Patients underwent surgical evaluation 4-8 weeks after radiation
• Endpoints:
  – Toxicity scored with CTCAE vs 4.0
  – 2-yr PFS, locoregional control, distant control, OS
OPTIMA

• Characteristics
  – 62 patients
    • Low risk: 82% T1-2, 89% N2b
    • High risk: 56% T1-2, 53% N2b
  – More than 50% with any tumor size reduction
    • Low risk (all completed): 71%
    • High risk (33/34 completed): 71%
  – 82% of patients received some form of de-escalated treatment

Seiwert et al Annals of Oncology 2018
## OPTIMA

<table>
<thead>
<tr>
<th>Patients with pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 Gy arm</td>
</tr>
<tr>
<td>45 Gy + TFHX</td>
</tr>
<tr>
<td>75 Gy + TFHX</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2-yr</th>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>95%</td>
<td>94%</td>
</tr>
<tr>
<td>OS</td>
<td>100%</td>
<td>97%</td>
</tr>
<tr>
<td>LC</td>
<td>100%</td>
<td>97%</td>
</tr>
<tr>
<td>DC</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

No statistical differences between two groups
De-escalation arms with less mucositis, dermatitis, and needing a PEG tube (all statistically significant)

Conclusion: Radiation alone after induction chemotherapy could be an option for low-risk patients with complete response after IC. Radiation dose reduction even with chemotherapy reduces toxicity

<table>
<thead>
<tr>
<th></th>
<th>RT50</th>
<th>CRT45</th>
<th>CRT75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute G3+ mucositis</td>
<td>30%</td>
<td>63%</td>
<td>90%</td>
</tr>
<tr>
<td>Acute G3+ dermatitis</td>
<td>0%</td>
<td>20%</td>
<td>45%</td>
</tr>
<tr>
<td>% requiring a PEG tube</td>
<td>0%</td>
<td>31%</td>
<td>82%</td>
</tr>
</tbody>
</table>
UCLA/UC Davis study: Phase II

• Pts: Stage III/IV (T1-4, N0-3)
• Treatment
  – IC: 175 mg/m² paclitaxel and carboplatin AUC 6 for 2 cycles 21 days
  – IMRT/VMAT dose stratified by response on CT using RECIST:
    • If CR or PR
      – 54 Gy in 27 fx with 30 mg/m² paclitaxel
      – 43 Gy to uninvolved areas
    • If SD*
      – 60 Gy in 30 fx with 30 mg/m² paclitaxel
      – 48 Gy to uninvolved areas
• Endpoints: 2-yr PFS, OS, toxicity assessed with CTCAE (early = within 90 days, late)

*patients with PD required surgical salvage

Chen et al Lancet Oncol 2017
UCLA/UC Davis study

• Characteristics
  – 44 analyzable patients with T1-2 (77%), N2 (83%)
  – All but 1 completed IC (allergic reaction)
  – Response after IC at all sites
    • 54% with PR or CR received 54 Gy
  – Median f/u 30 months
UCLA/UC Davis study

- CTCAE Grade 3 events during (two most common)
  - IC: leukopenia (39%), Neutropenia (11%)
  - ChemoRT: dysphagia (9%), mucositis (9%)
    • No differences in grade 3+ muco-esophageal toxicity between 54 vs 60 Gy @ 2 years ~ 15%

- 2-yr PFS: 92%
  - 1 patient with distant failure, 3 with locoregional failure

- 2-yr OS: 95%

- Conclusion: RT reduction for higher risk (T3-4, bulky T2b, > 10 year PYH) HPV+ OPX produces high rates of control at 2 years but differences in toxicity benefit of 54 Gy is unclear

Chen et al Lancet Oncol 2017
Proposed Ways to De-Escalate Treatment

1) Induction chemotherapy (IC) and response dependent RT de-escalation
2) Reduce RT Dose
   - UNC/Florida
3) Change Cisplatin to Cetuximab
4) Surgery + Adjuvant RT+/- Chemo
UNC/Florida Phase II

- Pts: T0-T3, N1-2 < 10 PYH or > 10 PYH with 5 years cessation
- Intervention
  - RT to 60 Gy with cisplatin (above)
    - Subclinical disease treated to 54 Gy
  - Chemo
    - Cisplatin (30 mg/m2) weekly (cetuximab, carboplatin, or carboplatin/paclitaxel not allowed)
  - Surgery
    - If CR on CT at the primary, direct visualization and biopsies performed. If PR, then minimal surgery (i.e. TORS)
    - Patients with N+ disease underwent removal of initially involved nodes only (limited dissection)

Chera et al Cancer 2018
UNC/Florida

• Endpoints
  – pCR (primary), LC, regional control, LRC, DMFS, OS
  – Toxicity including CTCAE, patient reported (PRO)-CTCAE and EORTC-Quality of Life Questionnaire (QLQ)
UNC/Florida

• Characteristics
  – 45 patients with T1-2 (80%), N+ (91%) disease
  – 70% completed all six doses of cisplatin
  – Median f/u 36 months
    • 3-yr LC, RC, LRC, CSS and DMFS: all 100%
    • 3-yr OS: 95% (1 stroke, 1 GBM)
    • pCR at primary: 98% (per discussion)
    • pCR at nodes: 84% (per discussion)
UNC/Florida Phase II

- **CTCAE Acute Grade 3+ Toxicity**
  - 39% dysphagia, 35% mucositis, 2% xerostomia
  - Chemo related: 11% hematologic, 18% nausea, 5% vomiting
- **PRO-CTCAE Grade 3+**
  - 75% xerostomia, 55% dysphagia, 45% mucositis
  - Increased dry mouth and xerostomia compared to baseline

**EORTC-QLQ (below)**
- Improved quality of life but residual dry mouth and sticky saliva
- No major changes in swallowing

![Graph showing improvement in quality of life and symptoms over time]

Higher = improved quality of life

Lower the number means improved symptoms

Chera et al. Cancer 2018
UNC/Florida

• De-escalated chemoRT for favorable risk HPV+ OPSCC is feasible
  – Both RT and chemo de-escalated

• Limitations
  – Unclear how much “non-definitive” neck dissection affects control rates
  – No comparison for toxicity data
Proposed Ways to De-Escalate Treatment

• 1) Add Induction chemotherapy and de-escalate well for responding patients
• 2) Reduce RT Dose
• 3) Change Cisplatin to Cetuximab
  – De-ESCALaTE
  – RTOG 1016
• 4) Surgery + Adjuvant RT+/- Chemo
De-ESCALaTE trial: Phase III

- Pts: T3N0-T4N0, T1N1-T4N3, non-smokers or less than 10 PYH
- Intervention: RT in both 70 Gy in 35 fx
  - Arm 1: Cisplatin 100 mg/m² (days 1, 22, and 43)
  - Arm 2: Cetuximab 450 mg/m² at week 1, 250 mg/m² weekly after

- Endpoints
  - Acute and late CTCAE
  - OS, recurrences
  - QoL and swallowing

Mehanna et al Lancet 2019
De-ESCALaTE trial

• Characteristics
  – 334 patients (166 in cis arm, 168 in cetux arm)
  – Median follow-up 25.9 months
  – T1-2 (65%) N2-3 (76%)
  – 38% complete all 3 cycles of cis (51% completed 2 cycles)
  – 79% received all 8 cycles of cetux

Mehanna et al Lancet 2019
De-ESCALaTE trial

- No differences in EORTC QLQ-30
- No differences in swallowing (per MDA dysphagia index)

<table>
<thead>
<tr>
<th>2-yr</th>
<th>Cis Arm</th>
<th>Cetux</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTCAE G3-5 events per patient</td>
<td>29.2</td>
<td>30.1</td>
</tr>
<tr>
<td>Acute CTCAE per patient</td>
<td>20.0</td>
<td>20.4</td>
</tr>
<tr>
<td>Late CTCAE per patient</td>
<td>0.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Mehanna et al Lancet 2019
De-ESCALaTE trial

- 2-yr OS (all significant)
  - 97.5% cisplatin vs 89.4% cetuximab
    - Subgroup analysis
      - Stage I/II: 98.4% cisplatin vs 93.2% cetuximab
      - Stage III/IV: 93.3% cisplatin vs 67.1% cetuximab

- Recurrences: 6% cisplatin vs 18% cetuximab (all significant)
  - LRC: 3 vs 12%
  - Distant: 3 vs 9%

Mehanna et al Lancet 2019
RTOG 1016: Phase III

• Pts: All patients with +HPV OPSCC except T1-2N1

• Intervention: Accelerated RT in both, 70 Gy in 35 fx (BID once per week)
  – Arm 1: Cisplatin 100 mg/m² (days 1, 22)
  – Arm 2: Cetuximab 450 mg/m² at week 1, 250 mg/m² weekly after

• Endpoints
  – OS (primary), LRC, DM
  – CTCAE
RTOG 1016: Results

• Characteristics
  – 805 patients (399 cetuximab, 406 cisplatin)
  – Median f/u 4.5 years
  – T2-3 (66%), N2 disease (86%)
  – 85% completed 7 doses of cetuximab
  – 88% completed 2 cycles of cisplatin

Gillison et al. Lancet 2019
RTOG 1016: Results

- OS inferior with cetuximab (HR 1.03-2.05, p = 0.016)
  - 5 yr: 77.9% (cetux) vs 84.6% (cisplatin)
- PFS was inferior in cetux group (67.3% vs 78.4% @ 5-years)
  - LR failure 39% in cetuximab vs 30% in cisplatin arm
- LRC was inferior in cetux group (9.9% vs 17.3% @ 5-years)
- No differences in DM

Gillison et al Lancet 2019
RTOG 1016: Results

- Proportion of patients with 1 or more Grade 3-4 acute AE:
  - 77.4% cetuximab vs 81.7% cisplatin (not significant)
- More hearing impairment in cisplatin arm
- EORTC QLQ H&N scores higher in cetuximab arm @ 1 year but differences not clinically meaningful (7.6 vs 2.5 p = 0.0382)
Proposed Ways to De-Escalate Treatment

• 1) Add Induction chemotherapy and de-escalate well for responding patients
• 2) Reduce RT Dose
• 3) Change Cisplatin to Cetuximab
• 4) Surgery + Adjuvant RT+/- Chemo
  – MC1273
  – ECOG 3311 (data pending)
MC1273: Phase II

- 80 pts with T104, N0-3
- Eligibility: ENE or intermediate risk factor (LVI, PNI, 2 or more involved lymph nodes, any lymph node greater than 3 cm, ≥ T3 disease), < 10 PYH
- Treatment:
  - Margin-clearing surgery
  - RT dose stratified by pathology
    - Cohort A: 30 Gy in 1.5 Gy fxS BID on days 1-5, 8-12 with docetaxel
    - Cohort B (with ENE): 36 Gy in 1.8 Gy fxS BID on same days as Cohort A
  - Docetaxel 15 mg/m² on days 1 and 8 in both arms

Ma et al JCO 2019
MC1273

• RT Design
  – 30 Gy target volumes
    • Ipsilateral dissected nodal volumes (II-IV, +/- IB, V, and retropharyngeal)
    • If base of tongue (BoT) primary OR tonsillar primary with either > 1 cm BoT or soft palate involvement
      – Included contralateral level II-IV
  – 36 Gy target volumes
    • Simultaneous integrated boost
    • Included nodal volumes with ENE only

• Endpoints
  – Locoregional control, PFS, OS
  – Toxicity: swallowing function, CTCAE vs 4.0, EORTC-QLQ
  – Financial analysis
MC1273

• Patient Characteristics
  – Cohort A = 37 pts, Cohort B = 43 patients
  – Median f/u 35.7 months (all patients had 2-yr follow-up)
  – T1-2 (81%), N1-2 (87.3%)

• Any CTCAE Toxicity: pre-RT, 1 yr and 2 yrs
  – Grade 2: 11.4%, 2.5%, 1.4%
  – Grade 3 or worse: 0.0%, 6.7%, 0.0%
  – Most common grade 2 events were oral mucositis, dysphagia, xerostomia

• No patients required a PEG tube by 1 month after treatment

<table>
<thead>
<tr>
<th>2-years</th>
<th>Cohort A</th>
<th>Cohort B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional control</td>
<td>100%</td>
<td>96.2%</td>
</tr>
<tr>
<td>Distant mets free survival</td>
<td>94.9%</td>
<td>91.9%</td>
</tr>
</tbody>
</table>
• Quality of Life (@ 1 year compared to baseline)
  ‒ Improved EORTC-QLQ H&N Score
  ‒ Improved swallowing function on barium swallow

• Financial Analysis
  ‒ Average cost of treatment = $45,884 = $17,791 (chemotherapy) + $28,093 (radiation)
  ‒ Average cost of standard adjuvant treatment = $57,845 = $26,603 (chemotherapy) + $31,242 (radiation)

• Conclusion: Aggressive adjuvant radiation dose de-escalation appears to provide comparable locoregional control to historical controls and results in significant improvements in toxicity. It is unclear if this treatment can be applied to heavy smokers as they were excluded
ECOG-ACRIN 3311: Phase II

- Results not released but our patient enrolled in this trial
- Patients with cT1-2, cN1-N2b undergo TORS + neck dissection
- Risk determination based on pathology
  - Low: T1-2, N0-1 with clear (≥ 3mm margins) without ECE or PNI/LVI
  - High: Positive margins OR extensive ECE (> 1 mm) OR ≥ 5 positive LNs
  - Intermediate: Close margins OR minimal ECE OR N2a, N2b (≤ 6 cm) OR +PNI or +LVI
ECOG-ACRIN 3311

• Guidelines for Target Volume Delineation
  – CTV-P60: post-operative bed influenced by intra-operative assessment of the invasive base of the tumor
  – CTV-N60: dissected nodal volumes with metastasis
  – CTV-N50: either dissected nodal volumes that were negative or undissected volumes
    • Ipsilateral involved nodal volumes adjacent to disease
    • Lateral retropharyngeal nodes if ipsilateral level II or primary extends to posterior pharyngeal mucosa
    • Contralateral retropharyngeal nodes covered if ipsilateral retropharyngeal nodes involved
    • Contralateral undissected neck levels II-IV
      – Can be omitted if
        » Tumor is > 1 cm from midline
        » BoT tumors without medial margin involvement
      – Required if
        » N2c disease
        » Ipsilateral retropharyngeal involvement

• Note: If randomized to the 50 Gy arm, CTV-P60 and CTV-N60 are treated to 50 Gy
Case: Surgical Pathology

• Right neck dissection
  – Levels 1B, 2B, 3, and 4 all negative
  – Level 2A: 2 of 3 nodes positive measuring 0.8 and 0.3 cm without ENE

• TORS performed 2 weeks later
  – 3.1 cm squamous cell carcinoma without LVI but with PNI
  – Initial deep margin was positive but final margins were negative

• TNM Stage:
  – AJCC 7th: pT2N2b – Stage IVA
  – AJCC 8th: pT1N1 – Stage I

• All trials mentioned used prior AJCC 6th and 7th edition staging. Stage III-IV accrued in trials is most likely early stage disease by AJCC 8th standards
Case: Radiation Planning

- The patient was randomized to 50 Gy arm of intermediate risk disease group
  - CTV-P60 – post-op cavity
  - CTV-N60 – right level 2A
  - CTV-N50 – R level IB and V, bilateral II-IV (minus right 2A)
- PTV = CTV + 3 mm
- All volumes treated to 50 Gy
Case: Radiation Planning

- Ensure PTV50 receives 95% of the prescribed dose
- Spinal Cord: 1 cc < 45 Gy
- R or L parotid: V20 < 50% (Mean < 26 Gy for both which was met for this case)
- Brainstem: 1 cc < 54 Gy
- Endolarynx: 1 cc < 50 Gy (V30 < 50%)
- Cricopharyngeus: 1 cc < 50 Gy (V30 < 50%)
- Submandibular gland: V35 < 50%
Case: Follow-up

- **Adverse events during and at the end of treatment:**
  - Notable mucositis and ulcer at the surgical site around 32 Gy
  - Decreased oral intake secondary to pain and lack of taste
  - Required multiple infusions of fluids because of dehydration
  - Moist desquamation of the neck

- **1-month follow-up**
  - Pain resolved along with mucositis and ulceration
  - Improved fatigue and taste
  - Cleared to return to work

- **21-month follow-up:**
  - Mentions minor xerostomia that does not bother him
  - CT larynx and indirect laryngoscopy negative for recurrent disease
Case Radiation Planning

• Endolarynx description per ECOG311
  – “This volume will consist of the tissues medial and contained within the laryngeal cartilage and will include the endolaryngeal structures from the level of the tip of the suprahyoid epiglottis to the inferior extent of the cricoid cartilage that does not overlap with any adjacent PTV”
General Conclusions

- Treatment de-intensification using induction chemotherapy, definitive chemoradiation, and adjuvant radiation approaches appears to be promising producing control rates comparable to historical data with significant reductions in toxicity
  - Await Phase III data
- Cetuximab is not a substitute for cisplatin therapy in the definitive setting in HPV+ low risk cancers
  - Inferior outcomes even when only 2 cycles of cisplatin are given
- Choice of de-escalation method should be tailored towards patient risk factors
  - Smoking history (> 10 years vs ≤ 10 years)
  - Extent of disease (i.e. induction chemo to reduce burden followed by smaller RT volumes/dose)
  - Surgical pathology (ENE, + margins)
  - Performance status (surgical candidate?)