Current Approaches to the Treatment of Head and Neck Cancer Patients

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Head and Neck Cancer Facts

- Approximately 50,000 people are diagnosed with Oral, Head and Neck Cancer every year in the United States.

- Worldwide, over 550,000 new cases of Oral, Head and Neck cancer are diagnosed each year.

- In the US, a new head and neck cancer case is diagnosed every 10 minutes and a person dies from this disease every 45 minutes.

- It is estimated that approximately $3.2 billion is spent in the United States each year on treatment of head and neck cancers.
What we know in HNSCC

- HNSCC are chemosensitive tumors
- Locally advanced, combining chemotherapy with radiation is better than alone
- There are better induction regimens than others
- EGFR is an important pathway
FDA Approved Chemotherapy Regimens for HNSCC

- **Locally Advanced**
  - Cetuximab with radiation

- **Induction in Locally Advanced**
  - Docetaxel + Cisplatin + 5FU

- **Metastatic**
  - Cetuximab single agent after platinum failures
  - Cetuximab with platinum + 5/FU

- **Clinical Usage**
  - Platinum combinations, Cisplatin with radiation, Whatever one feels like
Head and Neck Cancer Facts

- Which month is Head and Neck Cancer Awareness Month?
  - April

- What color is the head and neck cancer ribbon?
# Head and Neck Cancer Treatment: Multidisciplinary Care Team

- HN Surgery
- HN Radiation
- HN Medical Oncology
- Radiology
- Speech Therapist
- Nutrition
- Dental/Oral Surgery
- Mid-levels and Nursing
- Plastic Surgery
- Navigators
- Survivorship
- Integrative Medicine
- Social Worker
- Psychiatry
Levine Cancer Institute: Multidisciplinary Head and Neck Service

- **Head and Neck Surgical Oncology**
  - Zvonimir Milas, David Fisher

- **Head and Neck Medical Oncology**
  - Edward Kim, Asim Amin, Gary Fernette

- **Head and Neck Radiation Oncology**
  - Bob Fraser, Michael Haake, Anthony Crimaldi

- **Oral Medicine/Dental**
  - Peter Lockhart, Michael Brennan
Head and Neck Cancer Treatment

Stage of Disease

- Early stage
- Advanced (resectable)
- Locoregionally advanced (nonresectable)
- Metastatic, Recurrent (nonresectable)

Surgery

Radiotherapy

Chemotherapy

Investigational
Case 1

- 57 yo male
- Presented with right neck mass
- FNA – Squamous cell carcinoma
- Physical exam:
  - Bulky exophytic mass right tonsil (>4 cm)
  - Invades soft palate
  - Extends to the vallecula
- MRI:
  - 3.5 cm mass in R tonsil
  - 3.4 cm right upper IJ node, additional non-specific nodes
T3N2bM0
Management

- Induction CT → CRT
- Induction CT → RT alone
- CRT
  - CDDP
  - Erbitux
Rationale for Induction Therapy

- Reduce local tumor burden prior to radiotherapy
- Deliver a full dose of chemotherapy to potentially reduce the rate of distant relapse
- Allow interim assessment of response and individualized follow-up therapy
- Meta-analysis of induction chemotherapy with cisplatin + fluorouracil demonstrated a 5% improvement in survival at 5 years compared with other doublets
**Vermorken et al (TAX 323)**

**TPF Induction (n=177)**
- Docetaxel 75 mg/m² day 1
- cisplatin 75 mg/m² day 1
- fluorouracil 750 mg/m²/day days 1–5
- 4 cycles, q 3 wk

**PF Induction (n=181)**
- cisplatin 100 mg/m² day 1
- fluorouracil 1000 mg/m²/day days 1–5
- 4 cycles, q 3 wk

**Follow-up**
- 12 weeks after RT and thereafter

*Conventional fractionation or accelerated/hyperfractionated.

**Primary endpoint: Progression-free survival**

TAX 323: Overall Survival

Hazard ratio: 0.73
95% CI: [0.56-0.90]
Unadjusted Log-rank test: $P = .0052$

Median: 18.6 mo
Median: 14.2 mo
Sequential multimodality therapy: Induction therapy with TPF vs PF followed by concurrent chemoradiotherapy (CRT)

**TPF Induction (n=255)**
- Docetaxel 75 mg/m² day 1
- cisplatin 100 mg/m² day 1
- fluorouracil 1000 mg/m²/day days 1–4
- 3 cycles, q 3 wk

**PF Induction (n=246)**
- cisplatin 100 mg/m² day 1
- fluorouracil 1000 mg/m²/day days 1–5
- 3 cycles, q 3 wk

Concurrent CRT
- carboplatin (AUC 1.5) weekly; 7 doses maximum
- Radiation

Primary endpoint: Overall survival

Posner et al. (TAX 324)

- Select eligibility criteria
  - Stage III, IVA, IVB unresectable and potentially resectable
    - Low surgical curability
    - Goal of organ preservation
  - Locally advanced HNSCC (oral cavity, oropharynx, larynx, hypopharynx)
  - No prior chemotherapy, radiation therapy, or surgery for SCCHN
  - WHO PS ≤1

- Primary endpoint: Overall survival

- Secondary endpoints
  - Progression-free survival, response rates after induction chemotherapy, and toxic effects

Posner et al (TAX 324): Overall Survival

- **TPF (n=255)**
  - Median 70.6 months
  - (95% CI: 49.0 to not reached)

- **PF (n=246)**
  - Median 30.1 months
  - (95% CI: 20.9–51.5)

- 30% reduction in the risk of death
  - HR = 0.70
  - 95% CI: 0.54–0.90
  - P = .0058
Response rates to induction chemotherapy are higher with TPF compared to PF

Induction chemotherapy with TPF improves survival compared to PF, primarily due to increased locoregional control

Rate of distant failure is low with both TPF and PF

It is unknown whether induction chemotherapy is superior to upfront chemoXRT

It is unknown whether the improved survival with TPF would be observed in the setting of definitive treatment with concurrent cisplatin / XRT
Case 2

- 46yo M
- Hypertension
- Dysphagia
- 2-3 beers/day for 20 yrs
- Chewing tobacco and smoking
- Appliance repair man
Case 2

- Neck swelling: right submandibular and jugular chain
- Visual: mass involving posterior right hypopharynx, obliterates right AE fold
- Biopsy: squamous
- CXR: clear
- CT HN: right oropharyngeal lesion and LN
- T2N3M0 hypopharynx
Case 2: CT Baseline
Case 2

- Treatment: concurrent chemo-xrt
- 2 years later, hemoptysis
- Recurrent disease in chest
- CT with lobe collapse
- Palliative XRT to chest (obstructing lesion)
- Entered clinical trial
Case 2
June 03
Summary: Treatment Outcomes for Recurrent and/or Refractory HNSCC

Recurrent Disease
- Partial response rate: 35-40%
- Median survival: 6-9 months
- 1-year survival: 20-25%

Refractory to Chemotherapy
- Median survival: short
- 1-year survival: uncommon
## Novel Therapies in HNSCC

<table>
<thead>
<tr>
<th>Single Agent</th>
<th>Phase</th>
<th>N</th>
<th>RR</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib (Soulieres)</td>
<td>II</td>
<td>115</td>
<td>4.3%</td>
<td>38%</td>
</tr>
<tr>
<td>Gefitinib (Cohen)</td>
<td>II</td>
<td>47</td>
<td>11%</td>
<td>45%</td>
</tr>
<tr>
<td>Sorafenib (SWOG)</td>
<td>II</td>
<td>44</td>
<td>3%</td>
<td>45%</td>
</tr>
<tr>
<td>Cetuximab (Vermorken)</td>
<td>II</td>
<td>103</td>
<td>13%</td>
<td>33%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combination</th>
<th>Phase</th>
<th>N</th>
<th>RR</th>
<th>SD</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cis, Docetaxel, Erlotinib</td>
<td>II</td>
<td>48</td>
<td>66%</td>
<td>25%</td>
<td>11 mon</td>
</tr>
<tr>
<td>(Kim)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plat, 5FU, Cetuximab</td>
<td>III</td>
<td>442</td>
<td>nr</td>
<td>nr</td>
<td>10.1 mon</td>
</tr>
<tr>
<td>(Vermorken)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib + Bevacizumab</td>
<td>II</td>
<td>48</td>
<td>14%</td>
<td>54%</td>
<td>6.8 mon</td>
</tr>
<tr>
<td>(Vokes)</td>
<td></td>
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</tbody>
</table>
Other Targeted Therapies Being Studied in HNSCC

- **EGFR**
  - Lapatinib (Glaxo), Panitumumab (Amgen), Afatinib (BI)

- **IGFR**
  - A12 (ImClone), OSI-906 (OSIP)

- **Angiogenesis**
  - AZD2171 (AstraZeneca), Bevacizumab (Genentech), Sorafenib

- **Other**
  - Imatinib (pdgf), Dasatinib (src), Everolimus (mTOR)

- **Chemotherapies**
  - Pemetrexed (Eli Lilly), S1 (Sanofi)
EGFR

Cetuximab
Panitumumab
Gefitinib
Erloinib
Afatinib
EXTREME: Phase III Platinum/5FU ± Cetuximab in 1st Line RM HNSCC

Treatment-naïve refractory and/or metastatic SCCHN*

Stratification
Prior chemotherapy
KPS <80 vs ≥80

*No prior EGFR testing required for study entry
†EITHER carboplatin (AUC 5, d1) OR cisplatin (100 mg/m² IV, d1) + 5-FU (1000 mg/m² IV, d1-4) q3w for a maximum of 6 cycles
‡Cetuximab 400 mg/m² initial dose then 250 mg/m² weekly until progression or unacceptable toxicity

Primary: OS
Secondary: ORR, duration of response, TTP, QOL, Safety

n=222
n=220

Vermorken NEJM 2008
### EXTREME: Efficacy Data

#### Table 2. Responses to Treatment and Survival.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cetuximab plus Platinum–Fluorouracil (N = 222)</th>
<th>Platinum–Fluorouracil Alone (N = 220)</th>
<th>Hazard Ratio or Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival — mo†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>10.1 (8.6–11.2)</td>
<td>7.4 (6.4–8.3)</td>
<td>Hazard ratio, 0.80 (0.64–0.99)</td>
<td>0.04‡</td>
</tr>
<tr>
<td>Progression-free</td>
<td>5.6 (5.0–6.0)</td>
<td>3.3 (2.9–4.3)</td>
<td>Hazard ratio, 0.54 (0.43–0.67)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td><strong>Best response to therapy — %</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Overall</td>
<td>36 (29–42)</td>
<td>20 (15–25)</td>
<td>Odds ratio, 2.33 (1.50–3.60)</td>
<td>&lt;0.001§</td>
</tr>
</tbody>
</table>

* Data in the treatment columns are median (95% CI). The P values, hazard ratios, and odds ratios are stratified according to receipt or non-receipt of previous chemotherapy and the Karnofsky performance score at randomization.

† The number of months was estimated with the use of the Kaplan–Meier method.
‡ The P value was calculated with the use of the log-rank test.
§ The P value was calculated with the use of the Cochran–Mantel–Haenszel test.

¶ Disease control includes complete response, partial response, and stable disease. Time to treatment failure was defined as the time from randomization until the first occurrence of one of the following events: disease progression as assessed by the investigator, discontinuation of treatment because of disease progression, discontinuation of treatment because of an adverse event, initiation of any new anticancer therapy, or withdrawal of consent or death within 60 days after the final tumor assessment or randomization.

Data on the duration of response were available for 62 patients in the cetuximab group and 36 patients in the chemotherapy-alone group; data on disease progression in these patients were available at the time of the analysis. The number of months was estimated with the use of the Kaplan–Meier method.
Cetuximab for Platinum-Refractory HN Cancers

- Eligibility Criteria
  - Recurrent / metastatic HNSCC progressing within 30 days of platinum-based therapy

- Study Design
  - Single-arm, phase 2 study with 103 patients

- Results
  - response rate: 13%
  - recurrence-free survival: 70 days (~ 2 months)
  - overall survival: 178 days (~ 6 months)

*Cetuximab is indicated as salvage therapy based on this data!!??!*

Vermorken JCO 2007
EGFR TKIs in HNSCC

- **Erlotinib 150 mg/day:**
  - 4% RR in recurrent disease
  - PFS: 2.3 / OS 6 mos (Soulieres JCO 2004)

- **Gefitinib 250 mg/day:**
  - 1.4% RR in recurrent disease (0-5 previous CT)
  - PFS: 1.8 / OS: 5.5 mos (Cohen CCR 2005)

- **Gefitinib 500 mg/day:**
  - 11% RR in recurrent disease
  - PFS: 3.4 / OS 8 mos (Cohen JCO 2003)
Final Results of a Phase II Study of Erlotinib, Docetaxel and Cisplatin in Patients with Recurrent/Metastatic Head and Neck Cancer

Edward S. Kim, MD
MS Kies, BS Glisson, AS Tsao, LE Ginsberg, FC Holsinger, BJ Burke, M Truong, V Papadimitrakopoulou, WK Hong, SM Lippman
Efficacy
N = 48

- Complete response 4 pts (8%)
- Partial response 28 pts (58%)
- Stable disease 13 pts (25%)

- Overall response rate of 66%
- Disease control rate of 91%
- Only 3 pts progressed after 2 cycles of treatment
Overall Survival

11 months
(95% CI, 8.34 to 17)
1 yr survival 48%
Case 2

June 03    July 14
Patient W.E.

June 7, 2004  
July 28, 2004
Patient B.A.

Aug 9, 2004

Sept 21, 2004
Phase Ib Study of Erlotinib in SCCHN

Eligible patients with SCCof HN for whom surgical resection is planned

Obtain adequate baseline tumor specimen (archival or new biopsy)

Stratification factors:
- Mucosal vs. non-mucosal
- Current vs. former/never smoker

Randomize

Surgery

BLOOD-BASED BIOMARKERS AT WEEK 2 AND WITHIN 2 WEEKS PRIOR TO SURGERY (OPTIONAL)

POST-TREATMENT BIOMARKERS IN TUMOR TISSUE

CT scan

Standard dose: erlotinib 150 mg/day

High dose: erlotinib 200 mg/day (former / never smoker) or 300 mg/day (current smokers)

William et al. 2012
Phase Ib Study of Erlotinib in SCCHN

Response rates (28 evaluable patients)

- 7 responses (2 CR, 5 PR) – 25%
- 20 SD – 71%
- 1 PD – 4%
- 35% RR in oral cavity tumors

William et al. 2012
Preoperative Erlotinib Trial - Responses

Baseline

After 4 weeks of erlotinib 200 mg/day

pCR
Systemic Therapy for HN Cancer

- Chemosensitizer for concurrent therapy
- Induction chemotherapy
- Recurrent/Metastatic Disease
- Biologic Therapies: Cetuximab

Future Research

- EGFR: Afatinib, Necitumumab
- Nab-paclitaxel, Ramucirumab
- Immunotherapy (PD-1, PDL-1)

- Discover novel biomarkers
Thank you for your attention!