The Evolving Role of EGF Receptor Inhibition in Cancer of the Head and Neck

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Conflict of Interest

- Research support from Novartis
EGF-receptor

homo- or heterodimerization

Growth factors (EGF, TGF-α)

SOS Grb2

PI3K

PTEN

Ras-GDP

Ras-GTP

Raf

MEK

ERK

proliferation, anti-apoptosis, angiogenesis, survival metastasis
EGF Receptor inhibitors:

- EGF receptor overexpressed in >90% of cases
- member of the ErbB/HER family of receptors tyrosine kinases
- extracellular N-terminal ligand binding domain, a transmembrane region and a C-terminal intracellular domain
- transforming growth factor - α as the predominant autocrine growth factor in SCCHN
Anti-EGFR strategies

- targeting the EGF-R has been achieved by:
  » Antibody binding to the extracellular domain of the receptor with subsequent internalization of the antibody/receptor complex,
  » Competitive antagonism at the ATP binding site thus inhibiting EGF-R autophosphorylation and activation and
  » down-regulation of the EGF-R by using antisense DNA or siRNA.
  » Used in
    ■ recurrent disease,
    ■ combined chemoRT
    ■ sequential (induction) chemotherapy
1. EGF R inhibitors in metastatic disease
Phase II Trial of Gefitinib – 500mg

- Metastatic or recurrent SCC
- ≤ 1 prior therapy for recurrent disease
- PS 0-2
- Intact organ function

Gefitinib 500mg QD PO or G-tube

- Reassess q 4 weeks
- CT/MRI q 8 weeks
- RECIST criteria

Planned accrual 46
Primary endpoints: RR, TTP
Gefitinib 500mg Response (n=47)

- ORR: 11% (95% CI: 3.5-23.1)
- Disease control (CR/PR/SD): 53%
- Median TTP 3.4 months
- Median OS 8.1 months

Phase II Study Gefitinib – 250mg

- Planned accrual 63 patients.
- Primary endpoint: objective response rate (CR + PR).
- Rationale based on IDEAL trials in NSCLC

**REGISTRATION**

**Gefitinib 250mg QD**

- TUMOR BIOPSY
- VEGF LEVEL
- QoL
- EGFR GENOTYPING

- QoL q weekly for 4 weeks then q 4 weeks

- TUMOR BIOPSY
- VEGF LEVEL
- (WEEK 7 OR 8)

**RESPONSE ASSESSMENT – 8 WEEKS (RECIST CRITERIA)**

Response Gefitinib 250mg

- **ORR 1%**
- Median TTP 1.8 months
- Median OS 5.2 months
- Suggests dose-response relationship in SCCHN
  - Contrasts with NSCLC

Rash and EGFR Blockade

Median survival 11.1 vs 5.3 months, p=0.001

### Gefitinib 250mg and Rash

<table>
<thead>
<tr>
<th>Grade of skin rash</th>
<th>PD/NE</th>
<th>SD/PR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>(81.82)</td>
<td>(18.18)</td>
<td>(100.00)</td>
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<tr>
<td>1</td>
<td>17</td>
<td>9</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>(65.38)</td>
<td>(34.62)</td>
<td>(100.00)</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>(36.36)</td>
<td>(63.64)</td>
<td>(100.00)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>(0.00)</td>
<td>(100.00)</td>
<td>(100.00)</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>21</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>(65.00)</td>
<td>(35.00)</td>
<td>(100.00)</td>
</tr>
</tbody>
</table>

- Proportion of SD or PR increases as severity of skin rash increases (Wilcoxon rank-sum test, p=0.007)

ECOG 5397: Phase III cisplatin +/- Cetuximab

- Randomized phase III
- 117 patients with metastatic or recurrent SCCHN
- PS 0-1
- Cisplatin 100mg/m2 +/- Cetuximab 400/250mg/m2
- Primary endpoint PFS

Progression-free survival by treatment group

One-sided log-rank $P = .09$

<table>
<thead>
<tr>
<th>Arm</th>
<th>Total</th>
<th>Event</th>
<th>Censored</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>C225</td>
<td>60</td>
<td>58</td>
<td>2</td>
<td>4.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>56</td>
<td>55</td>
<td>1</td>
<td>2.7</td>
</tr>
</tbody>
</table>

ECOG 5397: Phase III cisplatin +/- Cetuximab

- Response rate 26% vs 10% (p=0.03)
ECOG 5397: Phase III cisplatin +/- Cetuximab

- Response rate 26% vs 10% (p=0.03)
- PFS 4.2 vs 2.7mo (p=0.09)
ECOG 5397:
Phase III cisplatin +/- Cetuximab

- Response rate 26% vs 10% (p=0.03)
- PFS 4.2 vs 2.7mo (p=0.09)
- OS 9.2 vs 8.0mo (p=0.21)
Phase I/II Study Erlotinib and Bevacizumab Recurrent/Metastatic SCCHN

- 48 patients in phase II portion
- Not more than one line of prior therapy
- Treatment with Bevacizumab 15mg/kg q3wk and erlotinib 150mg
- Primary endpoint in phase II response rate and PFS

Phase II Portion

Cycle # 1=28 days
Erlotinib Days 1-28
Bevacizumab Day 15

Subsequent Cycles=21 days
Erlotinib Days 1-21
Bevacizumab Day 1

## Best Response (Phase II) N = 48

<table>
<thead>
<tr>
<th>Response</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2 (4)</td>
</tr>
<tr>
<td>PR</td>
<td>5 (10)</td>
</tr>
<tr>
<td>SD</td>
<td>26 (54)</td>
</tr>
<tr>
<td>PD</td>
<td>15 (31)</td>
</tr>
</tbody>
</table>

Cetuximab: EXTREME trial

Design:
- randomized trial comparing PF alone with PF plus cetuximab
- 442 patients in first line therapy for recurrent disease.
- Overall survival was the primary endpoint.

Results:
- Median survival 7.4 months in the PF arm compared with 10.1 months for the PFC arm (p=0.036).
- This was one of the longest median survival times in this patient group ever recorded and the first randomized trial to demonstrate a survival advantage in the recurrent setting for head and neck cancer.

Questions:
- PFC versus treating with PF followed by C on progression?
- patients with incurable SCCHN are likely to benefit from treatment with an EGF-R inhibitor at some point but when?

Cetuximab: Side Effects

- Acneiforme rash is frequent (80% overall, 3% severe) and interestingly correlates with a tumor response.
- EGF-R expression as measured by immune-histochemistry in this study was not a reliable predictor of tumor response.
- Due to the chimeric nature of this antibody, allergic reactions occur in ~3% of patients who receive Cetuximab and are more frequent in some geographic areas.
- The allergic reactions are due to carbohydrates added to the antibody during manufacturing.

The insulin-like growth factors as target

- IGF-I along with its IGF binding protein 3 (IGFBP-3) have been implicated in cancer progression and metastasis.
- IGF-I acts though the IGF receptor 1 (IGF- R1), which allows IGF-I to exert its mitogenic effect on both normal and cancer cells.
- The IGF-IR is a RTKI which activates ras and phosphatidylinositol 3'-kinase-related signal transduction pathways.
- Involved in angiogenesis, suppression of cellular apoptotic pathways and facilitates cell growth.
- EGF-R inhibition may depend on cross-talk between EGF- and IGR-receptors.
- Serum IGF-1 and serum IGFBP-3 levels have also been found to predict second primary cancer risk.
IMC-A12

- IMC-A12 is a recombinant human IgG1 monoclonal antibody, antagonist of IGF-I and IGF-II ligand binding and signaling.
- effecting the internalization and degradation of IGF-IR
- IMC-A12 does not bind to or recognize the human insulin receptor
- The most significant adverse event to date has been hyperglycemia
- Rare SE include infusion reaction, anemia, psoriasis, pruritus, rash, acne, arthralgia, dizziness, fatigue, and nephrotoxicity
IMC-A12 study

- Open label randomized phase 2 study
- IMC-A12 +/- Cetuximab
- in ~ 90 patients with recurrent or metastatic HNSCC and prior Platinum-based therapy
- single agent IMC-A12 10 mg/kg over 1 hour every 2 weeks versus
- IMC-A12 10 mg/kg i.v. followed by cetuximab 500 mg/m2 i.v. repeated every 2 weeks
Alternative Anti-EGF-R Strategies

- Other anti-EGF-R strategies include
  - down-regulation of the EGF-R receptor by direct injection of antisense DNA.
  - Anti EGF vaccination

- Limited experience, only at specialized centers, effectiveness unknown
EGF-R inhibition in curative, locally advanced HN cancer
Cetuximab and radiotherapy in locally advanced HN cancer

- 424 Patients with stage III or IV, nonmetastatic, measurable squamous-cell carcinoma of the oropharynx, hypopharynx, or larynx
- randomly assigned to treatment with high-dose radiotherapy alone (213 patients) or high-dose radiotherapy plus weekly cetuximab (211 patients)
- The primary end point was the duration of control of locoregional disease;
- secondary end points were OS, PFS, RR, safety
The Cetuximab/Radiotherapy Phase III Trial

Stratify by:
- Karnofsky score: 90-100 vs. 60-80
- Regional Nodes: Negative vs. Positive
- Tumor stage: AJCC T1-3 vs. T4
- RT fractionation: Concomitant boost vs. Once daily vs. Twice daily

QD, BID or ACB Allowed

Bonner, NEJM, 2006
Cetuximab and Radiotherapy: Bonner et al

- 400 mg per square meter of body-surface area, followed by 250 mg per square meter weekly for the duration of radiotherapy.

<table>
<thead>
<tr>
<th>Table 1. Radiotherapy Regimens.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regimen</strong></td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Once daily</td>
</tr>
<tr>
<td>Twice daily</td>
</tr>
<tr>
<td>Concomitant boost</td>
</tr>
</tbody>
</table>

Overall Survival By Treatment: Median Follow-up 60 Months

Stratified Logrank p = 0.018, HR=0.73 (0.56-0.95)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total</th>
<th>Death</th>
<th>Alive</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation Alone</td>
<td>213</td>
<td>130</td>
<td>83</td>
<td>29.3</td>
</tr>
<tr>
<td>RT + Cetuximab</td>
<td>211</td>
<td>110</td>
<td>101</td>
<td>49.0</td>
</tr>
</tbody>
</table>

_Bonner, ASTRO, 2008_
Cetuximab and Radiotherapy: Bonner et al

Results:
- The median duration of locoregional control was 24.4 vs 14.9 months (HR 0.68; P=0.005).
- The median duration of overall survival was 49.0 months among patients treated with combined therapy vs 29.3 months (HR 0.74; P=0.03).
- Progression-free survival favored combined therapy as well (HR 0.70; P=0.006).
- No effect on the rate of distant metastasis was noted.

With the exception of acneiform rash and infusion reactions, the incidence of grade 3 or greater toxic effects, including mucositis, did not differ significantly between the two groups.
Cetuximab with Radiotherapy

- rate of esophageal stenosis among survivors at 1 year was 17% with radiotherapy and 19% with the combination.

- importantly, no effect on the rate of distant metastasis was noted. An unplanned analysis showed that patients with oropharynx primary and those who received concomitant boost radiation derived the most benefit from the combination.

- it is still unclear whether there is a difference in outcome of cetuximab combined with radiotherapy over platinum based chemoradiation. (RTOG 0522)
EGF inhibitors in Induction Therapy
Sustained Survival Advantage At 5 Years For Patients Receiving TPF Versus PF: Median Overall Survival 71 Versus 30 Months (HR 0.74, P=0.0129)
Phase I study of C-TPF in patients with locally advanced SCCHN

- 30 patients with previously untreated SCCHN were enrolled.
- FU cohorts were 700, 850, and 1,000 mg/m²/d for 4 days via continuous infusion.
- TPF given every 3 weeks for three cycles and C was given weekly for a total of 9 weeks, starting on day 1 of TPF.
- All patients received chemoradiotherapy after C-TPF
- 92% had stage 4 disease, 71% were oropharynx, and 100% had a performance status of 0

### Phase I study of C-TPF: Schema

#### 3 Cycles of Chemotherapy

| T | 1 | 1 | 1 |
| P | 1 | 1 | 1 |
| F | 1-4 | 1-4 | 1-4 |
| C | 1 | 8 | 15 | 1 | 8 | 15 | 1 | 8 | 15 |

#### Platinum-based Chemoradiotherapy

- XRT

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T: Docetaxel, P: Cisplatin, F: 5-fluorouracil, C: Cetuximab. XRT: Radiation therapy
Phase I study of C-TPF in patients with locally advanced SCCHN

- No dose-limiting toxicity (DLT) was encountered on dose levels 1 and 2.
- At dose level 3 of 1000 mg/m$^2$, one DLT was encountered and three more patients were enrolled with no DLTs. In the expansion cohort at the MTD, three DLT's were encountered.
- 5FU down from 1,000 mg/m$^2$ to dose level 2 of 850 mg/m$^2$. A total of 13 patients were enrolled at the MTD of 850 mg/m$^2$.

## First- Cycle dose- limiting toxicities

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>N</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>0/3</td>
<td>None</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>0/3</td>
<td>None</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>1/6</td>
<td>Mucositis/FN</td>
</tr>
<tr>
<td>Expansion Cohort 3</td>
<td>3/6</td>
<td>GI Bleed(2), FN1</td>
</tr>
<tr>
<td>Expansion Cohort 2</td>
<td>1/9</td>
<td>Mucositis</td>
</tr>
</tbody>
</table>
EGFR inhibitors in head and neck cancer: Summary

- EGFR inhibitors have become an established part of modern SCCHN treatment.
- Used in metastatic, concurrent and induction setting and adds clinically significant benefit.
- Combination treatment with traditional and biologic agents are emerging.