Targeting the ErbB Family in Head and Neck Cancer

a report by
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Head and neck cancer is the sixth most common cancer, representing about 5% of all cancers. Each year, more than half a million new cases are diagnosed worldwide. Over the past decade, the important role of different growth factors and their receptors and signal transduction pathways in the genesis and progression of tumours has been well recognised, and their mechanism of action and interaction is gradually being unravelled. The ErbB family comprises four members: human epidermal growth factor receptor (EGFR; HER 1), HER2 (c-erb-B2), HER3 (c-erb-B3) and HER4 (c-erb-B4).

Epidermal Growth Factor Receptor
EGFR and its ligand-transforming growth factor-alpha (TGF-α) are overexpressed in the vast majority of cases of squamous cell carcinoma of the head and neck (SCCHN). EGFR overexpression is an early event in carcinogenesis and steadily increases in parallel with histological abnormalities from hyperplasia, through carcinoma in situ to invasive carcinoma. EGFR overexpression is the result of an enhanced transcription or a gene amplification. There is a large body of evidence indicating that EGFR overexpression is a strong, independent and unfavourable prognostic factor for loco-regional control, disease-free survival and overall survival in SCCHN. Two of the potential EGFR-targeting strategies are currently in use. Monoclonal antibodies (MAbs) are directed at the extracellular domain of the receptor and at the small-molecule and adenosine tri-phosphate (ATP)-competitive tyrosine kinase inhibitors (TKIs) (see Table 1).

Monoclonal Antibodies
MAbs targeting EGFR that are under clinical development include IMC225 (cetuximab), EMD-72000 (matuzumab), ABX-EGF (panitumumab), h-R3 (nimotuzumab), Z8 (zalutumumab) and ICR62. The first MAb to enter the clinic was cetuximab (IMC225). Pre-clinically, it has antitumoral activity on its own and acts synergistically with chemotherapy and radiotherapy.

Cetuximab
Cetuximab is a chimeric human/murine immunoglobulin IgG1 antibody that binds with higher affinity to the EGFR than the natural ligands EGF and tumour necrosis factor-alpha (TNF-α). The cetuximab-bound EGFR is internalised and degraded without receptor phosphorylation and activation. The availability of EGFR on the cell surface is reduced and the receptor downregulated. The most common side effects are fever, chills, asthenia, nausea, transaminase elevation and skin toxicity. Severe skin reactions were observed by others when cetuximab was added to a taxane-containing triplet (Vermorken, personal communication).

Cetuximab was added to cisplatin and concomitant boost radiotherapy in a pilot phase II study conducted at the Memorial Sloan-Kettering Cancer Center. Twenty-two previously untreated patients with stage III or IV non-metastatic SCCHN were enrolled. The study was closed before it reached planned accrual because of toxicity concerns. Two patients died while still on study (one from pneumonia and one from an unknown cause). After that, three more non-fatal but serious adverse events occurred (one bacteraemia, one atrial fibrillation and one myocardial infarction), prompting study closure. However, three-year overall survival, progression-free survival (PFS) and loco-regional control rates were 76, 5 and 71%, respectively. Despite the early deaths, outcome compared favourably with those reported in the literature for patients with locally advanced SCCHN who were treated with chemoradiation alone. Moreover, in retrospect the significant adverse events were not clearly attributable to the investigational therapy. Therefore, although this regimen could not be recommended outside a clinical trial, the results were compelling enough to launch a randomised phase III Radiation Therapy Oncology Group (RTOG) study comparing this regimen with standard cisplatin-based chemoradiation. This trial will hopefully help to elucidate the question of how cetuximab fits into the current treatment strategies for loco-regionally advanced SCCHN. Kies et al. added cetuximab to weekly paclitaxel 135mg/m² and carboplatin area under the curve (AUC) 2 as induction regimen in treatment-naive locally advanced SCCHN. After six weekly administrations of the regimen all patients had a response, with 27% of these complete responses. Severe skin toxicity occurred in 47% of the patients. Severe skin reactions were observed by others when cetuximab was added to a taxane-containing triplet (Vermorken, personal communication).

Cetuximab has been studied extensively in recurrent and metastatic disease, both in first- and second-line treatment (see Table 2). In terms of first-line treatment, Burtner et al. randomised 117 patients with recurrent or metastatic SCCHN to cisplatin plus placebo or cisplatin plus cetuximab. No prior chemotherapy for recurrent and/or metastatic disease had been given to these patients. Objective response rate was 26% in the cetuximab arm and 10% in the placebo arm. PFS was longer in the cetuximab arm (4.2 versus 2.7 months). However, this difference was not statistically significant. This was probably due to the longer than expected
Head and Neck Cancer

Table 1: Epidermal Growth Factor Receptor-targeting Agents Under Clinical Investigation in Squamous Cell Carcinoma of the Head and Neck

<table>
<thead>
<tr>
<th>Monoclonal Antibodies</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>IgG1, Skin</td>
</tr>
<tr>
<td>Matuzumab</td>
<td>IgG1, Skin</td>
</tr>
<tr>
<td>Nimotuzumab h-R3</td>
<td>IgG1, Skin</td>
</tr>
<tr>
<td>Alutumumab 2F8</td>
<td>IgG1, Skin</td>
</tr>
<tr>
<td>Panitumumab ABX-Egf</td>
<td>IgG2, Skin</td>
</tr>
</tbody>
</table>

Table 2: Activity of Cetuximab in Platinum-refractory Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>RR (%)</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab monotherapy</td>
<td>103</td>
<td>13</td>
<td>5.9</td>
</tr>
<tr>
<td>Cetuximab + cisplatin/carboplatin monotherapy</td>
<td>96</td>
<td>10</td>
<td>6.7</td>
</tr>
<tr>
<td>Cetuximab + cisplatin</td>
<td>131</td>
<td>10</td>
<td>5.3</td>
</tr>
<tr>
<td>Platinum-refractory historical controls</td>
<td>151</td>
<td>3</td>
<td>3.4</td>
</tr>
</tbody>
</table>

RR = response rate.

As second-line treatment, three phase II trials examined the role of cetuximab in platinum-resistant disease. Baselga et al.36 added weekly cetuximab to platinum-based chemotherapy in 96 patients with platinum-refractory head and neck cancer (SCCHN). The objective response rate in the multivariate phase II study was 10% and the median time to progression and overall survival were 85 and 183 days, respectively. Herbst et al.37 studied the combination of cetuximab and chemotherapy in a heterogeneous population of 130 patients with recurrent and/or metastatic SCCHN. Patients either had stable disease after two cycles or had progressed under cisplatin-based chemotherapy. After the addition of cetuximab to the same regimen, 13% of the patients achieved a partial response. Median duration of response was about four months in the patients with progressive disease at the time they entered the study and 7.4 months in those who had stable disease. Responses in these two studies could be attributed to the reversal of cisplatin resistance or to the effect of cetuximab alone. The results of the third phase II trial38 suggest that the latter may be the case. In a population of 103 patients with platinum-resistant disease, a response rate of 13% and a median time to progression and survival of 2.3 and 5.9 months, respectively, were observed. These results are not dissimilar to the results of the add-on trials. Interestingly, the survival of up to six months achieved with cetuximab in platinum-resistant disease was similar to that seen with first-line therapy without cetuximab and represented an increase in survival of 2.5 months compared with platinum-refractory historical controls.39 Based on these results, cetuximab monotherapy seems to be a good option in patients with recurrent/metastatic SCCHN who have progressed on platinum-based chemotherapy.

**Other Monoclonal Antibodies**

Matuzumab (EMD72000)35–38 is a humanised IgG1 mouse anti-EGFR antibody that is in phase II testing in SCCHN. In phase I, the maximum tolerated dose was 1,600mg/week, with headache and fever as dose-limiting toxicities and acniform rash being the most common grade 1 or 2 toxicity. It has a prolonged half-life that allows for administration every two or three weeks. The optimal biological dose was 1,200mg every three weeks. Panitumumab (ABX-EGF) is a human IgG2 antibody.35 It blocks ligand binding and induces internalisation of the receptor with no receptor degradation. Side effects include pruritus, skin rash, dyspnoea, fatigue, abdominal pain, asthma and diarrhoea. Panitumumab at a weekly dose of 2.5mg/kg has an acceptable tolerability and encouraging clinical activity in patients with a variety of tumour types.36 Panitumumab is being studied as a single agent, in combination with chemotherapy in recurrent or metastatic disease and in combination with induction chemotherapy and chemoradiation in locally advanced SCCHN. Nimotuzumab (h-R3)37–39 is a humanised IgG1 mouse antibody. Preliminary data suggest that therapeutic levels of h-R3 can be achieved without eliciting skin toxicity. This is the most common side effect of the other anti-EGFR directed antibodies. In phase I studies h-R3 was added to radiation.
in patients with locally advanced SCCHN. The optimal dose for further phase II testing was determined to be 200mg/m².52,53 Zalutumumab (ZB4) is a fully human IgG1 EGFR-directed MAb that also exerts antibody-dependent cell-mediated cytotoxicity. The frequency of the acneiform skin rash observed with this antibody increases with dose. In a phase III trial by the Danish Head and Neck Cancer Study Group (DAHANCA), no dose-limiting toxicities were observed at doses of up to 8mg/kg/week. Metabolic responses, as evaluated by fluorodeoxyglucose (FDG) positron emission tomography (PET), were observed in six of the 15 evaluable patients and response evaluation by computed tomography (CT) showed a partial response in two of the 16 evaluable patients.52 Zalutumumab is currently undergoing phase III testing in patients with cisplatin refractory disease. The rat EGFR-directed antibody ICR62 is a rat MAb to the EGFR.54 A phase I clinical trial with a single dose of ICRI62 demonstrated that this antibody could be administered safely to patients with SCCHN and non-small-cell lung cancer (NSCLC). Four out of 20 patients developed human antirat antibodies. ICRI62 could be found in metastatic tumour sites in biopsies taken 24 hours after administration. MDX-447 (Humax(®) is a bispecific antibody comprising humanised Fab anti-CD64 and humanised Fab anti-EGFR. MDX-447 recognizes the CD64 receptor and directs the cytotoxic effector cells to the EGFR-expressing tumour cells. The dose-limiting toxicity is hypotension.

Epidermal Growth Factor Receptor-targeted Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKIs) compete with ATP for the cytoplasmatic catalytic domain of EGFR. Gefitinib and erlotinib are reversible specific EGFR TKIs and belong to the group of quinazoline TKIs. This group also includes: PD153035 and GW 572016 (lapatinib), which are reversible dual EGFR/HER-2 inhibitors; EKB-569, which irreversibly inhibits the EGFR and HER-2 TK, and the irreversible pan-ERBB TKI CI 1033 (cetinabtib). PKI-166 (dual EGFR/Erbb-2) belongs to the pyrrolotriazine TKIs, which also include AEE788 (dual EGFR/Erbb-2) and BMS 599626. ARRY-334543 (dual EGFR/Erbb-2) and PD1578 belong to the pyridopyrimidine TKIs.55 In a phase II trial in 52 patients with recurrent or metastatic disease, 85% of whom had received prior chemotherapy, the overall response rate with gefitinib 500mg/day was 10.6%. The only grade 3 toxicity was diarrhoea, which occurred in 6% of the patients. Median time to progression was 3.4 months and median overall survival was 8.1 months. Forty-seven patients with locally recurrent and/or metastatic SCCHN were enrolled in an expanded access programme of gefitinib at the Royal Marsden and St George’s hospitals.56 Patients were eligible if they had received prior radiotherapy and/or chemotherapy or were medically unfit for chemotherapy. The patients received 500mg/day and the only grade 3 toxicity was folliculitis, which occurred in 8%. The observed clinical response rate was 8%. Median time to progression was 2.6 months and median overall survival was 4.3 months.

Wheeler et al.57 treated 20 patients who had received only chemotherapy as their primary management for localised disease with gefitinib 500mg/day and observed three objective responses (15%), with a median response duration of six months. There were no objective responses in 12 patients with chemotherapy-refractory disease. Grade 3 toxicities were skin rash and gastrointestinal, and were observed in eight of the 32 patients. There was no association between rash and response. Median time to progression was three months and median overall survival was six months. In a multicentre phase II trial in the US, 70 patients58 with recurrent and/or metastatic SCCHN were treated with gefitinib 250mg/day. Grade 3 toxicities included diarrhoea (2%), rash (1%), pulmonary toxicity (1%) and nausea (1%). Median PFS was 1.8 months. The response rate of 1.4% contrasted unfavourably with the response rates observed with a daily dose of 500mg in the prior studies, suggesting that there may be a dose-response relationship for gefitinib in SCCHN. This latter aspect was tested in a large phase III trial (1839 IL/I0704).59 In the trial, 486 patients with recurrent and/or metastatic SCCHN unresponsive to or unfit for platinum were randomised to receive weekly methotrexate, gefitinib 250mg/day or gefitinib 500mg/day. Overall response rates were 3.9, 2.7% and 7.6%, respectively. Median overall survival times were 6.7, 5.6 and 6 months, respectively (p=0.39). Soulieres et al.60 treated 115 patients with recurrent and/or metastatic SCCHN with erlotinib at an initial dose of 150mg/day. Ninety-seven per cent of these had previously been irradiated and 37% had received prior chemotherapy. The most common drug-related toxicities were rash and diarrhoea, which was grade 1 or 2 in the vast majority of cases. Response rate was 4.3%. Median PFS was 9.6 weeks and median overall survival was six months. No difference was detected based on HER1/EGFR expression, but patients who developed at least grade 2 skin rash had a significantly better survival (see Table 3).

The optimal way of integrating the TKI into the current treatment strategies for head and neck cancer has yet to be determined, taking into consideration the experience with EGFR TKIs in NSCLC, where adding erlotinib or gefitinib to standard chemotherapy did not improve the outcome compared with chemotherapy alone.61-63 The radiosensitising and chemosensitising properties of gefitinib are sequence-dependent in several SCCHN lines.64-62 Synergy was observed when gefitinib was applied before radiation or before or during cisplatin and 5-FU. However, antagonism occurred when gefitinib application followed chemotherapy.60 Other investigators detected synergism when gefitinib was applied during or after docetaxel or gemcitabine, but antagonism in some cell lines when gefitinib preceded docetaxel.61,62 Induction chemotherapy followed by concomitant chemoradiation is a treatment paradigm that has recently gained much attention. Cohen et al.63 treated 69 patients with stage III or IV SCCHN with two cycles of induction chemotherapy (carboplatin and paclitaxel) followed by an alternating chemotherapy and radiation regimen and added gefitinib 250mg/day. After chemoradiation, gefitinib was continued for two years. Thirty-seven of the 42 evaluable patients (88%) had a complete response. Grade 3/4 toxicities were consistent with prior chemoradiation trials using the same regimen. After a median follow-up of 294 days, two patients had progressive disease and four patients had died.

Doss et al.64 added gefitinib 250mg/day to an induction regimen of docetaxel 60mg/m² and carboplatin (AUC 5) given on days one and 22, 5-FU given as a continuous infusion at a dose of 200mg/m² on days one to
Head and Neck Cancer

43. Beginning on day 43, patients received radiotherapy (68.4 in daily fractions of 1.8Gy) concurrently with docetaxel 20mg/m²/week and gefitinib 250mg/day. Forty-five patients entered the study. Grade 3/4 myelosuppression was common and all patients experienced grade 3/4 mucositis during the combined modality programme. There was one treatment-related death. Thirty-five patients had completed the regimen and were evaluable for response. Response was evaluated by CT scan and endoscopy. There was a complete response in 32% of patients and a partial response in 53%. Erlotinib 150mg/day can be safely combined with concurrent chemoradiation and weekly docetaxel 20mg/m².65 or cisplatin 100mg/m² every three weeks, without jeopardising timely administration of radiotherapy. Complete response rates were 83 and 84%, respectively. Phase II trials are planned or being considered. However, as there are data suggesting that when erlotinib is added to weekly docetaxel lowering of the dose of both drugs may be necessary, caution is still warranted when combining chemotherapy and TKIs.

In a so-called ‘window of opportunity’ study, Delord et al.68 treated 35 patients who had resectable SCCHN with erlotinib 150mg/day for the 14–27 days between diagnosis and surgery. As expected, rash and diarrhoea were the most frequent side effects. Twenty-five subjects were assessable for efficacy, of whom 36% responded (all partial responses). No delay in surgery was observed. Normal and tumour tissue biopsies were taken before and after treatment. Laboratory studies included EGFR TK mutation analysis and immunohistochemistry, including EGFR, phosphorylated-EGFR, phosphosytrophosine (p-Tyr), phospho-Akt (p-Akt), signal transducer and activator of transcription 3 (STAT3), phosphorylated extracellular signal-regulated kinase (pERK) 1/2, p21 and p27. No mutations in the catalytic domain of the EGFR TK were found. Interestingly, p21 expression was found to predict response to erlotinib (p=0.0002). Therefore, this trial demonstrated a useful prospective method to potentially aid patient selection and improve the design of post-operative adjuvant treatment combinations. In vitro and in vivo data suggest that combined targeting of the extracellular ligand-binding domain by an anti-EGFR antibody and the intracellular receptor kinase domain by a TKI has a complementary effect on downstream signalling, apoptosis, proliferation and tumour xenograft growth.69–70

Epidermal Growth Factor Receptor Mutations

The search for EGFR mutations is an area of active investigation. An EGFR mutation of particular importance is EGFRvIII. It is a ligand-independent, constitutively phosphorylated form of EGFR with enhanced tumourigenicity and radioresistance in pre-clinical models.71–73 EGFRvIII involves deletion of exon 2-7A and is frequently present in glioblastoma. It was detected by Sok et al.74 in 14 out of 33 SCCHN specimens by immunostaining and reverse transcription polymerase chain reaction (PCR) for EGFRvIII expression. An EGFRvIII transfected SCCHN cell line showed an increased proliferation and growth in vitro and in vivo, decreased apoptosis in response to cisplatin and decreased growth inhibition by cetuximab compared with vector transfected controls. Somatic activating mutations in the EGFR kinase domain were first described in NSCLC.75–76 In NSCLC, EGFR mutations in the TK domain are more frequent in never-smokers, females, patients of East Asian origin and patients with adenocarcinoma. Eighty-six per cent of the EGFR mutations in NSCLC occur in exon 19 or 21. The most common mutations are deletions in exon 19 and a missense mutation in exon 21 (L858R). The exon 19 deletions L858R, L861Q and G719A/C/S are consistently associated with in vitro and in vivo sensitivity to gefitinib and erlotinib, while exon 20 insertions and the T790M mutation are associated with resistance to gefitinib and erlotinib. The significance of other mutations is not yet entirely clear.77–82 In vitro NSCLC cell lines harbouring EGFR mutations were more sensitive to gefitinib, but their sensitivity to cetuximab was similar to that of EGFR wild-type cell lines.83 Gefitinib-sensitising EGFR mutations have been described in an oesophageal cancer cell line84 and in oesophageal tumours.85

The incidence of EGFR mutations in SCCHN is currently not known and varies from series to series.86–92 Lee et al.93 analysed the EGFR gene in 41 SCCHN and detected three (7.3%) deletions in exon 19 in a Korean population. Willmore-Payne94 detected two mutations in 24 tumours of the head and neck, one exon 20-activating mutation (N771I/VinsG) and one exon 19-activating mutation (G729E). Loeffler-Raggi95 detected an EGFR missense mutation in one out of 100 tumour samples of SCCHN patients. In a series of 82 patients, of whom eight had a gefitinib-responsive tumour, Cohen et al.90 did not find any EGFR TK-activating mutation. They did detect one ERbB2 mutation within exon 20. Also, Delord et al.68 did not find any mutation in 35 patients with newly diagnosed resectable SCCHN. Moreover, Mojica et al.96 did not detect any mutation in exon 19 or 21 in 11 SCCHN tumour specimens at Roswell Park Cancer Institute. The exact incidence of specific mutations and their possible predictive role in SCCHN have yet to be determined. Preliminary data suggest that EGFR mutations may be associated with a better outcome in tongue and tonsil cancer.92

Human Epidermal Growth Factor 2

HER2 (or ErbB2) is expressed in 40–60% of SCCHN and is also associated with a worse outcome.93 The ErbB2-directed antibody trastuzumab was added to paclitaxel and carboplatin in a phase II study that included patients with metastatic or recurrent SCCHN.94 The response rate (36%) was not higher than expected with this chemotherapy regimen alone. Lapatinib is a selective and potent dual competitive reversible inhibitor of the EGFR and HER2 TK.95 As a single agent, lapatinib is well tolerated but appears to have little, if any, activity in either EGFR inhibitor-naïve or -refractory patients with recurrent or metastatic SCCHN.95 Abidoye et al.95 did not observe any objective responses in 42 patients and found a median PFS of six weeks. The combination of lapatinib with conventional radiation (70Gy) and cisplatin 100mg/m² every three weeks was tested in a phase I dose-escalating study.96 The optimal dose was determined to be 1,500mg/day. Seventeen of the 22 patients were evaluable and 74% achieved a complete response. The others had a partial response. Toxicities were no different to those typically observed with concurrent cisplatin and radiotherapy.

Combinations of Targeting Agents

Cyclo-oxygenase 2 (COX-2) expression was found to be an independent prognostic predictor of disease-free survival in some series of oral squamous cell carcinoma.97–100 EGFR and COX-2 signalling pathways form a positive feedback loop.100–102 The EGFR ligands EGF and TGF-α induce COX-2 expression, and COX-2 induces transactivation or increased EGFR expression. The combination of the TKI AG1478 or gefitinib and celecoxib inhibits, either additively or synergistically, the growth of five SCCHN cell lines.103–105 EGFR TKIs and COX-2 inhibitors have a non-overlapping toxicity profile. The combination of celecoxib and gefitinib was tested in a phase I dose-finding study at the Dana Farber Cancer Institute.115 All patients had previously been treated with chemotherapy or radiochemotherapy. At doses of 400 and 500mg twice-daily, no dose-limiting toxicities were encountered. The incidence of diarrhoea and rash was similar to the reported incidence of these toxicities in phase II studies of gefitinib 250 or 500mg/day in SCCHN. The response rate was 22%. The median duration of response was 4.8 months; the median progression and overall survival...
were three and six months, respectively. The majority of studies examining the prognostic significance of vascular endothelial growth factor (VEGF) expression observed a worse outcome in patients with SCCHN expressing VEGF and VEGF receptor-2.111 Mauer et al.12 combined erlotinib 150mg/day with the humanised VEGF-A directed antibody bevacizumab, which was administered every three weeks in doses increasing from 5 to 15mg/kg. There were no dose-limiting toxicities. After two cycles of treatment, seven of the nine evaluable patients had stable disease and a partial response was documented in one. The dose of bevacizumab could be safely raised to 15mg/m² every three weeks. This dose was subsequently taken into a phase II study. Preliminary data on 28 evaluable patients were reported.113 Five out of 28 patients had a response (two complete responses and three partial responses). Median progression-free survival was 127 days and median overall survival was 226 days. Pre-clinical data14 suggest synergene when gefitinib and irradiation are combined with AZD2171, a highly potent, orally active, VEGF signalling inhibitor.

Conclusion
EGFR is an obvious target for therapy as it is overexpressed in virtually all SCCHN. The EGFR-directed MAb cetuximab has activity as a single agent in platinum-resistant disease and acts synergistically with radiotherapy and first-line platinum-based chemotherapy. Thus far, the results with EGFR TKIs are less promising. Areas of investigation are the integration of targeted therapies into existing treatment strategies and the combined use of agents targeting the same pathway at multiple levels or targeting multiple pathways.


