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Novel Chemoradiotherapy Regimens Incorporating Targeted Therapies in Locally Advanced Head and Neck Cancers

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1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide. The majority of cases present with locally advanced, non-metastatic HNSCC for which the survival rates are approximately 50% at 5 years. Primary surgery followed by chemoradiotherapy (CRT) or definitive platinum-containing CRT are the standard therapeutic approaches utilized in locally advanced HNSCC. In the updated MACH-NC meta-analysis, CRT resulted in an absolute 8% improvement in overall survival (OS) at 5 years (Pignon et al., 2007; Pignon et al., 2009). However, despite incremental therapeutic advances, the problems of locoregional recurrences, distant metastases, organ preservation, and toxicity amelioration remain a significant challenge.

Several molecular pathways are deregulated and activated in HNSCC making it attractive area for the evaluation of the recently available and in-development molecular targeted therapies. Among the pathways implicated in the development of HNSCC are the epidermal growth factor receptor (EGFR) pathway and the vascular endothelial growth factor (VEGF) receptor pathway. In this chapter we will review the current data with completed and ongoing trials with molecular targeted therapies in the management of locally advanced HNSCC.

2. Epidermal growth factor receptor inhibitors

EGFR is a member of the human epidermal growth factor receptor family of receptor tyrosine kinases that is overexpressed in most HNSCC cases. Signal activation with natural ligand fixation to EGFR leads to receptor homodimerization or heterodimerization with other HER receptors occurs which in turn leads to the activation of downstream signaling molecular pathways. These pathways, including the Ras/Raf/Mek/Erk and the phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) pathways, are involved in tumor proliferation, apoptosis, angiogenesis, and cell migration/invasion. Increased EGFR expression as well as a high EGFR gene copy number are associated with worsened survival outcomes (Grandis et al., 1998; Ang et al., 2002). EGFR inhibition is a promising strategy in HNSCC since it results in inhibition of tumor cell proliferation, potentiation of apoptotsis

and antiangiogenic effects (Ciardiello, 2005; Hirata et al., 2002). Currently available anti-EGFR therapeutic agents can be classified into monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs).

2.1 Monoclonal antibodies against EGFR

Monoclonal antibodies directed against EGFR inhibit activation of distinct EGFR signaling pathways and inhibit tumor growth through cell cycle arrest, pro-apoptotic effect, and inhibition of angiogenesis, invasion and metastasis, and possibly immune mechanisms (Baselga et al., 2000; Mendelsohn & Baselga, 2003). Moreover, anti-EGFR antibodies can augment the antitumor activity of RT and chemotherapy (Huan & Harari, 2000; Milas et al., 2004; Baselga et al., 1993; Fan et al., 1993).

Characteristic	Cetuximab	Nimotuzumab	Zalutumab	Panitumumab
Ig subclass	IgG1	IgG1	IgG1	IgG2
Type	Chimeric	Humanized	Fully human	Fully human
Status	Phase III	Phase III	Phase III	Phase III

Table 1. Current EGFR antibodies in evaluation in head and neck cancers

2.1.1 Cetuximab

Cetuximab is a chimeric human-murine monoclonal antibody that binds competitively to the EGFR with a higher affinity than its endogenous ligands. It has been studied extensively in HNSCC in several phase II and III studies and was approved by the FDA, in combination with RT for the treatment of patients with locally advanced head and neck cancer.

2.1.1.1 Cetuximab and radiotherapy alone

Bonner et al have published updated 5-year survival results of their pivotal phase III study which compared RT alone (n = 213 patients) with cetuximab plus RT (n = 211 patient) in patients locally advanced HNSCC of the oropharynx, hypopharynx, or larynx (Bonner et al., 2010). Patients were stratified by their Karnofsky performance score (60-80 versus 90-100), Tumor stage (T1-3 versus T4), N stage (N0 versus N1-3), and radiotherapy fractionation. The primary endpoint of the trial was duration of locoregional control and the secondary endpoints were quality of life and overall survival.

The updated median OS for patients treated with cetuximab and radiotherapy was 49 months versus 29.3 months in the RT alone group (p= 0.018). The 5-year OS rates for the cetuximab-RT and RT-alone groups were 45.6 months and 36.4 mmonths, respectively. Patients treated with cetuximab had a 26% reduction in the risk of death (hazard ratio [HR], 0.74%; 95% confidence interval [CI], 0.57-0.97) and a 9% absolute benefit in OS rate at 5 years. Though locoregional disease control was positively impacted with the addition of cetuximab (HR, 0.68; p = 0.005) there was no such impact upon distant disease control. In subgroup analysis, median OS values for patient receiving cetuximab-RT versus RT alone were statistically significantly different for primary tumor T1-T3 stage (69.5 months versus 41.4 months), N1-3 neck nodes (53 versus 26.9 months), stage II-III patients (69.5 months versus 46.9 months), and stage IV patients (43.2 months versus 24.2 months).

A forest plot analysis was done to assess whether certain patient groups benefitted with the addition of cetuximab to RT. In this analysis, factors which were associated with a potential increased benefit included presence of oropharyngeal tumors, concomitant boost RT, early T stage (T1-T3), high Karnofsky performance score (90%-100%), male sex, and age < 65 years. These results are provocative but given that the trial was not powered for this subgroup analysis, they should be interpreted with caution.

Patients who received cetuximab commonly developed an acneiform rash (83.7%); the severity of the rash was grade 3-4 in 16.8% patients. Infusion-related reactions were also seen in 15.4% patients; in 3.9% patients these were of grade 3/4 severity. However, in-field toxicities, such as mucositis, dermatitis, and dysphagia did not significantly increase with the addition of cetuximab to RT. Quality-of-life parameters were not adversely affected by the addition of cetuximab. This study allowed different RT fractionation regimens which may have impacted results and survival outcomes.

Based on the results of this study, the combination of cetuximab with RT is considered an alternative to platinum-based CRT for the treatment of locally advanced HNSCC and has been included in the National Comprehensive Cancer Network (NCCN) guidelines as an option for the treatment of locoregionally advanced HNSCC since 2007.

2.1.1.2 Cetuximab and chemoradiotherapy

The favorable results with the use of cetuximab plus RT have led to the adoption of this regimen in locally advanced HNSCC. A natural progression has been the evaluation of integration of cetuximab into existing chemoradiotherapy, typically involving platinum-based regimens. Several phase II studies from various groups have been conducted. Larger randomized trials have been launched and more recently the preliminary results of a randomized study evaluating the combination of cisplatin, cetuximab, and RT in this setting have been presented.

Multiple phase II studies have investigated the integration of cetuximab with standard platinum-based CRT regimens. A pilot study from the Memorial Sloan Kettering group evaluated 22 patients treated with accelerated fractionation by concomitant boost RT and cisplatin (100 mg/m2 on weeks 1 and 4) plus weekly cetuximab (Pfister et al., 2006). In this study, acute toxicities were typical of cisplatin-RT and cetuximab was related to grade 3/4 acneiform rash (10%) and infusion reactions (5%). However, the trial was closed prematurely due to significant adverse events including 2 deaths (one due pneumonia, one unknown cause), one myocardial infacrction, one bacteremia, and one atrial fibrillation. The 3-year PFS and OS rates were 76% and 56%, respectively.

In other studies, the combination of cisplatin and cetuximab concurrently with standard RT has not shown such an adverse event profile. This combination was evaluated in a phase II study by the Eastern Cooperative Oncology Group (ECOG) in patients with unresectable locally advanced HNSCC (E3303) (Langer et al., 2008). Cisplatin (75 mg/m2 every 3 weeks for 3 doses) was combined with weekly cetuximab followed by maintenance cetuximab for 6 months in responding patients with tolerable toxicity. Of 61 patients actually treated on study, the overall response rate was 48% with stable disease in 31% patients. The major grade 3/4 toxicities included neutropenia (26%), rash (28%), dermatitis (15%), mucositis (55%) and one death (neutropenic fever). The CR rate was 36.7% and maintenance

cetuximab could be given in 74.6% patients. The 2-year PFS was 44% and the median PFS was 17.4 months. The 2-year OS was 66% with a median OS of 34.2 months. The patterns of relapse included distant (54.2%), regional (16.6%), both distant and regional (8.3%), local and regional (8.3%) and local only in 1 patient (4.2%).

In a randomized phase II study from the Radiation Therapy Oncology Group, 238 high-risk patients with resected HNSCC were randomized to receive weekly cetuximab with either weekly cisplatin 30 mg/m2 or weekly docetaxel 15 mg/m2 with 60 Gy RT over a 6-week period (RTOG 0234) (Kies et al., 2009). Patients were considered high-risk based on positive margins, $\geq$ 2 involved lymph nodes or extracapsular nodal spread. Data were available on 203 patients, 97 in the cisplatin arm and 106 in the docetaxel arm. Major grade 3/4 toxicities in the cispaltin and docetaxel arms included neutropenia (28% and 14%), mucositis (37% and 33%) and dermatitis (33% each) in the cisplatin and docetaxel groups, respectively. The 2-year OS in the cisplatin and docetaxel arms were 69% and 79%, respectively. Likewise, the 2-year DFS in the cisplatin and docetaxel arms were 57% and 66%, respectively. The 2-years distant metastasis rates with docetaxel and cisplatin were 26% and 13%, respectively and this in turn was most likely responsible for the improvement in DFS in the docetaxel arm.

In an Italian study, Merlano et al have evaluated the combination of 3 cycles of every 3-weeks cisplatin (20 mg/m2/day X 5 days) and 5-fluorouracil (200 mgm2/day X 5 days) with weekly cetuximab and rapidly alternated to 3 split courses of RT (70 Gy) (Merlano et al., 2011). In 45 patients treated, the overall RR was 91% with a CR rate of 71%. Major grade 3/4 toxicities included stomatitis (65%), neutropenia (40%), thrombocytopenia (15%), and grade 3 radiodermatitis (74%) with 3 patients dying during therapy. The median PFS and OS were reported at 21+ months and 32.6+ months, respectively.

The combination of amifostine, cetuximab, weekly cisplatin (30 mg/m2) along with conformal/hypofractionated RT (2.7 Gy/fraction, total 21 fractions in 4 weeks) was evaluated in a Greek study by Koukourakis et al. (Koukourakis et al., 2010). In this study, 43 patients were treated with the dosing of amifostine individualized according to tolerance. High dose and standard dose amifostine were tolerated by 41.8% and 34.9% patients, respectively and high dose amifostine was linked to reduced RT delays. Grade 3/4 mucositis occurred in 16.2% patients, fungal infections occurred in 41.8% patients, and cetuximab interruptions due to acneiform rash were necessary in 23.3% of patients. The complete response rate was 68.5% and the 2-year local control and survival rates were 72.3% and 91% respectively.

Suntharalingam et al from the University of Maryland group evaluated cetuximab with weekly carboplatin (AUC 2), paclitaxel (40 mg/m2) and 70.2 Gy RT in 43 patients with unresectable disease (Suntharalingham et al., 2011). The planned cetuximab and chemotherapy cycles were completed in 70% and 56% patients, respectively. Major toxicities included grade 3 mucositis (79%), dysphagia (21%), radiodermatitis (16%), rash (9%), and grade 3/4 neutropenia (21%). The CR rate was 84% at end of therapy and the estimated 3-year locoregional control rate was 72%. Local and distant recurrences were seen in 6 and 10 patients, respectively. The 3-year actuarial OS and DFS rates were 59% and 58%, respectively.

Birnbaum et al from the Brown University Oncology Group have evaluated a short 4-week cetuximab "induction" period followed by cetuximab with weekly carboplatin (AUC 1),

paclitaxel (40 mg/m2) and concurrent RT to 66-72 Gy in 32 patients (Birnbaum et al., 2010). Patients were stratified by operable or inoperable disease. Patients with potentially resectable disease underwent interim tumor biopsy after 5 weeks CRT; positive biopsy patients underwent salvage surgery and the others completed CRT. Grade 3/4 radiodermatitis occurred in 53% patients which was increased compared to the prior experience with the chemotherapy regimen alone by these investigators. With a minimum follow-up of 3 years, the updated analysis shows the PFS and OS to be 53% and 59%, respectively. The rates of local, distant and combined recurrences were 22%, 15%, and 7%, respectively. The investigators detected no improvement in local control or distant metastasis free survival compared to their prior results with chemotherapy-RT alone.

Kao et al have evaluated the addition of cetuximab to the well-described non-platinum FHX regimen consisting of 5-fluorouracil, hydroxyurea, and hyperfractionated intensity modulated radiotherapy in 33 patients with locally advanced HNSCC (Kao et al., 2011). Prior organ-conserving surgery was allowed. RT was administered in 1.5 Gy fractions twice daily during weeks 1, 3, 5, and 7 to a median dose of 72 Gy. Grade 3 toxicity consisted of mucositis (33%), radiodermatitis (15%),neutropenia (12%) and thrombocytopenia (3%). The 2-year rates of locoregional control, DFS, and OS were 83%, 69%, and 86%, respectively. There were no grade 4 events and 64% patients completed treatment without requiring a feeding tube.

A large randomized phase III study was completed by the RTOG that compared accelerated fractionation RT by concomitant boost and cisplatin with or without cetuximab in patients with previously untreated, locally advanced HNSCC (Ang et al., 2011). A total of 940 patients with stage III-IV oropharynx, hypopharynx, and larynx cancers with Zubrod performance scores 0-1 were randomized to one either the experimental arm of cisplatin (100 mg/m2 every 3 weeks x 2 doses), weekly cetuximab and RT (42 fractions, total dose 70-72 Gy) over 6 weeks or the same regimen without cetuximab. Of 895 evaluable patients, 497 patients were randomized to the experimental arm and 448 patients to the standard arm. The primary tumor sites were oropharynx (70%) and larynx (23%). Among the experimental and standard arms, the distribution of stage IV disease (85% vs. 87%), T3-4 stage (60% vs. 62%) and node-positive disease (88% vs. 90%) were fairly well balanced.

The primary endpoint of this study was PFS and the secondary endpoints were OS, toxicity and early mortality. Interim analyses were planned at 108, 217, and 325 events and a planned subgroup analysis for interaction of p16 status with treatment outcomes was conducted. With a target accrual of 940 patients, the study was powered at 84% to detect a HR of 0.75. The trial was ended early after the third interim analysis showed that it was unlikely to meet its primary endpoint.

The cetuximab-containing arm had higher rates of grade 3/4 mucositis (43% versus 33%, p=0.003), in-field skin toxicity (25% versus 15%, p<0.001), out-of-field skin reactions (19% versus 1%, p < 0.001) but grade 3/4 dysphagia rates were similar (62% versus 66%, p=0.27). The rates of 30-day mortality were similar (2% versus 1.8%) as were the total grade 3-5 adverse event rates (92% versus 90%).

With a median follow-up of 2.4 years for surviving patients, there were no significant differences in 2-year PFS rates (63.4% versus 64.3%) or OS (82.6% versus 79.7%). The risk of distant metastases was numerically reduced in the experimental arm by 26% (HR 0.74,

p = 0.7) while the risk of locoregional progression was numerically higher in the cetuximab arm (HR 1.21, p=0.92). In a planned subgroup analysis, 321 of 628 patients with oropharynx cancer were evaluated for HPV p16 status. The p16 positivity rate was 73% (235 patients) and both PFS and OS did not differ according to the PFS status.

Treatment Regimen	Patients (n)	Responses	Toxicity	Reference
CETUXIMAB AND CRT ALONE				
CRT: cisplatin (2 cycles), cetuximab and RT over 6 weeks	22	RR: 94% 3-year PFS and OS: 56% and 76%	Major grade 3/4 cetuximab-related toxicities were rash (10%) and hypersensitivity (5%); study closed due to significant adverse events.	Pfister et al, 2006
CRT: cisplatin, cetuximab and RT Maintenance: cetuximab x 6 months (E3303)	61(unresectable)	RR: 48%2-year PFS and OS: 44% and 66%	Major grade 3/4 toxicities were neutropenia (26%), rash (28%), dermatitis (15%), mucositis (55%); one patient death	Langer et al, 2008
CRT:cetuximab, RT, plus weekly cisplatin or weekly docetaxel (RTOG 0234)	203 (postoperative)	2-year DFS: 57% (cisplatin) and 66% (docetaxel)	Major grade 3/4 toxicities were: radiodermatitis (39% each) and mucositis (37% vs. 33%)	Kies et al, 2009
CRT: cisplatin & 5-FU x 3 cycles, weekly cetuximab and split-course RT	45(unresectable)	RR: 91 CR: 71%% PFS: 21+ mths OS: 32.6+ mths	Major grade 3/4 toxicities were neutropenia (40%), stomatitis (65%)and radiodermatitis (73%); 3 patient deaths	Merlano et al, 2011
CRT:amifostine, cetuximab, weekly cisplatin, and RT	43	CR: 68.5% 2-year OS: 91%	Major grade 3/4 toxicities were mucositis (16%), fungal infections (42%); cervical strictures in (33%)	Koukourakis et al, 2010

Treatment Regimen	Patients (n)	Responses	Toxicity	Reference
CETUXIMAB AND CRT ALONE				
CRT: weekly carboplatin, paclitaxel, RT and cetuximab	43 (unresectable)	CR: 84% 3-year OS and DFS: 59% and 58%	Major toxicities were grade 3 mucositis (79%), dysphagia (21%), radiodermatitis (16%), rash (9%), and grade 3/4 neutropenia (21%)	Suntharalingam et al, 2011
CRT: cetuximab, 5-FU, hydroxyurea, hypefractionated RT	32	3-year OS and PFS: 54% and 53%	Major grade 3/4 toxicities were mucositis (69%); radiodermatitis (53%), acneiform rash (9%)	Birnbaum et al, 2010
CRT: weekly carboplatin, paclitaxel, RT and cetuximab	33	2-year DFS and OS: 69% and 86%	Major grade 3 toxicities were mucositis (33%), radiodermatitis (15%), and neutropenia (12%)	Kao et al, 2011

CRT: chemoradiotherapy; RT: radiotherapy; RR: response rate; CR; complete response; PFS: progression free survival; DFS: disease free survival; OS: overall survival

Table 2. Selected Trials Incorporating Cetuximab with Chemotherapy and Radiotherapy

2.1.1.3 Induction chemotherapy prior to cetuximab and radiotherapy

A French randomized phase II study (TREMPLIN) evaluated IC with 3 cycles of the TPF regimen followed by either every 3-week 100 mg/m2 cisplatin with RT (arm A) or cetuximab with RT (arm B) in patients with laryngeal or hypopharyngeal cancer. (Lefebvre et al., 2011) Patients with a less than 50% response to IC underwent salvage surgery while responding patients were randomized to either of the 2 combined modality regimens. The primary end point was laryngeal preservation. Of 153 enrolled patients, 116 patients could be randomized, 60 to arm A and 56 to arm B. There was no difference between cisplatin-RT and cetuximab-RT in terms of 3-month or 18-month larynx function preservation. At 32 months mean follow-up, there were more local failures in the cetuximab-RT arm (12 versus 5); however, 7 patients could be effectively salvaged in the cetuximab arm leading to equivalent ultimate local failure rates. The rates for OS for arm A and arm B were 85% and 85%; respectively. The cetuximab-RT arm was better tolerated leading to improved treatment delivery (71% versus 43%).

A Swedish phase II has evaluated has similarly evaluated 2 cycles of IC with TPF chemotherapy followed by cetuximab-RT in patients with locally advanced unresectable

HNSCC (Mercke et al., 2011). Among 90 patients enrolled upon this study, the 1-year DFS rate was 86%. This approach was associated with mostly acute toxicities but there were few long-term toxicities.

2.1.1.4 Cetuximab as part of Induction Chemotherapy (IC) regimens

In recurrent or metastatic HNSCC, cetuximab can augment the efficacy of chemotherapy. In a randomized study, 442 patients with recurrent or metastatic HNSCC were randomly assigned to therapy with platinum- containing doublet chemotherapy with or without cetuximab (Vermorken et al., 2008). The addition of cetuximab improved response rates by 16% and the median overall survival by 2.7 months, with a reduction in the risk of death of 20% (HR, 0.80); ($p = 0.04$). Consequently, cetuximab has been evaluated as part of induction therapy in a number of CRT trials in HNSCC.

The University of Pittsburgh group has published results evaluating IC consisting of docetaxel, cisplatin, and cetuximab (TPE) followed by RT, cisplatin, and cetuximab (XPE) which was followed by maintenance cetuximab for 6 months in 39 patients (Argiris et al., 2010). Among 37 evaluable patients, the overall objective response was 86% after IC and 100% after CRT. Using positron emission tomography scanning, the primary site complete response rates after IC and CRT were 59% and 77%, respectively. With a median follow-up of 36 months, the 3-year PFS and OS were 70% and 74%; respectively. Relapses were seen in locoregional sites (8 patients), distant (3 patients) or both (1 patient). Significant grade 3/4 hematologic toxicity was common during TPE, including neutropenia in 77% and febrile neutropenia in10%. Human paplilloma virus (HPV) positivity was not associated with treatment efficacy. This regimen was deemed was highly effective with promising long-term survival and was recommended for further testing in larger trials.

In a multicenter phase II study, the Eastern Cooperative Oncology Group (ECOG) evaluated a short 6-week IC regimen with weekly carboplatin, paclitaxel, and cetuximab (E2303) in operable locally advanced HNSCC (Wanebo et al., 2010). Induction was followed by CRT consisting of weekly doses of same agents. Primary site biopsies were done after completion of IC if if there was a clinical response. After the first 5 weeks of CRT (50 Gy), repeat primary site biopsy was done in all patients. At this point, biopsy-negative patients continued to receive CRT to a final dose of 68-72 Gy, whereas patients with biopsy-positive results underwent salvage surgery. Maintenance cetuximab was then administered to all patients for 6 months. Seventy patients underwent IC, 68 patients underwent CRT; 63 patients are available for analysis. Of 41 patients undergoing biopsy after IC, the pathologic complete response rate was 59%. After 5 weeks CRT, 60 patients underwent re-biopsies among whom the pathologic complete response rates were 95%. Of the 63 patients eligible for analysis, the pathologic complete response rate was 91%. Local, regional, and distant recurrence rates were 11%, 8% and 8%, respectively. At 2 years, primary site disease control was 83%, PFS was 66% and OS was 82%. HPV status did not correlate with responses or survival (Psyrri et al., 2011). These preliminary findings suggest that this approach produces high primary site pathologic complete response rates and survival rates. This approach of selective organ preservation has been previously tested by the authors using a similar regimen without cetuximab but is not standard practice (Ready et al., 2011; Wanebo et al., 2010).

Treatment Regimen	Patients (n)	Responses	Toxicity	Reference
IC: docetaxel, cisplatin, and cetuximab x 3 cycles CRT: cisplatin, cetuximab and RT Maintenance: 6 mths cetuximab	39 (resectable patients= 33)	RR: 86% after IC and 100% after CRT CR: 5% after IC and 24% after CRT 3-year PFS and OS: 70% and 74%	During IC: major grade 3/4 toxicities were neutropenia 77%, febrile neutropenia 10% During CRT: major grade 3/4 toxicities were mucositis 54%, dermatitis 27%, neutropenia 36%, thrombocytopenia 12%, febrile neutropenia 6%	Argiris et al, 2010
IC: paclitaxel, carboplatin , and cetuximab x 6 weeks CRT: paclitaxel, carboplatin, cetuximab and RT Maintenance: 6 mths cetuximab (E2303)	70 (operable patients)	Pathologic CR: 63% after IC and 97% after CRT 2-year DFS and OS: 62% and 82%	During CRT: major grade 3/4 toxicities were mucositis (32%) , neutropenia (31%), rash (9%), radiation dermatitis (13%); one patient death	Wanebo et al, 2010
IC: paclitaxel, carboplatin , and cetuximab x 6 weeks Follow-up therapy: surgery, RT or CRT	47 (resectable)	RR: 96% after IC CR: 19% after IC 3-year DFS and OS: 87% and 91%	During IC: grade 3 rash (45%), grade 3/4 neutropenia (21%), no deaths during IC	Kies et al, 2010
IC: docetaxel, cisplatin, 5-FU and cetuximab x 4 cycles CRT: cetuximab, RT	50 (unresectable patients)	RR: 78% after IC CR: 24% after IC 2-year DFS and OS: 42% and 60%	During IC: febrile neutropenia (26%); 2 deaths During CRT: grade 3/4 toxicities mucositis (56%), dermatitis (10%)	Mesia et al, 2010
IC: carboplatin, paclitaxel, cetuximab x 2 cycles CRT: either RT plus CetuxFHX (cetuximab, 5-FU, hydroxyurea) OR CetuxPX (cetuximab, cisplatin)	110	RR: 91.8% after IC 2-year OS: 89.5% with CetuxFHX and 91.4% with CetuxPX	During IC: major grade 3/4 toxicities were rash (16%) and neutropenia (36%) During CRT: major grade 3/4 toxicities in CetuxFHX were mucositis (91%), dermatitis (82%) and in Cetux PX were mucositis (94%) and dermatitis (50%)	Seiwert et al, 2011

Treatment Regimen	Patients (n)	Responses	Toxicity	Reference
IC: docetaxel, cisplatin, 5-FU (TPF) CRT: cisplatin plus RT versus cetuximab plus RT (TREMPLIN)	153 (resectable; 116 went on to CRT arms)	OS: 85% in both arms at 32 mths	More treatment delivery in cetuximab arm (71%) vs cisplatin arm (43%)	Lefebvre et al, 2011
IC: docetaxel, cisplatin, 5-FU (TPF) CRT: cetuximab, RT	90 (unresectable)	RR: 58% after IC DFS: 86% at 1-year	Grade 3 radiodermatitis 4%, cetuximab delays 20%, mostly acute toxicities	Mercke et al, 2011

IC: induction chemotherapy; CRT: chemoradiotherapy; RT: radiotherapy; RR: response rate; CR; complete response; PFS: progression free survival; DFS: disease free survival; OS: overall survival

Table 3. Selected Trials of Induction Chemotherapy Regimens incorporating Cetuximab.

The MD Anderson Cancer Center group has published results of their phase II study of dose-dense weekly IC regimen consisting of paclitaxel, carboplatin, and cetuximab for 6 weeks along with G-CSF. IC was followed by locoregional therapy with either surgery, RT alone, or cisplatin-RT. This regimen was highly active with a CR and OR rate of 19% and 96%, respectively. Six patients had relapses; locoregional in 4 patients, distant in 1 patient and both in 1 patient. The 3-year PFS and OS rates were 87% and 91%, respectively; HPV status was found to correlate with both PFS and OS (Kies et al., 2010).

The combination of docetaxel, cisplatin, 5-Fluorouracil plus cetuximab (TPF-C) as IC has been investigated in a Spanish multicenter phase II study (Mesia et al., 2009). Fifty patients with unresectable HNSCC were treated with 4 cycles of TPF-C chemotherapy along with G-CSF and antibiotic prophylaxis, followed by accelerated boost RT with concurrent cetuximab alone. The ORR after IC and end of CRT were 78% and 72%, respectively (intent-to-treat population) with only 86% patients starting CRT. Locoregional disease control at 1-year was 44%. With a median follow-up of 19 months, actuarial disease free survival and overall survival at 2 years were 42% and 60%, respectively.

Another approach as practiced by the University of Chicago group, has been to evaluate IC containing cetuximab, carboplatin, paclitaxel for 2 cycles followed by randomization to one of 2 CRT approaches: concurrent cetuximab, 5-fluorouracil, hydroxyurea and hyperfractionated RT (CetuxFHX) or cetuximab, cisplatin, and accelerated RT with concomitant boost (CetuxPX) (Seiwert et al., 2011). In the preliminary report, 110 patients had a overall response rate of 91.8% with IC. After end of all treatment, the 2-year OS in the CetuxFHX and CetuxPX arms was 89.5% and 91.4%, respectively. The 2-year PFS for CetuxFHX and CetuxPX was 82.3% and 89.7%, respectively. Even though the trial was marked by high rates of severe rash, dermatitis, mucositis, and neutropenia 95% of patients were able to complete all therapy. Survival outcomes between the two CRT arms were not significantly different.

2.1.2 Panitumumab

Panitumumab is a fully human IgG2 antibody that binds with high affinity to the EGFR and is approved in the setting of recurrent colorectal cancer. Panitumumab has been evaluated in preclinical studies for HNSCC (Lopez-Albaitero & Ferris, 2007; Kruser et al., 2008) which showed a favorable interaction between panitumumab and RT.

Wirth et al have conducted a phase I study of panitumumab in combination with CRT for which the preliminary results have been presented (Wirth et al., 2008). In this study, 19 patients with locally advanced HNSCC received IMRT (70 Gy) with concurrent weekly dosing of carboplatin (AUC 1.5) plus panitumumab (2.5 mg/kg) plus paclitaxel (2 dose levels, 15 and 30 mg/m^2) over a 7-week period. At the higher paclitaxel dose level 1 patient developed febrile neutropenia which was considered a dose limiting event. Major toxicities included grade 3 dysphagia (95%), grade 3 radiodermatitis (42%), and grade 3/4 mucositis (89%). Among evaluable patients, the primary site CR rate was 87%.

Panitumumab is being evaluated in the postoperative setting in resected locally advanced HNSCC with high-risk features (extracapsular nodal spread, > 2 nodes involved, perineural or angiolymphatic invasion, or < 1mm margins) (Ferris et al., 2010). The treatment consisted of RT (60-66 Gy) over 6-7 weeks concurrent with weekly panitumumab (2.5 mg/kg) and cisplatin (30 mg/m2). The planned accrual is 47 patients and final results of this study are awaited. Other trials with panitumumab in combination with CRT are currently ongoing.

2.1.3 Nimotuzumab

Nimotuzumab is a humanized IgG1 monoclonal antibody against EGFR developed in Cuba. This was originally a mouse IgG2a antibody (R3) which was humanized and the resulting antibody (h-R3) inhibits EGFR by binding to domain III of the extracellular domain. Nimotuzumab partially blocks the EGF binding site as well as stabilizes a receptor-protein configuration that is unfavorable for dimer formation. In pre-clinical evaluation, nimotuzumab reduced tumor proliferation, increased apoptosis, and had a lower binding affinity to EGFR than cetuximab.

2.1.3.1 Nimotuzumab and radiotherapy alone

Several early studies have been conducted with nimotuzumab as a single agent in combination with RT alone in locally advanced HNSCC. It is well tolerated as a single agent at weekly doses up to 400 mg and is associated with a very low incidence of rash (Boku et al., 2009).

In a phase I/II trial conducted in Cuba, Crombet et al enrolled 24 patients with unresectable HNSCC who received 6 weekly infusions of nimotuzumab administered concurrently with RT to a total dose of 60-66 Gy (Crombet et al., 2004). Initially, nimotuzumab doses were escalated from 50 mg to 400 mg weekly and the last 10 patients were treated at 200 mg or 400 mg weekly only. This combination was well tolerated without the development of skin toxicities while common adverse events were infusion reactions, grade 3 radiodermatitis (12.5%), grade 3 mucositis (20.8%), and grade 3 dysphagia (12.5%). The overall RR was 87.5% among 16 evaluable patients responded and the CR rate was 56%. The OS appeared to correlate with the administered dose level, with the 3-year survival rate ranging from 16.7% for the 2 lower doses to 66.7% for the 2 higher doses. Based on serum levels, the nimotuzumab dose of 200 mg/week was selected for further clinical testing.

In a follow-up study by the same group, Rodriguez et al performed a randomized phase II study in which they evaluated the combination of 6 weekly doses of nimotuzumab and RT (60-66 Gy) to patients treated with placebo plus RT in locally advanced unresectable HNSCC (Rodriguez et al., 2010). A total of 106 patients were enrolled; 54 on the nimotuzumab arm and 51 in the standard arm. Grade 1/2 events attributable to nimotuzumab included asthenia (14.6%), fever (9.8%), headache (9.8%), chills (7.8%), and anorexia (7.8%). Consistent with other reports, no acneiform skin rash was observed, differentiating nimotuzumab from other anti-EGFR antibodies. There was no significant exacerbation of adverse events with the addition of nimotuzumab to RT. Among 75 patients evaluable for response, the CR rates for the nimotuzumab and placebo groups were 59.5% and 34.2%, respectively. In the intent to treat analysis, the median OS differed significantly between the nimotuzumab and placebo arms at 12.5 months and 9.5 months, respectively. In a subset analysis, patients with at least weak EGFR-expression had an improvement in median OS compared to EGFR-negative patients (16.5 months versus 7.2 months, p=0.0038)

In a small Spanish study, Rojo et al evaluated nimotuzumab (200 mg and 400 mg doses) plus RT in 10 patients with advanced HNSCC felt to be unsuitable for CRT (Rojo et al., 2008). The overall response rate was 80% and median OS was 7.2 months. Nimotuzumab was well tolerated and no skin rash was observed again. Pharmacodynamic studies were conducted in this study which showed that nimotuzumab inhibited EGFR phopshorylation; molecular downstream effects included decrease of p-ERK and upregulation of p-AKT in tumor but not in the skin. There were no associations between doses or responses and pharmacodynamic effects in this study.

2.1.3.2 Nimotuzumab and chemoradiotherapy

In an open-label, phase IIb randomized study from India, Babu et al evaluated nimotuzumab in patients with locally advanced, inoperative HNSCC (Babu et al., 2010). Of 113 screened patients, 92 were randomized to receive a) RT alone, b) RT plus nimotuzumab, c) RT plus cisplatin, and d) RT plus cisplatin plus nimotuzumab. The nimotuzumab dose was 200 mg/week x 6 weeks, the cisplatin dose was 50 mg/week, and RT was given to a total dose of 60-6 Gy all over 6 weeks. Of 76 evaluable patients, the locoregional response rates were as follows: RT (37%), RT plus nimotuzumab (76%), RT plus cisplatin (70%), and RT plus cisplatin plus nimotuzumab (100%). Similarly, after 48 months follow-up the median OS rates were as follows: RT (12.7 months), RT plus nimotuzumab (14.3 months), RT plus cisplatin (21.9 months), and RT plus cisplatin plus nimotuzumab (not reached). The addition of nimotuzumab to CRT resulted in this small population resulted in significant reduction in the risk of death (HR 0.35, p=0.01).

Preliminary results of another study from India were reported by Gupta et al in which 17 patients with locally advanced HNSCC were treated with weekly doses of nimotuzumab 200 mg plus cisplatin 40 mg/m2 concurrent with RT (66 Gy in 33 fractions) (Gupta et al., 2010). All patients completed planned nimotuzumab treatments and were evaluated for the primary endpoint of responses and safety. No grade 3/4 adverse events were reported. The overall RR was 76% (CR 59%) while 2 patients progressed after therapy (one patient each in the 5th and 6th month). Additional clinical trials, including a randomized phase III evaluation in the postoperative treatment setting is planned.

2.2 EGFR tyrosine kinase inhibitors

EGFR tyrosine kinase inhibitors (EGFR-TKIs) are a class of oral drugs which bind intracellularly to EGFR and competitively inhibit the receptor activity resulting in inhibition of downstream signaling pathways (Steeghs et al., 2007). In HNSCC, the EGFR-TKIs which have been evaluated are erlotinib, gefitinib, and lapatinib.

2.2.1 Erlotinib

Erlotinib is an approved drug in advanced non-small cell lung cancer as monotherapy and in advanced pancreatic cancer in combination with gemcitabine. In recurrent or metastatic HNSCC, erlotinib has been evaluated as monotherapy and in combination with other chemotherapeutic agents.

In a phase I trial Savvides et al combined erlotinib with docetaxel and RT in locally advanced HNSCC (Savvides et al., 2006). The regimen consisted of weekly docetaxel (15 to 20 mg/m2) plus daily erlotinib (50 to 150 mg) with concurrent RT (70 Gy) followed by maintenance erlotinib for up to 2 years. One patient developed dose-limiting toxicities at each of the first 3 levels but no dose-limiting toxicity was observed at the 4th dose level. The CR rate was 83% (15 of 18 evaluable patients) and full dose erlotinib and docetaxel 20 mg/m^2 weekly were the recommended for phase II evaluation.

Herchenhorn et al conducted a phase I/II study in Brazil which evaluated the combination of erlotinib (50 to 150 mg), cisplatin (100 mg/m2 every 3 weeks x 3 doses), and RT (70.2 Gy) in 37 patients with locally advanced HNSCC (Herchenhorn et al., 2007). The phase II dosing of erlotinib at 150 mg dose was evaluated in 31 patients. The CR rate in these patients was 74%. Major grade 3/4 toxicities were radiodermatitis (51%), nausea (*48%*), mucositis (29%), dysphagia (35%), and vomiting (39%) were the most common adverse events (Herchenhorn et al., 2007). With a median follow-up of 37 months, the 3-year PFS and OS rates were 61% and 72%, respectively.

In a Spanish phase I study, de la Vega et al evaluated combination of erlotinib, weekly cisplatin, and RT (up to 63 Gy) in resected patients with locally advanced HNSCC (Arias de la Vega et al., 2011). Thirteen patients were treated and the recommended phase II evaluation dose was full dose erlotinib (150 mg) with weekly cisplatin (30 mg/m2) for 6 weeks. Further studies with erlotinib in patients with locally advanced HNSCCHN are ongoing.

2.2.2 Gefitinib

Gefitinib is an oral EGFR-TKI with modest single-agent activity in recurrent or metastatic HNSCC (Cohen et al., 2003; Cohen et al., 2005; Kirby et al., 2006). However, 2 phase III randomized trials did not show survival benefit of single-agent gefitinib over standard methotrexate (Stewart et al., 2009) or of docetaxel plus gefitinib versus docetaxel plus placebo in patients with recurrent or metastatic HNSCC (Argiris et al., 2009). Multiple studies of the combination of gefitinib with RT or CRT in locally advanced HNSCC have been conducted.

Rodriguez et al conducted a phase II trial of multiagent CRT including daily gefitinib (250 mg) with 2 cycles of infusional 96-hours of cisplatin and 5-fluorouracil, and concurrent

hyperfractionated RT (72-74 Gy) followed by maintenance gefitinib for 2 years (Rodriguez et al., 2009). Acute toxicities, including transient renal dysfunction and hospital admissions were significantly increased with the addition of gefitinib compared to historical controls. The 3-year estimates of freedom from recurrence and OS were 72% and 68%, respectively. Less than half the patients were projected to complete maintenance gefitinib. The investigators concluded that this regimen increased toxicity without improving efficacy.

The combination of weekly cisplatin (40 mg/m2) and gefitinib (250 mg) plus concomitant boost accelerated radiation (72 Gy) was evaluated by Rueda et al in 46 patients with unresectable locally advanced HNSCC (Reuda et al., 2007). Grade 3/4 toxicity included mucositis (47%), radiodermatitis (14%), rash (5%), diarrhea (2%), and grade 3 neutropenia (5%). Response evaluation at 3 months post therapy completion showed a RR of 63% and CR rate of 52%. With a median follow-up of 23 months, the 2-year PFS and OS were 47% and 56%, respectively.

A large, double blind, randomized phase II study was reported by Gregoire et al from Belgium (Gregoire et al., 2011). In this study, 226 patients with locally advanced HNSCC were randomized to gefitinib (250 mg or 500 mg) with cisplatin and RT followed by maintenance gefitinib or placebo. The primary objective was 2-year local disease control rate. The addition of gefitinib did not improve 2-year local control rates when given concurrently with CRT (32.7% versus 33.6%) or as maintenance (28.8% versus 37.4%).

Treatment Regimen	Patients (n)	Responses	Toxicity	Reference
Erlotinib and CRT				
CRT: weekly docetaxel, erlotinib and RT Maintenance: erlotinib x 2 years	23	CR: 83%	Mostly acute toxicities; one patient death	Savvides et al, 2006
CRT: cisplatin x 3 cycles, daily erlotinib and RT	37(unresectable)	CR: 74% 3-year PFS and OS: 61% and 72%	Major grade 3/4 toxicities were nausea (48%), vomiting (39%), radiodermatitis (52%), and mucositis (29%)	Herchenhorn et al, 2010
Gefitinib and CRT				
CRT: 2 cycles cisplatin and 5-FU, daily gefitinib and RT Maintenance: gefitinib x 2 years	60	3-year FFR and OS : 72% and 67%	Transient renal dysfunction (28%), re-hospitalization (83%), 5 patient deaths, increased diarrhea and rash with gefitinib	Rodriguez et al, 2009

Treatment Regimen	Patients (n)	Responses	Toxicity	Reference
CRT: weekly cisplatin, gefitinib, and RT	46 (unresectable)	RR: 63% CR: 52% 2-year PFS and OS: 47% and 56%	Major grade 3/4 toxicties were: mucositis (47%), rash (5%), radiodermatitis (14%).	Rueda et al, 2007
CRT: cisplatin, gefitinib (250mg vs. 500 mg) or placebo, and RT Maintenance: gefitinib x 1 year	226 (randomized phase II)	2-year LDCR: 33% each for gefitinib vs. no gefitinib	Increase in serious adverse events in gefitnib arms	Gregoire et al, 2011
IC: carboplatin, paclitaxel x 2 cycles CRT: RT, 5-FU, hydroxyurea, and gefitinib Maintenance: gefitinib x 2 years	69	CR: 90% after CRT 4-year PFS and OS: 72% and 74%	Major grade 3/4 toxicties during CRT were: neutropenia (16%), mucositis (85%), radiodermatitis (33%), infection (17%)	Cohen et al, 2010
IC: docetaxel, 5-FU, carboplatin, and gefitinib x 2 cycles CRT: docetaxel, gefitinib and RT Maintenance: gefitinib x 2 years	62	RR: 80% CR: 36% 3- year PFS and OS: 41% and 54%	Major grade 3/4 toxicties were: radiodermatitis (9%), mucositis (57%), hospitalizations (42%); one patient death	Hainsworth et al, 2009

IC: induction chemotherapy; CRT: chemoradiotherapy; RT: radiotherapy; RR: response rate; CR; complete response; PFS: progression free survival; DFS: disease free survival; OS: overall survival

Table 4. Selected Trials incorporating EGFR-TKI's in Chemoradiotherapy Regimens

Gefitinib was well tolerated during both phases but no efficacy improvement was noted.

Cohen et al have reported the University of Chicago experience with the addition of gefitinib to IC and subsequent CRT in a phase II trial (Cohen et al., 2010). Sixty-nine patients with locally advanced HNSCC were treated with 2 cycles of carboplatin and paclitaxel followed by fluorouracil, hydroxyurea, gefitinib, and twice daily RT followed by maintenance gefitinib for 2 years. Major grade 3/4 toxicity during CRT included mucositis (85%), radiodermatitis (33%), neutropenia (16%), and infection (17%). The CR rate was 90% after completion of CRT. After a median follow-up of 3.5 years, the 4-year PFS and OS s were 72% and 74%, respectively.

Finally, Hainsworth et al from the Sarah Cannon group treated 62 patients with locally advanced HNSCC with an IC regimen of 2 cycles of docetaxel (60 mg/m2) and carboplatin (AUC 5) every 3 weeks plus 6 weeks of daily infusional 5-FU (200 mg/m2) and gefitinib (250 mg) (Hainsworth et al., 2009). CRT consisted of RT (68.4 Gy) with weekly docetaxel (20 mg/m2) and daily gefitinib 250 mg/d followed by maintenance gefitinib for up to 2 years. IC resulted in major grade 3 mucositis (27%) and diarrhea (16%) as well as grade 3/4 neutropenia (30%). During CRT, the major grade 3/4 toxicities were mucositis (59%) and radiodermatitis (9%). The RR after IC and CRT was 46% and 80%, respectively. With a median follow-up of 33 months, the 3-year PFS and OS rates were 41% and 54%, respectively, which were not superior to survival results reported with CRT alone by the same group.

2.2.3 Lapatinib

Lapatinib is a dual-inhibitor which targets EGFR and HER-2 and may inhibit their dimerization as a result. In preclinical models, lapatinib has synergistic activity with chemotherapy and RT (Montemurro et al., 2007). Harrington et al have reported results of a phase I trial of the combination of lapatinib (500 mg, 1000 mg, 1500 mg), cisplatin (100 mg/m2 every 3 weeks x 3 cycles), and RT (66-70 Gy) in 31 patients (Harrington et al., 2009). No DLT's were observed in this evaluation and the recommended lapatinib dose of for phase II evaluation was determined as 1500 mg daily. The overall RR was 81% while radiodermatitis, mucositis, lymphopenia, and neutropenia were the most common side effects.

Harringtpon et al have also presented preliminary results of their phase II randomized evaluation of lapatinib or placebo, cisplatin, and RT as per the recommended schedule above followed by maintenance lapatinib or placebo (Harrington et al., 2010). In 67 patients randomized to lapatinib or placebo, the grade 3/4 toxicities were balanced with grade 3 rash and diarrhea being more common in the lapatinib arm. The CR rates in the lapatinib and standard arms were 53% and 36%, respectively. CRT dose intensities were not adversely impacted by lapatinib. Early data showed hazard ratios for PFS and OS by independent review of 0.71 and 0.70, respectively.

2.3 Predictors of outcome after treatment with EGFR inhibitors

The level of EGFR expression as detected by immunohistochemistry (IHC) has been evaluated as a potential biomarker of cetuximab efficacy in HNSCC. In patients with metastatic HNSCC, EGFR expression as determined using the DAKO assay with staining intensity graded on an ordinal scale 0-3 and staining density assessed according to the percentage of cells stained (Kies et al., 2007). High expression was defined as staining intensity 3 + on 80% of cells. EGFR expression was not predictive of response to cetuximab nor was there any association with survival.

The University of Pittsburgh group has reported results of evaluation of baseline serum biomarkers in their study evaluating cetuximab in locally advanced HNSCC (Ferris et al., 2009). A panel consisting of 31 cytokines were measured before and after 3 cycles of induction cetuximab-containing chemotherapy. Low baseline VEGF and IL-6 levels were potentially associated with complete response among patients evaluated by PET imaging post-therapy.

Fountzilas et al evaluated genetic biomarkers in patients undergoing cetuximab containing radiation in locally advanced HNSCC (Fountzilas et al., 2009). In this report, tumor EGFR, MET, ERCC1, and p-53 protein and/or gene expression were not associated with treatment response. However, a high level of matrix metalloproteinase MMP9 mRNA expression was found to be significantly associated with objective response.

Tumors of patients treated with cisplatin-chemotherapy with or without cetuximab on the phase III EXTREME registration study were evaluated for EGFR gene copy number FISH (Licitra et al., 2009). Tumors were classified as FISH positive or FISH negative using the Colorado scoring system. Patients with FISH positive tumors were evenly distributed across both arms. The FISH scores had no influence on the response rate in the cetuximab-containing arm and no effect on survival on either; thus EGFR gene copy number was not predictive of cetuximab efficacy in this setting. In patients treated with gefitnib, cisplatin and radiotherapy in locally advanced HNSCC, EGFR protein expression, FISH and mutation status did not predict for response or survival (Tan et al., 2011).

The most common adverse event associated with anti-EGFR agents that occurs in more than two-thirds of patients is skin rash which usually occurs in the first 3 weeks of treatment. It is likely related to EGFR expression in the skin and the severity of rash is associated with efficacy. Several studies in HNSCC have shown a direct correlation between the development of rash and better patient outcome after EGFR inhibitor therapy (Soulieres et al., 2004; Cohen et al., 2003; Baselga et al., 2005; Burtness et al., 2005; Herbst et al., 2005). In the Bonner study, patients with a grade 2 or greater rash had a significantly lower risk of death (Bonner et al., 2010). Patients with a prominent rash had significantly longer overall survival than those patients who had a mild rash (68.8 months vs. 25.6 months; HR 0.49; p=0.002). It is possible that occurrence of acneiform rash is a biomarker of an immunological response that is conducive for optimal outcome. It thus seems that currently occurrence of a high-grade rash may be the only biomarker predictive of favorable outcome with cetuximab containing therapy.

3. Vascular endothelial growth factor pathway inhibitors

VEGF was associated with an increased risk of death in HNSCC in a recent meta-analysis of 12 studies (Kyzas et al., 2005). In HNSCC, both VEGF and the VEGF receptor are upregulated and are important for tumor cell survival in hypoxic conditions (Moriyama et al., 1997; Denhart et al., 1997; Inoue et al., 1997; Petruzzelli et al., 1997). Pre-clinical studies have demonstrated that blockage of the VEGF pathways by anti-angiogenic drugs increases the anti-tumor effects of radiation. As such targeting the VEGF pathway through monoclonal antibodies and receptor tyrosine kinase inhibitors is a promising therapeutic approach in HNSCC. The currently available data with the use of bevacizumab in locally advanced HNSCC is reviewed below.

3.1 Bevacizumab

The humanized monoclonal antibody bevacizumab binds VEGF-A and is currently approved for clinical use in many advanced solid tumors, including colorectal cancer, non-small cell lung cancer, renal cell carcinoma, and glioblastomas. Bevacizumab inhibits angiogenesis and also facilitates chemotherapy delivery into tumors (Shirai & O'Brien, 2007;

Olsson et al., 2006). Antiangiogenic agents, in preclinical studies appear to overcome resistance and potentiate the effect of traditional therapies such as radiotherapy and chemotherapy (Seiwert & Cohen, 2008).

3.1.1 Bevacizumab and chemoradiotherapy

Various combinations of bevacizumab and radiotherapy have been evaluated in phase I/II trials in locally advanced HNSCC. Seiwert et al from the University of Chicago group have published results of a phase I evaluation of bevacizumab, 5-fluorouracil, hydroxyurea, and radiation (BFHX). In this study, 43 patients with recurrent, previously irradiated or poor prognosis, treatment-naïve HNSCC were treated with every 2-week regimen of bevacizumab (escalating doses from 2.5 to 10 mg/kg), hydroxyurea (500-1000 mg BID), and 5-FU (600-800 mg/m^2 as a continuous infusion for 5 days) in combination with RT (1.8-2 Gy once daily) on a week on-week off schedule (Seiwert et al., 2008). The MTD of the combination was bevacizumab (10 mg/kg), 5-FU (600 mg/m^2) and hydroxyurea (500 mg) and this cohort was expanded to 26 patients. The median OS was 10.3 months. Significant severe late toxicities were observed including development of fistula (5 patients), ulceration or tissue necrosis (4 patients), and thrombosis (3 patients).

Results of a follow-up phase II randomized study by the same group have been reported by Salama et al in which the BFHX regimen was compared to the prior FHX regimen (Salama et al., 2011). In this study, 26 patients with intermediate stage III-IV patients (excluding N2-N3 stage) were enrolled. The study was halted following unexpected locoregional progression in 4 patients with T4 tumors randomized to the BFHX regimen. The incidence of mucositis and dermatitis was not increased with the addition of bevacizumab to CRT. The pathologic CR rate on study was 77%. The 2-year OS was 68% and the DFS for BFHX and FHX were 59% and 89%, respectively. Two patients died during CRT and one patient died within 30 days after post-CRT surgery.

Savvides et al have presented preliminary results of a phase II study evaluating the combination of weekly docetaxel (20 mg/m^2) and every 2-week bevacizumab (5 mg/kg) with daily RT (70.2 Gy) followed by maintenance bevacizumab for up to 1 year (Savvides et al., 2008). Of 23 enrolled patients, 17 patients remained in CR and 4 patients recurred. No unexpected toxicities or severe bleeding episodes were noted while 8 patients required hospitalization during CRT. The estimated 1-year PFS and OS were 78% and 89%, respectively.

Preliminary results of a phase II study from the Sloan Kettering group which investigated the addition of bevacizumab (15 mg/kg every 3 weeks x 3 cycles) to cisplatin (50 mg/m^2 on days 1, 2, 22, 23, 43 and 44) and RT (70 Gy) have been presented by Pfister et al (Pfister et al., 2009). Plans for maintenance bevacizumab were discontinued after the occurrence of a grade 4 pulmonary hemorrhage. Major toxicities included grade 3 mucositis (76%) and grade 3/4 neutropenia (41%). Two patients died within 90 days of last treatment; one had a sudden death and another died from aspiration pneumonia. The estimated 1-year PFS and OS were 83% and 88%, respectively.

Preliminary results of a RTOG phase II trial of bevacizumab and CRT in patients with locally advanced nasopharyngeal carcinoma were reported by Lee et al (Lee et al., 2011). In this study, 44 patients were enrolled and received 3 cycles of bevacizumab (15 mg/kg), cisplatin (100 mg/m2), and IMR (70 Gy) followed by 3 cycles of adjuvant bevacizumab (15

mg/kg), cisplatin (80 mg/m2), and 5-fluorouracil (1000 mg/m2/day x 4 days). The most common grade 4 toxicity was hematologic and grade 3/4 mucositis was seen in 77% cases. The 2-year PFS and OS were 71.7% and 90.9%, respectively. These survival rates were favorable compared to prior RTOG data with regards to OS but not PFS.

3.1.2 Bevacizumab with induction chemotherapy and CRT

In a phase II study, Meluch et al evaluated IC with paclitaxel (200 mg/m2), carboplatin (AUC 6), and 5-FU (200 mg/m2/day x 3 weeks) plus bevacizumab (15 mg/kg) followed by concurrent RT (68.4 Gy) with paclitaxel (50 mg/mw/week), bevacizumab (15 mg/kg), and erlotinib (150 mg daily) in locally advanced HNSCC (Meluch et al., 2009). Of 60 enrolled patients, preliminary results in the first 48 patients showed that the most common grade 3/4 adverse events during IC were neutropenia (46%), neutropenic fever (6%), mucositis (14%), and diarrhea (14%); during CRT grade 3/4 mucositis occurred in 76% patients. The overall RR was 77% after completion of the entire treatment. After a median follow-up of 16 months, the 18-month PFS and OS were 85% and 87%, respectively. No unexpected toxicities were observed with this regimen.

4. Conclusion

The evaluation of targeted therapies in the management of locally advanced head and neck squamous cancers is evolving. Currently, randomized trials data support the use of the anti-EGFR monoclonal antibody cetuximab in combination with radiotherapy in this setting. Conversely, the currently available data do not support the use of cetuximab in combination with chemotherapy and radiotherapy in this setting based on the results of the RTOG 0522 study. As such, the use of combined targeted and chemotherapy regimens outside of a clinical trial is not recommended at present. The challenge in the appropriate use of anti-EGFR therapies is the determination of appropriate patients prospectively through the use of relevant biomarkers. Presently, the development of a high-grade rash is the only potential biomarker of benefit in the use of ant-EGFR therapy.

The clinical trials scenario is replete with ongoing randomized trials evaluating anti-EGFR monoclonal antibodies and tyrosine kinase inhibitors in combination with chemotherapy. Additional trials are investigating the role of anti-VEGF therapies and mTOR inhibitors are in early clinical trials. The results of these trials will shape the future of targeted therapies in this setting.

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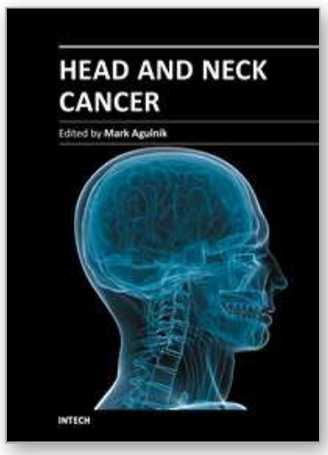
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Head and Neck Cancer provides an interesting and comprehensive overview of all aspects of head and neck cancer including overviews of the disease, basic science aspects pertaining to the disease, diagnosis, treatment and outcomes for patients with this disease. The chapters written by world renowned experts cover the entire discipline of head and neck oncology and include discussions of regional disparity is, advances in basic science understanding, advances in her radiotherapy, chemotherapy and targeted agents as well as a focus on reconstruction, prostheses, and aspects of quality of life and health outcomes. The book is designed to be both practical and comprehensive for every physician treating his complex disease.

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