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Balancing Safety and Efficacy of Epidermal Growth Factor Receptor Inhibitors in Patients With Squamous Cell Carcinoma of the Head and Neck

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Carcinoma • Squamous cell of head and neck • EGFR inhibitors

ABSTRACT

The epidermal growth factor receptor (EGFR) is overexpressed in more than 80% of squamous cell cancers of the head and neck (SCCHN). An evolving understanding of the role of EGFR in tumorigenesis has made the receptor an important therapeutic target in SCCHN. Several EGFR inhibitors (EGFRIs) are active in SCCHN, and their use is associated with improvement in progression-free survival and overall survival in various treatment settings. Nevertheless, EGFR inhibition is associated with significant mucocutaneous toxicity that must be balanced against its anticipated efficacy. This review summarizes the relevant clinical trial experience with EGFRIs, with attention to efficacy, toxicity, and methods of selecting patients most likely to benefit from therapy. ***The Oncologist*** 2015;20:1393–1403

Implications for Practice: Cetuximab and other inhibitors of the epidermal growth factor receptor (EGFR) have entered the medical oncologist's arsenal against squamous cell carcinoma of the head and neck (SCCHN). They are modestly active as single agents and in combination with chemotherapy and radiotherapy. Despite their efficacy across multiple treatment settings, cetuximab and other EGFR inhibitors (EGFRIs) have not supplanted platinum-based therapies, which remain a standard of care for SCCHN. The modest benefits of EGFRI therapy must take into consideration patient, disease, and treatment characteristics and must be balanced against potential treatment toxicity.

INTRODUCTION

Each year more than 500,000 patients globally are diagnosed with squamous cell carcinoma (SCC) of the head and neck (SCCHN), and more than 300,000 deaths are caused by the disease [1]. The majority of patients present with stage III/IV locoregionally advanced disease and are treated with combined modality therapy often incorporating surgery, radiotherapy (RT), and chemotherapy for patients with the most advanced locoregional disease [2]. Despite curative intent, approximately 70% of patients with locoregionally advanced disease relapse, underscoring the importance of primary locoregional control and of systemic therapies in recurrent or metastatic (R/M) disease [3]. Platinum compounds (cisplatin and carboplatin), 5-fluorouracil (5-FU), taxanes (paclitaxel and docetaxel), and methotrexate are among the most active chemotherapeutics in SCCHN [3]. Despite the activity associated with combination regimens, the absolute benefit of cytotoxic therapy in the curative and R/M settings is marginal [2, 3]. Moreover, the treatment of SCCHN is often complicated by patients' poor performance status and by medical comorbidities [4]. Consequently, efforts are ongoing to identify compounds with more favorable side effect profiles that maintain efficacy.

The epidermal growth factor receptor (EGFR) is a 170-kDa receptor tyrosine kinase expressed in epidermal tissues [5]. Ligand binding to the extracellular domain of EGFR promotes dimerization and autophosphorylation, activating the downstream mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), phosphatidylinositol-3-kinase (PI3K), the serine/threonine kinase AKT, and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways, which are associated with DNA synthesis, cell proliferation, and survival [6].

If mutated or overexpressed, EGFR can promote tumorigenesis across multiple tumor types. Whereas activating mutations in the gene encoding *EGFR* are seen in a subset of patients with non-small cell lung cancer (NSCLC) [7], such mutations are only very rarely seen in SCCHN [8]. Instead, some 80%–100% of SCCHNs are associated with EGFR protein

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overexpression and pathway activation, rendering EGFR a potential target in this disease [8]. EGFR-directed therapy is principally achieved with monoclonal antibodies (mAbs) or small molecule tyrosine kinase inhibitors (TKIs) [9]. Existing anti-EGFR mAbs target domain III of the EGFR and competitively inhibit the extracellular ligand-binding domain of the molecule, disrupting the EGFR pathway and promoting antibody-dependent cellular cytotoxicity (ADCC) [10]. The small molecule TKIs act on the intracellular portion of EGFR, impairing downstream signaling through inhibition of EGFR's intrinsic kinase domain without effecting ADCC [10].

The first and only molecularly targeted therapy approved for the treatment of SCCHN is cetuximab, a mAb directed against EGFR [11]. Since cetuximab's initial U.S. Food and Drug Administration approval in 2006, several other EGFR inhibitors (EGFRIs) in early phases of development have shown activity in SCCHN; these include panitumumab, zalutumumab, matuzumab, nimotuzumab, erlotinib, gefitinib, lapatinib, afatinib, and dacomitinib [10, 12]. The incorporation of these and other EGFRIs into the head and neck oncologist's armamentarium may be broadly considered in terms of three treatment settings: (a) locoregionally advanced disease for which surgery is the primary modality of therapy, with adjuvant chemoradiotherapy (CRT) offered to those with high-risk resected disease; (b) locally and regionally advanced disease in patients unfit or inappropriate for surgery whose therapy depends on definitive CRT; and (c) patients with R/M disease not amenable to salvage strategies, in whom systemic chemotherapy is the mainstay of therapy. CRT with high-dose cisplatin is the standard of care for high-risk resected disease and for definitive treatment of unresectable disease [13].

We reviewed the relevant published experience with EGFR inhibition in SCCHN, with attention to efficacy, toxicity, and methods of selecting patients most likely to benefit from therapy.

Materials and Methods

The PubMed, Embase, Cochrane Collaboration, and ClinicalTrials.gov databases and conference proceedings of the American Society of Clinical Oncology and the Multidisciplinary Head and Neck Cancer Symposium were queried. Search terms were *carcinoma*, *squamous cell*, *head and neck*, *epidermal growth factor receptor*, and *antagonist* or *inhibitor*. Results were limited to prospective clinical trials published as of January 2014. An additional search was performed in October 2014 with the same search terms. Publications were limited to those in English and involving human subjects. Both papers and abstracts were considered.

Evidence of Benefit

Adjuvant Therapy in Resected Disease

Table 1 summarizes relevant trials of EGFRIs in the adjuvant treatment of high-risk resected disease. Although such trials are under way, there are presently no published head-to-head comparisons of RT plus an EGFRI compared with conventional CRT in the adjuvant setting. The published experience of anti-EGFR therapy in the adjuvant setting is limited to single-arm studies of an EGFRI plus conventional CRT and to comparative studies of EGFRIs added to various CRT backbones.

Single-arm studies have demonstrated the feasibility and tolerability of RT/cisplatin in combination with cetuximab [14], panitumumab [15], matuzumab [20], and erlotinib [16, 21] in the adjuvant setting. Concurrent lapatinib plus RT/cisplatin has also been studied, but this combination failed to confer a disease-free survival benefit over RT/cisplatin in a placebo-controlled phase III study [17]. The randomized phase II trial RTOG 0234 demonstrated numerically superior 2-year overall survival (OS) with RT/docetaxel/cetuximab compared with RT/cisplatin/cetuximab (79% vs. 69%), driven principally by a reduction in distant recurrence (13% vs. 25%) [18]. In this latter trial, it is unclear whether and to what degree cetuximab contributed to the observed OS difference because the mAb was included in both treatment arms.

Future studies will focus on the optimal combination of EGFRIs and a CRT backbone. The RT/docetaxel/cetuximab combination used in RTOG 0234, for example, is being evaluated in the phase II/III RTOG 1216 trial, in which patients with SCCHN negative for human papillomavirus (HPV) undergo surgery and are randomized to adjuvant RT/cisplatin, RT/docetaxel, or RT/docetaxel/cetuximab [22]. In addition, a phase III study is under way investigating 18 months of adjuvant afatinib compared with placebo, following CRT [23]. A phase III comparison of CRT in combination with nimotuzumab or placebo in the adjuvant setting is also under way (ClinicalTrials.gov identifier NCT00957086).

Definitive Therapy for Unresectable Disease

For patients with locoregionally advanced, unresectable SCCHN, the mainstay of therapy is concurrent platinum-based CRT with curative intent [24]. EGFRIs have been combined with RT as single agents or with cytotoxic chemotherapy in this setting.

Table 2 summarizes the relevant published experience with RT plus an EGFRI for the definitive treatment of locoregionally advanced, unresectable SCCHN. The most influential study was the phase III trial by Bonner et al. that demonstrated an OS benefit with concurrent RT/cetuximab compared with RT alone (49 vs. 29 months), with a durable OS benefit at 5 years (45.6% vs. 36.4%) [39, 40].

Combination RT/EGFRI has been compared with RT/platinum in several contexts within the definitive setting. The phase II/III study by Ghi et al. randomized patients to induction docetaxel, cisplatin, and 5-FU or no induction chemotherapy, with a second randomization to RT/cetuximab or RT/cisplatin [30]. At a median follow-up of 41.3 months, induction chemotherapy was associated with improved complete response (CR) rates (43.5% vs. 28%), median progression-free survival (PFS; 29.7 vs. 18.5 months), and median OS (53.7 vs. 30.3 months). These benefits were independent of the agent administered with concomitant RT. Similarly, the phase II TREMPLIN study treated patients with induction chemotherapy followed by randomization to either RT/cetuximab or RT/cisplatin [34]. Although there were numerically fewer local recurrences in the RT/cisplatin arm, there were no significant differences in 3-month larynx preservation rates (93% vs. 95%), larynx function preservation rates (82% vs. 87%), or 18-month OS (89% vs. 92%). At first glance, these data suggest that induction therapy may abrogate the need for more intensive CRT regimens and that RT/cetuximab may be sufficient among patients treated first with induction chemotherapy; however, caution is advised in extrapolating these observations into

Table 1. Selected phase II and III clinical trials of adjuvant CRT with EGFR inhibitors

Study	Regimen	*N*	2-year DFS or PFS	2-year OS	Rate of grade ≥3 toxicity[a]
Peyrade et al., 2014 [14]	CRT + cetuximab	45	DFS: 60% (95% CI: 46–77)	79% (95% CI: 67.5–92.1)	Lymphopenia (52%) Mucositis (52%) Dermatitis (50%) Rash (29%)
Ferris et al., 2014 [15]	CRT + panitumumab	44	PFS: 73% (95% CI: 61–88)	76% (95% CI: 64–91)	Mucositis (41%) Hyponatremia (25%) Leukopenia (25%) Neutropenia (21%) Dysphagia (18%) Nausea/vomiting (14%) Anorexia (11%)
Arias et al., 2014 [16]	CRT + erlotinib	13	DFS: 65%	78%	RT-related: Mucositis (59%) Erythema (25%) CT-related: Mucositis (11%) Neutropenia (7%) Erlotinib-related: Skin toxicity (25%)
Harrington et al., 2014 [17]	CRT + lapatinib vs. CRT + placebo	688	Median DFS: 53.6 mo vs. NR	NR	NR
Harari et al., 2014 [18]	RT + cetuximab + cisplatin vs. RT + cetuximab + docetaxel	238	2-year DFS with cisplatin: 57% 2-year DFS with docetaxel: 66%	With cisplatin: 69% With docetaxel: 79%	Myelosuppression (cisplatin: 28%; docetaxel: 14%) Mucositis (cisplatin: 56%; docetaxel: 54%)
Zhao et al., 2012 [19]	Induction CT/nimotuzumab + radical surgery or CRT	40	1-year PFS: 80%	1-year OS: 83.3%	NR

[a]Grade ≥3 toxicities reported for ≥10% of patients in any group (regardless of relationship) or for reported treatment-related toxicities.
Trials were published between 2009 and 2014.
Abbreviations: CI, confidence interval; CRT, chemoradiotherapy; CT, chemotherapy; EGFR, epidermal growth factor receptor; DFS, disease-free survival; mo, months; NR, not reported; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

routine treatment decisions because these data are preliminary. Moreover, because these studies did not include an RT-alone comparator, it is not known whether RT/cetuximab confers an advantage over RT alone in this setting.

Trials of other EGFRIs in the definitive setting have been limited largely to early phase studies. Nimotuzumab, an anti-EGFR mAb available in Asia, Africa, and South America, has been shown in a phase II study to be active in combination with cisplatin/5-FU induction chemotherapy, yielding an objective response rate (ORR) of 87% with a pathologic CR rate of 15% [19]. In addition, nimotuzumab demonstrated its safety and tolerability in combination with RT [41]. A retrospective study of 835 patients with advanced carcinomas of diverse tissue types suggested that nimotuzumab was well tolerated in combination with CRT, without potentiating the toxicities of concurrent therapy [42]. Randomized phase II data demonstrated that nimotuzumab plus CRT improved median OS compared with RT alone [25, 28]. Similarly, sequential lapatinib and RT yielded improvements in ORR compared with placebo/RT (70% vs. 53%) in the definitive setting [26]. In contrast, concurrent RT/gefitinib was poorly tolerated and resulted in unexpectedly low median PFS and OS (6.7 and 8.5 months, respectively) [43].

Direct comparisons of RT/EGFRI to RT/platinum are scarce. The randomized phase II ARTFORCE trial will attempt to address this by randomizing unresectable SCCHN patients to RT plus either cetuximab or cisplatin [44]. A caveat with this forthcoming trial is that its comparator is low-dose cisplatin delivered weekly rather than conventional high-dose cisplatin administered every 21 days.

In lieu of published data comparing RT/EGFRI with RT/platinum, insight has been gained from studies of platinum-based CRT plus EGFRI. Early phase studies of EGFRIs given concurrently with RT/platinum have demonstrated feasibility and an attendant increase in both expected and unexpected toxicities [45]. A single-arm phase II study of RT/cisplatin/cetuximab, for example, demonstrated encouraging 3-year OS of 76% and 3-year PFS of 56%, but rates of adverse events (AEs) including myocardial infarction were unacceptably high [46]. When studied in a prospective comparative fashion, as occurred in the RTOG 0522 study, the addition of cetuximab to RT/cisplatin increased toxicity without improving PFS or OS [27]. Similarly, no significant improvements were seen when RT/platinum was combined with panitumumab [31], erlotinib [47], lapatinib [17], or gefitinib [37]. Analyses of outcomes among patients with HPV- and non-HPV-associated disease

Table 2. Selected phase II and III clinical trials of definitive CRT with EGFR inhibitors

Study	Regimen	*N*	Median DFS or PFS	Median OS	Rate of grade ≥3 toxicity[a]
Krishnamurthyreddy et al., 2009 [25]	RT vs. RT + nimotuzumab	76	DFS: 25.0 mo vs. NR	25.0 mo vs. NR	NR
	CRT vs. CRT + nimotuzumab		DFS: 21.3 mo vs. NR	22.0 mo vs. NR	
Del Campo et al., 2011 [26]	CRT + placebo vs. CRT + lapatinib	107	NR	NR	Mucositis (grade 3: 41% vs. 46%; grade 4: 0% vs. 4%)
Ang et al., 2014 [27]	CRT vs. CRT + cetuximab	891	3-year PFS: 61.2% vs. 58.9%	3-year OS: 72.9% vs. 75.8%	Dysphagia (57% vs. 53%) Radiation mucositis (33% vs. 43%) Skin reaction outside/inside portal (1%/15% vs. 20%/25%) Fatigue (9% vs. 14%)
Babu et al., 2010 [28]	Group A: RT vs. RT + nimotuzumab	76	NR	12.7 vs. 14.3 mo	NR
	Group B: CRT vs. CRT + nimotuzumab			21.9 mo vs. NR	
Bhatnagar et al., 2012 [29]	CRT vs. CRT + nimotuzumab	50	NR	NR	NR
Ghi et al., 2014 [30]	Arm A: CRT or cetuximab/RT vs. Arm B: induction CT + CRT or induction CT + cetuximab/RT	415	PFS: 18.5 mo 3-year PFS: 36.7% PFS: 29.7 mo 3-year PFS: 46.8%	30.3 mo 3-year OS: 45.7% 53.7 mo 3-year OS: 57.6%	NR
Giralt et al., 2012 [31]	CRT vs. CRT + panitumumab	150	PFS: 35% vs. 40%	HR 1.63; 95% CI: 0.88–3.02; $p = .12$	Mucosal inflammation (24% vs. 55%) Radiation skin injury (13% vs. 28%) Dysphagia (27% vs. 40%) Rash (0% vs. 11%)
Gupta et al., 2010 [32]	CRT + nimotuzumab	17	NR	NR	No grade 3 or 4 AEs
Hainsworth et al., 2011 [33]	Induction CT/bevacizumab + CRT/bevacizumab/ erlotinib	60	3-year PFS: 71%	3-year OS: 82%	Mucositis (78%) Radiation dermatitis (31%) Anorexia (24%) Fatigue (22%) Dehydration (17%) Nausea/vomiting (11%)
Lefebvre et al., 2013 [34]	Induction CT + CRT vs. induction CT + cetuximab/RT	116	NR	18-month OS: 92% vs. 89%	Acute toxicity: Mucositis (4% vs. 45%) In-field skin toxicity (26% vs 57%) Late toxicity: Xerostomia (10.3% vs. 8.9%)
Lim et al., 2012 [35]	CRT + nimotuzumab	25	1-year PFS: 80% (oropharynx) and 48% (nonoropharynx)	NR	NR
Merlano et al., 2011 [36]	CRT + cetuximab	45	Estimated PFS: 21 mo	Estimated OS: 32.6 mo	Radiodermatitis (74%) Stomatitis (65%) Leukopenia (40%) Neutropenia (40%) Thrombocytopenia (15%)
Singh et al., 2014 [37]	CRT vs. CRT + gefitinib	86	NR	NR	NR
Somani et al., 2013 [38]	CRT + nimotuzumab	57	NR	NR	No grade 3 or 4 AEs

[a]Grade ≥3 toxicities reported for ≥10% of patients in any group (regardless of relationship) or for reported treatment-related toxicities.
Trials were published between 2009 and 2014.
Abbreviations: AE, adverse event; CI, confidence interval; CRT, chemoradiation therapy; CT, chemotherapy; DFS, disease-free survival; EGFR, epidermal growth factor receptor; HR, hazard ratio; mo, months; NR, not reported; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

treated with RT/platinum/EGFRI have been mixed [17, 27]. Of interest, the addition of nimotuzumab to conventional RT/cisplatin appears to improve the CR rate (96% vs. 72%) [29] and 30-month OS (70% vs. 22%) [25] but does not appear to potentiate the toxicity of CRT compared with RT/cisplatin alone [25, 29, 32, 35, 38].

EGFR inhibition in combination with RT and two or more cytotoxic agents has also been studied with carboplatin/paclitaxel, carboplatin/5-FU, and cisplatin/5FU all as chemotherapy backbones. Regimens that include cetuximab [33, 36, 48–50] and erlotinib [33] have shown ORRs in excess of 70%, with a manageable increase in toxicities. The phase II REACH study is currently investigating RT/carboplatin/5-FU plus cetuximab [49], with preliminary results indicating a promising ORR of 92.9% and 2-year PFS of 63.3% [50].

A randomized phase II study demonstrated that concurrent RT/cetuximab followed by 12 weeks of cetuximab improved event-free survival compared with RT/cetuximab alone (23.7 vs. 18.4 months), although an OS benefit has not been demonstrated [51]. Maintenance EGFRI has not been compared with a nonmaintenance strategy in which EGFR-directed therapy is reinstituted at the time of relapse, and thus an OS benefit likely will not be observed. The benefit of maintenance cetuximab, however, appears to lose its significance after 2 years [51], suggesting that EGFR inhibition controls but cannot eradicate microscopic residual disease.

Chemotherapy in Recurrent or Metastatic Disease

The majority of studies of single-agent EGFRIs in R/M SCCHN are phase I and nonrandomized phase II studies. Selected randomized phase II and III trials of anti-EGFR therapy are provided in Table 3.

Single-agent studies included a phase II study of weekly cetuximab in patients with R/M disease that was associated with an ORR of 13%, a disease control rate (DCR) of 46%, and median OS of 25.4 weeks among patients with platinum-refractory disease [62]. Similarly, the efficacy of dacomitinib 45 mg/day is based on a phase II study that demonstrated a DCR of 69.8%, with median PFS and OS of 12.1 and 34.6 weeks, respectively [56]. Single-agent erlotinib and gefitinib were associated with numerically lower ORR (1.6%–10.6%) and DCR (34.0%–53%) in phase II studies [63–66].

Few trials have compared one EGFRI to another or to single-agent cytotoxic therapy. One of the most robust studies compared gefitinib with conventional methotrexate delivered intravenously on a weekly schedule [54]. Patients received gefitinib 250 mg/day, gefitinib 500 mg/day, or methotrexate 40 mg/m^2 i.v. weekly. There was no statistically significant difference in ORR (2.7%, 7.6%, and 3.9%, respectively) or median OS (5.6, 6.0, and 6.7 months, respectively). A randomized phase II comparison of afatinib 50 mg/day versus standard-dose cetuximab demonstrated a similar DCR (50% vs. 57%), with an increase in grade $\geq$3 AEs with afatinib, including diarrhea (15% vs. 0%), rash (18% vs. 8%), and mucositis (12% vs. 0%) [55]. This study's design allowed crossover, and tumor shrinkage was observed in 40% and 31% of patients who crossed over to afatinib or cetuximab, respectively. Although this observation raises the possibility that EGFR mAbs and TKIs do not promote cross-resistance, caution is warranted in overinterpreting these data because only 2 objective responses (shrinkage by $\geq$30%) were seen in 56% of patients who crossed over. Regarding safety, tolerability of afatinib among SCCHN patients was lower than that with cetuximab, reflected in the high rates of treatment discontinuation in this trial (23% vs. 5%). Due in part to tolerability concerns at the 50-mg/day dose, a phase III study comparing afatinib with methotrexate used a reduced afatinib dose [59]. In this study, LUX-Head & Neck 1, 483 patients with platinum-resistant R/M SCCHN were randomized to afatinib 40 mg/day or methotrexate 40 mg/m^2 i.v. weekly and followed for the primary and secondary endpoints of PFS and OS, respectively. At a median follow-up of 6.7 months, median PFS modestly favored afatinib (2.6 vs. 1.7 months; $p = .030$) without a statistically significant impact on median OS (6.8 vs. 6.0 months; $p = .70$). A trend toward improved ORR was seen with afatinib (10% vs. 5.6%; $p = .10$), although the observed ORR for methotrexate was quite low compared with historic patient cohorts treated with single-agent methotrexate (average approximately 30%) [67]. This may relate to patient selection factors because the study included only patients with platinum-refractory disease. Compared with the 50-mg/day dose, afatinib 40 mg/day was better tolerated; the most common grade 3/4 AEs included rash (9.7%) and diarrhea (9.4%) [59].

The combination of EGFRIs with platinum-based therapy has been studied extensively. In a placebo-controlled phase III study, the addition of cetuximab to conventional cisplatin increased ORR compared with cisplatin alone (26% vs. 10%), but this did not translate into an OS benefit (9.2 vs. 8.0 months) [53]. Although this study was underpowered to demonstrate a survival benefit, its hazard ratio for OS was comparable to more intensive regimens, such as platinum/5-FU/cetuximab [60, 67]. A single-arm phase II study demonstrated that among patients with R/M disease refractory to either cisplatin/paclitaxel or cisplatin/5-FU, the combination of cetuximab/cisplatin was associated with an ORR of 20% [68].

More intensive therapy with cetuximab in combination with platinum/5-FU, as studied in the EXTREME trial, has been associated with improvements in median PFS (5.6 vs. 3.3 months) as well as OS (10.1 vs. 7.4 months) compared with platinum/5-FU alone [60]. The EXTREME trial deserves particular attention because it remains the only robust trial of chemotherapy in R/M SCCHN to demonstrate an OS benefit. Importantly, the protocol allowed for either cisplatin- or carboplatin-based therapy for a maximum of six cycles. Patients in the cetuximab arm whose disease remained controlled—defined as CR, partial response (PR), or stable disease (SD)—received maintenance therapy with cetuximab until disease progression or unacceptable toxicity. Because of the trial's design, it is impossible to know whether the benefit seen in the cetuximab arm was related to upfront cetuximab therapy or whether maintenance cetuximab therapy conferred the majority of the benefit. A subgroup analysis demonstrated improved PFS with cetuximab/cisplatin/5-FU (5.8 vs. 3.8 months) and cetuximab/carboplatin/5-FU regimens (5.3 vs. 3.2 months), yet only the cisplatin-containing regimen was associated with improved OS (10.6 vs. 7.3 months). These data suggest that in fit patients with R/M SCCHN, cisplatin should be the preferred platinum agent when combined with cetuximab/5-FU. Cumulatively, these results have been used to support platinum/cetuximab-based

Table 3. Selected phase II and III clinical trials for EGFR inhibitors in recurrent/metastatic disease

Study	Regimen	*N*	Prior treatment	ORR	Median TTP, DFS, or PFS	Median OS	Rate of grade ≥3 toxicity[a]
Argiris et al., 2013 [52]	CT + placebo vs. CT + gefitinib	270	CT	6% vs. 13% ($p = .13$)	TTP: 2.1 vs. 3.5 mo	6.0 vs. 7.3 mo	Treatment related: Diarrhea (2% vs. 13%) Fatigue (16% vs. 11%) Dehydration (5% vs. 7%) Nausea (4% vs. 6%) Leukopenia (4% vs. 5%) Anorexia (2% vs. 7%) Lymphopenia (7% vs. 3%)
Burtness et al., 2005 [53]	CT + cetuximab vs. CT + placebo	117	RT	26% vs. 10%	PFS: 4.2 vs. 2.7 mo	9.2 vs. 8.0 mo	Fatigue (17% vs. 14%) Nausea (24% vs. 19%) Vomiting (15 vs. 17%) Hyponatremia (26% vs. 28%) Neutropenia (30% vs. 14%; $p = .04$) Thrombocytopenia (11% vs. 4%)
Stewart et al., 2009 [54]	Methotrexate vs. gefitinib 250 mg vs. gefitinib 500 mg	486	RT, CT	4% vs. 3% vs. 8% ($p = .57$ for gefitinib 250 mg vs. methotrexate; $p = .17$ for gefitinib 500 mg vs. methotrexate)	NR	6.7 vs. 5.6 vs. 6.0 mo ($p = .12$ for gefitinib 250 mg vs. methotrexate; $p = .39$ for gefitinib 500 mg vs. methotrexate)	Stomatitis (10% vs. 1% vs. 0%)
Seiwert et al., 2014 [55]	Stage 1: afatinib vs. cetuximab	124	CT	8% vs. 10% ($p = .78$)[b]	PFS: 13.0 vs. 15.0 wk	35.9 vs. 47.1 wk	Stage 1: Rash/acne (18% vs. 8%) Diarrhea (15% vs. 0%) Stomatitis (12% vs. 0%) Dehydration (8% vs. 0%) Fatigue (5% vs. 2%) Decreased appetite (5% vs. 0%)
	Stage 2: crossover from cetuximab to afatinib vs. crossover from afatinib to cetuximab	68		0% vs. 0%[b]	PFS: 9.3 vs. 5.7 wk		Stage 2: Rash/acne (25% vs. 13%) Diarrhea (11% vs. 0%) Dry skin (6% vs. 3%)
Abdul Razak et al., 2013 [56]	Dacomitinib 45 mg	63	Surgery, RT, CT	12.7%	PFS: 12.1 wk (95% CI: 11.1–17.9)	34.6 wk (95% CI: 29.4–52.1)	Diarrhea (15.9%)
Fury et al., 2012 [57]	Cetuximab 500 mg/m^2 vs. cetuximab 750 mg/m^2	61	≤2 prior CT	NR	PFS: 2.2 vs. 2.0 mo	7.0 vs. 9.4 mo	ALT elevation (3% vs. 21%)[b] Acneiform rash (11% vs. 0%)[b]
Hitt et al., 2012 [58]	Paclitaxel + cetuximab	46	CT	54% (95% CI: 39%–69%)	PFS: 4.2 mo (95% CI: 2.9–5.5)	8.1 mo (95% CI: 6.6–9.6)	Acne-like rash (24%) Asthenia (17%) Neutropenia (13%)
Machiels et al., 2015 [59]	Methotrexate vs. afatinib	483	Prior EGFR-based therapy	5.6% vs. 10% ($p = .10$)	PFS: 1.7 vs. 2.6 mo	6.0 vs. 6.8 mo	Afatinib-related: Rash/acne (9.7%) Diarrhea (9.4%)
Rosenthal et al., 2014 [21]	Erlotinib	31	Surgery	NR	2-year DFS: 45%	2-year OS: 56%	NR

(continued)

Table 3. (continued)

Study	Regimen	*N*	Prior treatment	ORR	Median TTP, DFS, or PFS	Median OS	Rate of grade ≥3 toxicity[a]
Vermorken et al., 2008 [60]	CT + cetuximab vs. CT alone	442	Untreated	36% (95% CI: 29-42) vs. 20% (95% CI: 15-25)	5.6 vs. 3.3 mo	10.1 vs. 7.4 mo	Anemia (13% vs. 19%) Neutropenia (22% vs. 29%) Thrombocytopenia (11% vs. 11%) Skin reactions (9% vs. <1%) Sepsis (9 cases vs. 1 case)
Vermorken et al., 2013 [61]	CT + cetuximab	66	≤1 prior systemic therapy (CRT), RT, surgery	29.3%	PFS: 4.4 mo (95% CI: 3.6–5.4)	9.7 mo (95% CI: 6.5–13.1)	Leukopenia (34.8%) Neutropenia (33.3%) Fatigue (24.2%) Skin rash/acne (15.2%) Anorexia (12.1%) Hypomagnesemia (10.6%) Infection (10.6%)

[a]Grade ≥3 toxicities reported for ≥10% of patients in any group (regardless of relationship) or for reported treatment-related toxicities.
[b]Cetuximab-related adverse events reported only.
Trials were published between 2009 and 2014.
Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; CRT, chemoradiation therapy; CT, chemotherapy; DFS, disease-free survival; EGFR, epidermal growth factor receptor; mo, months; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; TTP, time to progression; wk, weeks.

therapy in the first-line treatment of R/M SCCHN in the U.S. and Europe, although some have found the combination too expensive to justify the modest improvement in OS. A formal cost-effectiveness analysis in Canada, for example, suggested that the addition of cetuximab exceeded CAD$100,000 per quality-adjusted life-year gained and thus was felt to be not cost-effective despite the observed OS benefit [69, 70].

The combination of EGFRI plus a taxane has been similarly studied. A phase III study of combination gefitinib/docetaxel demonstrated that the doublet was well tolerated but did not improve median OS compared with docetaxel alone (7.3 vs. 6.0 months) [52]. A post hoc subgroup analysis suggested improved survival among younger patients treated with gefitinib, but its unplanned nature renders this analysis little more than hypothesis generating. In a phase II study of 46 patients deemed unlikely to derive benefit from cisplatin, combination cetuximab/paclitaxel was associated with a DCR of 80% and a CR rate of 22%, with acceptable rates of toxicity [58]. Randomized studies are necessary, but cetuximab/paclitaxel appears to be a reasonable option for patients who are not candidates for cisplatin-containing therapy.

Safety and Tolerability

The distinct mechanisms of action and largely nonoverlapping toxicities of EGFRIs and conventional cytotoxic chemotherapy have permitted the safe incorporation of EGFRIs into conventional chemotherapy regimens for SCCHN. Nevertheless, the immunogenicity of the mAbs and the widespread distribution of EGFR in epithelial tissues can lead to serious infusion-related reactions and mucocutaneous toxicities, rates of which vary by patient demographics, EGFRI used, concomitant cytotoxic agent administered, and concurrent use of RT.

Infusion reactions (IRs) complicate approximately 4% and 12%–19% of panitumumab and cetuximab administrations, respectively [71]. Their severity varies but is frequently grade 3–4, increasing resource utilization and cost of treatment [72]. Cetuximab-related IRs appear to be mediated by IgE directed against the oligosaccharide galactose-α-1,3-galactose [73], and levels of pretreatment anti-galactose-α-1,3-galactose IgE predict the occurrence of cetuximab-related IRs with high sensitivity and specificity [74]. Additional clinical risk factors include European ancestry and history of atopy [75]; geographic distribution also may play a role [73, 76], although this has not been found consistently [75]. Corticosteroids and antihistamines may limit the risk of EGFR mAb-associated IRs [71, 75], but proactive risk-benefit analysis and vigilant monitoring after treatment are prudent in regions with high incidence of IRs [76].

> Data from dermatology referral clinics suggest that underdetection and underreporting of EGFR-related skin-specific AEs is an ongoing problem.

The mucocutaneous toxicities of EGFRIs have been amply described and include acneiform rash, augmentation of radiation mucositis and dermatitis, and diarrhea. Randomized controlled trials suggest that the addition of an EGFRI to standard therapy affects AE rates only modestly. In the definitive setting, for example, the addition of cetuximab to RT has been associated with a 5% absolute risk increase in the rate of grade ≥3 radiation dermatitis and a 16% absolute risk increase in the rate of grade ≥3 acneiform rash compared with RT alone; in contrast, the addition of cetuximab to RT only modestly increases grade ≥3 mucositis rates compared with RT alone (56% vs. 52%) [39, 40]. Rates of grade ≥3 mucosal toxicity were increased across trials comparing CRT plus EGFRI with CRT alone, including those that evaluated lapatinib (46%

vs. 41%) [26], cetuximab (43% vs. 33%) [27], and panitumumab (55% vs. 24%) [31]. In the R/M setting, single-agent EGFRI causes grade ≥3 rash in up to 25% of patients [56, 54, 55, 57, 59], with fewer events among cetuximab-treated patients compared with those treated with afatinib [55]. Although in most cases the increased toxicity of EGFRIs was modest, it is worth noting that for some patients, including those with Asian ancestry, this toxicity can be quite severe [78].

Despite the modest increase in AE rates, clinical trial experience suggests that the addition of EGFRIs to conventional chemotherapy or CRT does not adversely affect quality of life [42, 79, 80]. Nevertheless, these reported observations are at odds with the experience of many medical oncologists and their patients [81], suggesting that patient-directed questionnaires used in early studies of EGFRIs may have been unable to detect subtle but meaningful effects on patients' quality of life. Data from dermatology referral clinics suggest that underdetection and underreporting of EGFR-related skin-specific AEs is an ongoing problem [82]. Together, these observations underscore the importance of a multidisciplinary approach toward the management of treatment-related AEs. Efforts are under way to improve upon the detection and reporting of skin-related and other AEs associated with EGFR inhibition [83].

Discussion

The array of biologic and cytotoxic agents available for the treatment of SCCHN has increased dramatically in the past decade. Among them, EGFRIs have shown encouraging but limited efficacy. Despite countless trials of myriad agents, few adequately powered comparative studies exist; therefore, it is difficult to make evidence-based decisions concerning choices of agents from the published literature.

We continue to favor RT/platinum in the adjuvant treatment of fit patients with high-risk resected disease and in the definitive treatment of nonsurgical candidates. Combination RT/EGFRI is certainly active, but randomized phase III studies have not yet demonstrated that RT/EGFRI is superior or at least noninferior to RT/platinum in these settings. In the R/M setting, randomized data regarding the benefit of EGFRI monotherapy are conflicting. Cetuximab, erlotinib, gefitinib, and dacomitinib yield modest response rates that are significantly inferior to those of single-agent chemotherapeutic agents. Compared with the ORR of single-agent chemotherapy (20%–30%) [67], the poor single-agent activity of EGFRIs raises the question of whether EGFRI monotherapy should be incorporated into the standard care of patients with R/M disease [67]. Afatinib may be an exception, but the modest 4-week PFS benefit compared with methotrexate is not compelling [59].

Precisely why one anti-EGFR agent may have superior activity over another is unknown, although clues are available in different agents' mechanisms of action. The mAbs may dually inhibit tumorigenesis through their disruption of EGFR signal transduction and via ADCC [84], whereas the small molecule TKIs inhibit the EGFR pathway but do not directly engage the immune system. Among mAbs, the robustness of ADCC may be an important component of therapeutic activity in SCCHN. IgG1 mAbs have greater ADCC potential compared with IgG2 agents; therefore, cetuximab may have greater activity than panitumumab [85]. Enhanced ADCC and improvements in clinical efficacy have been observed in patients with polymorphisms of the fragment C (Fc) receptor of immune cells that enhances their affinity for the Fc region [86]. Small molecule TKIs may be better suited to the rare patient whose tumor harbors the EGFRvIII truncation mutant; the tyrosine kinase domain of the EGFRvIII mutant is constitutively activated such that mAbs should have no activity [87]. Compared with mAbs, EGFR inhibition by currently available TKIs may be incomplete such that, at clinically achievable concentrations of TKI, sufficient EGFR activity persists to allow ongoing tumorigenesis [88]. Irreversible inhibition by second-generation EGFRIs such as afatinib theoretically may confer enhanced activity against EGFR compared with first-generation reversible inhibitors including erlotinib and gefitinib. Although the above discussion documents modestly improved activity with afatinib, this comes at the expense of increased toxicity compared with first-generation agents. Consequently, it remains to be seen whether irreversible TKIs should supplant the reversible inhibitors.

Compared with mAbs, EGFR inhibition by currently available TKIs may be incomplete such that, at clinically achievable concentrations of TKI, sufficient EGFR activity persists to allow ongoing tumorigenesis.

Across treatment settings, HPV status has emerged as an important prognostic factor among patients with SCCHN. Until recently, HPV status had not been routinely assayed or incorporated into clinical trial eligibility criteria; therefore, the preponderance of published data includes patients with and without HPV-associated disease. Patients with HPV-associated disease, as assessed by HPV in situ hybridization or P16 immunohistochemistry, are generally younger and present with more advanced nodal disease [89]. Deep sequencing of HPV-associated tumors has identified distinct molecular signatures: HPV-associated tumors rarely contain TP53 mutations or EGFR overexpression and instead are more commonly associated with activating mutations in PIK3CA [90]. In addition, clinical outcomes among HPV-associated SCCHN patients compare favorably with those of patients with non-HPV-associated disease [91]. Taken together, these clinicopathologic features suggest that HPV-associated SCCHN is a separate disease entity altogether, complicating the development, evaluation, and incorporation of EGFRIs into the treatment of SCCHN.

The favorable prognosis among patients with HPV-associated oropharyngeal SCC has prompted the practice of therapy de-escalation in this setting [92], which warrants further study. Several ongoing trials in patients with HPV-associated oropharyngeal SCC are comparing EGFRI-based concurrent chemoradiotherapy with standard platinum-based chemoradiotherapy. In RTOG 1016 (NCT01302834), for example, patients with low- and intermediate-risk disease (prior smokers allowed, T1–2 N2a–3 M0 or T3–4 N1–3 M0) receive accelerated RT (70 Gy over 6 weeks, with 6 fractions per week during weeks 2–6) with either conventional high-dose

cisplatin (100 mg/m^2 on days 1 and 22) or eight weekly cetuximab doses. Separately, in the Trans-Tasman Radiation Oncology Group 12.01 study (NCT01855451), patients with low-risk disease (for nonsmokers: T3 N0–1 M0 or T1–3 N2 M0; for smokers: T1-3 N0–2a M0) receive conventionally fractionated RT (70 Gy in 35 fractions over 7 weeks) with either low-dose weekly cisplatin (40 mg/m^2 for 7 weeks) or weekly cetuximab during RT. In the ongoing British DE-ESCALATE HPV trial (NCT01874171), patients with low-risk disease (for nonsmokers: T3–4 N0 M0 or T1–4 N1–3 M0; for smokers: T1–4 N1–2a) receive conventionally fractionated RT and either high-dose cisplatin (100 mg/m^2 on days 1, 22, and 43) or weekly cetuximab during RT. Finally, because RT alone may be sufficient in the lowest risk population, the National Cancer Institute-sponsored NRG-HN002 study (NCT02254278) enrolls patients with low-risk disease (T1–2 N1–2b M0 or T3 N0–2b M0) and randomizes to either accelerated RT alone (60 Gy over 5 weeks with 6 fractions per week) or to conventional RT (60 Gy over 6 weeks) plus weekly cisplatin (40 mg/m^2 for 6 weeks). Until results from these studies are available, one cannot conclude that either the substitution of cetuximab for cisplatin or a reduction in radiation dose is appropriate. We presently recommend against the routine de-escalation of therapy for patients with HPV-associated oropharyngeal SCC in the definitive and adjuvant settings.

Performance status remains a major factor in considering appropriate therapy. Retrospective series have demonstrated inferior survival in patients with SCCHN and poor performance status [93]. Whether patients with advanced age or poor performance status gain any benefit from cytotoxic therapy or EGFRIs remains unknown because patients with poor performance have historically been excluded from clinical trials in SCCHN. The Elderly Head and Neck Cancer (ELAN) group of trials is currently enrolling elderly patients into a series of three trials based on treatment setting and level of fitness determined by a pragmatic geriatric evaluation [94]. In the curative setting, unfit patients will be enrolled in the phase III ELAN-RT study of conventional RT versus hypofractionated split-course RT (NCT01864850); in the R/M setting, patients will be enrolled based on performance status into either the phase II ELAN-FIT trial, in which patients receive therapy similar to that in the EXTREME trial (NCT01864772), or the phase III ELAN-UNFIT trial comparing single-agent cetuximab with methotrexate (NCT01884623).

Despite the emergence of a substantial body of data regarding EGFRIs in the treatment of SCCHN in the past decade, the principles of management remain unchanged. EGFRIs have not displaced cisplatin as the preferred agent to be administered concurrently with RT; single-agent EGFRIs have not established themselves as preferred agents in the R/M setting; and the clinical benefit from the addition of cetuximab to a doublet conventional chemotherapeutic backbone brings only a modest clinically relevant benefit to these patients, along with substantial toxicity. Several ongoing trials (e.g., RTOG 1016 in the HPV-associated definitive setting) may change this, but data to date do not suggest that EGFRIs will provide a major leap forward.

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Disclosures

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