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Review

Anti EGFR therapy in the treatment of non-metastatic head and neck squamous cell carcinoma: The current evidence

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Abstract Head and neck squamous cell carcinoma (HNSCC) accounts for a large oncologic burden in the developing countries. In patients with locally advanced head and neck cancer multimodality treatment is warranted. Radiation therapy with concurrent chemotherapy has long been considered the standard for patients with disease involving the oropharynx, larynx and hypopharynx. However, addition of chemotherapy to radiotherapy increases treatment related toxicity by many folds and compliance rates decrease. In this context a systemic therapy, which when used concurrent with radiation with favorable toxicity profile is of great importance for improving disease control in locally advanced HNSCC. Anti-epithelial growth factor receptor targeted therapy emerged as a potential treatment option. In recent years many trials were conducted to find the optimum treatment option with the combination of these targeted agents. The initial trials showed excellent results with minimal morbidity and led to great enthusiasm across the globe to incorporate these regimens as a standard of care. However, subsequently many trials failed to maintain such results and now there is little agreement to the initial results achieved with these drugs. Based on the current evidence we cannot recommend the replacement of cisplatin with targeted therapy in concurrent setting. It may be considered in patients with altered renal parameters, hypersensitivity or intolerance to cisplatin. The addition of targeted therapy in addition to chemotherapy in the concurrent setting can't also be recommended as the benefit is doubtful and is associated with a significant increase in toxicity.

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Contents

Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for large oncologic burden in the developing countries [1]. A large majority of these patients present in locally advanced stage and require a multimodality therapy [2]. The treatment option varies from radio-chemotherapy, surgery followed by radiotherapy, induction chemotherapy followed by radio-chemotherapy, altered fractionation radiotherapy. The best outcome in inoperable oral cavity lesions and other locally advanced head and neck cancers has been with concurrent chemoradiation [3]. However, treatment related toxicity is often the limiting factor and may lead to radiotherapy treatment breaks and leads to survival detriment [4]. In addition end organ compromise and co-morbidity makes it challenging to treat such patient to the optimum. Epithelial growth factor receptor (EGFR) is found in about 80% of the patients of head and neck squamous cell carcinoma [5]. The research for alternate agents, have paved way for less toxic, equally effective targeted therapy. Cetuximab was the first drug to be shown to be effective in the concurrent setting in radically treated head and neck patients. The survival benefit by addition of Cetuximab to radiotherapy was in fact higher than that from concurrent chemotherapy reported from the meta-analysis. Trials further evaluated other agents like Panitumumab, other agents also in the concurrent setting. The good results in concurrent setting also led to trials evaluating the addition of targeted therapy along with chemotherapy and radiotherapy. We here intend to systematically review these trials in which targeted therapy has been used in a radical setting in head and neck squamous cell carcinoma.

Targeted therapy with radiotherapy

Radiotherapy with concurrent cisplatin was found to be the best therapeutic approach with 6.5% overall survival benefit at 5 years [6]. The results of the meta-analysis revealed the benefit of concurrent chemotherapy (CTRT) in all head and neck sub-sites. However, acute and late toxicity are the major limitation and compliance was a major issue. The HNSCC patients are often elderly and not suitable for chemotherapy because of end organ damage and multiple co-morbidities. This led researchers to find an alternate drug with similar efficacy but lesser toxicity and thus better tolerance among these patients. Epithelial growth factor receptor (EGFR) being over expressed in about 80% of the patients of head and neck squamous cell carcinoma was an excellent target. The initial phase I trial reported the addition of Cetuximab with radiotherapy in locally advanced head and neck cancer is well tolerated [7].

This led Bonner et al. to conduct a phase III randomized trial to see the survival benefit of addition of Cetuximab to radical radiotherapy. Bonner et al. in this land mark phase III trial, randomized 424 patients to receive radical radiation plus concurrent Cetuximab (400 mg/m^2 loading dose followed by 250 mg/m^2 weekly) versus radical radiation alone [8]. Cetuximab was found to significantly improve loco-regional progression-free survival (median 24.4 vs. 14.9 months) and overall survival (median 49 vs. 29.3 months) compared to radiation alone. The 5 year updated results showed an absolute 5 year benefit of 9.2% with addition of Cetuximab. 17% patients developed grade 3 or higher acneiform rash. It was also noted that patients who had a grade II or higher skin rash had significantly better survival than those with no or grade I rash.

The better survival benefit shown by Bonner trial must also be seen with the fact that 90% of the patients in Bonner trial could complete the scheduled treatment while the scheduled chemo radiation is generally possible in only 50% of the patients. The toxicity profile in patients in the Bonner trial was also encouraging as well as there were a few treatment interruptions in the Cetuximab arm when compared to those in historical radio chemotherapy patients. But, as of now, there is no randomized phase III trial comparing concurrent cisplatin vs. Cetuximab head on. Though, the survival benefit with concurrent Cetuximab appears higher than cisplatin [9.2 vs. 6.5] note must also be kept that the data regarding Cetuximab is based on a trial of 425 patients while the data on cisplatin is based on meta-analysis of more than 17,000 patients. When interpreting the results of the Bonner trial it must be also noted that the radiotherapy was not uniform, one group received conventional fractionation while there were groups with hyper fractionation and one group receiving concomitant boost.

There are also a few retrospective reviews that have addressed this issue. Lawrence Koutcher in a retrospective review of 174 patients aimed to compare concurrent cisplatin vs. Cetuximab in locally advanced head and neck cancers [9]. The results showed 2 year overall survival of 87.4% and 44.5% for the cisplatin and Cetuximab arm respectively. The survival difference that was proven in univariate analysis

continued to be significant in multivariate analysis. But the results of this study must be taken with a pinch of salt because of its retrospective nature and possible difference in selection bias between the two groups. It must be noted that the reported two year survival in the Cetuximab arm is even less than that in the standard radiotherapy alone arm further increasing the suspicion of selection bias.

Petrelli et al. did a systematic review and meta-analysis to compare concomitant platinum based chemotherapy vs. Cetuximab with radiotherapy for locally advanced head and neck cancer [10]. The analysis included fifteen trials, including a total of 1808 patients. It was concluded that concomitant radio chemotherapy significantly improved 2-year overall survival ($p = 0.02$) and 2-year progression free survival ($p = 0.002$) when compared to Cetuximab with radiotherapy. But the meta-analysis can't be considered as conclusive evidence as there are no phase III trials comparing head to head CTRT and bioradiotherapy (BioRT) and the retrospective trials may be biased toward recruiting patients in poor general condition to BioRT.

Other agents have also been tried in the concurrent setting. Giralt et al. in a phase II trial [CONSERT II] evaluated Panitumumab plus radiotherapy versus radio chemotherapy in patients with locally advanced squamous-cell carcinoma of the head and neck [11]. Progression-free survival events occurred in 39% of patients in the radio chemotherapy group and 59% of patients in the radiotherapy plus Panitumumab group ($p = 0.03$). Overall survival at 2 years in patients receiving radio chemotherapy was 71% vs. 63% in patients receiving radiotherapy plus Panitumumab.

Rodriguez et al. evaluated the role of Nimotuzumab with radiotherapy for unresectable squamous-cell carcinoma of the head and neck [12]. This double blind, randomized clinical trial included 106 patients of advanced squamous cell carcinoma of the head and neck. Analysis of data revealed median survival of the patients treated with Nimotuzumab and radiotherapy (RT) of 12.50 months while 9.47 months for placebo plus irradiation.

Hence based on available data we cannot recommend bio radiotherapy over chemo radiotherapy in locally advanced carcinoma of head and neck in the absence of definite evidence of superiority. But it can be used as a feasible option in patients who may not tolerate cisplatin due to age or those with impaired renal function. Also it may be considered in patients with poor performance status and patients with allergy to cisplatin.

Targeted therapy with radical radio-chemotherapy

Survival benefit and favorable toxicity profile of Cetuximab in the concurrent setting encouraged to start the RTOG 0522 trial which compared accelerated radiation plus concurrent cisplatin with or without Cetuximab for stage III and IV head and neck carcinoma [13]. The clinical rationale for this study was that Cetuximab enhances tumor response when added to cisplatin and radiotherapy thereby helping improve survival. This trial accrued 891 patients with stage III or IV (T2N2-3M0 or T3-4, any N, M0) squamous cell carcinoma of the oropharynx, hypopharynx, or larynx. Patients in the experimental arm had significantly higher rates of grade 3 and 4 skin reactions (both inside and outside radiation volumes), radiation mucositis, fatigue, anorexia, and hypokalemia up to 90 days from the start of therapy; however the difference did not persist after 90 days. In the efficacy analysis no significant differences were found in progression free survival (PFS), overall survival (OS), loco regional failure (LRF), or distant metastasis. The toxicity data of this study showed about a ten percent increase in grade 3 and 4 dermatitis and mucositis. The results also reported more frequent interruptions in radiation therapy (26.9% vs. 15.1%, respectively). The probable reason for no added benefit with addition of Cetuximab with radio chemotherapy may be due to similar mechanism of radio-sensitization for both Cetuximab and cisplatin. The high rate of toxicity burden and treatment interruptions also appears to have contributed to suboptimal results. Also note must be made that accelerated fractionation was used in this trial in both arms which may have contributed to more acute adverse reactions. Subset analysis revealed a better 3-year probability of PFS and OS for patients with p16-positive oropharyngeal carcinoma, compared with patients with p16-negative oropharyngeal carcinoma.

Martins et al. conducted a phase II trial evaluating the benefit of addition of erlotinib to cisplatin and radiotherapy in locally advanced squamous cell carcinoma of the head and neck [14]. 204 patients were randomly assigned to two arms containing radiotherapy with cisplatin with or without erlotinib. But the addition of erlotinib neither increased complete response rate or progression-free survival compared to cisplatin and radiotherapy alone.

Subsequently, other anti-EGFR agents were also evaluated in various phase II trials. Basavaraj et al. in a phase II study evaluated the benefit of adding Nimotuzumab to chemoradiation [15]. In this study which included 92 patients it was seen that EGFR expression showed a significant relationship to patient survival in patients treated with Nimotuzumab and chemoradiation ($p = 0.02$).

The CONCERT I trial randomized patients to receive radio chemotherapy with or without Panitumumab, a fully human monoclonal antibody that targets EGFR. This trial accrued locally advanced squamous-cell carcinoma of the head and neck (Stage III, IVa, or IVb, previously untreated) to receive radio chemotherapy (three cycles of cisplatin 100 mg/m^2) or Panitumumab plus radio chemotherapy (three cycles of intravenous Panitumumab 9.0 mg/kg every 3 weeks plus cisplatin 75 mg/m^2). Primary endpoint was local-regional control at 2 years. The trial reported local regional control of 68% in the standard arm compared to 61% in the experimental arm. The PFS and OS did not support the experimental arm [16]. Adverse events like grade 3 and 4 dysphagia (27% vs. 40%), mucosal inflammation (24% vs. 55%), and dermatitis (13% vs. 31%) were more common in the Panitumumab arm. Serious adverse events were reported in 43% patients in the Panitumumab plus chemo radio therapy group compared to 32% in the radio chemotherapy only group. Use of suboptimal dose of cisplatin (75 mg/m^2) may have contributed to inferior results in this trial. Point should be made that compromise in the total chemotherapy dose may not be compensated by addition of targeted therapy irrespective of the biomarker status.

Hence with the available data there is no benefit in adding targeted to concurrent chemo radiotherapy in locally advanced carcinoma of head and neck. In addition it adds significantly to the toxicity. Hence, selective addition of anti EGFR therapy to patients with EGFR over expression may be evaluated further.

Table 1 Summary of various trials that have evaluated the role of targeted therapy in radical setting.

Study	Type	Trial Design	Outcome	Toxicity	Comments
Magrini $n = 70$ [17]	Phase II	CTRT vs. BioRT (cetuximab)	Loco regional control, patterns of failure, and survivals were similar between the treatment arms	GI toxicities more in CTRT arm Cutaneous toxicity and the need for nutritional support more in BioRT arm	RT discontinuation for more than 10 days more in BioRT ARM(13% vs. 0%)
Sakashita $n = 33$ [18]	Retrospective	Cetuximab-based BioRT vs. CTRT	–	Higher incidence of Grade $\geqslant 3$ radiation dermatitis in BioRT (43% vs. 3%) Higher incidence of Grade $\geqslant 3$ mucositis/ stomatitis in BioRT (64.3% vs.41.4%) Lower incidence of inability to feed orally in BioRT (38.5% vs. 55.2%)	
Strom $n = 279$ [19]	Retrospective	CTRT vs. BioRT (cetuximab)	No difference in loco regional control, distant metastasis rate, or overall survival		
Levy $n = 124$ [20]		CBRT after Taxane based induction chemotherapy		Radio dermatitis (97%) Skin rash (65%)	Occurrence of rash – improved 3 year OS in patients
Petrelli $n = 1808$ [10]	Meta-analysis	CTRT vs. BioRT (cetuximab)	CTRT significantly improved • 2-year OS (RR = 0.66) • 2-year PFS (RR = 0.68)		
Thomson $n = 27$ [23]	Phase-I/II trial	Cetuximab with hypo fractionated RT	At a median follow-up of 47 months, overall cause-specific survival −79%	Grade 3 acute toxicities • Pain (81%) • Oral mucositis (78%) • Dysphagia (41%)	Used hypo fractionated IMRT, 62.5 Gy in 25 daily fractions
Shapiro $n = 360$ [24]	Retrospective	Cisplatin + RT Cetuximab + RT Carboplatin, 5FU + RT	Cetuximab– inferior 4-year OS and loco regional control	Late toxicity 5FU/carboplatin (25.0%) vs. Cisplatin (8.0%) vs. Cetuximab (7.7%)	Cetuximab arm • Patients with poor performance status, older age
Egloff $n = 60$ [25]	Phase II	RT + Cetuximab + Cisplatin	2 year OS −66%	Grade $\geqslant 3$ toxicities • Mucositis (55%) • Dysphagia (46%) • Neutropenia (26%)	HPV(+) patients had significantly longer OS and PFS ($p = 0.004$ and 0.036)
Saigal $n = 16$ [26]	Retrospective	Definitive carboplatin + Cetuximab + RT	Three-year loco regional recurrence −28.3%	3 patients experienced a treatment delay and three did not finish RT	
Wanebo $n = 64$ [27]	Phase II	Cetuximab, Paclitaxel, and Carboplatin used as induction therapy and concomitant with RT	OS −78% at 3 years EFS −55% at 3 years	24.2% Grade III hematological toxicity 15.75 Grade III rash 21.4% Radiation dermatitis	
Levy $n = 265$ [21]	Retrospective	Cisplatin-based CRT Cetuximab-based BioRT	2-year LRC: 76% for CRT vs. 61% for BioRT 2-year LRC: 81% for CRT vs. 68% for BioRT	BioRT patients had more G3-4 skin complications ($p < 0.001$) and CRT patients had higher rates of feeding tube placement ($p = 0.006$) and G3-4 gastrointestinal toxicities ($p < 0.001$)	Patients receiving BioRT • More pre-existing conditionsSubgroup analyses showed that T4 patients benefited significantly from CRT (vs. BioRT) in LRC
Ley $n = 47$ [22]	Retrospective	Cisplatin-based CRT Cetuximab-based BioRT	3 year DSS 83% in the cisplatin group vs. 31% in the cetuximab group	51% requirement for PEG tube in BioRT group	

Tang $n = 177$ [28]	Retrospective	Cetuximab monotherapy Cetuximab and chemotherapy combination Platinum-based chemotherapy without cetuximab	Patients treated with platinum-based concurrent chemoradiotherapy exhibited significantly better EFS and OS compared with those receiving cetuximab	Patients cetuximab monotherapy • Older • Lower karnofsky performance status • Higher charlson co morbidity scores

CTRT, chemoradiotherapy; BioRT, bioradiotherapy; CBRT, Chemobioradiotherapy; RT, radiotherapy; OS, overall survival; PFS, progression free survival; EFS, event free survival; LRC, loco regional control; DC, distant control; DSS, disease-specific survival; IMRT, intensity modulated radiotherapy.

A summary of various trials that have evaluated the role of targeted therapy in radical setting in patients with locally advanced head and neck cancer is given in Table 1 [10,17–28].

Targeted therapy with radical radiotherapy after induction chemotherapy

In the recent years organ preservation approach has become feasible without compromising on survival with the advent of radio-chemotherapy as well as neoadjuvant chemotherapy protocols. Neoadjuvant chemotherapy followed by radiation or radio-chemotherapy protocols for laryngeal or hypopharyngeal primary received great momentum. However, chemotherapy toxicity remains an important barrier to this. In this context less toxic anti-EGFR monoclonal antibody Cetuximab was evaluated in phase II trial for organ preservation in stage III and IV laryngeal or hypo pharyngeal cancers [TREMPLIN Trial] [29]. This phase II trial included 116 patients, TPF regimen 3 cycles were used for induction chemotherapy and patients with more than 50% response were randomized to receive radio chemotherapy with cisplatin vs. radiotherapy with Cetuximab. When data were analyzed there was no significant difference in larynx preservation at 3 months between the two arms. There was also no significant difference in overall survival at 18 months between the two arms. There was no difference in grade 3 and 4 mucositis between the two arms, but more grade 3 and 4 in-field skin toxicity was observed in the Cetuximab arm. Hematological toxicity and protocol modification due to toxicity was higher in cisplatin arm compared to Cetuximab.

Though this trial showed no difference in outcomes in bioradiotherapy vs. chemo radiotherapy in organ preservation, further phase III data may be required before routinely incorporating bioradiotherapy in organ preservation protocols. However, one may argue that bio radiotherapy may be an option in patients not suitable for chemotherapy without compromising the outcome.

Attempts have also been made to assess the feasibility of adding Cetuximab with radiation after induction chemotherapy for LAHNSCC. Ghi et al. randomly assigned 421 patients to 421 patients with LASCCHN of the oral cavity, oropharynx, hypopharynx, stage III-IV, ECOG PS 0-1 to one of four treatment options: Arm A1: CRT (cisplatin/5fluorouracil $\times$ 2 concomitant to standard RT fractionation); Arm A2: CET/RT; Arm B1: 3 cycles of TPF followed by the same CRT; and Arm B2: 3 cycles of TPF followed by CET/RT [30]. The authors reported radiological CR 43.5% in induction and 28% in concomitant arm ($p = 0.002$). Median PFS was 29.7 months in induction vs. 18.5 in concomitant arm with a 3-year PFS of 46.8% vs. 36.7% (HR: 0.73; 95%CI 0.57–0.94; $p = 0.015$), respectively. Median OS was 53.7 months in induction vs. 30.3 in concomitant arm with a 3-year OS of 57.6% vs. 45.7% (HR: 0.72; 95%CI 0.55–0.96; $p = 0.025$) respectively. Compliance to concomitant treatments was not affected by induction TPF. Italian INTERCEPTOR trial also aimed to assess feasibility of adding Cetuximab with radiation following induction chemotherapy. This randomized multicenter phase III study comparing CTRT versus induction chemotherapy followed by bioradiation (RT + Cetuximab). The primary endpoint is overall Survival and secondary end points are Response Rate (RR), Progression Free survival

Table 2 Summarizes different trials using Cetuximab in concurrent, induction setting for locally advanced HNSCC.

Author/year/Phase/N	Study arm	Results	Adverse effects
Magrini et al., 2015/Phase II/ 70	RT + Cisplatin versus RT + Cetuximab	Locoregional control, patterns of failure, and survivals were similar	Serious adverse events higher in the Cetuximab arm (19% *v* 3%, $p = .044$)
Argiris et al., 2010/Phase II/39	ICT (TPE) → RT + Cetuximab	3-year PFS and OS- 70% and 74%	Grade III/IV-neutropenic fever (10%), grade 3 or 4 oral mucositis (54%) and hypomagnesemia (39%)
Kies et al., 2010/Phase II/47	ICT (Paclitaxel + Carboplatin + Cetuximab) → RT/CTRT/ Surgery	3 year PFS, OS-87%, 91%	Grade III/IV-rash-45%, Neutropenia-21%
Mesía et al., 2016/Phase II/50	ICT (C-TPF) → sequential accelerated RT with concomitant boost (69.9 Gy) + weekly cetuximab	median overall survival (OS) was 40.7 months 2 year LRC-57%	Grade III/IV-neutropenia (24%), neutropenic fever (24%), and diarrhea (20%), Death 6%
Haddad et al., 2009/Phase I/30	ICT (C-TPF) → CTRT	overall response rate of 100%	Grade III-Rash 3%
Pfister et al., 2006/Phase II/22	RT + Cisplatin + Cetuxiamb	3 year PFS, OS, LRC-56%, 76%, 71%	Grade III/IV-Rash 10%, hypersensitivity-5%

RT, radiotherapy; ICT, induction chemotherapy; CTRT, chemoradiotherapy; OS, overall survival; PFS, progression free survival; LRC, locoregional control.

(PFS) role of Biomolecular prognostic factors (EGFR, HPV) and toxicities. Table 2 summarizes different trials using Cetuximab in concurrent or induction setting for locally advanced HNSCC [32–37].

Targeted therapy and HPV

Radiation therapy oncology group 1016 is a Phase III non-inferiority study that will evaluate whether the substitution of cisplatin with Cetuximab in concurrent radio chemotherapy regimens employing accelerated intensity modulated radiotherapy (70 Gy/6 weeks) achieves similar survival with lower toxicity in these favorable patients. In this regard Siu et al. published results of the first phase III de-escalation trial 320 patients were randomly assigned to receive standard fractionation radiation with concurrent cisplatin or accelerated fractionated radiation with concurrent Panitumumab. With a median follow-up of 46.4 months, PFS was not superior in the cisplatin arm compared to Panitumumab arm. However, the direct comparison is not possible as the trial did not have a Panitumumab with standard fraction radiation arm [31].

Conclusion

The targeted agents in head and neck cancer appeared with great enthusiasm to improve survival with or without limiting the toxicity of the conventional cytotoxic agents. The current evidence does not support replacement of cisplatin with targeted therapy in concurrent setting in patients who can tolerate cisplatin. It may be considered in patients with altered renal parameters, hypersensitivity or intolerance to cisplatin. The addition of targeted therapy in addition to chemotherapy in the concurrent setting leads to a significant increase in toxicity without additional survival benefit and thus cannot be recommended. The question of using Cetuximab in patients with good prognosis like those with HPV positivity needs to be further addressed. The results of the radiation therapy oncology group 1016 trial may be helpful in this regard.

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