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Cetuximab Therapy for Head and Neck Squamous Cell Carcinoma: A Systematic Review of the Data

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Abstract

Objective. To review the current state of the data on the use of cetuximab in head and neck squamous cell carcinoma (HNSCC).

Data Sources. The National Center for Biotechnology Information's PubMed and the Cochrane collection.

Review Methods. Search terms included *cetuximab* and *head and neck cancer*. These results were reviewed, and a second search was performed using limits: meta-analysis, randomized controlled trial, and clinical trial.

Results. The literature search yielded 412 articles. Fifteen were identified for analysis. For patients with recurrent/metastatic disease who received combination chemotherapy in phase I/II trials, the overall response (OR) was 18.7% (95% confidence interval [CI], 10.4%-27.0%). Phase III trial data for combination chemotherapy in recurrent/metastatic disease showed OR to be 17.0% (95% CI, 12.6%-21.4%) for platinum-based regimens and 34.2% (28.6%-39.7%) for platinum-based regimens with cetuximab. For this same group, the estimated aggregate hazard ratio comparing platinum-based therapy plus cetuximab to platinum therapy alone was 1.10 (95% CI, 0.78-1.54), indicating no significant improvement in overall survival in the aggregate analysis. Combination chemoradiation with cetuximab in both phase I/II trials and the single phase III trial shows enhanced responsiveness, but the data are difficult to interpret because it is not used with standard-of-care regimens for advanced-stage disease.

Conclusion. Early evidence has shown cetuximab to be effective in the treatment of HNSCC, and it should be used to enhance, but not replace, current treatment paradigms until further phase III data are available.

Keywords

Cetuximab, squamous cell carcinoma, head and neck cancer, chemotherapy, systematic review

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Epidermal growth factors are implicated in the autonomous and dysregulated growth and development of cancer cells. These factors bind to transmembrane tyrosine kinase receptors that dimerize and lead to signaling cascades within the cell that ultimately result in blood vessel ingrowth, inhibition of apoptosis, invasion, and active cancer cell proliferation.¹ Currently, novel strategies have been developed that target these specific receptors with receptor antagonists and monoclonal antibodies. Several therapeutic agents have been developed for multiple types of tumors, including erlotinib (non-small cell lung cancer and pancreatic cancer), gefitinib (non-small cell lung cancer), cetuximab (colorectal cancer and head and neck squamous cell carcinoma), and panitumumab (colorectal cancer).² However, the precise role of these drugs in the treatment of solid tumors is not entirely clear given the modest clinical response in the majority of patients and the lack of a first-line indication for most clinical scenarios.²

Epidermal growth factor receptor antagonist therapy appears to be a rational choice in the treatment of head and neck squamous cell carcinoma (HNSCC) because of a high rate of expression of epidermal growth factor (EGF), which has been associated with poorer survival in this patient population.^{1,3-5} Cetuximab received early favor as an exciting and promising new therapy with relatively mild side effects. Its mechanism of action differs significantly from that of traditional chemotherapeutic regimens, and therefore, it was anticipated that this drug would have fewer cross-toxicities with other agents while acting synergistically against the tumor.⁶ It has been evaluated in several early clinical trials, but its overall clinical effectiveness and specific roles in the treatment of HNSCC have not been

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broadly evaluated. This systematic review focuses exclusively on cetuximab because of its prevalent use for head and neck cancer to better understand the appropriate use of this therapy.

Methods

Literature Search

Two independent literature searches (2000-present) of the National Center for Biotechnology Information's PubMed and of the Cochrane collection were performed. Search terms included *cetuximab* and *head and neck cancer*. These results were reviewed, and then a second stage search was performed with the following search limits: meta-analysis, randomized controlled trial, and clinical trial. A cross-reference search was then performed in OVID/Medline and checked with the PubMed results to ensure that no trials had been neglected.

The review was limited to clinical trials of epidermal growth factor receptor inhibitors in patients with squamous cell carcinoma of the head and neck. Excluded studies included the following: (1) therapy other than cetuximab, (2) cancers outside of head and neck, (3) non-squamous cell cancers, (4) retrospective studies, and (5) non-English literature. Included studies were any prospective trial of cetuximab for head and neck cancer as a single agent, in combination therapy with other chemotherapeutic agents, in combination chemotherapy with concurrent radiation, or cetuximab monotherapy with radiation. Included studies were required to present at least one of the following outcome variables: (1) treatment response (none, partial, complete), (2) disease-free survival, (3) overall survival, and/or (4) toxicity.

The studies were sorted into 4 groups according to patient population, treatment, and trial design to improve homogeneity of included studies. The 4 groups included the following: (1) phase I/II trials with combination chemotherapy, including cetuximab; (2) phase III trials with combination chemotherapy; (3) phase I/II trials with chemotherapy and radiation therapy; and (4) phase III trials with chemotherapy and radiation therapy.

Each article was reviewed in detail by 2 reviewers with construction of a database that included study information along with summary measures of treatment response, toxicity, and survival. Gaps in available data are noted in the Results section as well as relevant figures and tables. Other important points are noted for providing context where appropriate, but often these were not amenable to data pooling for analysis because they were reported only in a minority of studies.

For the phase I and II clinical trials involving combination chemotherapy and combination chemoradiation, clinical responsiveness and median overall survival (OS) were the main end points reported. Pooled, available data were used to estimate partial response (PR), complete response (CR), overall response (OR = PR + CR), and a weighted average of median overall survival.

Only 2 phase III trials were available for review evaluating combination chemotherapy with cetuximab at the time of this writing. Although the data are limited, we

constructed weighted estimates of clinical responsiveness, median overall survival, percentage 1-year survival, and the hazard ratio of treatment with and without cetuximab. The single phase III trial of radiation therapy and cetuximab is discussed because of the important context that it provides but is not part of an aggregate analysis as it stands alone as the only phase III trial of this type.

Toxicity analysis was performed by examining the total numbers of grade III and IV events related to the therapeutic regimens. Cetuximab-related events and total patients with adverse events are not reported by the majority of the studies but are shown here only to provide context for the pooled data.

We obtained summary point and interval estimates using meta-analysis, a methodology that uses inverse variance weighted averages to combine estimates across studies.⁷ For pooled estimation of clinical response (CR, PR, and OR) rates, we assessed homogeneity of study means and fit random effects models where appropriate. However, for meta-analyses based on a small number of studies (3 or fewer), there is limited information to adequately estimate the variance of the random effect. Therefore, in such circumstances, we derived response estimates using a fixed effects modeling approach.

Because of inconsistencies in reporting of uncertainty (standard errors and 95% confidence intervals [CIs]) across studies, pooled estimates of median overall survival and percentage 1-year survival were obtained using inverse sample size weights. In addition, these OS summaries (median and 1-year percentage) ignore follow-up time differences owing to censoring and event rates, and this information is typically not reported in the literature. Because of this lack of complete information, we did not construct 95% CIs for median and percentage 1-year survival estimates. For the randomized phase III trials, a pooled hazard ratio (HR) estimate (for the overall survival end point) comparing platinum-based chemotherapy plus cetuximab to platinum-based therapy alone was constructed using methods described by Parmar et al.⁸ Specifically, we constructed a pooled HR estimate using the HR estimate from the Vermorken et al⁹ study together with counts of the number randomized and total number of deaths in each arm of the Burtneis et al¹⁰ study. Unlike median and percentage 1-year OS estimates, the hazard ratio accounts for censoring and differences in follow-up time across patient cohorts. This approach is particularly important in this setting to elucidate the survival advantage in the combined population given the differences in the individual study results. All analyses were performed using R statistical software (R version 10.1, 2009).¹¹ Meta-analyses for response end points were performed using the *rmeta* package in R (2009).

Results

Literature Search

The initial search in PubMed resulted in 412 articles that were screened for inclusion. Fifteen clinical trials were selected according to the inclusion/exclusion criteria as seen in **Table 1**. The secondary stage search yielded 34 articles

Table 1. Methodological Characteristics of Each Study Included in This Analysis

Phase	Study Characteristics	Agents	Level of Disease	Number of Patients
Phase I/II noncomparison groups				
I	Combination chemotherapy and cetuximab as induction therapy	Docetaxel/cisplatin/FU + cetuximab	Locally advanced disease	28
II	Previously untreated			
	Cetuximab monotherapy or combined therapy after failed platinum agent monotherapy	Cetuximab monotherapy or platinum agent + cetuximab	Recurrent or metastatic	103
I/II	Combination chemotherapy, first-line for recurrent/metastatic disease	5-FU/platinum agent + cetuximab	Recurrent or metastatic	53
II	Combination chemotherapy with cetuximab after failed platinum agent-based therapy	Platinum agent + cetuximab	Recurrent or metastatic	96
II	Combination chemotherapy with cetuximab after failed platinum agent-based therapy	Cisplatin/paclitaxel + cetuximab or cisplatin/fluorouracil + cetuximab	Recurrent or metastatic	130
I	Combination chemotherapy	Cisplatin + cetuximab	Recurrent or metastatic	12
II	Combination chemotherapy and cetuximab as induction therapy	Carboplatin/paclitaxel + cetuximab	Locally advanced disease	47
Radiotherapy + cetuximab				
I	Unresectable disease	Cetuximab only + RT	Locally advanced disease	16
II	No prior RT or chemotherapy			
II	New or recurrent disease	Cetuximab + cisplatin + RT	Locally advanced disease	21
III	No prior radiation therapy			
III	No metastatic disease	Cetuximab only ± RT	Locally advanced disease	424
III	Previously untreated			
III	No metastatic disease	Cetuximab only ± RT	Locally advanced disease	424
II	Previously untreated			
II	Inoperable disease after primary radiation or chemoradiation	Cetuximab + RT	Recurrent	7
Combination chemotherapy				
III	Untreated recurrent or metastatic disease	Cisplatin or carboplatin + 5-FU ± cetuximab	Recurrent or metastatic	442
III	Recurrent or metastatic disease after locoregional therapy	Cisplatin ± cetuximab	Recurrent or metastatic	117
Toxicity				
II	Toxicity analysis	Paclitaxel/carboplatin and RT + cetuximab	Locally advanced disease	32

Abbreviations: 5-FU, 5-fluorouracil; RT, radiation therapy.

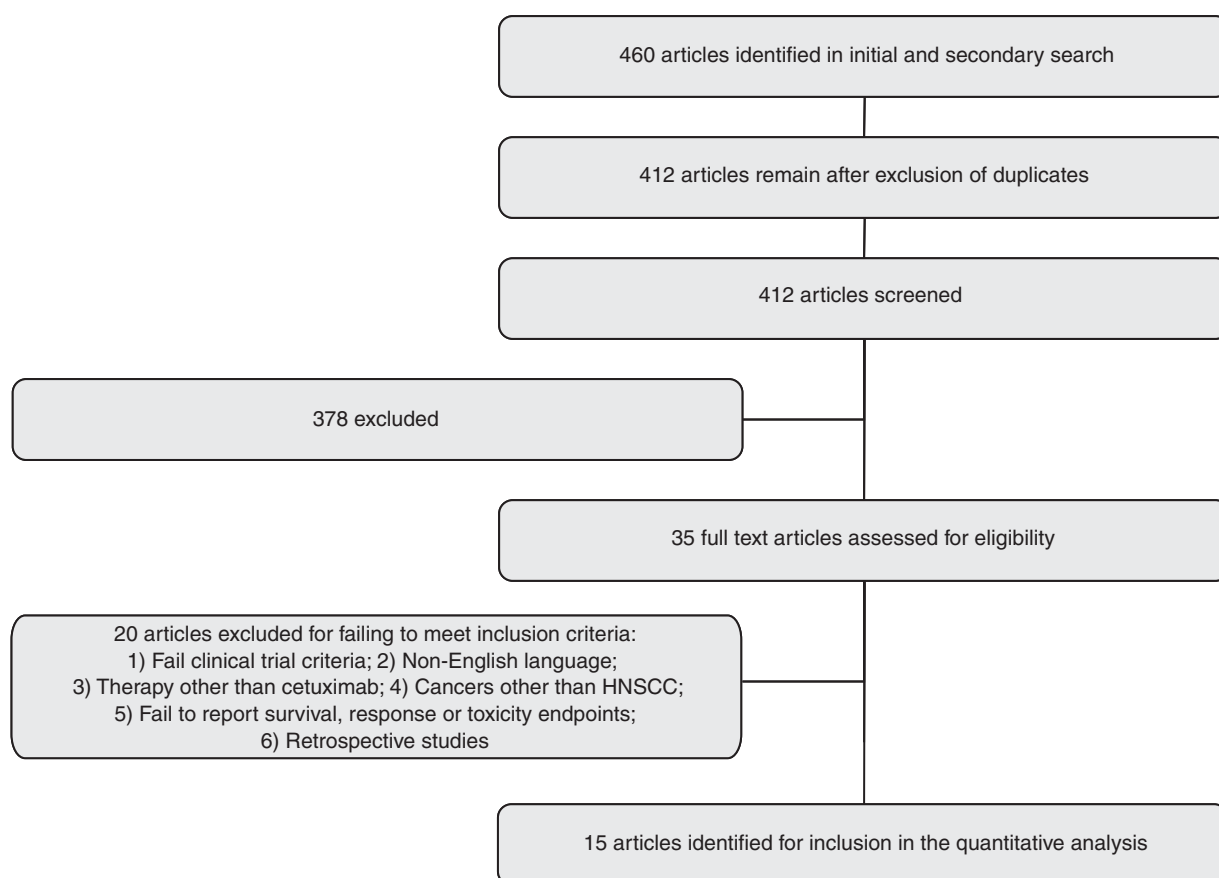


Figure 1. Summary flowchart of article identification, inclusion, and exclusion. HNSCC, head and neck squamous cell carcinoma.

in PubMed and 14 articles in OVID/Medline (these 14 were all duplicates from the secondary stage PubMed search). Of these 34 articles, a total of 12 trials were immediately excluded because they did not exclusively study HNSCC (included various solid tumors, esophageal cancers, nasopharyngeal carcinoma, salivary gland carcinoma, skin cancer, and lung cancers). Five results were not prospective clinical trials: a retrospective study, a letter to the editor, a review article, a clinical trials broadcast statement for RTOG 0522, and a study using a survey of EORTC institutes. Finally, 3 trials were excluded because their end points were radiation dosimetry, quality of life, and cost-effectiveness of treatment. Thus, a total of 14 trials were identified during the secondary stage search, and all were duplicate results from the initial PubMed search. A single trial from the initial search not found during the secondary stage was also included for a total of 15 trials eligible for analysis. Of note, the Bonner et al¹² trial from 2010 reports follow-up results from the 2006 data and does not provide any new or revised data points for our analysis. A summary of this process can be found in **Figure 1**.

Therapeutic Responses

Seven phase I and II trials followed patients treated with cetuximab in combination with other chemotherapy. Five of

the 7 studies were for patients with recurrent or metastatic disease, and the majority of these patients had received prior therapy and failed platinum-based chemotherapeutic regimens. The remaining 2 trials included previously untreated patients and administered the chemotherapeutic regimens as induction therapy. Therefore, this pooled data analysis included only these 5 of the 7 phase I and II trials. An aggregate analysis of these data shows a total of 394 patients all treated with cetuximab and another chemotherapeutic agent. An exception includes the Vermorken et al⁹ published in 2007 in which cetuximab is given to a fraction of patients as monotherapy. The test for homogeneity of means indicated significant heterogeneity across studies ($P = .001$), and a random effects model was used to estimate clinical response rates. Of these 394 patients, 15.7% (95% CI, 9.2%-22.2%) exhibited a partial response based on the criteria established for each study, and 2% of patients demonstrated a complete response (**Table 2**). The overall response rate was 18.7% (95% CI, 10.4%-27.0%), as seen in **Figure 2**.

Among the phase III trials for recurrent or metastatic disease using combination chemotherapy, there is no delineation between partial and complete disease response. However, aggregate data analysis is still feasible using the reported overall responsiveness; this shows a combined responsiveness of 17.0% (95% CI, 12.6%-21.4%) for

Table 2. Aggregate Analysis of Treatment Response for Combination Chemotherapy in Phase I and II Studies

Phase I/II Noncomparison Groups	No.	CR (Rate), No. (%)	PR (Rate), No. (%)	OR (Rate), No. (%)	Median OS, d
Shin et al, 2001 ¹³	12	2 (16.7)	4 (33.3)	6 (50.0)	NR
Baselga et al, 2005 ²³	96	0	10 (10.4)	10 (10.4)	183
Herbst et al, 2005 ²⁴	130	2 (1.5)	15 (11.5)	17 (13.1)	228
Bourhis et al, 2006 ²²	53	2 (3.8)	17 (32.1)	19 (35.8)	297
Vermorken et al, 2007 ⁹	103	0	13 (12.6)	13 (12.6)	178
Total average response rate, No. (%) ^a [95% CI ^a]	394	6 (NA)	59 (15.7) [9.2-22.2]	65 (18.7) [10.4-27.0]	213

This table represents the 5 studies that treated recurrent/metastatic disease with combination chemotherapy. CR and PR are reported in each study, and the OR is represented by PR + CR per the methods described. CI indicates confidence interval; CR, complete response; NR, not reported; NA, not applicable; OR, overall response; OS, overall survival; PR, partial response.

^aDerived using weighted responses; weights = inverse variance.

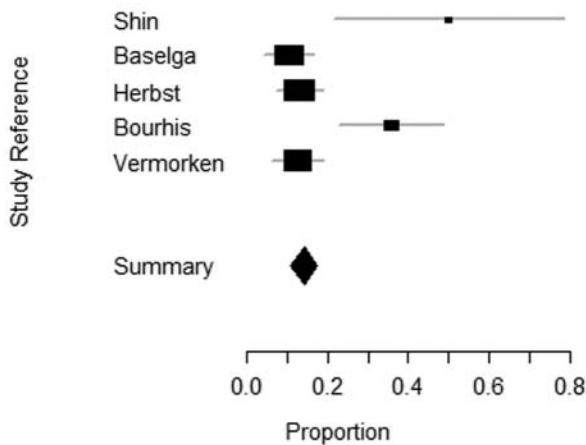


Figure 2. Forest plot representation of overall response for phase I/II trials using combination chemotherapy (with cetuximab) for recurrent and metastatic disease.

platinum-based regimens with placebo compared to 34.2% (28.6%-39.7%) for platinum-based therapy with cetuximab (**Table 3**). These data are presented also in **Figure 3A, B**.

The addition of cetuximab to radiation therapy enhances its effectiveness, as seen by overall response compared to

radiation alone. The small phase I and II trials (**Table 4**) together studied a total of 44 patients and showed an overall response of 85.5% (95% CI, 75.7%-95.2%) (**Figure 4**). The single phase III trial comparing radiotherapy alone to radiotherapy and cetuximab reports a higher response rate (74% vs 64%) with the addition of cetuximab (**Table 5**).

Survival

Four of the 7 phase I and II trials on combination chemotherapy plus cetuximab summarize overall survival, and it is universally poor given the severity of disease studied in these populations. A weighted average of the median survival is only 213 days for an aggregate population of 382 patients (**Table 2**). This is consistent with the pooled data seen in the 2 phase III trials (**Table 3**) for a similar treatment population in which the treatment arms (platinum-based therapy plus cetuximab) show a median survival of 9.9 months. This is only a modest increase in survival when compared to the control arm's 7.5-month median survival. The 1-year survival is also improved for the population treated with combined platinum and cetuximab therapy when compared to platinum-based therapy only. Combined data show 54.3% and 39.8% for the 1-year overall survival in the treatment and control arms, respectively (**Table 3**). The aggregate HR is an estimate of survival advantage and

Table 3. Combined Phase III Trial Data for Combination Chemotherapy

Randomized Trials		No.	Responders (Rate), No. (%) [95% CI]	I-Year OS, %	Median OS, mo
Burtneess et al, 2005 ¹⁰	Cisplatin + placebo	60 (57.5)	6 (10)	31.7	8.0
	Cisplatin + cetuximab	57 (54.5)	15 (26)	38.6	9.2
Vermorken et al, 2007 ⁹	Cisplatin/5-FU baseline	220	44 (20)	41.9	7.4
	Cisplatin/5-FU + cetuximab	222	80 (36)	58.6	10.1
Pooled data	Platinum therapy alone	280 (277.5)	50 (17.0) ^a [12.6-21.4] ^a	39.8	7.5
	Platinum therapy + cetuximab	279 (276.5)	95 (34.2) ^a [28.6-39.7] ^a	54.3	9.9

Pooled estimates of median overall survival and percentage 1-year survival were obtained using inverse variance sample size weighting. Responsiveness for the individual studies were derived from the primary source and pooled to calculate response rates.

^aDerived using weighted responses; weight = inverse variance.

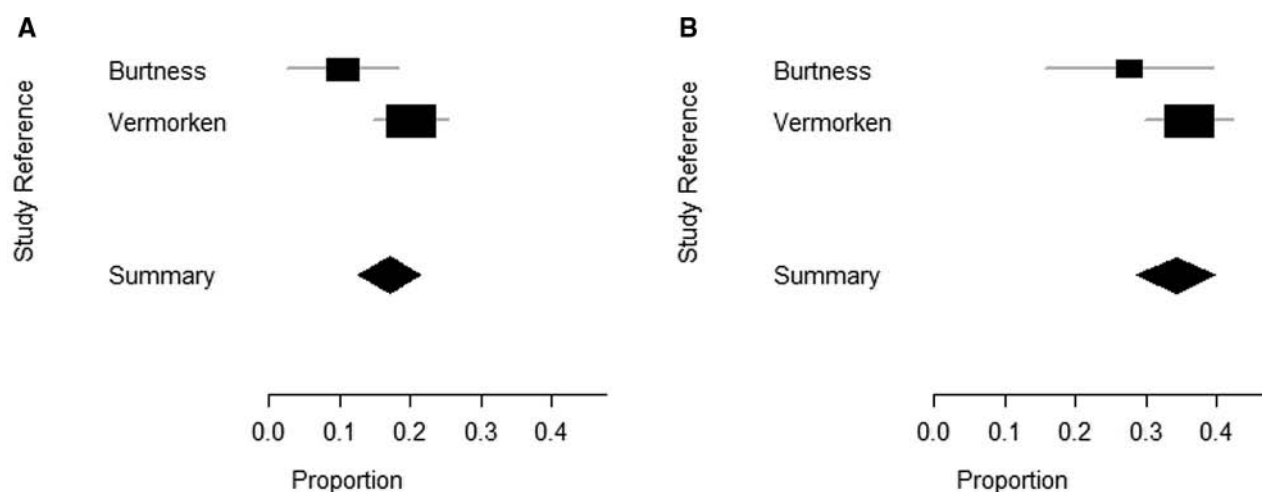


Figure 3. (A) Forest plot representation of overall response for the phase III control arms of combination chemotherapy (without cetuximab) for recurrent and metastatic disease. (B) Forest plot representation of overall response for the phase III treatment arms of combination chemotherapy (with cetuximab) for recurrent and metastatic disease.

Table 4. Aggregate Analysis of Treatment Response for Combination Chemoradiation in Phase I and II Studies

RT + Cetuximab	Phase	No.	CR (Rate), No. (%)	PR (Rate), No. (%)	OR (Rate), No. (%)
Robert et al, 2001 ²⁵	I	16	13 (81)	2 (13)	15 (94)
Pfister et al, 2006 ²⁶	II	21	2 (10)	13 (62)	15 (71)
Balermipas et al, 2009 ²⁷	II	7	2 (29)	2 (29)	4 (57)
Total average response rate, No. (%) ^a [95% CI ^a]		44	17 (30.9) [20.9-40.9]	17 (30.9) [18.9-42.8]	34 (85.5) [75.7-95.2]

This table represents the studies that used chemotherapy and radiation therapy. As before, CR and PR are reported in each study, and the OR is represented by PR + CR using inverse-variance weighting. CI indicates confidence interval; CR, complete response; OR, overall response; PR, partial response.

^aDerived using weighted responses; weights = inverse variance.

combines the data from the 2 studies to compare platinum-based therapy plus cetuximab to platinum-based therapy

alone. Only 1 of the studies reports significance in OS, so this technique is critical in this setting to elucidate if there is a change in survival for the combined population. Using this technique, the HR is 1.10 (95% CI, 0.78-1.54), indicating no significant improvement in overall survival for the experimental arm in the aggregate analysis.

For combination radiation therapy and cetuximab, the phase I and II trials do not report median survival. The single phase III trial shows a significant improvement in median survival times at 49 months for combination therapy compared to 29 months for radiation therapy alone. This was primarily seen for the oropharyngeal subsite and should be interpreted with caution when extrapolating to all sites in the head and neck.

Toxicity

Overall, cetuximab is thought to be a relatively well-tolerated therapeutic option, but certain toxicities specifically associated with this agent include skin rash of varying severity and rarely anaphylaxis. Our analysis focused primarily on grade III and IV reactions as outlined by the common toxicity criteria that define specific objective findings to categorize the severity of side effects and drug

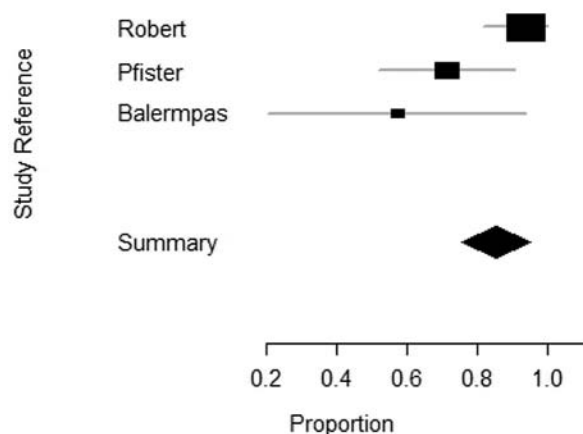


Figure 4. Forest plot representation of overall response for phase I/II trials using combination radiation and chemotherapy (including cetuximab).

Table 5. Phase III Trial Data for Chemoradiation Therapy

RT + Cetuximab (Bonner et al, 2006 ¹⁶)	No.	Percentage Responders	OR ^a	Median OS
RT + cetuximab	211	74	156 or 157	49.0
RT alone	213	64	136 or 137	29.3

As the only phase III trial on combination chemoradiation using cetuximab, the data reported here are simply a summary of relevant information derived from the primary source. OR indicates overall response; OS, overall survival; RT, radiation therapy.

^aCalculated.

Table 6. Combined Toxicity Data from All Studies

	No.	Total Grade III/IV SAEs	% with Grade III/IV	# with Cetuximab-Related SAEs
Chemotoxicity analysis				
Haddad et al, 2009 ²¹	28	NR	NR	NR
Vermorken et al, 2007 ⁹	103	NR	70.9	24.0
Bourhis et al, 2006 ²²	53	41	NR	NR
Baselga et al, 2005 ²³	96	57	42.7	15.0
Herbst et al, 2005 ²⁴	131	152	NR	NR
Shin et al, 2001 ¹³	12	13	NR	NR
Kies et al, 2010 ¹⁷	47	93	NR	NR
Burtneess et al, 2005 ¹⁰				
Cisplatin + cetuximab	58	277	89.6	NR
Cisplatin + placebo	58	166	72.4	NR
ChemoXRT toxicity analysis				
Birnbaum et al, 2010 ²⁸	32	94	96.9	NR
Robert et al, 2001 ²⁵	16	33	NR	NR
Pfister et al, 2006 ²⁶	21	68	NR	NR
Balermipas et al, 2009 ²⁷	7	19	NR	NR
Bonner et al, 2006 ¹⁶				
RT only	212	NR	NR	NR
RT + cetuximab	208	NR	NR	NR

Abbreviations: NR, not reported; RT, radiation therapy; SAE, severe adverse effect.

reactions for each major body system. Of the total 397 patients studied in all trial types with combination chemotherapy only, there were 633 grade III and IV reactions (Table 6). Four studies report the total number of patients with this level of reaction to combination therapy; of these 257 patients, the incidence of grade III/IV reactions is 64.6% (95% CI, 58.4%-70.4%). Of course, a number of these toxicities are attributed to the well-known side effects of the other chemotherapeutic agents of the baseline regimens. Cetuximab-related events are only recorded in 2 studies, and the incidence in these 199 patients is 19.6%. One of the 2 randomized controlled trials reports on the frequency of adverse reactions in the treatment (platinum-based therapy and cetuximab) and control arms (platinum-based therapy). These showed that 90% and 73% of patients in the treatment arm and control arm, respectively, suffered grade III/IV reactions; however, when controlled for the number of treatment cycles, the rate of specifically hematologic toxicity was not changed.¹⁰

A total of 287 patients received both cetuximab and radiation therapy in all the phase I, II, and III trials. Grade III

and IV count data were available for 76 patients. In these 76 patients, there were a total of 214 adverse grade III and IV reactions.

Discussion

Epidermal growth factor receptor antagonists are the result of research to target specific cancer-causing mechanisms. Overexpression of EGF receptors is implicated as one of the methods by which HNSCC evades normal cellular regulation of proliferation and growth.³⁻⁵ Initial studies with cetuximab demonstrated its affinity for the EGF receptor along with sufficient clinical response to encourage further investigation.^{13,14} The results of these and subsequent studies are reviewed in detail here to highlight the current state of the data as a way of prudently and critically evaluating the administration of a relatively novel therapy in the face of fairly extensive, early usage.

First, it should be noted that the standard of care at our institution for primary treatment of advanced-stage (stage III and IV) HNSCC (without distant metastasis) is surgical excision with adjuvant radiation (with or without

chemotherapy depending on adverse features seen on final pathologic examination) or primary concurrent radiation and chemotherapy (platinum based in combination with taxol analog) with surgical salvage as indicated for persistent disease. The one exception is HNSCC of the oral cavity in which surgery followed by adjuvant radiation ($\pm$ chemotherapy) is the preferred primary treatment. The standard for metastatic disease or recurrence that has failed other therapies is combination chemotherapy or clinical trial drug if available. We undertook this study to better understand the possible additive role that cetuximab could serve within these evidence-based treatment paradigms.

With respect to treatment response, cetuximab has been shown to have a consistent antineoplastic effect in each study reviewed. However, the primary patients enrolled in the combination chemotherapy trials had recurrent or metastatic disease that was often refractory to other therapies, proving that these patients had the most aggressive disease processes with the poorest prognosis. Thus, the modest treatment responses reported in our Results section may not be an entirely fair assessment of this therapy's true effectiveness in a general HNSCC population. The 2 randomized controlled trials that pursued combination chemotherapy with and without cetuximab confirm these moderate effects. The slight improvement seen in these phase III trials is likely the result of reporting best overall response rate and objective response rate instead of the complete and partial responses reported separately in the phase I/II trials.^{10,15}

The addition of cetuximab to radiation therapy, not surprisingly, showed a significant increase in responsiveness compared to the phase I/II trials of combination chemotherapy; this is confirmed by a single randomized controlled trial.¹⁶ However, there are 2 caveats to interpreting these phase III data: (1) the control population with advanced HNSCC is treated with what is presently non-standard-of-care radiation therapy alone, and (2) the majority of the response is seen only for the oropharynx subsite. Therefore, future studies (which are currently in progress) are needed to better evaluate the use of this new therapy within current treatment paradigms and for a variety of patients with differing disease factors.

Ultimately, there may be specific patient factors that help to guide cetuximab usage. EGF receptor (EGFR) expression may prove to be an important predictor in treatment response, although the primary studies that evaluated this factor did not find conclusive results to guide current usage.^{10,17} Human papillomavirus (HPV) status, however, does appear to correlate with cetuximab's efficacy. Kies et al¹⁷ report that those individuals who never smoked were more likely to achieve a complete response to treatment with induction chemotherapy that included cetuximab; further, these nonsmoking patients were more likely to be HPV positive. This is consistent with the results of HPV-related patient demographics found in other studies.¹⁸⁻²⁰ If, in fact, HPV-related HNSCC is more sensitive to cetuximab therapy, this may help to explain the preponderance of treatment

response seen in the oropharyngeal subsite in the phase III trial by Bonner et al¹² of radiation plus cetuximab. A prospective trial evaluating this critical factor is needed to better delineate patient selection.

Survival with cetuximab therapy parallels the modest efficacy data for each of the trials that study it in combination with other therapeutic agents (for both phase I/II and III trials). Median survival data indicate only an increase in weeks to months, and there are no correlative statistics that compare this increase in survival time to improvements in quality of life. Again, this fact is complicated by the fact that the patients studied here often have the most aggressive tumors with the poorest prognosis. Nevertheless, the evidence for using this treatment in the palliative setting would be strengthened if future trials demonstrate that the limited improvement in survival is accompanied by significant improvements in quality of life, tumor morbidity, and pain control.

The toxicity profile of cetuximab appears to be relatively benign with respect to the other chemotherapeutic agents currently in use. In almost all instances, the majority of adverse events seem to be attributable to the standard regimens currently used to treat HNSCC. However, there is a recognizable increase in total adverse events with the addition of another drug, and with the addition of cetuximab, severe skin rashes and rarely anaphylactic infusion reactions can be anticipated in a small percentage of patients.⁴ These manageable but serious side effects must be considered in the treatment planning and emphasize that the addition of another agent to already toxic regimens should include careful patient selection and full disclosure of the expected benefits over harms.

Conclusion

Early evidence has shown cetuximab to be an effective agent for the treatment of HNSCC, and it will likely develop into a frequently used drug in the armamentarium against these aggressive neoplasms. Although an effective antineoplastic agent, the current data on this therapy do not provide solid support for its use in replacing current treatment regimens or for broad use in all patient populations and subsites. However, the data do support its use as an additional agent to augment and enhance standard-of-care regimens, particularly for patients with advanced disease. Its usage in HPV-associated HNSCC, concurrent chemoradiation regimens, and treatment of premalignant lesions has not been fully elucidated and needs to be further studied based on the preliminary results of the studies highlighted here. There are dozens of clinical trials that are currently seeking to answer these questions, and cetuximab's definitive role in our current treatments will be better defined by the results of these studies.

Author Contributions

Travis D. Reeves, primary literature review and initial statistical analysis; **Elizabeth G. Hill**, final statistical analysis; **Kent E.**

Armstrong, final statistical analysis; M. Boyd Gillespie, primary literature review and initial statistical analysis.

Disclosures

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