Cetuximab therapy for head and neck squamous cell carcinoma: a systematic review of the data
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CRD summary
This review concluded that cetuximab was effective in the treatment of head and neck squamous cell carcinoma and should enhance, but not replace, standard treatment regimens, until further phase III trials become available. Limitations in the review, including unclear trial quality and small data sets, mean that the reliability of this conclusion is uncertain.

Authors' objectives
To determine the efficacy of cetuximab in the treatment of head and neck squamous cell carcinoma.

Searching
PubMed and The Cochrane Library were searched (from 2000); search terms were reported. A cross-reference search was performed in MEDLINE. Only English-language publications were included.

Study selection
Prospective clinical trials of cetuximab (alone, with radiation, with other chemotherapy, or with both), in patients with head and neck squamous cell carcinoma, were eligible for inclusion. Trials were required to report at least one of the following outcomes: treatment response (none, partial, or complete), disease-free survival, overall survival, and toxicity.

Included trials assessed cetuximab alone or with cisplatin, paclitaxel, 5-fluorouracil, carboplatin, an unspecified platinum agent, or radiotherapy. Most of the included trials were phase I or II; three phase III trials were included. Clinical responsiveness and median overall survival were the primary endpoints for the phase I and II trials of combination chemotherapy and combination chemoradiation. The level of disease included locally advanced disease and recurrent or metastatic disease.

The authors did not state how many reviewers selected studies.

Assessment of study quality
The authors did not state that the validity of the included trials was formally assessed.

Data extraction
Two reviewers extracted the data to calculate clinical responsiveness, weighted average of median overall survival, percentage one-year survival and the hazard ratio for treatment with or without cetuximab, along with 95% confidence intervals. The total numbers of grade III and IV events with each therapeutic regimen were extracted.

Methods of synthesis
Where trials were pooled, summary estimates and 95% confidence intervals were calculated using a fixed-effect model. Where significant heterogeneity was found a random-effects model was used, unless there were fewer than four trials for the analysis. Pooled estimates of median overall survival and percentage one-year survival were calculated, using inverse sample size weights (95% confidence intervals were not constructed due to lack of complete information).

Trials were grouped according to treatment and design: phase I or II trials with combination chemotherapy, phase III trials with combination therapy, phase I or II trials with chemotherapy and radiation, and phase III trials with chemotherapy and radiation.

Results of the review
Fourteen trials, in 15 articles, were included in the review (1,528 patients); 11 were phase I or II trials (seven of...
cetuximab with other chemotherapy, three of radiotherapy and cetuximab, and one toxicity analysis) and three were phase III trials (two of combination therapy and one of radiotherapy and cetuximab that was reported in two articles).

With other chemotherapy, cetuximab overall response rate for recurrent or metastatic disease in phase I or II trials was 18.7% (95% CI 10.4 to 27.0; five trials; 394 patients).

In phase III trials, the overall response rate for recurrent or metastatic disease was 17.0% (95% CI 12.6 to 21.4; two trials; 280 patients) for platinum therapy alone and 34.2% (95% CI 28.6 to 39.7; two trials; 279 patients) for platinum therapy with cetuximab; median survival was 7.5 months without cetuximab and 9.9 months with it. One-year survival was 39.8% without cetuximab and 54.3% with cetuximab. No statistically significant difference between groups was found for overall survival (two trials).

A significant improvement was demonstrated in median survival in favour of combination therapy compared with radiation alone (49 months versus 29 months, one phase III trial). The overall response in phase I or II trials, for cetuximab with radiation therapy was 85.5% (95% CI 75.7 to 95.2%; 44 patients). The one phase III trial demonstrated a higher response rate with cetuximab (74% versus 64%).

Based on four trials reporting toxicity, the incidence of grade III or IV reactions was 64.6% (95% CI 58.4 to 70.4) with combination therapy. The incidence of cetuximab-related events was 19.6%, based on two trials (199 patients).

Authors' conclusions
Early evidence indicated that cetuximab was effective in the treatment of head and neck squamous cell carcinoma and should be used to enhance, but not replace, the standard treatment regimens, until further phase III trials become available.

CRD commentary
The review question was supported with defined inclusion criteria. The search was limited to two electronic databases and inclusion was restricted to published trials in English, raising the possibility of language and publication bias. It was unclear whether appropriate steps were taken to reduce the likelihood of error and bias in the selection of trials, and it does not appear that the validity of the included trials was evaluated. Where trials were pooled, many estimates were based on a small number of small trials.

Limitations in the review process mean that the reliability of the results is not clear.

Implications of the review for practice and research
Practice: The authors suggested that the data supported the use of cetuximab as an addition to standard regimens, especially in patients with advanced disease. The manageable, but serious side-effects should be considered in treatment planning including careful patient selection and full disclosure of the expected benefits and harms.

Research: The authors stated that a prospective trial should investigate specific patient factors, such as whether head and neck squamous cell carcinoma related to human papillomavirus was more sensitive to cetuximab.

Funding
No funding received.

Bibliographic details

PubMedID
21493327

DOI
10.1177/0194599811399559

Original Paper URL
http://oto.sagepub.com/content/144/5/676.abstract

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Antibodies, Monoclonal /therapeutic use; Antibodies, Monoclonal, Humanized; Antineoplastic Agents /therapeutic use; Carcinoma, Squamous Cell /surgery; Cetuximab; Head and Neck Neoplasms /drug therapy; Humans

**AccessionNumber**
12011005151

**Date bibliographic record published**
09/11/2011

**Date abstract record published**
19/10/2012

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.