Anti-epidermal growth factor receptor therapy for advanced head and neck squamous cell carcinoma: a meta-analysis

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CRD summary
The review concluded that anti-epidermal growth factor receptor monoclonal antibodies, but not tyrosine kinase inhibitors, were effective for the treatment of locoregionally advanced and recurrent/metastatic head and neck squamous cell carcinoma. The small number of trials and potential for error and bias in the review process mean the reliability of the authors’ conclusion is not clear.

Authors' objectives
To evaluate the efficacy and safety of anti-epidermal growth factor receptor (EGFR) therapy for advanced head and neck squamous cell carcinoma.

Searching
Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE databases were searched from inception to 2011. The Web of Science database was searched (search dates not provided), as were conference proceedings from the American Society of Clinical Oncology and the European Society of Medical Oncology (2000-2011). Search terms were reported. Only studies written in English were considered.

Study selection
Randomised controlled trials (RCTs) that compared anti-epidermal growth factor receptor therapy (alone or in combination with conventional therapy) with non-anti-epidermal growth factor receptor therapy in patients with biopsy-proven locoregionally advanced or recurrent/metastatic head and neck squamous cell carcinoma were eligible for inclusion. Trials had to report at least one of the following outcomes: overall response rate; overall survival; progression free survival; or grade three to four adverse effects. Trials for carcinoma of the nasopharynx or oesophagus were excluded.

Treatment included anti-epidermal growth factor receptor therapy monoclonal antibodies (zalutumumab alone, cetuximab plus radiotherapy or CT (not defined), and nimotuzumab plus chemoradiotherapy or radiotherapy) or tyrosine kinase inhibitors (gefitinib alone or in combination with CT, and lapatinib plus chemoradiotherapy). Control arms included conventional therapy. Performance status criteria varied across trials; Eastern Cooperative Oncology Group (ECOG) was 2 or less, Karnofsky Performance Status (KPS) was 60 or greater and World Health Organisation (WHO) was 2 or less. Most participants were male and mean age across trial groups ranged from 55 to 65 years. Most trials were multinational.

The authors did not state whether an independent procedure was used in the screening process.

Assessment of study quality
The quality of the included trials was assessed using the five-point Jadad scale, which considers reported randomisation, blinding and withdrawals/drop-outs. The authors did not state how many reviewers assessed trial quality.

Data extraction
All authors independently extracted relevant data to allow the calculation of overall hazard ratios (HR) for overall survival and progression free survival, and relative risks (RRs) for overall response rate and adverse effects. If HR and its 95% confidence interval (CI) were not reported methods reported by Williamson and colleagues were used to extract estimates of these statistics. Any discrepancies were resolved by consensus.

Methods of synthesis
Summary HRs and RRs, along with their associated 95% CIs, were calculated using a random effects model. Subgroup analyses were performed based on cancer stage (locoregionally advanced or recurrent/metastatic), anti-epidermal growth factor receptor drug type (monoclonal antibodies or tyrosine kinase inhibitors), and phase of trial (II or III).
Statistical heterogeneity was investigated using the Q test and the $I^2$ statistic (heterogeneity was deemed high if $p<0.1$). Where significant statistical heterogeneity was found sensitivity analyses were carried out (exclusion of trials that potentially biased results). Publication bias, using Begg’s and Egger’s tests, was assessed for meta-analyses including seven or more trials.

**Results of the review**

Twelve RCTs, from ten reports, were included (2,396 participants; sample sizes ranged from 67 to 486). Seven trials used monoclonal antibodies and five trials used tyrosine kinase inhibitors. All but one trial received a Jadad score of ≥3 (range 2 to 5).

A statistically significant difference was found for overall response rate (RR 1.36, 95% CI 1.12 to 1.67; 10 RCTs) and progression free survival (HR 0.63, 95% CI 0.55 to 0.71; seven RCTs) in favour of anti-epidermal growth factor receptor therapy compared with conventional therapy. No significant between group difference was found for overall survival. Evidence of significant heterogeneity was found for overall response rate ($p<0.005$, $I^2=61.5\%$) and overall survival ($p=0.013$, $I^2=57.2\%$); no single study was found to be responsible. No publication bias was found.

Subgroup analyses of patients with either locoregionally advanced or recurrent/metastatic head and neck squamous cell carcinoma by drug type found a significant difference in favour of monoclonal antibodies compared with conventional therapy for all efficacy outcomes in both tumour stage groups. Overall response rate for locoregionally advanced was RR 1.21 (95% CI 1.08 to 1.37; three RCTs) and recurrent/metastatic was RR 1.88 (95% CI 1.40 to 2.54; two RCTs). Overall survival for locoregionally advanced was HR 0.72 (95% CI 0.59 to 0.89; four RCTs) and for recurrent/metastatic was HR 0.79 (95% CI 0.67 to 0.94; two RCTs). Progression free survival for locoregionally advanced was HR 0.66 (95% CI 0.53 to 0.83; three RCTs) and for recurrent/metastatic was HR 0.61 (95% CI 0.52 to 0.71; three RCTs). There was no evidence of statistically significant heterogeneity. Tyrosine kinase inhibitors were not found to significantly improve outcomes in either tumour stage group.

Separate subgroup analyses by tumour stage, and by drug type and trial phase were also presented.

Anti-epidermal growth factor receptor therapy was associated with a significantly greater risk of rashes (RR 14.34, 95% CI 5.02 to 41.02), diarrhoea (RR 2.36, 95% CI 1.15 to 4.87) and anorexia (RR 2.49, 95% CI 1.11 to 5.56).

**Authors' conclusions**

Anti-epidermal growth factor receptor monoclonal antibodies, but not tyrosine kinase inhibitors, were found to be effective for the treatment of locoregionally advanced and recurrent/metastatic head and neck squamous cell carcinoma.

**CRD commentary**

The review addressed a clearly defined question. Several databases and sources of grey literature were searched, which minimised potential for publication bias. Only trials written in English were considered which raised possibility of language bias. Appropriate steps were taken to minimise the likelihood of reviewer error or bias in the data extraction. However, it was unclear how many reviewers selected studies for inclusion or assessed trial quality and reviewer error and bias could not be excluded at these stages. Only summary results were reported for the quality assessment and some important criteria, such as allocation concealment, were not included. Trials were pooled in meta-analyses and heterogeneity investigated.

The authors’ conclusions are largely based on estimates in which only a small number of trials contributed. This, and the potential for error and bias in the selection and quality assessment of the included trials, reduces the reliability of the authors’ conclusions.

**Implications of the review for practice and research**

**Practice:** The authors recommend that anti-epidermal growth factor receptor monoclonal antibodies were used for both first or second line treatment for advanced head and neck squamous carcinoma. Skin reactions and some gastrointestinal reactions should be monitored during anti-epidermal growth factor receptor treatment.

**Research:** The authors stated that more RCT evidence was needed to draw a more exact conclusion relating to some of the subgroup analyses.
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