Risk of skin rash associated with erlotinib in cancer patients: a meta-analysis

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CRD summary
The review concluded that there was a significant risk of all-grade and high-grade rash associated with erlotinib use in cancer patients, which may be modified by chemotherapy. Due to potential limitations with the review process, uncertainties about the quality of included studies and presence of significant heterogeneity, the authors’ conclusions should be interpreted with caution and may not be reliable.

Authors' objectives
To evaluate the risk of skin rash associated with use of erlotinib in cancer patients.

Searching
PubMed was searched from 1990 to October 2008. Search terms were reported. Web of Science was also searched. The abstracts of conferences of American Society of Clinical Oncology were also searched from 2004 to October 2008. The manufacturer's website was searched.

Study selection
Prospective phase II or phase III randomised controlled trials (RCTs) that compared erlotinib (an epidermal growth factor receptor (EGFR) inhibitor) versus a control without EGFR inhibitors and that assessed the risk of rash in cancer patients were eligible for inclusion. Phase I trials and single-arm phase II trials were excluded due to a lack of controls. RCTs where erlotinib was used as a single agent or combined with other agents were eligible for inclusion. Patients in the intervention group had to be treated with a starting dose of 150mg daily. Data had to be available regarding events or incidence of skin rash and study sample sizes. Some trials compared erlotinib alone with placebo or in combination with chemotherapy versus placebo and/or chemotherapy.

The included studies reported incidence of skin rash of grade 1 to 5 (all grades) or grade ≥3 (high grade) using Common Terminology Criteria for Adverse Events of the National Cancer Institute versions 2 and 3 (relevant descriptions were reported). Rash was not mentioned as a pre-existing condition in any trial. The most common underlying malignancy was non-small cell lung cancer; there were individual trials of patients with renal cell cancer, glioblastoma multiforme and colorectal cancer.

The authors did not report how many reviewers performed the selection.

Assessment of study quality
No formal assessment of methodological quality was made, but relevant data were reported for blinding, loss to follow-up and duration of follow-up.

Data extraction
The number of events for each outcome was extracted in order to calculate relative risk (RR) and 95% confidence intervals (95%CI). Efforts were made to contact authors and the manufacturer of erlotinib for missing data. The authors did not report how many reviewers performed data extraction.

Methods of synthesis
Relative risks and 95% CIs were pooled using fixed-effect and random-effects models. Pooled results were presented by incidence of skin rash grade (all grades and high grade). Statistical heterogeneity was determined using the Cochrane Q statistic (p<0.1), in which case a random-effects model was used. Subgroup analyses were conducted by intervention: erlotinib alone or in combination with chemotherapy.

Results of the review
Nine RCTs were identified (n=3,631, range 59 to 1,172). Four RCTs were double-blind. Three RCTs were phase III
and the others were phase II. Overall loss to follow-up was 19.9% (range 0 to 61.3%) and two studies had a relatively high loss to follow-up (35.0% and 61.3%). Median duration of follow-up was reported for three RCTs (range 3.8 to 9.8 months).

The overall incidence of all-grade skin rash associated with erlotinib was 70.4% (95% CI 67.2% to 73.4%; five RCTs), for single-agent erlotinib treatment it was 75.2% (95% CI 71.3% to 78.7%; two RCTs) and for erlotinib combination it was 63.5% (95% CI 58.1% to 68.6%; three RCTs). There was a significant risk in overall all-grade rash associated with erlotinib versus controls (RR 3.43, 95% CI 2.13 to 5.52, I²=85.2%), erlotinib alone (RR 4.72, 95% CI 3.56 to 6.20, I²=56.1%) and erlotinib combination (RR 2.34, 95% CI 1.64 to 3.34, I²=58.4%).

For high-grade skin rash, overall incidence was 9.4% (95% CI 8.0% to 11.0%; eight RCTs), for single-agent erlotinib treatment it was 9.1% (95% CI 7.0% to 11.7%; four RCTs) and for erlotinib combination it was 9.2% (95% CI 6.4% to 13.1%; five RCTs). There was a significant risk in overall high-grade rash associated with erlotinib compared with controls (RR 11.27, 95% CI 5.74 to 22.14), erlotinib alone (RR 14.27, 95% CI 3.36 to 60.54) and erlotinib combination (RR 10.09, 95% CI 4.80 to 21.24).

There was a significant decrease in risk of all-grade rash in patients treated with combined erlotinib plus chemotherapy versus erlotinib alone (RR 0.84, 95% CI 0.77 to 0.93), but there was no significant difference in risk for high-grade rash.

Subgroup analyses did not significantly effect the results.

**Authors’ conclusions**
Erlotinib is associated with substantial skin toxicity in cancer patients that may be modified by chemotherapy.

**CRD commentary**
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched and unpublished studies were considered. It was unclear whether language restrictions were applied, in which case some studies could have been missed. Publication bias was not assessed. Study quality was not assessed formally but some relevant data were provided. The authors did not report whether efforts had been made to reduce error and bias in the review process (such as independent screening for relevant studies by more than one reviewer). Some relevant study details were reported, but no details of the age and sex of patients was reported. There were no details of treatment doses, regimens or durations. Statistical heterogeneity was assessed and there was evidence for heterogeneity. The statistical method used for the meta-analysis of the RCTs seemed appropriate. There were very wide confidence intervals for some findings, which questioned their reliability. Two studies, one of which was a large study, had a high loss to follow-up.

In view of some potential limitations in the review process, uncertainties about the quality of included studies and presence of significant heterogeneity, the authors’ conclusions should be interpreted with caution and may not be reliable.

**Implications of the review for practice and research**
**Practice:** The authors recommended that appropriate early intervention was used for rashes associated with erlotinib treatment in cancer patients. The authors stated that clinical trials were conducted in major centres and institutes in patients with adequate organ function and may not be applicable to patients with organ dysfunction treated in the community.

**Research:** The authors identified a need for further studies to investigate risk factors and pathogenesis and to develop effective measures for prevention and treatment of skin toxicity.

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