Risk of rash in cancer patients treated with vandetanib: systematic review and meta-analysis

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CRD summary
This review concluded that vandetanib was associated with a significantly increased risk of developing rash in patients with advanced cancer. Potential for bias in the review methods and the unclear quality of and variation in the evidence mean that the conclusions should be considered with a note of caution.

Authors' objectives
To determine the incidence and risk of rash in cancer patients who received vandetanib.

Searching
PubMed and Web of Science were searched from January 1966 to July 2011 for studies published in English; search terms were reported. Abstracts and presentations from American Society of Clinical Oncology annual meetings (2004 to 2011) were searched.

Study selection
Prospective phase II and phase III clinical trials that assessed 300mg of vandetanib as a single agent in cancer patients and that reported on the incidence of rash were eligible for inclusion. Rash outcomes could be rash, rash or desquamation, and dermatitis acneiform (National Cancer Institute Common Toxicity Criteria version 2 or Common Terminology Criteria for Adverse Events version 3). Only rash of grade one or above was included. Trials that combined vandetanib with chemotherapy were excluded.

Patients in the included studies had non-small cell lung cancer, medullary thyroid cancer, small cell lung cancer and metastatic breast cancer. Treatments in the phase II studies were vandetanib as a single agent or in combination with paclitaxel and carboplatin. Control arms were gefitinib or placebo with paclitaxel and carboplatin, and placebo. All the phase III trials evaluated 300mg vandetanib compared with 150mg erlotinib or placebo.

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

Assessment of study quality
The authors did not report that they assessed study quality.

Data extraction
The number of patients with all-grade and high-grade rash were extracted from each trial and used to calculate proportions with exact 95% confidence intervals (CI). For placebo-controlled studies the relative risk (RR) of rash for vandetanib compared to placebo was calculated.

The authors did not report how many reviewers performed the data extraction.

Methods of synthesis
Statistical heterogeneity was assessed using Cochran’s Q statistic with a p-value of 0.10. Where heterogeneity was detected, possible reasons were explored and relative risks were pooled using a random-effects model. Otherwise both fixed-effect and random-effects models were used. Analyses to compare cancer types were performed (analysis method not reported).

Results of the review
Nine trials were included (2,961 participants, range 30 to 1,237): three phase III trials, five randomised phase II trials and one single-arm phase II trial. All trials were sponsored by a pharmaceutical company.

Incidence of all-grade rash ranged from 29.2% to 71.2% with a pooled value of 46.1% (95% CI 40.6% to 51.8%; nine trials, 1,751 participants treated with vandetanib; statistically significant heterogeneity p=0.001).
Incidence of high-grade rash ranged from 2% to 4.1% with a pooled value of 3.5% (95% CI 2.5% to 4.7%; eight trials, 1,134 participants treated with vandetanib; no evidence of heterogeneity p=1.0).

Further results for rash incidence by type of cancer were reported in the paper.

Vandetanib increased the risk of all-grade rash compared with control (RR 2.43, 95% CI 1.37 to 4.29; four trials). There was statistically significant heterogeneity (p=0.001). A similar result was seen when the one trial with placebo plus paclitaxel and carboplatin as the control was excluded. No significant difference between vandetanib and control was seen for high-grade rash.

**Authors' conclusions**
Vandetanib was associated with a significantly increased risk of developing rash in patients with advanced cancer.

**CRD commentary**
This review specified inclusion criteria for study design, interventions, participants and outcomes. Only two databases were searched. Abstracts from scientific meetings were searched. Only papers in English were included which put the review at risk of language and publication biases. Whether study selection and data extraction were performed in duplicate was not reported so risks of error or bias could not be ruled out. No formal assessment of the quality of the evidence was made. The methods of meta-analysis appeared appropriate.

Potential for bias in the review methods and the unclear quality of and variation in the evidence mean that the conclusions should be considered with a note of caution.

**Implications of the review for practice and research**
**Practice:** The authors stated that as vandetanib may cause photosensitivity the importance of adequate photo-protective measures and avoidance of exposure to the sun should be emphasized to patients.

**Research:** The authors stated that further studies were needed to investigate differences in the risk of skin toxicity between tumour types. More research was needed into the relationship between rash and response to vandetanib treatment.

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