The risk of nail changes with epidermal growth factor receptor inhibitors: a systematic review of the literature and meta-analysis

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CRD summary
The review found that epidermal growth factor receptor inhibitors were associated with a significant risk of nail toxicity in patients with advanced cancer regardless of the specific type used. The review had weaknesses that included a limited search, lack of information about study quality and questionable statistical methods. The conclusions require cautious interpretation.

Authors' objectives
To evaluate the risk of nail toxicity associated with the use of epidermal growth factor receptor inhibitors by cancer patients.

Searching
PubMed was searched from 1998 to July 2011. Search terms were reported. Web of Science and conference proceedings of the American Society of Oncology (2004 to 2011) were searched.

Study selection
Eligible studies were phase II and II clinical trials reporting the incidence of nail changes in cancer patients assigned to receive epidermal growth factor receptor inhibitors (cetuximab, erlotinib, panitumumab or lapatinib) at approved doses.

Participants in the included studies were patients with a range of underlying malignancies, the most common being non-small cell lung cancer and metastatic colorectal cancer. None of the studies reported nail disorders as a pre-existing condition. Epidermal growth factor receptor inhibitors used in the included studies were erlotinib, panitumumab and cetuximab. In the only controlled study in the review – a randomised controlled trial (RCT) – the control group received best supportive care. Nail changes in most of the included studies were reported in accordance with versions 2 and 3 of the Common Terminology Criteria for Adverse Events of the National Cancer Institute. Outcomes reported in the review were all-grade and high grade nail toxicity.

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

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

Data extraction
Data were extracted on the incidence of nail changes in each study group, with 95% confidence intervals (CIs).

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

Methods of synthesis
Data were combined to calculate pooled incidence rates of nail change across all studies. Q and I² statistics were used to assess heterogeneity. Both fixed-effect (inverse variance) and random-effects models were used unless there was significant heterogeneity (p<0.1), in which case a random effects model was used. Incidence rates in all intervention groups were compared with the incidence rate in the control arm of the RCT to calculate relative risks and 95% confidence intervals. Subgroup analyses were conducted by type of epidermal growth factor receptor inhibitor.

Results of the review
Twenty-two studies were included: one randomised controlled trial (463 participants) and 21 single arm (uncontrolled) phase II trials (1,642 participants, range 24 to 346).

Incidence of all-grade nail toxicity ranged from 5.7% to 48.1% and when data were pooled the overall incidence was
17.2% (95% CI 13.8% to 21.3%; 20 studies; random-effects model; I²=74%).

Incidence of high-grade nail toxicity ranged from 0.1% to 5.0% and when data were pooled the overall incidence was 1.4% (95% CI 0.9% to 2.1%; 22 studies; fixed-effect model; I²=0%).

Compared to controls that received best supportive care, the intervention group had a relative risk of all-grade nail toxicity of 0.77 (95% CI 0.41 to 1.45) and a relative risk of high-grade nail toxicity of 0.13 (95% CI 0.04 to 0.46).

Subgroup analyses showed no significant difference in nail toxicity between different types of epidermal growth factor receptor inhibitor.

Authors' conclusions
Epidermal growth factor receptor inhibitors were associated with a significant risk of nail toxicity in patients with advanced cancer regardless of the specific type used.

CRD commentary
The objectives and inclusion criteria of the review were clear. Some relevant sources were searched for studies but the search was rather narrow as it was limited to two databases. It was not reported whether the search was limited by language so the potential for language bias could not be assessed. It was unclear whether steps were taken to limit the risk of reviewer bias and error in study selection and data extraction and it did not appear that study quality was systematically assessed. These factors made it difficult to assess the reliability of the review findings.

Incidence rates of all-grade nail toxicity varied very widely and the pooled analysis had very high heterogeneity so it was questionable whether it was appropriate was appropriate to combine these data. Pooling of all intervention groups versus the RCT control group was of doubtful validity as the clinical comparability of the groups was unclear. The findings of the randomised comparison were not reported. The authors suggested that nail toxicities were under-reported as studies of lapatinib and other potentially eligible studies failed to report this outcome and that lack of specificity in newer nail toxicity grading scales may inhibit reporting. The authors noted that the review findings may not be generalisable to a private or community setting.

The review had weaknesses that included a limited search, lack of information about study quality and questionable statistical methods. The conclusions require cautious interpretation.

Implications of the review for practice and research
Practice: The authors stated that adequate detection and early intervention for nail changes is important in cancer patients receiving epidermal growth factor receptor inhibitors as this may help prevent debilitating toxicity and ensure the optimal treatment dose.

Research: The authors stated a need for further research into the pathogenesis of nail changes and risk factors for nail changes. Effective evidence-based strategies needed to be developed for their management.

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