Meta-analysis of incidence and risk of hypomagnesemia with cetuximab for advanced cancer


CRD summary
The review concluded that cetuximab was associated with a significant risk of hypomagnesaemia in cancer patients. The authors’ conclusions broadly reflected the evidence presented and appear likely to be reliable.

Authors’ objectives
To evaluate the risks of hypomagnesaemia in patients undergoing treatment with cetuximab-based therapy.

Searching
PubMed, EMBASE, The Cochrane Library and Web of Science were searched without language restrictions to December 2009; search terms were reported. Meeting abstracts from American Society of Clinical Oncology (2000 to 2009) and references of identified studies and reviews were checked.

Study selection
Phase II or III trials of cancer patients who received cetuximab and that reported incidence of hypomagnesaemia were eligible for inclusion. Cetuximab dosage had to be 400mg/m$^2$ intravenously on day one followed by 250mg/m$^2$ weekly. Trials that assessed variations in dosage and timing were excluded. The primary outcome was incidence of hypomagnesaemia.

Most studies used cetuximab as a first-line treatment for head and neck, colorectal, non-small cell lung, ovarian, gastric or oesophageal cancer. Cointerventions commonly included platinum, capecitabine and paclitaxel. Where stated, mean age ranged from 52 to 66 years.

The authors did not state how many reviewers selected studies.

Assessment of study quality
The quality of randomised controlled trials (RCTs) was assessed using the Jadad scale of randomisation, blinding and completion of follow-up. The maximum score was 5 points.

It appeared that two reviewers independently performed the assessments.

Data extraction
Two reviewers independently extracted data (consensus was reached on all items) on incidence of all-grade and grade 3/4 hypomagnesaemia to enable calculation of event rates or odds ratios (OR) with 95% confidence intervals (CI).

Methods of synthesis
Event rates or odds ratios, with 95% CI, were pooled using a fixed-effect model. Heterogeneity was assessed using the Q test and $I^2$. A random-effects model was used where heterogeneity was present. Further analyses explored effects of tumour type, trial phase, trial design and treatment line.

Results of the review
Nineteen studies with 4,559 patients (3,081 took cetuximab) were included. One of the six RCTs (sample size range 117 to 1,298) scored 5 points on the Jadad scale, four scored 3 and one scored 2. The 13 single-armed trials (sample size range eight to 1,123) were not quality assessed.

Incidence of grade 3/4 hypomagnesaemia was 5.6% (95% CI 3.0% to 10.2%, $I^2$=96%; 19 studies). Incidence of all-grade hypomagnesaemia was 36.7% (95% CI 22% to 54.4%, $I^2$=88%; seven studies). The authors reported that heterogeneity remained when sensitivity and subgroup analyses were performed.
In RCTs that compared cetuximab-based therapy with non-cetuximab-based therapy, cetuximab was associated with a significantly greater risk of grade 3/4 hypomagnesaemia (OR 5.3, 95% CI 2.3 to 12.2, $I^2=0\%$; six trials) and all-grade hypomagnesaemia (OR 4.75, 95% CI 3.7 to 6.2, $I^2=26\%$; four RCTs).

**Authors' conclusions**
Cetuximab was associated with a significant risk of hypomagnesaemia in cancer patients.

**CRD commentary**
The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify all relevant studies in any language were undertaken by searching electronic databases and checking references and conference proceedings. Suitable methods were employed to reduce risks of reviewer error and bias for the processes of data extraction and assessing study quality; the authors did not report whether such methods were used to select studies for inclusion. A basic assessment of study quality was made and Jadad scores were provided with no further details, which made it difficult for the reader to fully assess the risk of bias in individual studies. Basic study details were provided and appropriate methods were used to pool RCT data. Highly significant heterogeneity was found when pooling all studies and investigated, but no likely causes could be identified. However, significant heterogeneity was not associated with the randomised evidence.

The authors' conclusions broadly reflected the evidence presented and appear likely to be reliable.

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

**Practice:** The authors stated that early monitoring and effective management of hypomagnesaemia was important for patients who received cetuximab-based therapy.

**Research:** The authors did not state any implications for research.

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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.