Treatment-related mortality with vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy in patients with advanced solid tumors: a meta-analysis

CRD summary
The review concluded that vascular endothelial growth factor receptor tyrosine kinase inhibitors were associated with a significant increase in the risk of fatal adverse events in patients with advanced solid tumours. Limitations in the quality of the evidence base and the low event rates mean the authors' conclusions should be considered tentative.

Authors' objectives
To evaluate whether single agent therapy with vascular endothelial growth factor receptor tyrosine kinase inhibitors is associated with an increased rate of fatal adverse events in patients with advanced solid tumours.

Searching
PubMed and American Society of Clinical Oncology meetings were searched from January 2001 to May 2011 for relevant studies published in peer reviewed journals in English; search terms were reported.

Study selection
Randomised controlled trials (RCTs, phase II or III) of patients with cancer where treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitors was compared with control (standard of care, placebo or best supportive care) were eligible. Trials were required to include data on treatment-emergent non disease-related fatal adverse events.

In the included studies, most participants had a baseline Eastern Cooperative Oncology Group status of zero or one; they had either locally advanced and metastatic renal cell carcinoma, advanced pancreatic neuroendocrine tumours, metastatic or advanced breast cancer, advanced hepatocellular carcinoma, advanced gastrointestinal stromal tumours, advanced non-small cell lung cancer or metastatic small cell lung cancer. They were assigned to either single agent vascular endothelial growth factor receptor tyrosine kinase inhibitors (sorafenib, sunitinib, pazopanib or vandetanib) or control (placebo, interferon alpha, cytotoxic chemotherapy, epidermal growth factor receptor tyrosine kinase inhibitors or no therapy). Mean progression-free survival ranged from 2.5 months to 11.4 months.

The authors did not state how many reviewers selected studies for the review.

Assessment of study quality
Studies were assessed for quality using the Jadad scale of randomisation, double blinding and description of withdrawals and drop-outs.

The authors did not state how many reviewers assessed studies for quality.

Data extraction
Data were extracted on treatment-emergent non disease-related fatal adverse events to enable calculation of relative risks (RR) with 95% confidence intervals (CI).

Two reviewers independently extracted data. Discrepancies were resolved by consensus.

Methods of synthesis
Study results were pooled in meta-analyses and summary effect relative risks with 95% CIs were calculated using a random-effects model (where heterogeneity was identified) or a fixed-effect model. Continuity corrections were applied where cells had zero events. Heterogeneity was assessed by the X² test (p<0.05 evidence of significant heterogeneity) and quantified using the I² value. Subgroup analyses investigated placebo versus active comparator controls, studies with the same cancer type, studies that explored the same vascular endothelial growth factor receptor tyrosine kinase inhibitors and specific fatal adverse event categories.
Results of the review

Thirteen RCTs (5,164 patients, range 55 to 1,240) were included in the review. Six trials were randomised, double-blinded and placebo controlled. Mean overall Jadad score was 3.2 (range 1 to 5) out of the maximum 5; overall study quality was considered fair.

When compared with control, vascular endothelial growth factor receptor tyrosine kinase inhibitors were associated with an increased rate of fatal adverse events (RR 1.64, 95% CI 1.16 to 2.32; 13 studies; random-effects model, no significant heterogeneity; incidence 2.26% versus 1.26%).

In subgroup analyses, an increased risk of fatal adverse events was found with vascular endothelial growth factor receptor tyrosine kinase inhibitors in studies of renal carcinoma patients (RR 1.62, 95% CI 1.04 to 2.51; four studies; no significant heterogeneity), studies where control was placebo (RR 1.69, 95% CI 1.06 to 2.67; six studies; no significant heterogeneity) and in studies of sorafenib (RR 1.85, 95% CI 1.10 to 3.13; three studies; no significant heterogeneity). There was a non-significant trend towards an increased risk of fatal adverse events in studies of non-small cell lung cancer studies (three studies), where control was active comparators (six studies) and in studies of vandetanib (four studies). There was no evidence of a significant difference between groups in studies of sunitinib (five studies).

Authors' conclusions

Vascular endothelial growth factor receptor tyrosine kinase inhibitors were associated with a significant increase in the risk of fatal adverse events in patients with advanced solid tumours.

CRD commentary

The review addressed a clear research question supported by appropriate inclusion criteria. A limited number of sources were searched; attempts were made to find unpublished studies but potential for publication bias was not evaluated formally. The restriction to studies written in English meant that language bias could not be ruled out. Appropriate methods were used to extract data but the authors did not state how many reviewers selected studies or assessed them for quality so reviewer error and bias could not be ruled out. Quality assessment used a valid tool. The identified studies were considered overall to be fair quality.

The authors acknowledged difficulties in extracting data on fatal events; some studies did not clearly differentiate disease-related from non-disease-related fatal events; these difficulties were experienced for both arms of the trials which minimised the chance of differential under or over reporting. The authors noted that the significant finding in the subgroup of trials of renal carcinoma could be related to longer follow-up in this group compared with studies of other types of tumours. Due to low event rates, the subgroup analyses were likely to be underpowered to distinguish between types of intervention, types of control and tumour types. Insufficient information was provided on the causes of the fatal adverse events. Synthesis of the studies and assessment of heterogeneity was appropriate.

Limitations in the quality of the evidence base and the low event rates mean the authors' conclusions should be considered tentative.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further research should focus on careful documentation and uniform reporting of the causes of fatal adverse events.

Funding

None.

Bibliographic details

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.