Risk of high-grade bleeding in patients with cancer treated with bevacizumab: a meta-analysis of randomized controlled trials

CRD summary
This review concluded that the addition of bevacizumab to cancer chemotherapy significantly increased the risk of high-grade bleeding. The risk may be dose-dependent and may vary with tumour type. These conclusions reflected the evidence presented but should be interpreted with caution because of the lack of full details on study quality.

Authors’ objectives
To assess the risk of high-grade bleeding in cancer patients who received bevacizumab therapy.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to September 2010. There were no language restrictions. Abstracts and meeting presentations from American Society of Clinical Oncology conferences between January 2000 and September 2010 were searched. Search terms were reported. Reference lists of relevant publications were screened. Experts in the field were consulted for any additional studies.

Study selection
Phase II and phase III randomised controlled trials (RCTs) that evaluated bevacizumab versus a control in addition to concurrent chemotherapy and/or treatment with a biological agent in cancer patients were eligible for inclusion. Eligible studies had to report data on the incidence of bleeding and sample size. High grade bleeding was defined as grade three or above using the Common Terminology Criteria for Adverse Events.

In the included studies, patients’ malignant diseases were non-small cell lung cancer, colorectal cancer, breast cancer, renal-cell carcinoma, pancreatic carcinoma, gastric cancer and mesothelioma. The baseline Eastern Cooperative Oncology Group performance status for most patients was between 0 and 1. The comparator was either placebo or active controls. Where reported, the duration of follow-up of included studies ranged from 6.7 to 46.2 months. The dose of bevacizumab administered was either 2.5 or 5mg/kg per week. Concurrent therapies varied across the studies and included docetaxel, cisplatin, paclitaxel, carboplatin, fluorouracil and capecitabine.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
Study quality was assessed using the five-point Jadad scale of randomisation, blinding and withdrawal. Studies with a score of more than 2 were classified as good quality.

Two reviewers independently performed validity assessment.

Data extraction
Data were extracted on event rates to enable calculation of relative risks (RRs) with 95% confidence intervals (CIs). Where necessary the authors of trials were contacted for missing data.

Two reviewers independently performed data extraction, with any disagreements resolved by a third reviewer.

Methods of synthesis
Pooled relative risks with 95% CIs were calculated using a random-effects model. Statistical heterogeneity was assessed using the Q and I² statistics. Subgroup analyses were performed on different malignant diseases and different doses of bevacizumab. Publication bias was assessed using a funnel plot.

Results of the review
Twenty-two RCTs were included in the review (14,277 participants). Eight trials were double-blinded. A random
allocation sequence was generated in all trials. Jadad scores for each study were not reported.

Compared with non-bevacizumab treatment, addition of bevacizumab to cancer chemotherapy was significantly associated with an increased risk of high-grade bleeding (RR 1.60, 95% CI 1.19 to 2.15; 20 RCTs).

In patients who received high doses of bevacizumab at 5mg/kg per week (versus non-bevacizumab treatment) there was a significantly higher risk of high-grade bleeding for those with non-small-cell lung cancer (RR 3.41, 95% CI 1.68 to 6.91; three RCTs), renal cell carcinoma (RR 6.37, 95% CI 1.43 to 28.33; two RCTs) and colorectal cancer (RR 9.11, 95% CI 1.70 to 48.79; two RCTs).

In patients who received low doses of bevacizumab at 2.5 mg/kg per week (versus non-bevacizumab treatment) there was a significantly higher risk of high-grade bleeding for those with non-small cell lung cancer (RR 2.48, 95% CI 1.01 to 6.10; two RCTs) but not in patients with colorectal cancer.

No significant heterogeneity was observed on these outcomes. There was no evidence of publication bias.

**Authors’ conclusions**
The addition of bevacizumab to cancer chemotherapy significantly increased the risk of high-grade bleeding. The risk may be dose-dependent and may vary with tumour type.

**CRD commentary**
The review inclusion criteria were clear. Relevant databases were searched. Efforts were made to find both published and unpublished studies without language restrictions, which minimised potential for language and publication biases. Sufficient efforts were made to minimise reviewer errors and bias in the review process. Appropriate criteria were used to assess study quality. The results of assessing study quality were not reported in full. Statistical heterogeneity was assessed and appropriate methods were used to pool the results.

The authors’ conclusions reflected the evidence presented but should be interpreted with caution because of the lack of full details on study quality.

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

**Practice:** The authors stated that clinicians should be aware of the possibility that any patient treated with bevacizumab may develop high-grade bleeding (especially patients at high risk).

**Research:** The authors stated that further studies were required to investigate risk reduction and the possible use of bevacizumab in selected patients.

**Funding**
None.

**Bibliographic details**

**PubMedID**
21243343

**DOI**
10.1007/s00228-010-0988-x

**Original Paper URL**
http://www.springerlink.com/content/vpx044u0m3037377/

**Indexing Status**
Subject indexing assigned by NLM
MeSH
Angiogenesis Inhibitors /adverse effects /therapeutic use; Antibodies, Monoclonal /adverse effects /therapeutic use; Antibodies, Monoclonal, Humanized /adverse effects /therapeutic use; Antineoplastic Agents /adverse effects /therapeutic use; Bevacizumab; Dose-Response Relationship, Drug; Hemorrhage /chemically induced /drug therapy /epidemiology; Humans; Incidence; Neoplasms /drug therapy /epidemiology; Randomized Controlled Trials as Topic; Risk; Risk Factors; Vascular Endothelial Growth Factor A

AccessionNumber
12011004315

Date bibliographic record published
05/10/2011

Date abstract record published
24/05/2012

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.