Increased risk of serious hemorrhage with bevacizumab in cancer patients: a meta-analysis
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CRD summary
The authors concluded that bevacizumab increased the risk of haemorrhage in patients with certain types of cancer. Risk may have varied by dose of bevacizumab and tumour type. Further research was needed. The authors’ conclusions reflect the evidence, but heterogeneity among the studies and potential for bias in the review suggest that the findings should be interpreted with some caution.

Authors' objectives
To assess the effects of bevacizumab on the overall risk of serious haemorrhage in the treatment of cancer.

Searching
PubMed and Web of Science were searched up to May 2009. Search terms were reported. Conference proceedings from American Society of Clinical Oncology meetings between 2000 and 2009 were searched. Grey literature and relevant reviews were searched. Reference lists of relevant trials were searched.

Study selection
Randomised controlled trials (RCTs) that compared the effects of treatment with bevacizumab versus control (placebo or best supportive care) in addition to concurrent treatment with chemotherapy or drugs in patients with solid tumours were eligible for inclusion. The outcome of interest was event or incidence of haemorrhage.

In the included trials, the underlying malignancy included the following types of cancer: colorectal, renal, non-small cell lung (non squamous cell), pancreatic, breast and mesothelioma. Patients were required to have adequate hepatic, haematological and renal functions. Patients were excluded from the included trials if they had significant uncontrolled hypertension, serious non-healing wounds, major surgery within the last 28 days, peripheral vascular disease, significant cardiovascular disease, more than grade 2 haemoptysis, pre-existing haemorrhage diathesis or thrombotic disorder, brain metastasis, were pregnant or lactating, regularly used aspirin or non-steroidal anti-inflammatory drugs and used oral or parenteral anticoagulants (with the exception of prophylactic anticoagulants) to maintain a vascular device access. Bevacizumab dose ranged between 1.5 and 5mg/kg/week. One trial did not include concurrent treatment. The other studies administered various concurrent treatments (such as cisplatin, gemcitabine, capecitabine, paclitaxel and carboplatin). The effects of bevacizumab on the risk of thrombocytopenia were assessed.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
Trial quality was assessed using criteria of allocation concealment, blinding, completeness of follow-up and objectivity of outcome measures.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
All four reviewers independently extracted number of events of haemorrhage and thrombocytopenia to calculate relative risks (RRs) and 95% confidence intervals (CIs). Haemorrhage was categorised in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events: all-grade haemorrhage, high-grade haemorrhage and fatal haemorrhage (as defined in the review). Primary authors were contacted for clarification, where necessary. Discrepancies were resolved by consensus.

Methods of synthesis
A fixed-effect model, or random-effects model where there was evidence of statistical heterogeneity, was used to combine relative risks and 95% CIs for overall haemorrhage and thrombocytopenia. Statistical heterogeneity was
assessed using Cochran's Q and $I^2$.

Subgroup analyses were undertaken based on type of haemorrhage (all-grade, high-grade and fatal), bevacizumab dosage (low dose 2.5 mg/kg/week versus high dose 5 mg/kg/week), type of tumour and site of haemorrhage.

Publication bias was assessed using Begg's and Egger's tests.

**Results of the review**

Twenty RCTs (n=12,617 participants, range 81 to 2,647) were included in the review: six Phase II and 14 Phase III trials. All trials were reported to be of acceptable quality; all trials reported allocation concealment and seven trials were reported to be double blind. Median follow-up duration ranged from 6.7 to 28 months.

Bevacizumab statistically significantly increased the risk of overall haemorrhage (RR 2.48, 95% CI 1.93 to 3.18, $I^2$=53%; 20 RCTs). The increased risk with bevacizumab compared to controls remained for each type of outcome: all-grade haemorrhage (RR 2.88, 95% CI 2.07 to 4.0; 10 RCTs), high-grade haemorrhage (RR 1.91, 95% CI 1.36 to 2.68; 19 RCTs) and risk of fatal haemorrhage (RR 3.56, 95% CI 1.71 to 7.41; 14 RCTs).

Subgroup analyses showed that risk of haemorrhage was significantly higher than controls for both high-dose (RR 2.99, 95% CI 2.46 to 3.64, $I^2$=9.9%; 14 RCTs) and low-dose bevacizumab (RR 2.01, 95% CI 1.43 to 2.83, $I^2$=59%; 10 RCTs). There was a slight discrepancy in the relative risk reported for high dose; we have reported the figure from the forest plot.

Subgroup analyses showed that risk of haemorrhage varied by type of cancer and by haemorrhage site. Patients with non-small cell lung cancer (non squamous) were at highest risk for fatal haemorrhage (RR 5.16, 95% CI 1.38 to 19.24, three RCTs) followed by non-small cell lung cancer (RR 5.02, 95% CI 1.52 to 16.66, four RCTs).

There were no statistically significant differences in risk of thrombocytopenia between patients who received bevacizumab and controls (11 RCTs).

There was no evidence of publication bias according to Begg's and Egger's tests.

**Authors' conclusions**

Bevacizumab significantly increased the risk of serious or fatal haemorrhage in patients with certain types of cancer. Risk may vary by dose of bevacizumab and tumour type. Further studies are needed for the prevention and treatment of severe haemorrhage.

**CRD commentary**

The review question and supporting inclusion criteria were clearly stated. The literature search was adequate. It was unclear whether the search was restricted by language. Publication bias was formally assessed and no evidence of bias was found. Trial quality was assessed with appropriate criteria, but individual data were not reported so it was difficult to make an independent assessment regarding the quality of the trials. The authors undertook data extraction in duplicate. It was unclear whether the same was true for study selection and validity assessment, so reviewer error and bias could not be ruled out.

Few patient and study details were provided. The authors acknowledged that there was significant patient and study heterogeneity. There was some evidence of statistical heterogeneity, so pooling of the trials may not have been appropriate. The authors acknowledged the restrictions for inclusion criteria in the included studies, which may have limited the generalisability of the findings to other patient groups (such as patients with organ dysfunctions and those in the community). Some findings may be limited by sample size.

The authors' conclusions appear to reflect the evidence, but heterogeneity among studies and potential for bias in the review mean the findings should be interpreted with some caution.
Implications of the review for practice and research

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

Research: The authors state that further research was needed to assess the risk of bleeding in patients who required both anticoagulants and treatment with bevacizumab and further assess the effects on different sites of haemorrhage.

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