Anti-vascular endothelial growth factor antibody bevacizumab reduced the risk of anemia associated with chemotherapy: a meta-analysis

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CRD summary
The review concluded that bevacizumab may have significantly reduced the risk of anaemia with chemotherapy in cancer patients. This was a generally well-conducted review and the authors' cautious conclusion appears likely to be reliable.

Authors' objectives
To determine the effect of bevacizumab on the risk of anaemia in cancer patients treated with chemotherapy

Searching
PubMed, Web of Science, EMBASE and The Cochrane Library were searched without language restrictions up to May 2010. Search terms were reported. Conference abstracts presented at the American Society of Clinical Oncology (ASCO) between January 2000 and May 2010 as well as FDA submissions, updated manufacturer's package inserts, relevant letters, editorials and reviews were also searched. References from relevant articles were checked for additional studies.

Study selection
Prospective phase II and III randomised controlled trials (RCTs) of patients with solid tumours that compared bevacizumab and chemotherapy with chemotherapy alone and reported event or incidence of anaemia.

In most trials the bevacizumab dose was 5mg/kg per week; three trials included a dose of 2.5mg/kg per week. All trials included concurrent treatment including interferon alfa, docetaxel. Underlying malignancies included: renal cell carcinoma; non-small cell lung carcinoma, non-squamous cell cancer; mesothelioma; pancreatic cancer; breast cancer. The Eastern Cooperative Oncology Group status for most patients was between 0 and 1 and patients were required to have adequate functions of major organs and haematological profiles. Patients taking regular aspirin, non-steroidal anti-inflammatory drugs (NSAIDs, greater than 325mg/day) and oral or parenteral anticoagulants (excepting prophylactic anticoagulants to maintain vascular device) were excluded. Other patient exclusion criteria were also reported. The authors stated that use of growth factors, including erythropoietin, was not specified.

Two reviewers independently reviewed citations for inclusion in the review.

Assessment of study quality
Trial quality was assessed using criteria that included adequacy of allocation concealment, completeness of follow-up, and objectivity of outcome measures. The authors did not state how many reviewers were involved in the validity assessment.

Data extraction
Two reviewers independently extracted data from the included trials and any discrepancies were resolved through discussion. The incidence of anaemia was calculated and the proportion of patients with anaemia, and 95% confidence interval (CI), was extracted from each trial. Relative risks (RRs) were calculated. Occurrence of anaemia was assessed and recorded according to the National Cancer Institute’s common toxicity criteria (version 2 or 3). Bevacizumab was classified into low (5% or 7.5% mg/kg per dose per schedule) or high dose (10 or 15 mg/kg per schedule). Where a discrepancy in the data was found in duplicate publications information was taken from the safety report of the most recent package insert instead of the original publication.

Methods of synthesis
Relative risks and their associated 95% confidence intervals were pooled and summary estimates calculated using a fixed-effect model unless significant heterogeneity was found, in which case a random-effects model was used. Heterogeneity was assessed using the Q statistic (p<0.1 was considered significant) and I². The effect of dose was also
explored. Publication bias of the primary end point (RR of anaemia) was assessed using the Begg and Egger's test.

**Results of the review**

Eleven RCTs were included in the review (6,439, range 115 to 1,043); two phase II trials and nine phase III trials. Randomised treatment allocation sequences were generated in all trials and six trials were of double-blind placebo controlled design. All trials were deemed to have adequate follow-up (median, 6.7 to 25.9 months).

Bevacizumab and chemotherapy was found to significantly reduce the relative risk of all-grade anaemia (RR 0.79, 95% CI 0.66 to 0.94; four RCTs) and high-grade anaemia (RR 0.72, 95% CI 0.57 to 0.90; 11 RCTs). No evidence of significant heterogeneity was found.

The relative risk of high-grade anaemia was 0.71 (95% CI 0.54 to 0.94; 10 RCTs) with bevacizumab 5mg/kg/week and 0.74 (95% CI 0.53 to 1.03; three RCTs) with bevacizumab 2.5mg/kg/week compared with chemotherapy alone; no significant difference was found between the dose levels (p=0.88). The effect of bevacizumab on high-grade anaemia was not significantly affected by tumour histology (p=0.78) or chemotherapy regimen (single agent vs. doublet combination p=0.98 and platinum versus non-platinum p=0.43). No significant correlation was found between RR of high-grade anaemia and hazard ratios of progression-free survival or overall-survival.

No evidence of publication bias was found.

**Authors' conclusions**

Bevacizumab may have significantly reduced the risk of anaemia with chemotherapy in cancer patients.

**CRD commentary**

The review question was supported by clearly defined inclusion criteria and several sources were searched without language restriction for relevant trials. Appropriate steps were taken to minimise error and bias in the selection of trials and data extraction, but the authors did not state whether similar procedures were undertaken for validity assessment. The quality of the included trials was assessed using relevant criteria. Although individual trial results were not reported all trials were considered to have had adequate allocation concealment. Standard meta-analytic techniques were used to calculate summary estimates and heterogeneity was assessed.

The authors acknowledged a number of limitations including that the reporting of all-grade anaemia was limited to four of 11 RCTs, high-grade anaemia included combined grades (3 to 4), and baseline haemoglobin levels were not reported in any trial. In addition, given the included patient populations, generalisability to community populations (included trials were mostly carried at academic centres and major research institutions) and in the setting of organ dysfunction may be questioned. Overall, this was a reasonably well-conducted review and the authors' cautious conclusion is likely to be reliable.

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

**Practice:** The authors did not state any implication for practice.

**Research:** The authors suggest further trials examining risk factors influencing bevacizumab on anaemia were needed, and that serial measurements of reticulocyte counts during therapy might help with understanding the mechanism by which bevacizumab protects against chemotherapy-related anaemia. Trials to investigate the effect of vascular endothelial growth factor inhibitors on erythrocytosis and haemoglobin change as a bio-marker for anti-vascular endothelial growth factor therapy were strongly recommended.

**Funding**

Research Foundation of State University of New York (SUNY) at Stony Brook.

**Bibliographic details**


**PubMedID**
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.