Haematologic toxicities associated with the addition of bevacizumab in cancer patients
Schutz FA, Jardim DL, Je Y, Choueiri TK

CRD summary
The authors concluded that bevacizumab was associated with a higher risk of neutropenia, thrombocytopenia and febrile neutropenia, but a reduced risk of anaemia. Due to potential limitations in the review process, evidence of publication bias and limited reflection on the clinical significance of findings, the authors' conclusions may not be reliable.

Authors' objectives
To determine the incidence and risk of haematologic toxicities associated with bevacizumab.

Searching
PubMed (1966 to 2010) and Web of Science databases were searched; search terms were reported. Conference abstracts from the American Society of Clinical Oncology were searched from 2004-2010.

Study selection
Eligible trials were phase 2 or phase 3 randomised controlled trials (RCTs) in cancer patients. Only one of the groups received bevacizumab and all groups received similar chemotherapy or immunotherapy. Adequate haematologic safety data were required. All studies needed to be published in English.

Approximately two-thirds were phase three trials. Median patient age (where reported) ranged from 46 to 69 years. Underlying malignancies included non-small cell lung cancer, breast cancer, colorectal cancer and renal cell cancer. A wide variety of different chemotherapy treatments were provided in the trials including FOLFOX6 (fluorouracil, leucovorin and oxaliplatin), docetaxel, CAPIRI (capecitabine and irinotecan) and pemetrexed. Most trials used high dose bevacizumab (5mg/kg/week) but a number also provided low dose bevacizumab (2.5mg/kg/week). Progression free survival was also assessed. Median treatment duration ranged from 2.1 to 11.5 months.

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

Assessment of study quality
Authors assessed type of report (full publication versus conference abstract), if trial was double-blind and if it was a phase 2 or phase 3 trial.

Data extraction
All-grade and high-grade haematological adverse events (anaemia, neutropenia, thrombocytopenia and febrile neutropenia) defined according to the criteria of the National Cancer Institute's Common Toxicity Criteria were extracted to calculate risk ratios (RR) and 95% confidence intervals (CI). Where cells contained zero events, 0.5 was added as a continuity correction.

Data extraction was conducted by two reviewers independently with any differences resolved by consensus.

Methods of synthesis
Data were pooled using an inverse variance fixed-effect model unless substantial heterogeneity was identified. Where this was present a DerSimonian and Laird random-effects model was used. Subgroup analyses were conducted based on the quality assessment criteria above: concomitant therapy (chemotherapy vs immunotherapy) and bevacizumab dose (2.5 vs 5mg/kg/week).

Substantial heterogeneity (defined as p less than 0.1) was identified by Cochran's Q statistic and I².

Publication bias was examined using funnel plots and formally using Begg and Egger tests (p less than 0.05 was considered statistically significant).
Results of the review
There were twenty-three trials of 25,867 patients but only data from 15,263 were included in the meta-analysis. Eleven trials were double-blind. Median follow-up (where reported) ranged from six to 43.5 months. Progression-free survival ranged from 2.9 to 14.1 months.

There was a statistically significant increased risk of all-grade neutropenia (RR 1.15; 95% CI 1.01 to 1.30; seven studies; I²=0%) for the bevacizumab group compared with controls. There was also an increased risk of high-grade neutropenia (RR 1.08; 95% CI 1.02 to 1.13; 21 studies; I²=29.2%) and febrile neutropenia (RR 1.31; 95% CI 1.08 to 1.58; 16 studies; I²=0%) for the bevacizumab group compared with controls.

The bevacizumab group had an increased risk for all-grade thrombocytopenia (RR 1.22; 95% CI 1.00 to 1.48; seven studies; I²=0.1%). There did not appear to have been a difference in risk between the bevacizumab group and controls for high-grade thrombocytopenia (RR 1.10; 95% CI 0.79 to 1.54; 15 studies; I²=45.5%).

Bevacizumab was associated with a decreased risk of all-grade (RR 0.81; 95% CI 0.68 to 0.96; five studies; I²=0%) and high-grade anaemia (RR 0.73; 95% CI 0.60 to 0.89; 15 studies; I²=6.3%).

There was no evidence of differences in risk of haematological adverse events between groups when different doses of bevacizumab were compared, whether the trials used chemotherapy or immunotherapy or on the basis of quality assessment criteria.

There was some evidence of publication bias identified for high-grade incidence of anaemia, neutropenia and thrombocytopenia.

Authors' conclusions
The authors concluded there was an increased risk of all- and high-grade neutropenia and all-grade thrombocytopenia for patients who received bevacizumab concurrently with chemotherapy or immunotherapy. It was also concluded that bevacizumab reduced risk of anaemia.

CRD commentary
The review question and inclusion criteria were clear. Appropriate sources were searched. Only studies in English were included which may have led to language bias and relevant studies being missed. Rigorous methods to reduce bias and error for data extraction were used. However, it was unclear whether such methods were used for study selection and quality assessment.

The quality assessment was very limited and did not take into account a variety of important factors such as method of randomisation or allocation concealment. Pooling of data appeared to be justified as most reported analyses showed low heterogeneity. The authors did not appear to discuss what absolute or relative difference in risk for each haematological outcome would be considered to have been clinically meaningful. In addition, there was evidence of clinical heterogeneity, and including only patients with organ function may have limited generalisability.

As there was potential for missed studies, limited information provided on study quality, limited discussion on the clinical significance of the haematological risks and benefits and some evidence of publication bias, the authors' conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors stated that physicians and patients should be aware of the haematological risk associated with bevacizumab and that frequent monitoring should be provided when using this treatment.

Research: The authors stated that further research should be conducted to assess the potentially protective role of vascular endothelial growth factor (VEGF) inhibition during erythropoiesis.

Funding
The Trust Family Research Fund for Kidney Cancer.

Bibliographic details

PubMedID
21470847

DOI
10.1016/j.ejca.2011.03.005

Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Angiogenesis Inhibitors /adverse effects /therapeutic use; Antibodies, Monoclonal, Humanized /adverse effects /therapeutic use; Bevacizumab; Bone Marrow /drug effects; Double-Blind Method; Erythropoiesis /drug effects; Female; Humans; Male; Middle Aged; Neoplasms /blood /drug therapy; Neutropenia /chemically induced; Placebos; Randomized Controlled Trials as Topic; Risk; Thrombocytopenia /chemically induced

AccessionNumber
12011003353

Date bibliographic record published
30/03/2012

Date abstract record published
07/08/2012

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.