Bevacizumab increases risk for severe proteinuria in cancer patients
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CRD summary
This review found that addition of bevacizumab to chemotherapeutic regimens significantly increased the risk of high-grade proteinuria in patients with cancer. The authors’ conclusions reflect the evidence presented, but a limited search, potential for language bias and limitations in the data acknowledged should be considered.

Authors’ objectives
To evaluate the overall risk and risk factors in cancer patients of high-grade proteinuria with treatment with bevacizumab.

Searching
PubMed and Web of Science were searched from inception to September 2009 for relevant trials; search terms were reported. Abstracts from the American Society of Clinical Oncology conferences between January 2000 and September 2009 were searched to identify additional trials. The updated manufacturer's package insert was reviewed to identify relevant information.

Study selection
Randomised controlled trials in which combinations of chemotherapeutic treatment with bevacizumab were compared to chemotherapy without bevacizumab in patients with cancer were eligible for inclusion. Trials were required to report on the event or incidence of Grade 3-4 proteinuria and sample size. High grade proteinuria was the primary outcome of the review.

The malignancies of the patients in the trials were colorectal cancer, non-small cell lung cancer, breast cancer, pancreatic cancer, renal cell carcinoma and malignant mesothelioma. Exclusion criteria varied widely between studies. Dosage of bevacizumab was either 2.5 or 5.0mg/kg per week. A range of concurrent chemotherapeutic agents was given in the studies. The patients were required to have adequate hepatic, renal and haematological function on entry to the studies and Eastern Cooperative Oncology group status for most patients was 0-1. Baseline renal function was not uniformly defined across the included studies and included normal, adequate or serum creatine less than 1.8 or 2.0mg/dL. Follow-up in the trials ranged from 6.7 to 27.6 months.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Methodological quality was assessed in terms of concealment of randomisation, completeness of follow-up and use of objective outcome measurements.

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

Data extraction
Data were independently extracted by three reviewers to calculate relative risks (RR) and 95% confidence intervals (CI). The authors of the included trials were contacted where relevant data were unclear. Any discrepancies between the reviewers were resolved by consensus.

Methods of synthesis
Pooled relative risks and 95% CIs were calculated with both random-effects and fixed-effect models. Statistical heterogeneity was assessed using the Cochran Q-statistic and the $I^2$ test. When the Cochran Q-statistic was p<0.1, results of the random-effects model were reported and causes of heterogeneity were explored. The Begg test was used to evaluate publication bias.
Subgroup analyses were conducted on the basis of bevacizumab dosage, malignancy type and use of platinum-based chemotherapy. The relationship between high grade proteinuria and clinical outcomes were evaluated.

**Results of the review**

Sixteen RCTs (n=12,268) were included in the review. Methodological quality of the trials was regarded as acceptable, with randomised allocation sequences generated in all trials,

Incidence of high grade proteinuria for patients who received bevacizumab was 2.2% (95% CI 1.2 to 4.3%, I²=94%) in all 16 included trials. Risk of high-grade proteinuria was significantly higher for patients treated with bevacizumab (RR 4.79 (95% CI 2.71 to 8.46, Q=19.989, I²= 25%; 16 trials), as was risk of nephrotic syndrome (RR 7.78, 95% CI 1.80 to 33.62, Q=0.48, I²<0.001; four trials).

There were statistically significant increases in risk of high-grade proteinuria observed with both lower doses of bevacizumab compared to chemotherapy alone (2.5mg/kg/week, RR 2.62, 95%CI 1.61 to 4.28, I²<0.001; seven trials) and higher doses of bevacizumab compared to chemotherapy alone (5.0mg/kg/week, RR 8.56, 95% CI 4.09 to 17.92, I²=1.958; 10 trials). There appeared to be a dosage-dependent risk of high grade proteinuria, as the differences in risk between high-dose and low-dose bevacizumab was statistically significant (p=0.009).

Risk of high-grade proteinuria varied according to tumour type. There were statistically significant increases in risk of high-grade proteinuria with all malignancy types except malignant mesothelioma. Of the malignancy types with higher risks of proteinuria, the highest risk was observed for renal cell carcinoma (RR 48.76, 95% CI 9.73 to 244.40) and the lowest risk was for colorectal cancer (RR 2.52, 95% CI 1.54 to 4.15). Comparison between the relative risks associated with bevacizumab treatment in renal cell carcinoma and other malignancies showed a significantly higher risk with renal cell carcinoma (p=0.001).

There were no differences observed in risk of high-grade proteinuria associated with bevacizumab when it was compared with platinum- and non-platinum-based chemotherapeutic regimens.

For patients treated with bevacizumab, statistically significant benefits in progression-free survival and overall survival were observed for patients with non-small cell lung cancer and colorectal cancer and for progression-free survival in patients with breast cancer and renal cell carcinoma (data not reported).

The results of the Begg test indicated that there was no evidence of publication bias.

**Authors’ conclusions**

The addition of bevacizumab to chemotherapeutic regimens significantly increased the risk of high-grade proteinuria in patients with cancer. This risk may be modified by dosage and tumour type, therefore, it is important that future studies investigate risk reduction and effective treatment of proteinuria.

**CRD commentary**

The review addressed a defined question and criteria for the inclusion of studies was clearly stipulated. Some relevant sources were searched. It was unclear whether language restrictions were applied, so there was potential for language bias. Steps to minimise errors and bias were reported for data extraction, but not for study selection or the assessment of methodological quality. The reviewers’ decision to combine the studies in a meta-analysis appeared to be justified. Reasons for heterogeneity were appropriately explored. Patients were required to have adequate hepatic, renal and haematological function on entry to the trials, which may restrict the generalisability of the results. The authors of the review acknowledged some limitations relating to the applicability of the results to the population of patients with cancer in the community or who did not have adequate organ function. Other limitations in the results were noted appropriately.

Honoraria from Onyx Pharmaceuticals, Novartis, Wyeth and Pfizer were noted.

The authors’ conclusions reflect the evidence presented, but the limited search, potential for language bias and limitations in data should be borne in mind.
Implications of the review for practice and research

**Practice:** The authors stated that patients with cancer who received treatment with bevacizumab should be monitored before each treatment; this was particularly important for patients with renal cell carcinoma and those who received high-dose bevacizumab. Preventive measures may include optimal control of hypertension and use of angiotensin-converting enzyme inhibitors. Dose reductions of bevacizumab may also be feasible to reduce the risk of persistent high-grade proteinuria when the treatment was required for tumour control.

**Research:** The authors stated that further research was required to establish the dose relationship between bevacizumab and high-grade proteinuria and clinical outcomes such as survival.

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