Adverse events risk associated with bevacizumab addition to breast cancer chemotherapy: a meta-analysis


CRD summary
The authors concluded that bevacizumab was associated with an increased risk of hypertension, proteinuria, left ventricular dysfunction and bleeding, but not of gastrointestinal perforation, arterial or venous thromboembolic events and fatal events, in patients with metastatic breast cancer. Given the unclear quality and small number of included trials, the reliability of the authors' conclusions is unclear.

Authors' objectives
To assess the risk of severe adverse events with the addition of bevacizumab to chemotherapy in patients with metastatic or locally recurrent breast cancer.

Searching
MEDLINE was searched for articles from 1966 to March 2011. Search terms were reported. Abstracts from oncology meetings were searched.

Study selection
Phase III clinical trials investigating bevacizumab plus combination therapy, as a first or second treatment, for metastatic or locally recurrent breast cancer, were eligible for inclusion. Trials had to report the incidence of adverse events of severity grade three or higher, according to the National Cancer Institute Common Toxicity Criteria.

The included trials evaluated bevacizumab with either capecitabine, paclitaxel, taxane, anthracycline, docetaxel, gemcitabine or vinorelbine. Control conditions were chemotherapy alone or placebo. In most trials, bevacizumab was given in five doses per week. All trials targeted metastatic breast cancer; some patients had locally recurrent breast cancer. Treatment was first or second line and most patients were human epidermal growth factor receptor 2 (HER2) negative. The median age of patients ranged from 51 to 57 years and their median progression-free survival ranged from 4.9 to 11.8 months in the bevacizumab groups and from 4.2 to 8.2 months in the control groups.

The authors did not state how many people selected trials.

Assessment of study quality
The authors did not state that they assessed the quality of the included trials.

Data extraction
The number of grade three or higher adverse events in the following categories were extracted for each group; arterial thromboembolic events, venous thromboembolic events, gastrointestinal perforation, hypertension, proteinuria, haemorrhage, left ventricular dysfunction, and febrile neutropenia. These were used to calculate odds ratios, with 95% confidence intervals, using the Woolf method.

Two investigators independently extracted the data and disagreements were resolved by consensus.

Methods of synthesis
Pooled odds ratios with 95% confidence intervals were calculated. Statistical heterogeneity was assessed using Cochran's Q and I². Where significant statistical heterogeneity was found (p<0.10 and I²>25%), a random-effects model was used for the meta-analysis, otherwise the Mantel-Haenszel fixed-effect model was used. Where there were no events in one group, a correction value was added to each cell, and this was calculated using the group ratio imbalance and the estimated pooled odds ratio (details were reported).

Subgroup analyses were carried out for the dose of bevacizumab, the type of combination therapy, and the year of publication, using meta-regression. Publication bias was assessed using the Begg and Egger tests and by visual
Results of the review

Five clinical trials were included in the review, with 3,784 patients.

Patients receiving bevacizumab were at significantly increased risk of developing proteinuria (OR 27.68, p<0.0001), haemorrhagic events (OR 4.07, p=0.006), and left ventricular dysfunction (OR 2.25, 95% CI 1.16 to 4.37), compared with those not receiving bevacizumab. There was no evidence of significant statistical heterogeneity for these outcomes. Patients receiving bevacizumab were more than twelve times more likely to present with severe hypertension than control patients (OR 12.76, 95% CI 2.93 to 55.53). There was evidence of significant statistical heterogeneity (I²=70%).

The meta-regression, for the outcome of hypertension, found a significantly higher risk of hypertension in trials published before 2008 (OR 58.97, p<0.001 for before 2008 versus OR 5.047, p=0.004 for after 2008). The risk of hypertension was not associated with any type of combination therapy, but it was close to significant for the dose of bevacizumab (p=0.055).

Bevacizumab was not associated with an increased risk of arterial or venous thromboembolic events, total vascular events, febrile neutropenia, and gastrointestinal perforation. Bevacizumab was not associated with an increased risk of severe (grade five) adverse events. There was evidence of moderate statistical heterogeneity for the outcome of vascular events (I²=52.1%), but not for the other outcomes (I²=0).

There was evidence of publication bias for the outcome of proteinuria (p=0.022). No publication bias was reported for the other outcomes, but there were few included trials.

Authors' conclusions

Bevacizumab was associated with an increased risk of hypertension, proteinuria, left ventricular dysfunction and bleeding, but not gastrointestinal perforation, arterial or venous thromboembolic events and fatal events, in patients with metastatic breast cancer.

CRD commentary

The review question was largely clear. The inclusion criteria for the intervention and outcomes were well defined. The abbreviation LR was not defined, but was assumed to be locally recurrent. The search was restricted to one database and oncology meeting abstracts. Therefore important data may have been missed. It is unclear whether the search was restricted by language and language bias cannot be ruled out. Attempts were made to identify unpublished data and publication bias was assessed, but there were too few trials for a reliable assessment and publication bias cannot be ruled out. It was unclear whether attempts were made to minimise reviewer error and bias in the study selection process, but they were made for data extraction.

The authors do not appear to have assessed quality, and no information was given on the quality of the included trials, so the reliability of the data is unclear. Given the rarity of some adverse events, the number of trials and participants may have been too small to detect significant between-group differences. The authors acknowledged that the longer progression-free survival with bevacizumab might have introduced a bias towards detecting more adverse events in this group. Suitable methods were used to combine the trial data and statistical heterogeneity was assessed and investigated. The results reported in the text of the review differed from the results in forest plots provided by the authors. This did not alter the significance of the results, but it raises questions about their reliability.

Given the unclear quality and small number of included trials, the reliability of the authors' conclusions is unclear.

Implications of the review for practice and research

Practice: The authors stated that bevacizumab should be discontinued in patients who had symptoms of possible bowel obstruction or who had a history of colitis or diverticulitis.

Research: The authors stated that further research was needed into bevacizumab and febrile neutropenia, using time-dependent analyses to investigate the impact of longer patient follow-up on the incidence of febrile neutropenia.
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