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REVIEW ARTICLE

Risk profile of bevacizumab in patients with non-small cell lung cancer: A meta-analysis of randomized controlled trials

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Abstract

Background. Severe adverse events (AEs) have been reported in cancer patients treated with bevacizumab. Currently, safety of bevacizumab in patients with non-small cell lung cancer (NSCLC) is not clear. We conducted a meta-analysis to evaluate the risk profile of bevacizumab in NSCLC patients. *Methods*. Relevant trials were identified by searching databases and conference proceedings. Data on treatment-related deaths and grade 3 or 4 AEs were extracted and pooled to calculate relative risks (RRs) with 95% confidence interval (CI) for bevacizumab compared with chemotherapy alone. *Results*. A total of 2210 patients were included in the analysis. Compared with chemotherapy alone, high-dosage (15 mg/kg) bevacizumab was associated with an increased risk of treatment-related deaths (RR = 2.04, 95% CI = 1.18–3.52), but not for low-dosage (7.5 mg/kg) group (RR = 1.20, 95% CI = 0.60–2.41). In addition, treatment with bevacizumab was associated with several grade 3 or 4 AEs in patients with NSCLC, especially in high-dosage bevacizumab group. *Conclusion*. The use of the bevacizumab increases the risk of treatment-related deaths and several grade 3 or 4 AEs in patient with NSCLC. The risk may be dose-dependent. Close monitoring and adequate management are recommended to decrease severe AEs.

Tumor vascularization is a vital process for the progression of a neoplasm from a small localized tumor to an enlarging tumor with the ability to metastasize [1]. Angiogenesis is a complex process regulated by several growth factors among which vascular endothelial growth factor (VEGF) plays an important role [2]. Evidence from *in vitro* and *in vivo* experiments have shown that increased VEGF expression is associated with tumor growth and metastasis, whereas the inhibition of VEGF signaling results in suppression of both tumor-induced angiogenesis and tumor growth [3].

Bevacizumab (rhuMab Avastin, Genentech Inc, South San Francisco, CA, USA), a recombinant humanized monoclonal antibody targeting the VEGF ligand, has shown benefits in the treatment of many types of malignancy including head and neck cancer, non-small cell lung cancer (NSCLC), colorectal cancer, breast cancer and so on [4–11]. As with many therapeutic agents, severe adverse events (AEs) have been reported in cancer patients treated with the widely used angiogenesis inhibitor bevacizumab in combination with chemotherapy, including hypertension, proteinuria, hemorrhage, rash, gastrointestinal perforation, and congestive heart failure [7–14]. Currently, the specific role of bevacizumab in the development of severe AEs in NSCLC patients remains controversial.

In recent years, several systematic reviews and meta-analyses were performed to assess safety of bevacizumab in combination with chemotherapy in patients with NSCLC [15–18]. However, some systematic reviews were incomplete in that published studies were omitted in their analyses. Moreover, some clinically relevant AEs, such as gastrointestinal perforation, leukopenia, diarrhea, nausea, and headache have not yet been systematically evaluated. Thus, safety of bevacizumab in patients with NSCLC needed further investigated. Therefore, we conducted a meta-analysis on relevant randomized controlled clinical trials (RCTs) to evaluate the risk profile of bevacizumab in patients with NSCLC.

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Patients and methods

Identification and eligibility of relevant studies

We carried out a search in MEDLINE, EMBASE databases, covering all papers published up to March 2011, using the following search terms: bevacizumab (as well as its commercial name, Avastin) and non-small cell lung cancer. The abstracts of relevant scientific meetings were examined to ensure complete review of the available studies. To ensure that all relevant trials were included, we checked the clinical trial registry (www.clinicaltrials.gov) for the existence of unpublished trials. All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. If studies had partly overlapped subjects, only the most recent or complete study was selected.

Inclusion criteria

We included all randomized controlled trials that evaluated the administration of bevacizumab plus chemotherapy versus chemotherapy alone. Phase I and single-arm phase II trials were excluded due to their lack of control groups. Two investigators reviewed the articles independently to exclude irrelevant and overlapping studies. The results were compared, and disagreements were resolved by discussion and consensus.

Data extraction and clinical endpoints

From each study, the following information was extracted: first author's surname, year of publication, ethnicity, histological of enrolled patients, trial phase, number of subjects, treatment arms, and number of AEs in experimental and control arms. The AEs of included studies were assessed and recorded according to the National Cancer Institute's common toxicity criteria (version 2 or 3; http://ctep.cancer.gov). We have included the incidences of treatment-related deaths and AEs (grades 3 or 4) for the analyses.

Statistical analysis

For each trial, data on treatment-related deaths and severe AEs (grades 3 or 4) were extracted and pooled to calculate relative risks (risk ratios, RRs) with 95% confidence interval (CI) for bevacizumab compared with chemotherapy alone or plus placebo. To explore a dosage-effect relationship, we divided bevacizumab therapy into low-dosage (7.5 mg/kg) and high-dosage (15 mg/kg) [8,10]. The significance of the combined RR was determined by the Z-test, in which $p < 0.05$ was considered significant. The χ^2-based Q statistic test was used for the assessment of the between-study heterogeneity, and it was considered significant for $p < 0.1$ [19]. When the effects were assessed to be homogenous, the fixed-effect model was used; otherwise, the random-effect model was applied [20]. We also used the statistic of I^2 to efficiently test for the heterogeneity, with $I^2 < 25\%$, 25–75% and $>75\%$ to represent low, moderate and high degree of inconsistency, respectively [21]. An estimate of potential publication bias was carried out by the funnel plot. The Egger's test detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the standardized effect estimates against their precision [22].

All analyses were done by using the Stata (Version10.0, Stata Corporation) and Review Manager (version 5.0.1, The Cochrane Collaboration), using two sided *p*-value.

Results

Literature search and study characteristics

The electronic database searches identified 592 citations. Of these, 514 citations were excluded after the first screening based on abstracts or titles, leaving 78 articles for full-text review. In these articles, 73 studies were excluded due to containing no relative outcomes, phase 1 trials, single-arm phase 2 trials, overlapped subjects, and bevacizumab used in both experiment and control group. Lastly, five RCTs were selected for final inclusion in the meta-analysis, including three phase 2 trials and two phase 3 trials [7–11]. Figure 1 shows the detailed screening and selection process that we applied in our meta-analysis. Of five studies, three trials used a mixed population

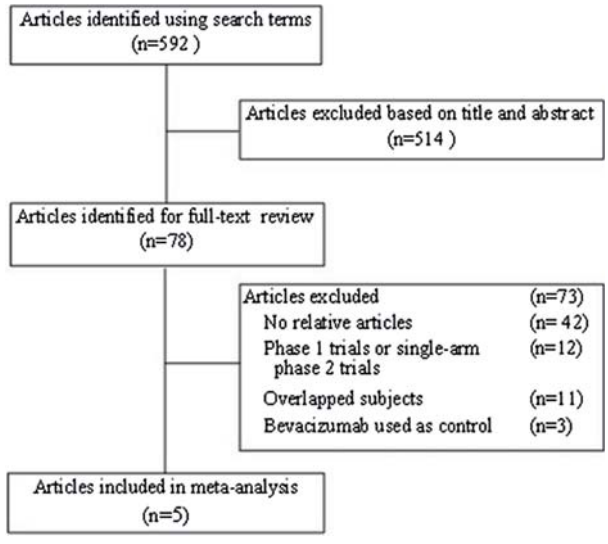

Figure 1. Flow diagram of the literature search and trial selection process.

Table I. Characteristics of randomized controlled clinical trials included in the meta-analysis.

Source	Trial phase	No. of patients	Populations	Histology	Patients	Interventions
Herbst et al. 2007 [7]	II	120	Mixed	Large-cell carcinoma, adenocarcinoma, other	Recurrent or refractory NSCLC	15 mg/kg of bevacizumab plus chemotherapy, bevacizumab plus erlotinib, or chemotherapy alone
Johnson et al. 2004 [8]	II	99	American	Adenocarcinoma, large-cell anaplastic, squamous cell, other	Advanced or metastatic NSCLC	7.5/15 mg/kg of bevacizumab plus chemotherapy, or chemotherapy alone
Nishio et al. 2009 [9]	II	180	Japanese	NA	Advanced or recurrent NSCLC	15 mg/kg of bevacizumab plus chemotherapy, or chemotherapy alone
Reck et al. 2009 [10]	III	1043	Mixed	Adenocarcinoma, large cell, other	Advanced or recurrent non-squamous NSCLC (stage IIIB or IV)	Chemotherapy plus placebo, or 7.5/15 mg/kg of bevacizumab
Sandler et al. 2006 [11]	III	878	Mixed	Adenocarcinoma, large cell cancer, bronchioloalveolar carcinoma, other	Recurrent or advanced NSCLC (stage IIIB or IV)	15 mg/kg of bevacizumab plus chemotherapy, or chemotherapy alone

NA, Not available; NSCLC, Non-small cell lung cancer.

[7,10,11], one trial was conducted with Japanese patients [9] and one with American patients [8]. The total population for analysis included 2210 patients. In addition, 949 of the bevacizumab-treated patients received a low-dosage (7.5 mg/kg), and 362 received a high-dosage (15 mg/kg). The study characteristics are summarized in Table I.

Meta-analyses

We pooled RRs of bevacizumab versus control for treatment-related deaths and severe AEs (grades 3 or 4) separately. As shown in Figure 2, the RR of treatment-related deaths in the group treated with high-dosage bevacizumab was 2.04 (95% CI = 1.18–3.52; $p = 0.27$, $I^2 = 23\%$ for heterogeneity; fixed model)

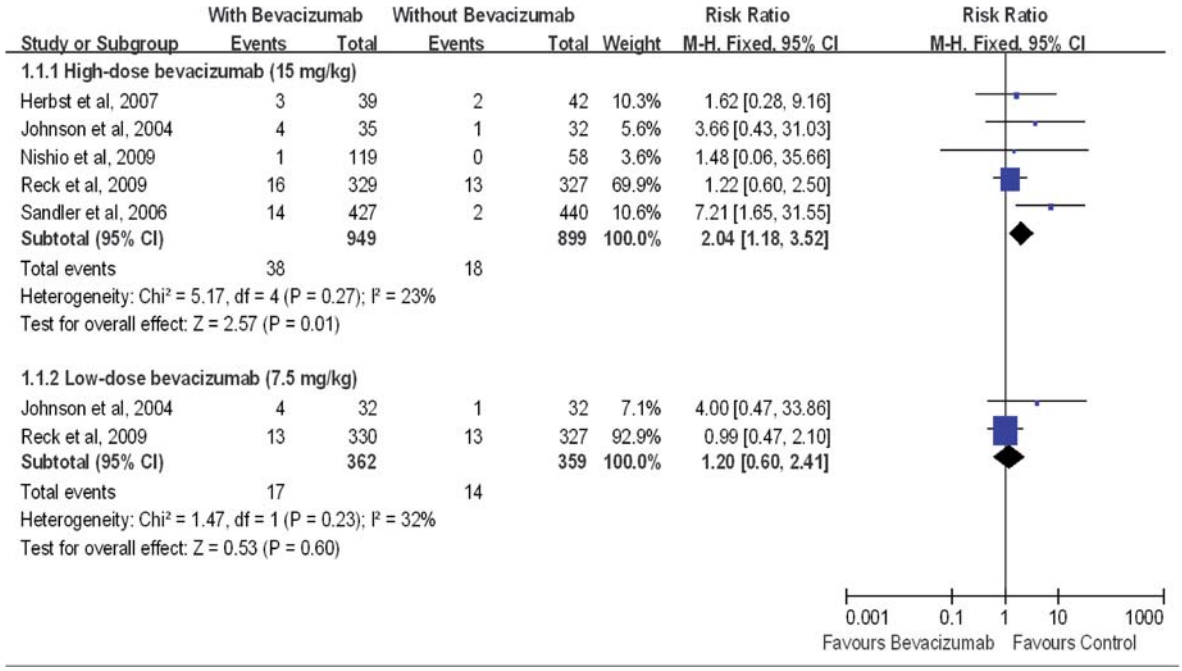

Figure 2. Relative risks of treatment-related deaths associated with bevacizumab versus control among patients with non-small cell lung cancer.

Table II. Relative risks with 95% confidence intervals for common adverse events (Grade ≥ 3).

	High-dosage bevacizumab (15 mg/kg)							Low-dosage bevacizumab (7.5 mg/kg)						
Adverse event	No.[a]	Subjects	RR [95% CI]	*p*	I^2 (%)	p[b]	Effects model	No.[a]	Subjects	RR [95% CI]	*p*	I^2 (%)	p[b]	Effects model
Hypertension	5	949/899	6.93 [3.58,13.39]	<0.00001	0	0.73	Fixed	2	362/359	3.28 [1.38,7.81]	0.007	55	0.13	Fixed
Bleeding events	5	949/899	3.48 [1.80,6.73]	0.0002	0	0.73	Fixed	2	362/359	2.98 [1.24,7.15]	0.01	7	0.30	Fixed
Neutropenia	3	795/809	1.28 [1.09,1.51]	0.003	36	0.21	Fixed	1	330/327	1.26 [1.02,1.55]	0.03	–	–	–
Thrombocytopenia	4	830/841	1.11 [0.85,1.46]	0.45	30	0.23	Fixed	2	362/359	1.16 [0.89,1.51]	0.27	NA	NA	NA
Anemia	3	795/809	0.75 [0.50,1.13]	0.17	38	0.20	Fixed	1	330/327	0.77 [0.50,1.17]	0.21	–	–	–
Rash	3	501/514	5.15 [1.14,23.38]	0.03	NA	NA	NA	1	32/32	NA	NA	–	–	–
Headache	2	462/472	6.26 [1.66,23.58]	0.007	0	0.82	Fixed	1	32/32	3.00 [0.13,71.00]	0.50	–	–	–
Proteinuria	2	756/767	18.30 [2.46,136.11]	0.005	0	0.57	Fixed	1	330/327	2.97 [0.12,72.71]	0.50	–	–	–
GI perforation	2	368/369	1.03 [0.18,5.79]	0.98	0	0.36	Fixed	1	330/327	0.20 [0.01,4.11]	0.30	–	–	–
Thrombotic event[c]	3	403/401	0.99 [0.60,1.63]	0.97	21	0.28	Fixed	2	362/359	1.07 [0.63,1.84]	0.79	0.57	0	Fixed
Leukopenia	2	74/74	2.25 [1.09,4.66]	0.03	33	0.22	Fixed	1	32/32	1.43 [0.62,3.28]	0.40	–	–	–
Diarrhea	2	74/74	2.75 [0.12,65.18]	0.53	NA	NA	NA	1	32/32	7.00 [0.38,130.26]	0.19	–	–	–
Vomiting	3	403/401	2.42 [1.32,4.43]	0.004	0	0.77	Fixed	2	362/359	1.91 [0.99,3.67]	0.05	0	0.63	Fixed
Nausea	2	74/74	1.98 [0.38,10.49]	0.42	0	0.92	Fixed	1	32/32	1.00 [0.07, 15.30]	1	–	–	–

[a]number of studies; [b]p-value of Q-test for heterogeneity test; [c]venous or arterial thrombotic event; NA, Not applicable; GI, gastrointestinal.

compared with patients who did not receive bevacizumab. The pooled result was not significantly affected after exclusion of one trial including patients with squamous cell carcinoma (SCC) [8] (RR = 1.95, 95% CI = 1.11–3.42; $p = 0.19$, $I^2 = 36\%$ for heterogeneity; fixed model). However, no significant increase risk of treatment-related deaths in the group treated with the low-dosage bevacizumab versus control was found (RR = 1.20, 95% CI = 0.60–2.41; $p = 0.23$, $I^2 = 32\%$ for heterogeneity; fixed model).

The risk of grades 3 or 4 AEs in patients treated with bevacizumab versus control is presented in Table II. Compared with control group, bevacizumab was associated with a significantly increase risk of hypertension (high dose: RR = 6.93, 95% CI = 3.58–13.39; low dose: RR = 3.28, 95% CI = 1.38–7.81), bleeding events (high dose: RR = 3.48, 95% CI = 1.80–6.73; low dose: RR = 2.98, 95% CI = 1.24–7.15), and neutropenia (high dose: RR = 1.28, 95% CI = 1.09–1.51; low dose: RR = 1.26, 95% CI = 1.02–1.55) in both high-dosage and low-dosage groups. Considering bleeding events happened frequently in patients with SCC, we further performed an analysis by exclusion those patients and statistically similar results were obtained (high dose: RR = 3.52, 95% CI = 1.79–6.91; low dose: RR = 2.31, 95% CI = 0.90–5.94). There was a significant increase risk of rash (RR = 5.15, 95% CI = 1.14–23.38), headache (RR = 6.26, 95% CI = 1.66–23.58), leucopenia (RR = 2.25, 95% CI = 1.09–4.66), and vomiting (RR = 2.42, 95% CI = 1.32–4.43) in high-dosage bevacizumab group versus control group; while those risks were not found in low-dosage bevacizumab group. In addition, no statistically significant differences were found for thrombocytopenia, anemia, gastrointestinal perforation, thrombotic event (venous and arterial), diarrhea, or nausea related to treatment with bevacizumab.

Publication bias

We used Funnel plot and Egger's regression asymmetry test to access the publication bias of literatures. The data suggested that there was no evidence of publication bias for the RR of treatment-related deaths in comparison of bevacizumab-treated patients versus controls ($t = 1.26$, $p = 0.336$).

Discussion

The AEs of bevacizumab is somewhat different from that of traditional cytotoxic chemotherapy. Rather than digestive system toxicity and bone marrow suppression which are commonly associated with chemotherapy, frequently reported side effects of bevacizumab include hypertension, bleeding events, and rash [7–14]. Moreover, treatment-related deaths

have been reported in cancer patients treated with bevacizumab [15]. The present meta-analysis, including 1311 NSCLC patients received bevacizumab and 899 controls from five RCTs, shows a significant increased risk of treatment-related deaths in patients with high-dosage bevacizumab in the pooled analysis. For low-dosage bevacizumab, no association with treatment-related deaths was found. However, there are only two studies included in the analysis with limited sample sizes (362 patients received bevacizumab and 359 controls) in low-dosage bevacizumab group; therefore, the result should be interpreted with caution. More studies should be conducted to further examine this association.

An important cause of treatment-related deaths associated with bevacizumab was fatal pulmonary hemorrhage. Sandler et al. found that baseline cavitation of tumor is the only potential risks factor of early onset pulmonary hemorrhage in NSCLC [23]. In addition, study has shown that bevacizumab associated with pulmonary hemorrhage in patients with SCC [8]. We further performed an analysis by removing patients with SCC. However, the result showed that even in patients with non-SCC NSCLC, high-dosage bevacizumab significantly increased the risk of treatment-related deaths.

Compared with control group, bevacizumab was associated with a significantly increased risk of hypertension, bleeding events, and neutropenia. In addition, there were no differences between high- and low-dosage of bevacizumab, suggesting that the low-dosage was enough to trigger these AEs. Although the exact mechanism for these associations was not clear, it was biologically possible that they might be related to inhibitory effect of bevacizumab on VEGF signaling [24]. However, some AEs associated with bevacizumab treatment may be attributable to known risk factors, including age, race, sex and bevacizumab dose [14,16,25–27]. In our analyses, we have identified a relationship between bevacizumab dosage and rash, headache, leukopenia, and vomiting. Thus, dosage reduction may be a reasonable approach to reduce the risk of some AEs.

In our study, we did not find any association between bevacizumab and thrombocytopenia, anemia, gastrointestinal perforation, thrombotic event, diarrhea, or nausea. Although congestive heart failure associated with bevacizumab has been reported frequently in several trials [28,29], no such association was found in patients with NSCLC. The variety AEs of bevacizumab in patients with different cancers is puzzling but may be due to biology of underlying cancer and host factors [30]. Efforts on further studies may lead to a better insight of those issues.

As bevacizumab is widely used in patients with NSCLC, it will be especially important to recognize the risk and intervene promptly to reduce its incidence of mortality and AEs. Our study not only shows that there is a significant increase risk of treatment-related deaths associated with high-dosage bevacizumab but also provides a better representation of the overall risk of severe AEs. Such evidence on the safety of bevacizumab in patients with NSCLC might help physicians and patients to a better understanding of the risk of treatment. More importantly, it would be of great help for clinicians to choose bevacizumab therapy in an individualized manner, and to monitor and treat side effects timely and appropriately.

Some limitations of this meta-analysis should be acknowledged. First, as a meta-analysis, we were not able to assess confounding factors, such as age, sex and duration time at the patient level and incorporate them into the analysis. Second, in some analysis, the sample of sizes was relatively small, with not enough statistical power to explore the real association. Finally, exclusion criteria added during the study when a grade 5 pulmonary hemorrhage occurred in one trial [11], which might cause bias of the reported incidence rates and make some findings less relevant for the daily practice.

In conclusion, the use of the bevacizumab increases the risk of treatment-related deaths and several grade 3 or 4 AEs in patient with NSCLC. Physicians and investigators should optimize the balance between oncologic clinical benefit and life-threatening AEs. The use of bevacizumab in an individualized manner and dosage reduction may be reasonable approaches to reducing the risk of some AEs.

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