Risk of hypertension with bevacizumab, an antibody against vascular endothelial growth factor A: a systematic review and meta-analysis

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INTRODUCTION

Tumor angiogenesis is critical for tumor progression. The vascular endothelial growth factor (VEGF) promotes angiogenesis and over expression of the VEGF has been correlated with poor prognosis in various malignancies.1,2 There are 2 main targets in the VEGF signaling pathway: VEGF ligands and VEGF receptors (VEGFRs). Bevacizumab, a humanized antibody against VEGF, is effective in the treatment of patients with many cancers, such as metastatic colorectal cancer, non-small-cell lung cancer, and breast cancer, shown by several phase III studies.1,4 There also are promising phase II clinical trials in patients with pancreatic cancer, renal cell cancer, and prostate cancer. However, as with many therapeutic agents, significant side effects are associated with bevacizumab. Hypertension is one of the predominant toxicity. We performed a systematic review and meta-analysis of published clinical trials of bevacizumab to quantify the risk of hypertension. 15 studies following PRISMA guidelines and matching inclusion and exclusion criteria were collected in which a group of patients were either treated with Bevacizumab and a concurrent chemotherapy and another group treated with Placebo and the same chemotherapy. Relative risk (RR) was calculated. P<0.05 was considered statistically significant. RevMan 5.3 software was used for the analysis. A total of 13,070 patients were included. Bevacizumab was associated with a significant increased risk of overall hypertension (RR=3.509; 95% C.I:2.451 to 5.023). 11 trials are included for determining the risk of Grade 3 hypertension including 8799 patients with a significant increased risk (RR=3.909; 95% C.I:1.983 to 7.707). 7 trials are included for determining the risk of hypertension at low dose (2.5 mg/kg/cycle) including 3691 patients associated with a significant increased (RR=2.640; 95% C.I: 1.408 to 4.950). 10 trials are included for determining the risk of hypertension at high dose (5 mg/kg/cycle) including 9379 patients associated with a significant (RR=4.036; 95% C.I: 2.948 to 5.525). Our meta-analysis has demonstrated that bevacizumab may be associated with a significantly increased risk of hypertension in patient with a variety of metastatic solid tumors irrespective of dosage.

Keywords: Bevacizumab, Anti-cancer, Placebo, Hypertension

ABSTRACT

Bevacizumab, a humanized antibody against VEGF, is effective in the treatment of patients with many cancers. However, as with many therapeutic agents, significant side effects are associated with bevacizumab. Hypertension is one of the predominant toxicity. We performed a systematic review and meta-analysis of published clinical trials of bevacizumab to quantify the risk of hypertension. 15 studies following PRISMA guidelines and matching inclusion and exclusion criteria were collected in which a group of patients were either treated with Bevacizumab and a concurrent chemotherapy and another group treated with Placebo and the same chemotherapy. Relative risk (RR) was calculated. P<0.05 was considered statistically significant. RevMan 5.3 software was used for the analysis. A total of 13,070 patients were included. Bevacizumab was associated with a significant increased risk of overall hypertension (RR=3.509; 95% C.I:2.451 to 5.023). 11 trials are included for determining the risk of Grade 3 hypertension including 8799 patients with a significant increased risk (RR=3.909; 95% C.I:1.983 to 7.707). 7 trials are included for determining the risk of hypertension at low dose (2.5 mg/kg/cycle) including 3691 patients associated with a significant increased (RR=2.640; 95% C.I: 1.408 to 4.950). 10 trials are included for determining the risk of hypertension at high dose (5 mg/kg/cycle) including 9379 patients associated with a significant (RR=4.036; 95% C.I: 2.948 to 5.525). Our meta-analysis has demonstrated that bevacizumab may be associated with a significantly increased risk of hypertension in patient with a variety of metastatic solid tumors irrespective of dosage.

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INTRODUCTION

Tumor angiogenesis is critical for tumor progression. The vascular endothelial growth factor (VEGF) promotes angiogenesis and over expression of the VEGF has been correlated with poor prognosis in various malignancies.1,2 There are 2 main targets in the VEGF signaling pathway: VEGF ligands and VEGF receptors (VEGFRs). Bevacizumab, a humanized antibody against VEGF, is effective in the treatment of patients with many cancers, such as metastatic colorectal cancer, non-small-cell lung cancer, and breast cancer, shown by several phase III studies.1,4 There also are promising phase II clinical trials in patients with pancreatic cancer, renal cell cancer, and prostate cancer. However, as with many therapeutic agents, significant side effects are associated with bevacizumab, including thrombosis, wound-healing complications, bleeding, gastrointestinal perforation, and renal toxicity. Hypertension is the predominant toxicity.3 Severe hypertension including hypertensive crisis may cause significant cardiovascular damage with a possible life-threatening consequence, and limit the use of bevacizumab. The incidences of high-grade (grade 3-4) hypertension in patients receiving bevacizumab varied
substantially among clinical trials. The overall risk of hypertension in patients with cancer on bevacizumab therapy is unclear. We performed a systematic review and meta-analysis of published clinical trials of bevacizumab to quantify the risk of hypertension. The use of Bevacizumab in cancer has been increasing nowadays in India, due to lack of many systematic reviews determining the risk of this novel anticancer agent we decided to perform a meta-analysis.

**METHODS**

**Step 1: Identification and literature search**

The search was done based on preferred reporting system for meta-analysis and systemic review (PRISMA) guideline. All the scientific database like clinical trials.gov, Pubmed central, NCBI, NIH, Cochrane Library and Google scholar were used for search cancer, Bevacizumab, side-effects, hypertension. All the trials published after January 2004 to till date were included in search.

**Step 2: Criteria for selection of studies**

All study related randomised controlled trials (RCTs) using either:

- An adequate method of allocation concealment (e.g. sealed opaque envelopes),
- Studies that were double-blind, single-blind or unblinded,
- Studies that were in Phase 2 or Phase 3 trial were only included.

**Step 3: RCT enrolment criteria**

**Inclusion criteria**

Inclusion criteria were the study must include the participants greater than or equal to 18 years of age; the studies which included bevacizumab plus a concurrent therapy and placebo with a concurrent therapy were only included; the dose of bevacizumab should be 2.5 mg/kg/week or 5 mg/kg/week.

**Exclusion criteria**

Exclusion criteria were studies including patients prior treated with bevacizumab or another drug that targets VEGF-A pathway or other malignancies within 5 years (unless low risk of recurrence); also the studies with history of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess, clinical signs or symptoms of gastrointestinal obstruction, and/or requirement of parenteral nutrition, non-healing wound, ulcer. Bone fracture, bleeding diathesis, coagulopathy, known CNS disease (except for treated brain metastasis), clinically significant cardiovascular disease, a major surgical procedure within 28 days of enrollment or anticipated to occur while participating in study were excluded from the analysis; unpublished research work or trials.

**Database searched from Google Scholar, Science Direct, Pubmed Library, NCBI, NIH, Clinical trials.gov: Total=72,700**

**Studies screened by relevance of title N=507**

**Studies after removal of duplication studies and removing of all phase 1 trials and including only phase 2 and 3 trials N=78**

**Potentially relevant studies that met eligibility criteria N=21**

**Studies qualified for meta-analysis N=15**

**Figure 1: PRISMA flow diagram of included articles.**

**Step 4: Type of intervention**

Patients treated by bevacizumab with concurrent chemotherapy and placebo with concurrent chemotherapy in clinical trial (phase 2 or 3) of cancer.

**Step 5: Outcome measure of side effect**

Outcome for measurement of Hypertension and grade was according to National Cancer Institute Common Terminology criteria version 3. Outcome was measured after 6 cycles for 6 studies and till overall survival in 9.

**Step 6: Data extraction**

Data were extracted from studies meeting above criteria. Those studies in which data was unclear asked from respective authors. In some studies, data could not obtain by enquiry were excluded.

**Step 7: Nullification of bias**

Authors assured to include studies in which allocation of both the groups were adequately randomized and there was no any conflict of interest as well as match to
inclusion and exclusion criteria. Also the concurrent treatment was same for the group with bevacizumab therapy and placebo therapy.

**Step 8: Measurement of relative risk**

The outcome of the occurrence of hypertension (both any grade and above grade 3) was recorded from both the groups (bevacizumab and placebo) and relative risk (RR) was calculated with 95% confidence interval and funnel as well as forest plot was obtained. RevMan®Version 5.38 was used for analysis. P value less than 0.05 were considered significant.

**RESULTS**

Individual searches yield total of studies, from which 15 included all grade hypertension, 11 studies included grade 3 hypertension and above, 7 studies included bevacizumab with dose 2.5 mg/kg/cycle and 10 studies included bevacizumab with dose 5 mg/kg/cycle. The trials of Miles et al, and Reck et al, had both dosing cycles so were included in both low and high dosing regimens.10,18

| Table 1: Characteristics of randomized controlled clinical trials included in the meta-analysis. |
| Study name | Underlying malignancy | Concurrent treatment | Bevacizumab dose |
|------------|-----------------------|----------------------|-----------------|
| Ohtsu et al6 | Advanced gastric cancer | Fluropyrimidine-cisplatin | 2.5 mg/kg/every week |
| Escudier et al7 | Metastatic renal cell carcinoma | Interferon alfa | 5 mg/kg/week |
| Aghajanian et al8 | Recurrent epithelial ovarian, primary peritoneal, or | Gemcitabine plus carboplatin; | 5 mg/kg every week |
| Zhou et al9 | Recurrent non squamous non small cell lung cancer | Pacitaxel or carboplatin | 5 mg/kg every week |
| Miles et al10 | HER 2- metastatic breast cancer | Docetaxel | 2.5 mg/kg/week |
| Miles et al10 | HER 2- metastatic breast cancer | Docetaxel | 5 mg/kg/week |
| Cutsem et al11 | Metastatic pancreatic cancer | Gemcitabine and erlotinib | 2.5 mg/kg/week |
| Kabbinavar et al12 | Metastatic colon cancer | Bolus fluorouracil and leucovorin | 2.5 mg/kg every week |
| Hurwitz et al13 | Metastatic colon cancer | Irinotecan, bolus fluorouracil, and leucovorin | 2.5 mg/kg every week |
| Hurwitz et al14 | Metastatic colorectal cancer | Irinotecan/fluorouracil/leucovorin | 2.5 mg/kg/week |
| Hurwitz et al15 | Metastatic colorectal cancer | Oxaliplatin-based, irinotecan based | 5 mg/kg/week |
| Kindler et al16 | Advanced pancreatic cancer | Gemcitabine | 5 mg/kg/week |
| Kindler et al17 | Malignant mesothelioma | Gemcitabine and cisplatin | 5 mg/kg every week |
| Reck et al18 | Nonsquamous non–small-cell lung cancer | Cisplatin and gemcitabine | 2.5 mg/kg every week |
| Reck et al18 | Nonsquamous non–small-cell lung cancer | Cisplatin and gemcitabine | 5 mg/kg every week |
| Robert et al19 | HER 2–locally recurrent or metastatic breast cancer | Capecitabine, taxane, anthracycline | 5 mg/kg every week |
| Burger et al20 | Ovarian cancer | Carboplatin and Pacitaxel | 5 mg/kg every week |

| Table 2: Characteristics of randomized controlled clinical trials included in the meta-analysis. |
| Study name | Trial phase | Number for analysis bevacizumab group (N) | Number for analysis placebo group (N) | Hypertension in bevacizumab group | Hypertension in placebo group |
|------------|-------------|--------------------------------|-------------------------|-------------------------------|-------------------------------|
| Ohtsu et al6 | 3 | 386 | 381 | 24 | 2 |
| Escudier et al7 | 3 | 337 | 304 | 88 | 28 |
| Aghajanian et al8 | 3 | 247 | 233 | 43 | 1 |
| Zhou et al9 | 3 | 140 | 134 | 7 | 1 |
| Miles et al10 | 3 | 252 | 231 | 2 | 3 |
| Miles et al10 | 3 | 247 | 231 | 11 | 3 |
| Cutsem et al11 | 3 | 296 | 287 | 60 | 26 |
| Kabbinavar et al12 | 2 | 100 | 104 | 32 | 5 |
| Hurwitz et al13 | 2 | 393 | 397 | 88 | 33 |
| Hurwitz et al14 | 3 | 109 | 98 | 37 | 37 |
| Hurwitz et al15 | 3 | 1990 | 1773 | 153 | 29 |
| Kindler et al16 | 3 | 277 | 263 | 10 | 3 |

Continued.
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| Study name       | Trial phase | Number for analysis bevacizumab group (N) | Number for analysis placebo group (N) | Hypertension in bevacizumab group | Hypertension in placebo group |
|------------------|-------------|------------------------------------------|---------------------------------------|-----------------------------------|-----------------------------|
| Kindler et al17  | 2           | 53                                       | 55                                    | 23                                | 9                           |
| Reck et al18     | 3           | 330                                      | 327                                   | 21                                | 5                           |
| Reck et al18     | 3           | 329                                      | 327                                   | 28                                | 5                           |
| Robert et al19   | 3           | 817                                      | 413                                   | 81                                | 4                           |
| Burger et al20   | 3           | 608                                      | 601                                   | 139                               | 43                          |

Table 3: Relative risk of all grade hypertension in bevacizumab versus placebo.

| Study          | Bevacizumab (N) | Placebo (N) | Relative risk | 95% CI         | z     | P value | Weight (%) |
|----------------|-----------------|-------------|---------------|----------------|-------|---------|------------|
|                | Fixed           | Random      |               |                |       |         |            |
| Ohtsu et al6   | 24/386          | 2/381       | 11.845        | 2.819 to 49.771| 0.94  | 3.74    |            |
| Escudier et al7| 88/337          | 28/304      | 2.835         | 1.908 to 4.213 | 12.34 | 8.37    |            |
| Aghajanian et al8| 43/247        | 1/233       | 40.563        | 5.631 to 292.193| 0.50  | 2.44    |            |
| Zhou et al10   | 7/140           | 1/134       | 6.700         | 0.835 to 53.732| 0.45  | 2.25    |            |
| Miles et al10  | 2/252           | 3/231       | 0.611         | 0.103 to 3.625 | 0.61  | 2.83    |            |
| Miles et al10  | 11/247          | 3/231       | 3.429         | 0.969 to 12.137| 1.21  | 4.32    |            |
| Cutsem et al11 | 60/296          | 26/287      | 2.238         | 1.455 to 3.442 | 10.44 | 8.22    |            |
| Kabbinavar et al12| 32/100        | 5/104       | 6.656         | 2.702 to 16.399| 2.38  | 5.87    |            |
| Hurwitz et al13| 88/393          | 33/397      | 2.694         | 1.851 to 3.919 | 13.76 | 8.46    |            |
| Hurwitz et al14| 37/109          | 37/98       | 0.899         | 0.624 to 1.295 | 14.53 | 8.50    |            |
| Hurwitz et al15| 153/1990        | 29/1773     | 4.701         | 3.177 to 6.955 | 12.61 | 8.39    |            |
| Kindler et al16| 10/277          | 3/263       | 3.165         | 0.881 to 11.373| 1.18  | 4.26    |            |
| Kindler et al17| 23/53           | 9/55        | 2.652         | 1.354 to 5.193 | 4.29  | 7.02    |            |
| Reck et al18   | 21/330          | 5/327       | 4.162         | 1.588 to 10.905| 2.09  | 5.57    |            |
| Reck et al18   | 28/329          | 5/327       | 5.566         | 2.176 to 14.237| 2.19  | 5.69    |            |
| Robert et al19 | 81/817          | 4/413       | 10.237        | 3.777 to 27.740| 1.95  | 5.42    |            |
| Burger et al20 | 139/608         | 43/601      | 3.195         | 2.314 to 4.413 | 18.56 | 8.66    |            |
| Total (fixed effects) | 847/6911 | 237/6159 | 3.288 | 2.865 to 3.774 | 16.936 | <0.001 | 100.00 100.00 |
| Total (random effects) | 847/6911 | 237/6159 | 3.509 | 2.451 to 5.023 | 6.859  | <0.001 | 100.00 100.00 |

Heterogeneity, Q=78.7471, degree of freedom = 16, p<0.0001, I² (inconsistency) = 79.68%

There are 15 trials for determining the risk of all grade hypertension including 13,070 patients (6911 in bevacizumab and 6159 in placebo group). The relative risk of hypertension with the patients treated with bevacizumab and concurrent therapy was 3.509 times more than placebo and concurrent therapy with 2.451 to 5.023 C.I and the p value statistically significant in random effect model.

There are 11 trials for determining the risk of grade 3 hypertension including 8799 patients (4550 in bevacizumab group and 4249 in placebo group). The
relative risk of hypertension with the patients treated with bevacizumab and concurrent therapy was 3.909 times more than placebo and concurrent therapy with 1.983 to 7.707 CI and the p value statistically significant in random effect model.

**Table 4: Relative risk of hypertension with bevacizumab of grade 3 and above.**

| Study            | Bevacizumab (N) | Placebo (N) | Relative risk | 95% CI   | z      | P value | Weight (%) |
|------------------|-----------------|-------------|---------------|----------|--------|---------|------------|
| Escudier et al$^7$ | 11/337          | 2/304       | 4.961         | 1.109 to 22.206 | 2.40   | 7.71    |            |
| Aghajanian et al$^8$ | 43/247         | 1/233       | 40.563        | 5.631 to 292.193 | 1.38   | 6.04    |            |
| Zhou et al$^9$   | 7/140           | 1/134       | 6.700         | 0.835 to 53.732 | 1.25   | 5.72    |            |
| Cutsem et al$^{11}$ | 10/296          | 3/287       | 3.232         | 0.899 to 11.624 | 3.29   | 8.59    |            |
| Kabbinavar et al$^{12}$ | 16/100        | 3/104       | 5.547         | 1.667 to 18.456 | 3.73   | 8.91    |            |
| Hurwitz et al$^{13}$ | 43/393         | 9/397       | 4.826         | 2.385 to 9.766 | 10.86 | 10.91  |            |
| Hurwitz et al$^{14}$ | 20/109         | 3/98        | 5.994         | 1.837 to 19.554 | 3.86   | 8.99    |            |
| Hurwitz et al$^{15}$ | 153/1990       | 29/1737     | 4.701         | 3.177 to 6.955 | 35.16 | 11.88  |            |
| Kindler et al$^{16}$ | 10/277         | 3/263       | 3.165         | 0.881 to 11.373 | 3.30   | 8.59    |            |
| Kindler et al$^{17}$ | 23/55          | 9/55        | 2.622         | 1.354 to 5.193 | 11.95 | 11.03  |            |
| Burger et al$^{18}$ | 24/608         | 43/601      | 0.552         | 0.339 to 0.897 | 22.80 | 11.63  |            |
| Total (fixed effects) | 360/4550   | 106/4249    | 3.225         | 2.606 to 3.990 | 10.781| <0.001 | 100.00     |
| Total (random effects) | 360/4550   | 106/4249    | 3.909         | 1.983 to 7.707 | 3.937 | <0.001 | 100.00     |

Heterogeneity Q=64.6768, degree of freedom=10, p<0.0001, I² (inconsistency) =85.54%.

**Table 5: Relative risk of hypertension at low dose (2.5 mg/kg/cycle) in bevacizumab versus placebo.**

| Study          | Bevacizumab (N) | Placebo (N) | Relative risk | 95% CI   | z      | P value | Weight (%) |
|----------------|-----------------|-------------|---------------|----------|--------|---------|------------|
| Ohtsu et al$^6$ | 24/386          | 2/381       | 11.845        | 2.819 to 49.771 | 2.10   | 9.73    |            |
| Miles et al$^8$  | 2/252           | 3/231       | 0.611         | 0.103 to 3.625 | 1.36   | 7.65    |            |
| Cutsem et al$^{11}$ | 60/296         | 26/287      | 2.238         | 1.455 to 3.442 | 23.33 | 18.08  |            |
| Kabbinavar et al$^{12}$ | 32/100        | 5/104       | 6.656         | 2.702 to 16.399 | 5.32  | 14.05  |            |
| Hurwitz et al$^{13}$ | 88/393         | 33/397      | 2.694         | 1.851 to 3.919 | 30.76 | 18.46  |            |
| Hurwitz et al$^{14}$ | 37/109         | 37/98       | 0.899         | 0.624 to 1.295 | 32.47 | 18.53  |            |
| Reck et al$^{16}$ | 21/330          | 5/327       | 4.162         | 1.588 to 10.905 | 4.66  | 13.50  |            |
| Total (fixed effects) | 264/1866      | 111/1825    | 2.312         | 1.887 to 2.833 | 8.082 | <0.001 | 100.00     |
| Total (random effects) | 264/1866      | 111/1825    | 2.640         | 1.408 to 4.950 | 3.026 | 0.002  | 100.00     |

Heterogeneity Q=40.2178, degree of freedom= 6, p<0.0001, I² (inconsistency) =85.08%.

**Table 6: Relative risk of hypertension at high dose (5 mg/kg/cycle) in bevacizumab versus placebo.**

| Study          | Bevacizumab (N) | Placebo (N) | Relative risk | 95% CI   | z      | P value | Weight (%) |
|----------------|-----------------|-------------|---------------|----------|--------|---------|------------|
| Escudier et al$^7$ | 88/337          | 28/304      | 2.835         | 1.908 to 4.213 | 2.233 | 18.76  |            |
| Aghajanian et al$^8$ | 43/247         | 1/233       | 40.563        | 5.631 to 292.193 | 0.90  | 2.31    |            |
| Zhou et al$^9$   | 7/140           | 1/134       | 6.700         | 0.835 to 53.732 | 0.81  | 2.10    |            |
| Miles et al$^{10}$ | 11/247         | 3/231       | 3.429         | 0.969 to 12.137 | 2.19  | 5.02    |            |
| Hurwitz et al$^{15}$ | 153/1990       | 29/1773     | 4.701         | 3.177 to 6.955 | 22.81 | 18.88  |            |
| Kindler et al$^{16}$ | 10/277         | 3/263       | 3.165         | 0.881 to 11.373 | 2.14  | 4.92    |            |
| Kindler et al$^{17}$ | 23/53          | 9/55        | 2.652         | 1.354 to 5.193 | 7.75  | 12.03  |            |
| Reck et al$^{18}$  | 28/329          | 5/327       | 5.566         | 2.176 to 14.237 | 3.97  | 7.89    |            |
| Robert et al$^{19}$ | 81/817         | 4/413       | 10.237        | 3.777 to 27.740 | 3.52  | 7.24    |            |
| Burger et al$^{20}$ | 139/608        | 43/601      | 3.195         | 2.314 to 4.413 | 33.58 | 20.85  |            |
| Total (fixed effects) | 583/5045       | 126/4334    | 4.134         | 3.426 to 4.988 | 14.817| <0.001 | 100.00     |
| Total (random effects) | 583/5045       | 126/4334    | 4.036         | 2.948 to 5.525 | 8.704 | <0.001 | 100.00     |

Heterogeneity Q=17.1782, degree of freedom= 9, p=0.0462, I² (inconsistency) =47.61%.
There are 7 trials for determining the risk of hypertension at low dose (2.5 mg/kg/cycle) including 3691 patients (1866 in bevacizumab group and 1825 in placebo group). The relative risk of hypertension with the patients treated with bevacizumab and concurrent therapy was 2.640 times more than placebo and concurrent therapy with 1.408 to 4.950 C.I and the p value statistically significant in random effect model.

There are 10 trials for determining the risk of hypertension at high dose (5 mg/kg/cycle) including 9379 patients (5045 in bevacizumab group and 4334 in placebo group). The relative risk of hypertension with the patients treated with bevacizumab and concurrent therapy was 4.036 times more than placebo and concurrent therapy with 2.948 to 5.525 C.I and the p value statistically significant in random effect model.

**DISCUSSION**

Our meta-analysis shows that bevacizumab is associated with a significant increased risk of hypertension in patients who received treatment for metastatic cancers of lung, ovarian, colorectum, pancreatic and kidney which were similar to the results of study of Xiaolei Zhu, Shenhong Wu, William L. Dahut, Chirag R. Parikh. With the increasing use of angiogenesis inhibitors in patients with several metastatic cancers because of the associated survival benefit, it is important that oncologists, internists, and nephrologists monitor and manage these side effects appropriately to ensure that patients receive maximum benefit from bevacizumab therapy.

As expected, hypertension of grade 3 or higher was significantly more common with bevacizumab than without it. Although the risk of hypertension appeared to be cumulative.21,22 The clinical significance of severe hypertension is evident because of associated cardiovascular complications. Indeed, severe hypertension can require hospitalization or discontinuation of bevacizumab in many of patients; complications may include hypertensive encephalopathy, central nervous system hemorrhage, reversible posterior leukoencephalopathy, and congestive heart failure.23 In addition, high-grade hypertension may lead to arterial thromboembolic events, which were significantly increased in cancer patients treated with bevacizumab.24 Therefore, it is particularly important for all health-care providers and patients to recognize the risk, and to monitor and treat hypertension timely and appropriately.

Efforts are ongoing to understand the mechanism of hypertension associated with angiogenesis inhibitors. The binding of VEGF to its corresponding receptors can enhance microvascular permeability, initiate cell division and migration, and impede apoptosis and senescence. Inhibition of VEGF effect may cause decreased endothelial renewal capacity and increased apoptosis. In addition, it interferes with endothelial cell production of vasodilators such as nitrous oxide and prostacyclin, leading to vasoconstriction. Similar effects of VEGF antagonism in kidneys may contribute to the development of hypertension. Appropriate VEGF expression in endothelial cells and podocytes of kidneys maintains a normal glomerular structure and function. Disruption of the VEGF signaling pathway leads to inhibition of nitric oxide synthase, thereby reducing nitric oxide and prostacyclin synthesis. This in turn renders a vasoconstrictive effect and decreased sodium ion renal excretion, resulting in elevated blood pressure. In addition, hypertension may be related to vascular rarefaction, a functional decrease in the number of arterioles and capillaries generating an increase in peripheral vascular resistance.25

In clinical trials, bevacizumab-associated hypertension was managed with oral antihypertensive medications. The choice of antihypertensive therapy for management of this secondary hypertension is still under debate.

**CONCLUSION**

The association of hypertension with new agents presents a challenge for recognition because many RCTs may not be powered to reveal a significant relationship. Our meta-analysis of 15 RCTs has overcome this limitation of individual trials and demonstrated that bevacizumab may be associated with a significantly increased risk of hypertension in patients with a variety of metastatic solid tumors irrespective of dosing.

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