Treatment-Related Mortality With Bevacizumab in Cancer Patients
A Meta-analysis

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A fatal adverse event (FAE) is defined as a death caused in all likelihood by a drug and is a major cause of fatality in the United States. In prospective studies, the reported incidence of FAEs is 0.3%, and adverse drug reactions account for 4.6% of all hospital fatalities. In cancer patients, the overall risk of FAEs may be higher due to serious toxic effects commonly associated with chemotherapy. Therefore, it is important to develop risk reduction strategies.

Vascular endothelial growth factor (VEGF) plays an important role in tumor growth, invasion, and metastasis by promoting tumor angiogenesis. Bevacizumab, a humanized monoclonal antibody that inhibits VEGF activity, was approved in combination with chemotherapy for treating many types of advanced cancer, including colorectal cancer, non–small cell lung cancer (NSCLC), breast cancer, renal cell carcinoma, and glioblastoma multiforme. Because of the important role of VEGF in vascular function and physiological angiogenesis, its inhibition by bevacizumab has been noted to cause serious adverse events, including wound dehiscence, bleeding, thromboembolic events, bowel perforation, and neutropenia. Even though a number of FAEs have been reported in patients treated with bevacizumab, its role in the development of these fatal events has not been definitively established. Data across bevacizumab trials reveal conflicting results regarding its associations with FAEs. Most trials showed...
no significant association between bevacizumab and FAEs, with the exception of 2 trials involving patients with NSCLC or prostate cancer. To better understand the overall risk of FAEs with bevacizumab and its risk factors, we conducted a systematic review and meta-analysis of published randomized controlled trials (RCTs) to determine whether bevacizumab is associated with increased rates of FAEs in cancer patients.

**METHODS**

**Data Sources**

We conducted an independent review of citations from PubMed between January 1, 1966, and October 30, 2010. Key words were bevacizumab, Avastin, and cancer and the search was limited to randomized controlled clinical trials. The search strategy also used text terms such as fatal events, angiogenesis, and vascular endothelial growth factor to identify relevant information. Abstracts and virtual meeting presentations containing the terms bevacizumab or Avastin from the American Society of Clinical Oncology conferences (http://www.asco.org/ASCOv2) between January 2000 and October 30, 2010, were also referenced to identify relevant clinical trials. We also performed independent searches using EMBASE or the Web of Science database between January 1, 1966, and October 30, 2010, to ensure that no clinical trials were overlooked. We examined each publication, and only the most recent or complete report of a clinical trial was incorporated when duplicate publications were found. Efforts were made to contact investigators and the manufacturer of bevacizumab when relevant data were unclear. The updated manufacturer's package insert of bevacizumab was also reviewed to identify pertinent information.

**Study Selection**

The primary goal of our study was to establish the association of bevacizumab with development of FAEs in cancer patients. Thus, only RCTs with a direct comparison between bevacizumab in combination with chemotherapy (or biological therapy) and chemotherapy (or biological therapy) alone were incorporated in the analysis. Phase 1 trials and single-group phase 2 trials were omitted from analysis because of lack of controls. Clinical trials that met the following criteria were included: (1) prospective phase 2 or 3 trials involving cancer patients; (2) random assignment of participants to bevacizumab treatment or control (placebo or best supportive care) in addition to concurrent therapy using a chemotherapeutic or biological agent; and (3) available data regarding events or incidence of FAEs and sample size. The quality of reports of clinical trials was assessed and calculated using the 7-item Jadad scale including randomization, double-blinding, and withdrawals as previously described.

**Data Extraction and Clinical End Point**

The primary end-point FAE definition is based on currently accepted criteria. Fatal adverse events were deaths related to adverse events as reported according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) criteria, version 2 or 3. Overall, these versions are the same in defining FAEs (grade 5), with the only difference being more focus on attribution to specific adverse events in version 3. Version 2 does not have requirements for specifying causes of FAEs. However, many trials had specified causes of FAEs. In CTCAE, version 3, grade 5 events are attributed to a particular adverse event as much as possible; in the rare situation in which death cannot be reported as a specific CTCAE adverse event, grade 5 or “death unrelated to an adverse event—select” or the “other (specify)” option is available. The National Cancer Institute strongly discourages the use of the “other (specify)” category because of the difficulty assessing aggregate data associated with this category. For death unrelated to an adverse event, the guidelines also require that any death that occurs within 30 days of intervention with an investigational therapy be reported and that all late deaths that are possibly attributable to the investigational intervention be reported.

Data extraction was performed for patient characteristics, treatment information, results, and follow-up time from selected trials. Incidences FAEs and sample sizes were extracted from the safety profile for each trial. Independent data extraction was performed by all 3 authors. Any discrepancies among reviewers were resolved by consensus.

**Statistical Analysis**

All statistical analyses were performed using Comprehensive Meta-analysis software, version 2 (Biostat, Englewood, New Jersey). For the calculation of incidence, the number of patients with FAEs and the number of patients receiving bevacizumab were extracted from the selected clinical trials; the proportion of patients with FAEs and 95% confidence interval (CI) were derived for each study. For the calculation of relative risk (RR), patients assigned to bevacizumab in combination with chemotherapy were compared with those assigned to chemotherapy alone in the same trial. For meta-analysis, both a fixed-effects model (weighted with inverse variance) and a random-effects model were considered. For each meta-analysis, the Cochran Q statistic and P score were first calculated to determine heterogeneity among the proportions of the included trials. For P<.10 values of the Cochran Q statistic, the assumption of homogeneity was deemed invalid and a random-effects model was reported. The causes of heterogeneity were also explored in this context. Otherwise, results from the fixed-effects model were reported. A 2-tailed P<.05 was considered statistically significant.

Prespecified subgroup analysis was performed to identify risk factors for FAEs with bevacizumab-based therapy. To explore a dose-effect relationship, bevacizumab therapy was further divided into low-dose (2.5, 5, or 7.5 mg/kg per schedule, equivalent to a weekly dose of...
2.5 mg/kg) and high-dose (10 or 15 mg/kg per schedule, equivalent to a weekly dose of 5 mg/kg). The designation of low dose vs high dose is relatively arbitrary. We previously have shown that the risks of gastrointestinal tract perforation, hypertension, and proteinuria with bevacizumab may be dose-dependent.15-17 Subgroup analyses were also performed according to year the study was performed, tumor type, and chemotherapy regimens. Q statistics were used for comparison of subgroup results.

RESULTS

Search Results
Our literature search yielded 385 potentially relevant clinical studies on bevacizumab, and a total of 16 RCTs were selected for the purpose of analysis (FIGURE 1). These trials include 4 phase 2 and 12 phase 3 studies, and their characteristics are listed in Table 1.

Study Quality
Randomized treatment allocation sequences were generated in all trials. Five trials were double-blinded and placebo-controlled,10,24,29,31,32 4 other trials had placebo controls,18,20,21,23 and the rest had active treatment controls. Fatal adverse events were assessed as the primary endpoint of the study and recorded according to CTCAE criteria, version 2 or 3, in these trials (Table 1). Follow-up time was adequate for each trial. Jadad scores are listed for each trial in Table 1; the mean score was 2.9, with a range between 1 and 4. Therefore, the overall quality of all trials was fair. The association of bevacizumab with FAEs did not vary significantly with Jadad scores ($P = .18$). Relative risks of FAEs were 1.54 (95% CI, 1.0-2.39) and 1.39 (95% CI, 0.95-2.04), respectively, for studies with scores of 3 or lower vs higher than 3.

Table 1. Characteristics of Randomized Controlled Trials Included in the Meta-analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>Trial Phase</th>
<th>No. of Participants</th>
<th>Follow-up, Median (Range), mo</th>
<th>Underlying Malignancy</th>
<th>Concurrent Treatment</th>
<th>Bevacizumab Dose, mg/kg per wk</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurwitz et al,2004</td>
<td>3</td>
<td>813/790</td>
<td>18.0 (NA)</td>
<td>Colorectal cancer</td>
<td>Irinotecan, bolus fluorouracil, and leucovorin</td>
<td>2.5</td>
<td>3</td>
</tr>
<tr>
<td>Kabbinavar et al,2005</td>
<td>2</td>
<td>209/204</td>
<td>14.8 (NA)</td>
<td>Colorectal cancer</td>
<td>Bolus fluorouracil and leucovorin</td>
<td>2.5</td>
<td>2</td>
</tr>
<tr>
<td>Saltz et al,2008</td>
<td>3</td>
<td>1401/1369</td>
<td>27.6 (NA)</td>
<td>Colorectal cancer</td>
<td>Oxaliplatin, fluorouracil, and leucovorin or capcitabine and oxaliplatin</td>
<td>2.5</td>
<td>4</td>
</tr>
<tr>
<td>Kabbinavar et al,2003</td>
<td>2</td>
<td>104/102</td>
<td>17.6 (NA)</td>
<td>Colorectal cancer</td>
<td>Fluorouracil and leucovorin</td>
<td>2.5 or 5</td>
<td>1</td>
</tr>
<tr>
<td>Giantonio et al,2007</td>
<td>3</td>
<td>829/806</td>
<td>28 (NA)</td>
<td>Colorectal cancer</td>
<td>Oxaliplatin, fluorouracil, and leucovorin</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Johnson et al,2004</td>
<td>3</td>
<td>99/98</td>
<td>14.7 (NA)</td>
<td>NSCLC</td>
<td>Paclitaxel and carboplatin</td>
<td>2.5 or 5</td>
<td>5</td>
</tr>
<tr>
<td>Reck et al,2009</td>
<td>3</td>
<td>1043/986</td>
<td>NA</td>
<td>NSCLC</td>
<td>Cisplatin and gemcitabine</td>
<td>2.5 or 5</td>
<td>4</td>
</tr>
<tr>
<td>Herbst et al,2007</td>
<td>2</td>
<td>122/120</td>
<td>15.8 (NA)</td>
<td>NSCLC</td>
<td>Docetaxel or pemetrexed</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Sandler et al,2006</td>
<td>3</td>
<td>878/867</td>
<td>19.0 (NA)</td>
<td>NSCLC</td>
<td>Paclitaxel and carboplatin</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Miles et al,2010</td>
<td>3</td>
<td>736/730</td>
<td>10.2 (0-17.5)</td>
<td>Breast cancer</td>
<td>Docetaxel</td>
<td>2.5 or 5</td>
<td>3</td>
</tr>
<tr>
<td>Miller et al,2005</td>
<td>3</td>
<td>462/444</td>
<td>14.8 (NA)</td>
<td>Breast cancer</td>
<td>Capcitabine</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Miller et al,2007</td>
<td>3</td>
<td>722/711</td>
<td>25.9 (NA)</td>
<td>Breast cancer</td>
<td>Paclitaxel</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Escudier et al,2007</td>
<td>3</td>
<td>649/641</td>
<td>13.3 (0-25.6)</td>
<td>Renal cell carcinoma</td>
<td>Interferon alfa</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Rini et al,2008</td>
<td>3</td>
<td>732/715</td>
<td>NA</td>
<td>Renal cell carcinoma</td>
<td>Interferon alfa</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Van Cutsem et al,2009</td>
<td>3</td>
<td>607/583</td>
<td>6.7 (NA)</td>
<td>Pancreatic cancer</td>
<td>Gemcitabine and erlotinib</td>
<td>2.5</td>
<td>4</td>
</tr>
<tr>
<td>Kelly et al,2010</td>
<td>3</td>
<td>1050/1040</td>
<td>25 (NA)</td>
<td>Prostate cancer</td>
<td>Docetaxel</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: NA, data not available; NSCLC, non–small cell lung cancer.

The number enrolled is the number of patients recruited for the original study; the number analyzed (in this meta-analysis) is the number of patients actually exposed to the study drugs; numbers of patients were combined for analysis when there were 2 bevacizumab groups.

The dose schedule was converted from a milligrams-per-kilogram schedule.

Study quality was assessed on the 7-item Jadad scale, with a score range of 0 to 5.12
Incidence and Relative Risk (RR) of FAEs With Bevacizumab According to Dose, Tumor Type, and Chemotherapy Type

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>No. of Studies</th>
<th>Total No. of Participants</th>
<th>Incidence of FAEs, % (95% CI)</th>
<th>RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bevacizumab</td>
<td>Control</td>
<td>Bevacizumab</td>
<td>Control</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>5</td>
<td>34/1775</td>
<td>29/1406</td>
<td>2.1 (1.5-3.0)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>4</td>
<td>56/1231</td>
<td>18/841</td>
<td>5.3 (3.2-8.6)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>3</td>
<td>12/1079</td>
<td>10/806</td>
<td>0.9 (0.3-3.1)</td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td>2</td>
<td>11/703</td>
<td>11/653</td>
<td>1.8 (1.0-3.2)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1</td>
<td>26/296</td>
<td>16/287</td>
<td>8.8 (6.0-12.6)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>1</td>
<td>23/524</td>
<td>6/526</td>
<td>4.4 (2.9-6.5)</td>
</tr>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 mg/kg per wk</td>
<td>4</td>
<td>54/1483</td>
<td>44/1463</td>
<td>3.7 (1.6-8.3)</td>
</tr>
<tr>
<td>5.0 mg/kg per wk</td>
<td>8</td>
<td>59/2833</td>
<td>24/2521</td>
<td>1.9 (1.1-3.4)</td>
</tr>
<tr>
<td>Chemotherapeutic agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum or taxanes</td>
<td>5</td>
<td>48/1915</td>
<td>11/1639</td>
<td>3.3 (2.5-4.3)</td>
</tr>
<tr>
<td>Nonplatinum or nontaxanes</td>
<td>3</td>
<td>11/918</td>
<td>13/882</td>
<td>1.6 (0.9-2.9)</td>
</tr>
<tr>
<td>Overall</td>
<td>16</td>
<td>162/5606</td>
<td>90/4609</td>
<td>2.9 (2.0-4.2)</td>
</tr>
</tbody>
</table>

**Table 2.** Incidence and Relative Risk (RR) of FAEs With Bevacizumab According to Dose, Tumor Type, and Chemotherapy Type

**Abbreviations:** CI, confidence interval; FAE, fatal adverse event; NSCLC, non–small cell lung cancer.

**a**P = .04 for overall RR; P = .06 for variation in RRs by tumor type; P = .32 for variation in RRs by dose; P = .006 for variation in RRs by chemotherapy type.

**b**Bevacizumab was given at the same dose of 5 mg/kg per week for these trials. The incidences and RRs were calculated from trials included in this meta-analysis as described in the "Methods" section of the text.

Patients
A total of 10,217 patients (bevacizumab, n = 5608; control, n = 4609) from 16 clinical trials were included in the analysis. The baseline Eastern Cooperative Oncology Group status for most of the patients was between 0 and 1. Patients were required to have adequate hepatic, renal, and hematologic functions. The exclusion criteria for these studies included the following conditions: significant cardiovascular disease, peripheral vascular disease, uncontrolled hypertension, serious nonhealing wounds, major surgery within previous 28 days, preexisting bleeding diathesis, brain metastasis, regularly used aspirin (>325 mg/d) or nonsteroidal anti-inflammatory drugs, pregnant or lactating women, and current use of oral or parenteral anticoagulants, with the exception of prophylactic anticoagulants to maintain patency of vascular device access. Underlying malignancies included colorectal cancer (5 studies), NSCLC (4 studies), breast cancer (3 studies), renal cell cancer (2 studies), pancreatic cancer (1 study), and prostate cancer (1 study). In all trials, patients were randomly assigned to either a control or bevacizumab group, with 3 three-group studies, each having 2 bevacizumab treatment groups in which patients received different dose levels or combinations.

Incidence of FAEs
A total of 5608 patients receiving bevacizumab in 16 RCTs were available for analysis. There were 162 total FAEs among these patients. The highest incidence (13.4%; 95% CI, 7.1%-23.8%) was observed in a phase 2 lung cancer trial, and the lowest incidence was observed in a phase 3 breast cancer trial in which no FAEs occurred. Using a random-effects model (heterogeneity test: Q = 74.39; P < .001; I² = 79.84), the summary incidence of FAEs in patients receiving bevacizumab was 2.9% (95% CI, 2.0%-4.2%).

We further explored the causes of the heterogeneity. As shown in Table 2, the incidence of FAEs varied significantly by tumor type (P = .001), suggesting that tumor type or associated treatment may play a major role in the absolute risk of FAEs.

Relative Risk of FAEs
Among the 10,217 patients in the 16 RCTs, the summary RR was 1.33 (95% CI, 1.02-1.73; P = .04; incidence, 2.9% vs 2.2%) for the association of bevacizumab with FAEs using a fixed-effects model (FIGURE 2). These findings suggest a significantly increased risk of FAEs associated with the addition of bevacizumab to chemotherapy or a biological agent. No significant heterogeneity was found among these studies despite clear disparity in tumor type and concurrent chemotherapy (Q = 20.46; P = .71; I² = 26.67).

Patients with squamous cell histology of lung cancer are no longer treated with bevacizumab because of a high risk of pulmonary hemorrhage. After excluding the trial containing squamous cell lung cancer, the RR with bevacizumab remained similar and was 1.43 (95% CI, 1.07-1.91; P = .02). We also explored the relationship between the year studies were performed and the RR of FAEs with bevacizumab. No significant association was found with the year of study performance (P = .32).

Risk of FAEs and Bevacizumab Dose.
From 8 trials (bevacizumab, n = 2833; controls, n = 2521) of bevacizumab at an equivalent of 5.0 mg/kg per week, the high-dose administration was associated with significantly increased risk, with an RR of 1.98 (95% CI, 1.20-3.27; P = .008; incidence, 1.9%...
vs 1.0%). From 4 trials (bevacizumab, n=1483; controls, n=1463) for bevacizumab at 2.5 mg/kg per week, the low-dose administration was not associated with an increased risk of FAEs (RR, 1.22; 95% CI, 0.82-1.81; P=.33; incidence, 3.7% vs 2.8%). Overall, no statistically significant difference was found for rate of FAEs between the high and low doses of bevacizumab (P=.32). The lack of statistical significance between high and low doses may be due to lack of statistical power. Additional future studies may result in significant findings.

Risk of FAEs and Tumor Type. We further determined RRs of FAEs with bevacizumab according to tumor type. The highest RRs were observed in patients with prostate cancer (RR, 3.85; 95% CI, 1.58-9.37; incidence, 3.3% vs 1.0%) and lung cancer (RR, 3.85; 95% CI, 1.58-9.37; incidence, 3.7% vs 1.1%) and the lowest RRs (RR, 0.59; 95% CI, 0.30-1.62; incidence, 0.9% vs 1.3%). Relative risks of FAEs did not vary significantly by tumor type (P=.06). However, the wide variation in RRs may indicate that the association of bevacizumab with FAEs may be different among these tumor types.

Risk of FAEs and Chemotherapy Regimen. To determine whether the type of chemotherapeutic agent may alter the association of bevacizumab with risk of FAE, we performed a subgroup risk analysis stratified according to drug class such as platinum (cisplatin, carboplatin, or oxaliplatin) and taxanes (paclitaxel or docetaxel) vs others (nonplatinum- and nontaxane-based chemotherapies or cytokines including fluorouracil, irinotecan, gemcitabine, erlotinib, and interferon alfa). Relative risks were calculated for a consistent dose of bevacizumab to exclude potential confounding by different doses across the clinical trials. Bevacizumab at 5 mg/kg per week (8 trials) but not at 2.5 mg/kg per week (4 trials) provided an adequate number of trials for subgroup analysis. The RR for bevacizumab with platinum- or taxane-containing regimens was 3.49 (95% CI, 1.82-6.66; P<.001; incidence, 3.3% vs 1.0%) vs 0.83 (95% CI, 0.37-1.85; P=.65; incidence, 1.6% vs 1.6%) for nonplatinum- or nontaxane-based regimens. This difference in risk of FAEs with bevacizumab among these chemotherapeutic classes was statistically significant (P=.006).

Risk of Specific FAEs. Among the total of 162 FAEs with bevacizumab therapy, 67 (41.4%) had specified adverse events attributable to the death, while the rest of the FAEs (n=95 [68.6%]) had unspecified causes. In comparison with chemotherapy alone, bevacizumab was associated with an increased risk of specified FAEs (RR, 1.76; 95% CI, 1.10-2.82; P=.02) but not with risk of unspecified FAEs (RR, 1.09; 95% CI, 0.79-1.51; P=.61). Common specific causes of FAEs included hemorrhage (23.5%), neutropenia (12.2%), gastrointestinal tract perforation (7.1%), pulmonary embolism (5.1%), and cerebrovascular accident (5.1%). Pulmonary (14/23) and gastrointestinal hem-

### Figure 2. Relative Risk (RR) of Fatal Adverse Events Associated With Bevacizumab vs Control

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events/Total No. of Patients</th>
<th>RR (95% CI)</th>
<th>Favors Bevacizumab</th>
<th>Value</th>
</tr>
</thead>
</table>
| Miller et al,27 2005 | 0/215 2/229 | 0.21 (0.01-4.41) | .32 | Control
| Kabbinavar et al,19 2005 | 4/100 7/104 | 0.59 (0.18-1.97) | .39 | Favors Bevacizumab
| Miles et al,25 2010 | 10/499 7/231 | 0.66 (0.26-1.71) | .40 | Control
| Rini et al,30 2008 | 3/366 4/349 | 0.72 (0.16-3.17) | .66 | Favors Bevacizumab
| Hurwitz et al,16 2004 | 10/393 11/397 | 0.92 (0.40-2.14) | .84 | Control
| Escudier et al,29 2007 | 8/337 7/304 | 1.03 (0.38-2.80) | .95 | Favors Bevacizumab
| Kabbinavar,21 2003 | 2/67 1/35 | 1.05 (0.10-11.13) | .97 | Control
| Herbst et al,25 2007 | 4/78 2/42 | 1.08 (0.21-5.64) | .93 | Favors Bevacizumab
| Reck et al,24 2009 | 23/524 6/526 | 1.11 (0.58-2.13) | .76 | Control
| Saltz et al,26 2008 | 14/894 10/875 | 1.38 (0.61-3.04) | .45 | Favors Bevacizumab
| Van Cutsem et al,31 2009 | 26/296 16/287 | 1.58 (0.86-2.87) | .14 | Control
| Miller et al,29 2007 | 2/265 1/346 | 1.90 (0.17-20.81) | .60 | Favors Bevacizumab
| Johnson et al,23 2004 | 8/87 1/32 | 3.82 (0.50-29.26) | .20 | Control
| Giantonio et al,28 2007 | 4/521 0/285 | 4.93 (0.27-91.26) | .28 | Control
| Sandler et al,32 2006 | 15/427 2/440 | 7.73 (1.78-33.59) | .006 | Favors Bevacizumab
| Overall | | | | |
| Fixed-effects model | 162/5608 90/4609 | 1.33 (1.02-1.73) | .04 | Control
| Random-effects model | 162/5608 90/4609 | 1.33 (0.95-1.86) | .09 | Favors Bevacizumab

Overall summary risk of fatal adverse events was calculated using fixed- and random-effects models. For studies with 0 events in a cell, 0.5 was added to the cell frequency before calculation of the relative risk. CI indicates confidence interval.

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Incidence of FAEs, % (95% CI)

Overall 16 162/5608 90/4609 2.9 (2.0-4.2) 2.2 (1.4-3.2) 1.33 (1.02-1.73)
Pulmonary embolism 5 5/1133 4/1111 0.7 (0.3-1.5) 0.6 (0.2-1.4) 1.10 (0.34-3.10)
Gastrointestinal hemorrhage 2 6/733 1/741 0.9 (0.3-2.3) 0.2 (0-1.0) 3.71 (0.58-23.63)
Neutropenia 3 12/1154 3/803 1.1 (0.6-1.9) 0.6 (0.1-2.7) 2.37 (0.61-9.18)
Gastrointestinal tract perforation 5 7/2318 1/2039 0.3 (0.9-1.7) 0.2 (0-1.0) 2.45 (0.63-9.51)
Pulmonary hemorrhage 5 14/1568 0/1145 1.3 (0.4-4.2) 0.3 (0.1-1.2) 3.96 (1.03-15.25)
Hemorrhage 7 23/2403 3/1737 1.3 (0.6-2.9) 0.5 (0.1-1.7) 2.77 (0.63-9.51)
Unspecified 12 95/3878 62/3167 2.6 (1.7-3.8) 2.5 (2.0-3.2) 1.09 (0.73-1.62)

**Table 3. Incidence and Relative Risk (RR) of Specific FAEs With Bevacizumab**

<table>
<thead>
<tr>
<th>FAEs</th>
<th>No. of Studies</th>
<th>Total No. of Participants</th>
<th>Incidence of FAEs, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specified</td>
<td>13</td>
<td>67/4219/3503</td>
<td>2.1 (1.7-2.7)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>12</td>
<td>95/3878/3216</td>
<td>2.6 (1.7-3.8)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>7</td>
<td>23/2403/3173</td>
<td>1.3 (0.6-2.9)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>5</td>
<td>14/1568/0/1145</td>
<td>1.3 (0.4-4.2)</td>
</tr>
<tr>
<td>Gastrointestinal tract perforation</td>
<td>5</td>
<td>7/2318/1/2039</td>
<td>0.3 (0.9-1.7)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>12/1154/3/803</td>
<td>1.1 (0.6-1.9)</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>2</td>
<td>6/733/1/741</td>
<td>0.9 (0.3-2.3)</td>
</tr>
<tr>
<td>Pulmonary hemorrhage</td>
<td>5</td>
<td>5/1133/4/1111</td>
<td>0.7 (0.3-1.5)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>2</td>
<td>5/733/1/741</td>
<td>0.7 (0.3-1.7)</td>
</tr>
<tr>
<td>Overall</td>
<td>16</td>
<td>162/5608/90/4609</td>
<td>2.9 (2.0-4.2)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; FAE, fatal adverse event. The incidences and RRs were calculated from trials included in this meta-analysis as described in the "Methods" section of the text. Other rare causes of bevacizumab-associated FAEs include wound dehiscence, liver failure, lung abscess, chronic obstructive pulmonary disease, aspiration pneumonia, septic shock, and respiratory failure.

We also investigated the prevalence of specific FAEs associated with bevacizumab (Table 3). The highest incidence was hemorrhage (1.3%, 95% CI, 0.6%-2.9%), followed by neutropenia (1.1%; 95% CI, 0.6%-1.9%). Bevacizumab was associated with a higher risk of fatal bleeding (RR, 2.77; 95% CI, 1.07-7.16; P = .04). In addition, bevacizumab was associated with a higher rate of fatal pulmonary hemorrhage in NSCLC (RR, 3.96; 95% CI, 1.03-15.25; P = .045), non–squamous cell NSCLC (RR, 3.86; 95% CI, 0.84-17.69; P = .08), and gastrointestinal bleeding (RR, 3.71; 95% CI, 0.58-23.63; P = .17). We did not find an association of bevacizumab with risk of FAES secondary to neutropenia (RR, 2.37; 95% CI, 0.61-9.18; P = .21), gastrointestinal tract perforation (RR, 2.44; 95% CI, 0.63-9.49; P = .20), pulmonary embolism (RR, 1.10; 95% CI, 0.34-3.61; P = .88), or stroke (RR, 3.60; 95% CI, 0.59-22.02; P = .35).

**COMMENT**

Historically, studies on drug-related fatal events were performed on the basis of retrospective chart reviews. The causal association between a study drug and death was established on the basis of known adverse effects of the drug, concurrent treatment, and the review committee’s consensus. The inherent difficulty in single-group retrospective or prospective studies was to determine the attribution of FAEs to a drug because of comorbidities and polypharmacies. Based on 16 RCTs, our study has demonstrated that the addition of bevacizumab to systematic antineoplastic therapy is associated with a significantly increased risk of FAEs, with an RR of 1.33 (incidence, 2.9% vs 2.2%) in cancer patients. Given that the absolute risk of treatment-related mortality appears low, the use of bevacizumab should be considered in the context of overall survival benefits. Because bevacizumab is increasingly used in cancer patients, it is particularly important for all health care practitioners and patients to understand and recognize the risk of treatment-related mortality.

In this study, a substantial number of bevacizumab-associated FAEs were attributed to specific causes (41.4%). Bevacizumab was associated with an increased rate of specified FAEs. The main specified FAEs associated with bevacizumab were hemorrhage, gastrointestinal tract perforation, and neutropenia. Bevacizumab was associated with an increased risk of fatal hemorrhage and pulmonary hemorrhage. The association of bevacizumab with fatal pulmonary hemorrhage may be related to squamous cell histology because of necrosis and major bronchial localization. In non–squamous cell NSCLC, bevacizumab was associated with a higher risk of fatal pulmonary hemorrhage. Bleeding in lungs is difficult to control and can cause immediate respiratory failure and death. Further studies are needed to identify the risk factors of major hemorrhage.

Other causes of FAEs associated with use of bevacizumab were neutropenia and gastrointestinal tract perforation. However, these associations were not statistically significant. This could be due to a limitation of sample size. Further research is warranted to evaluate the risk and risk factors for bevacizumab-associated fatal neutropenia and gastrointestinal tract perforation. In addition, there were a relatively large number of unspecified causes of FAEs that occurred in association with bevacizumab use. These need to be elucidated in future trials.

We evaluated associations of bevacizumab with FAEs according to tumor type, bevacizumab dose, and chemotherapy agent. The incidence of FAEs varied significantly with different tumor types, reflecting the nature of underlying tumor biology or associated treatment. However, our study showed that the RR of FAEs with bevacizumab did not vary significantly with tumor types (P = .06). However, RRs for associations of bevacizumab with FAEs may differ substantially.
across distinct tumor types (RRs ranging from 0.69 to 3.85). Further studies are needed.

The association of bevacizumab with FAEs was statistically significant among the trials that used higher doses of bevacizumab (5.0 mg/kg per week) but was not statistically significant among the trials that used lower doses of bevacizumab (2.5 mg/kg per week). However, there was no significant difference between the high and low doses of bevacizumab \((P = .32)\). Our results suggest a possible dose dependency for the association of bevacizumab with FAEs, but this is unclear with the sample size in this analysis.

Notably, our study showed that the association of bevacizumab with FAEs varied significantly among patients receiving different classes of chemotherapy agents. This result may reflect an interaction between bevacizumab and certain chemotherapy agents in causing severe toxic effects. Further subgroup analysis showed a higher risk of FAEs due to pulmonary hemorrhage when bevacizumab was combined with platinum or taxanes compared with other regimens (RR, 4.49 vs 2.71). However, this association was not statistically significant \((P = .96)\).

Based on our findings, the following approaches may be considered to reduce the association of bevacizumab with risk of FAEs. Patients treated with bevacizumab should be monitored carefully for bleeding, gastrointestinal tract perforation, and neutropenia. Risk reduction includes selecting appropriate patients for therapy, prophylactic granulocyte colony-stimulating factor, early assessment of toxic effects, and adequate management of serious adverse events. Indeed, prospective monitoring of a phase 3 trial in colorectal cancer suggested that early assessment of adverse events may improve treatment-related mortality.\(^1\)

Our study has several limitations. First, these studies were conducted at various institutions by different investigators internationally and may have potential bias in reported incidences or specification of FAEs. In particular, determining whether late-occurring FAEs are attributable to bevacizumab therapy is associated with some subjectivity and the assessment of investigators. Fatal adverse events were not primary outcome measures in the included studies. The reported incidence of FAEs had significant heterogeneity among the included studies. Nevertheless, we attempted to adjust for the heterogeneity using a random-effects model to calculate the incidence of FAEs. However, the incidence of FAEs for breast cancer or overall may underestimate the actual event rate because studies without FAEs receive disproportionate weight in the weighted average scheme of the meta-analysis. Second, these studies were conducted at major academic institutions among patients with adequate major organ function and may not reflect the general patient population in the community or patients with organ dysfunction. Third, the risk of FAEs observed herein may have been affected by a lack of experience with bevacizumab toxic effects in early studies and may not reflect the risk of current therapy. However, we found that the relative risk of FAEs with bevacizumab was not associated significantly with the year of studies performed \((P = .52)\). Finally, this is a meta-analysis at the study level; therefore, confounding variables at the patient level cannot be assessed properly and incorporated into the analysis.

In summary, this study has demonstrated that the addition of bevacizumab to concurrent antineoplastic therapy is associated with an increased rate of FAEs in cancer patients. The use of taxanes or platinum may increase the risk of FAEs associated with bevacizumab. The increased risk of FAEs associated with bevacizumab may vary with bevacizumab doses or tumor types. Further efforts are needed to reduce FAEs due to hemorrhage, neutropenia, and gastrointestinal perforation in association with bevacizumab therapy. It is important for physicians and patients to recognize the risks as well as the benefits associated with bevacizumab treatment and to monitor closely to identify and treat serious adverse effects.

Author Contributions: Dr Wu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wu.

Acquisition of data: Ranpura, Hapani, Wu.

Analysis and interpretation of data: Ranpura, Hapani, Wu.

Drafting of the manuscript: Ranpura, Wu.

Critical revision of the manuscript for important intellectual content: Ranpura, Hapani, Wu.

Statistical analysis: Ranpura, Hapani, Wu.

Administrative, technical, or material support: Wu.

Study supervision: Wu.

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REFERENCES