Intracranial hemorrhage in patients with cancer treated with bevacizumab: the Memorial Sloan-Kettering experience

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Background: Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor approved for recurrent glioblastoma (GBM), metastatic breast, colorectal and non-small-cell lung cancers (NSCLC). There has been a potentially increased risk of intracranial hemorrhage (ICH) in patients receiving bevacizumab.

Methods: We retrospectively identified patients with ICH who received bevacizumab between 1 January 2001 and 10 January 2009.

Results: We identified 1024 patients with ICH, 4191 patients who received bevacizumab and 12 (0.3%) who met both our criteria. There were eight women and four men with a median age of 66 years. Primary cancers were ovarian (n = 3), NSCLC (n = 3), colon (n = 1), angiosarcoma (n = 1) and GBM (n = 4). Intracranial tumors were present in 9 of the 12 patients; the remaining three (25%) had no evidence of intracranial pathology. Two hundred and fifty-seven patients with these same primary pathologies and brain tumors were treated with bevacizumab; ICH was seen in nine (3.7%), which was comparable to the 3.6% frequency seen in comparable patients not receiving bevacizumab.

Conclusions: ICH with bevacizumab treatment in this population is rare and does not appear to increase its frequency over the baseline rate of ICH in a comparable population. Most bevacizumab-related ICH occurs into central nervous system tumors but spontaneous hemorrhages were seen.

Key words: bevacizumab, intracranial hemorrhage, metastatic brain tumors, primary brain tumors, vascular endothelial growth factor

introduction

Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF) currently approved for several malignancies including recurrent glioblastoma (GBM) in the United States and metastatic colorectal and non-small-cell lung cancers (NSCLCs) in the United States and Europe. Bevacizumab is thought to produce its therapeutic effect by binding to the VEGF molecule, thereby limiting new vessel formation, decreasing vascular permeability and limiting oxygen supply to the growing tumor [1]. In addition to the desired therapeutic effect, patients may also develop hypertension, proteinuria and bleeding, including into the central nervous system (CNS). The systemic cancers for which bevacizumab has been approved commonly metastasize to the CNS, some of which, such as NSCLC, are associated with spontaneous hemorrhage into brain metastases.

Until recently, patients with intracranial metastases have been excluded from bevacizumab trials based upon an early case report of a 29-year-old man with hepatocellular carcinoma (HCC) who experienced a fatal intracranial hemorrhage (ICH) from a previously undiagnosed brain metastasis while in a phase I study of bevacizumab [2]. In addition, an increased risk of ICH was seen in patients with renal cell cancer (RCC) treated with small-molecule antiangiogenic therapies [3]. CNS metastases from some malignancies such as HCC and RCC have a greater propensity to bleed, which may have predisposed to the observed hemorrhages. Patients with HCC may also have a coagulopathy due to impaired liver function contributing to ICH risk. However, the exact risk of ICH in patients with brain metastases receiving bevacizumab is not well known, particularly for the common causes of brain metastases such as lung and breast cancer. The aim of this study was to define incidence and characteristics of ICH in bevacizumab-treated cancer patients and to assess the risk of cerebral hemorrhage in patients with CNS metastases treated with bevacizumab.

methods

We retrospectively identified all patients who were treated with bevacizumab or who developed an ICH at the Memorial Sloan-Kettering Cancer Center (MSKCC) between 1 January 2001 and 1 January 2009. In
developing the cohort of patients who were on bevacizumab and who also developed an ICH, we excluded patients with ICH before initiation of bevacizumab and those who bled after 6 months following the last dose of bevacizumab. In order to ascertain the risk associated with bevacizumab for ICH, a query was carried out in non-bevacizumab-treated patients to estimate the number of ICHs that occurred during the same period in patients with identical histology as the bevacizumab-treated patients; any ICH before the search period was excluded.

We reviewed the medical records of all patients with bevacizumab-associated ICH as well as their available neuroimaging studies. We then sought to ascertain whether the frequency of ICH appeared increased over the rate in comparable patients not receiving bevacizumab. For the same time period, we identified the following patient groups: (i) the total number of patients with each of the tumor histologies found in the cohort with ICH on bevacizumab, (ii) the number of patients who developed ICH with each of the tumor histologies and whether or not they were treated with bevacizumab and (iii) the number of patients who received bevacizumab for each tumor histology and whether or not they developed an ICH. This study was approved by the MSKCC Institutional Review Board.

results

A total of 4191 patients received bevacizumab during the study period, of whom 12 (0.3%) developed an ICH (Table 1). Of the 12 patients who developed ICH while on bevacizumab, there were eight women and four men with a median age of 66 years (Table 2). Four patients had GBM. Of the remaining eight patients, three each had ovarian cancer and NSCLC and one each had colon cancer and angiosarcoma (Figures 1–4). Of these 12 patients, 9 had an intracranial tumor, primary or metastatic. The three patients with ovarian cancer had no known intracranial tumor or other structural abnormality of the brain and had a spontaneous ICH. All hemorrhages occurred in the brain parenchyma; one patient with a GBM developed parenchymal hemorrhages with extension into the ventricular system. At the time of the ICH, 9 of the 12 patients had mildly elevated systolic blood pressure; 3 were normotensive (Table 2).

Seven patients had abnormal coagulation due to (i) therapeutic dose low-molecular weight heparin (LMWH) in four, (ii) thrombocytopenia in two and (iii) both thrombocytopenia and LMWH in one. All patients with thrombocytopenia had a platelet count >40 000/µl (Table 2). All three patients who developed ICHs without apparent brain lesions were on LMWH. None of the 12 patients were taking antiplatelet medications.

Of the nine patients with brain lesions, four had GBM, three had known brain metastases and two had brain metastases that were identified only at the time of ICH. Only three patients received prior brain radiotherapy (Table 2). Seven of the 12 (58%) patients died of their ICH, a median of 21 days from hemorrhage; four died after a median of 12 months following the ICH from extracranial progression of cancer. One patient with ovarian cancer is still alive. No patient had surgical evacuation of their ICH and no patient received medications such as factor VII to reverse hemorrhage. Bevacizumab was discontinued in all patients following the ICH.

Of the 587 patients with a primary or metastatic brain tumor who received bevacizumab during the study period, intratumoral hemorrhage occurred in 9 (1.5%). Of the 13 913 patients with brain tumors from all cancers who were treated at MSKCC during the same time period, 1024 (7.4%) developed ICH. We also examined bevacizumab use in all patients with primary tumors identical to those in our cohort who had an intracranial tumor and developed an ICH (GBM, NSCLC, colon and angiosarcoma). In 2760 patients with similar histologies, there were 106 (3.8%) ICHs (Table 1). Of these 106 IHCs, 100 (3.6%) were ICHs in patients with known brain tumors and 6 were in patients without brain tumors.

In patients from the above histologies and brain tumors who were also treated with bevacizumab (n = 257), there were 9 ICHs with a frequency of 3.5% (Table 3).

In no histological subtype did exposure to bevacizumab increase the risk of ICH except possibly for angiosarcoma (n = 1), but our patient number is too small to be certain of that association (Tables 2 and 4). In two of the patients, the ICHs occurred immediately after the last dose of bevacizumab. The median time between the last dose of bevacizumab and the ICHs was 3.5 weeks (range 1–23 weeks) (Table 2).

discussion

Life-threatening ICH has been a feared complication of bevacizumab. Although several reviews have shown a very low rate of intracranial bleeding even in the presence of CNS metastases [4, 5], and a study of bevacizumab in malignant gliomas reported no ICH [6], these patients are often excluded from clinical trials incorporating bevacizumab.

Our study demonstrates that ICH in cancer patients treated with bevacizumab is rare and the rate does not appear increased over the rate of spontaneous ICH in a comparable population. The majority of bevacizumab-related ICH occurred into

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Table 1. Frequency of primaries, brain metastases, bevacizumab use and ICH in the study period

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Total</th>
<th>BT</th>
<th>Bev</th>
<th>ICH</th>
<th>BT and Bev</th>
<th>ICH and BT</th>
<th>ICH and Bev</th>
<th>ICH, BT and Bev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian cancer</td>
<td>4811</td>
<td>141</td>
<td>301</td>
<td>10</td>
<td>20</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>NSCLC</td>
<td>2914</td>
<td>789</td>
<td>242</td>
<td>29</td>
<td>77</td>
<td>28</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Colon</td>
<td>1091</td>
<td>35</td>
<td>211</td>
<td>1</td>
<td>14</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>275</td>
<td>14</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>GBM</td>
<td>1781</td>
<td>1781</td>
<td>145</td>
<td>61</td>
<td>145</td>
<td>61</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total for above tumors</td>
<td>10 872</td>
<td>2760</td>
<td>900</td>
<td>106</td>
<td>257</td>
<td>100</td>
<td>12</td>
<td>9</td>
</tr>
</tbody>
</table>

Bev, Bevacizumab; BT, primary or metastatic brain tumor; GBM, glioblastoma; ICH, intracranial hemorrhage; NSCLC, non-small-cell lung cancer.
<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Primary BT</th>
<th>ICH location</th>
<th>Last bev to ICH (weeks)</th>
<th>Duration of Bev (months)</th>
<th>Bev dosing</th>
<th>Platelets (K/µl)</th>
<th>HTN BP</th>
<th>Anticoagulation</th>
<th>Survival (days)</th>
<th>Brain XRT before ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>Ovarian</td>
<td>No</td>
<td>Small L parietal and frontal</td>
<td>1</td>
<td>1.5</td>
<td>4 doses (q 2 weeks, 10 mg/kg)</td>
<td>463</td>
<td>Y</td>
<td>138/82</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>Ovarian</td>
<td>No</td>
<td>Pontine</td>
<td>2</td>
<td>5</td>
<td>7 doses (q 3 weeks, 15 mg/kg)</td>
<td>246</td>
<td>N</td>
<td>163/78</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>Sarcoma</td>
<td>Yes</td>
<td>Extensive</td>
<td>9</td>
<td>6</td>
<td>12 doses (q 2 weeks, 5 mg/kg)</td>
<td>43</td>
<td>N</td>
<td>142/80</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>Colon</td>
<td>Yes</td>
<td>Large L frontal</td>
<td>23</td>
<td>14</td>
<td>23 doses (q 2 weeks, 5 mg/kg)</td>
<td>253</td>
<td>N</td>
<td>118/81</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>NSCLC</td>
<td>Yes</td>
<td>Bifrontal</td>
<td>3</td>
<td>12</td>
<td>17 doses (q 3 wks, 15 mg/kg)</td>
<td>212</td>
<td>Y</td>
<td>125/76</td>
<td>N</td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>GBM</td>
<td>Yes</td>
<td>Intraventricular and R temporal</td>
<td>6</td>
<td>5</td>
<td>8 doses (q 2 weeks, 10 mg/kg)</td>
<td>116</td>
<td>N</td>
<td>152/94</td>
<td>N</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>GBM</td>
<td>Yes</td>
<td>Small L frontotemporal</td>
<td>13</td>
<td>1</td>
<td>3 doses (q 2 weeks, 10 mg/kg)</td>
<td>155</td>
<td>Y</td>
<td>151/86</td>
<td>N</td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>NSCLC</td>
<td>Yes</td>
<td>L frontal and R occipital</td>
<td>3</td>
<td>2</td>
<td>3 doses (q 3 weeks, 15 mg/kg)</td>
<td>146</td>
<td>N</td>
<td>140/71</td>
<td>N</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>GBM</td>
<td>Yes</td>
<td>L frontal</td>
<td>3</td>
<td>5</td>
<td>10 doses (q 2 weeks, 10 mg/kg)</td>
<td>489</td>
<td>Y</td>
<td>128/86</td>
<td>N</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>Ovarian</td>
<td>No</td>
<td>Cerebellar vermis</td>
<td>4</td>
<td>7</td>
<td>11 doses (q 3 weeks, 15 mg/kg)</td>
<td>476</td>
<td>N</td>
<td>153/85</td>
<td>≥381 N</td>
</tr>
<tr>
<td>11</td>
<td>81</td>
<td>GBM</td>
<td>Yes</td>
<td>Small L temporal</td>
<td>2</td>
<td>10</td>
<td>20 doses (q 2 weeks, 10 mg/kg)</td>
<td>168</td>
<td>N</td>
<td>179/81</td>
<td>N</td>
</tr>
<tr>
<td>12a</td>
<td>66</td>
<td>NSCLC</td>
<td>Yes</td>
<td>Large R frontal</td>
<td>4</td>
<td>3</td>
<td>5 doses (q 3 weeks, 15 mg/kg)</td>
<td>108*</td>
<td>N</td>
<td>142/81</td>
<td>N</td>
</tr>
</tbody>
</table>

*Fifty six by 1 week before ICH and 108 on the day of the MRI.

Bev, bevacizumab; BT, brain tumor; GBM, glioblastoma; ICH, intracranial hemorrhage; L, left; N, no; NSCLC, non-small-cell lung cancer; R, right; Y, yes; HTN, hypertension; BP, blood pressure; XRT, X-ray therapy.
preexisting primary or metastatic brain tumors. Simultaneous coagulopathy may increase the risk of bevacizumab-related ICH as five of our patients were receiving LMWH at the time of hemorrhage [7, 8]. Three of our patients had a spontaneous hemorrhage without underlying CNS pathology; all three were on therapeutic dose LMWH. Thrombocytopenia is a less common cause of ICH in patients with cancer, but three of our patients had a low platelet count at the time of bleeding; however, in all three, the platelet count exceeded the low levels usually associated with spontaneous bleeding (>40 000/µl).

Besse et al. [5] carried out a retrospective analysis of multiple datasets of patients with systemic cancer treated with bevacizumab and reported a low rate of ICH. The datasets included patients treated with bevacizumab (ICH = 0.9%), those with brain metastases previously treated with radiotherapy (ICH = 0.8%), those with unrecognized brain metastases at entry (ICH = 0.9%) and those who developed brain metastases during the clinical trial (ICH = 3.3%) [5]. The overall rate of ICH associated with bevacizumab administration in our study (1.3% (12/900)) is lower than the 3.3% aggregate rate reported by Besse et al. [5], but our incidence of ICH in bevacizumab-treated patients with primary or metastatic brain tumors [3.5% (9/257)] is comparable. For the primary pathologies in our 12 patients (GBM, angiosarcoma, NSCLC, ovarian and colon cancer), the incidence of ICH was similar in those who did (3.8%) or did not [3.6% (100/2760)] receive bevacizumab. An open-label trial for treatment of nonsquamous NSCLC enrolled patients with treated brain metastases. Of the 106 safety-assessable patients
who received a median of five cycles of bevacizumab (range 1–17 cycles), there were no reported episodes of grade 2 CNS hemorrhage [9].

The half-life of bevacizumab is 20 days [10]. However, there is evidence that the effects of bevacizumab can be measured in platelets for longer periods and concentrations as low as 1 µg/ml can block most of the VEGF stored in the α-granules of platelets [11]. Therefore, potential interruption of coagulation beyond the half-life of bevacizumab is possible and may contribute to some of the later hemorrhages seen in our patients.

The population treated at MSKCC may not reflect the general hospital cancer population, which could affect the rate of ICH we observed. The incidence of bevacizumab-related ICH could be underreported; e.g. catastrophic ICH of an MSKCC patient treated in the community would have been missed by our search.

Another limitation of our retrospective study is that we used search criteria, which would have missed patients who developed small or clinically asymptomatic ICH. However, it is likely that the reporting of such asymptomatic ICHs is similar whether patients received bevacizumab or not. In fact, the reporting of ICH may be higher in patients treated with bevacizumab due to the increased vigilance and perceived danger of ICH while on this drug. Hence, even if all ICHs were not identified in our search, it is unlikely that there was disproportionate underreporting of ICH in patients on bevacizumab.

Although the mechanism of bleeding observed with bevacizumab is not well understood, changes in the vascular endothelium caused by VEGF inhibition, which is required for endothelial renewal, may play a role. This also affects immature blood vessels that require VEGF to survive [12]. VEGF inhibition may therefore decrease the regenerative capacity of the endothelium in response to injury that in turn may increase bleeding risk [13]. Minor bleeding, predominantly from mucocutaneous membranes, is a common side-effect but severe bleeding is far less common, with an incidence of <5% observed in patients with metastatic colon cancer, not higher than the incidence in such patients treated with chemotherapy alone [14–17].

conclusions

ICH in cancer patients treated with bevacizumab was rare in our study and the rate does not appear increased over the ICH rate in a similar population not treated with bevacizumab. Most bevacizumab-related ICH occurred into preexisting primary or metastatic brain tumors, but spontaneous hemorrhages were also seen. Concurrent coagulopathy may increase the risk of bevacizumab-related ICH.

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disclosure
LDeA has served on an advisory board to Genentech. The other authors declare no conflicts of interest.

references