Drug Review: Safety and Efficacy of Bevacizumab for Glioblastoma and Other Brain Tumors

Yoshitaka Narita

Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, Tokyo, Japan

*For reprints and all correspondence: Yoshitaka Narita, Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: yonarita@ncc.go.jp

Received January 21, 2013; accepted March 14, 2013

Glioblastoma is a highly vascular tumor that expresses vascular endothelial growth factor, a key regulator of angiogenesis and tumor blood vessel permeability. Bevacizumab is a monoclonal antibody that inhibits vascular endothelial growth factor and the growth of gliomas. Bevacizumab monotherapy has proven effective for recurrent glioblastoma, and it extended progression-free survival and improved patient quality of life in various clinical trials. Some patients who receive bevacizumab experience improvements in neurological symptoms and steroid dose reductions. Bevacizumab induces a dramatic and rapid radiological response, but non-enhancing lesions are often detected on magnetic resonance imaging without enhancing lesions. Rebound phenomena such as rapid tumor regrowth are occasionally observed after the discontinuation of bevacizumab therapy. Therefore, Response Assessment in Neuro-Oncology criteria were recently devised to evaluate the efficacy and radiological response of bevacizumab treatment. Hypertension and proteinuria are characteristic adverse events associated with bevacizumab therapy. In addition, many fatal adverse events such as intracranial hemorrhage and venous thromboembolism are reported in patients treated with bevacizumab. However, these events are also associated with glioma itself, and careful attention needs to be paid to these events. Bevacizumab is used to treat various diseases including radiation necrosis and recurrent brain tumors such as brain metastases, schwannoma and meningioma, but additional clinical trials are necessary. The efficacy and current problems associated with bevacizumab in the treatment of glioblastoma and other brain tumors are reviewed.

Key words: bevacizumab – glioblastoma – glioma – brain metastases – rebound

INTRODUCTION

Glioblastoma (GBM), the most common malignant brain tumor, is associated with a survival time of 1–2 years. The standard therapy for a newly diagnosed GBM is maximum resection in patients without neurological deficits and radiotherapy (RT) plus the alkylating agent temozolomide (TMZ) (1). GBM is a highly vascular tumor, and an alternative therapeutic approach that inhibits angiogenesis is expected to inhibit the growth of GBM.

Vascular endothelial growth factor (VEGF), a key regulator of angiogenesis, is highly expressed in GBM (2–4). The expression of VEGF correlates with the grade of gliomas (5), and VEGF expression is also observed in meningioma and brain metastases (3). The molecular bases for the upregulation of VEGF gene expression in gliomas are as follows: (i) hypoxia or the hypoxia inducible factor (HIF)-related mechanism, (ii) epidermal growth factor receptor signaling, (iii) upregulation of the Forkhead box M1B (FoxM1B) transcription factor in GBM but not in low-grade glioma, which stimulates VEGF expression independently of HIF and (iv) upregulation of HuR, a member of the Elav family of RNA-binding proteins, in GBM, which suppresses the post-
transcriptional degradation of VEGF mRNA under hypoxia (6). VEGF signaling regulates angiogenesis and tumor blood vessel permeability, which promote endothelial cell proliferation, survival and migration and cerebral edema (6).

Monoclonal antibodies against VEGF have been demonstrated to inhibit the growth of GBM xenografts in an in vivo mouse model (7,8). Bevacizumab (Avastin®), a monoclonal antibody that inhibits the VEGF, is currently approved for metastatic colorectal, non-small-cell lung, breast, ovarian and renal cancers. Based on the results of many clinical trials of bevacizumab for the treatment of GBM, bevacizumab is currently recognized as a second-line chemotherapeutic agent for GBM. The application of bevacizumab for recurrent GBM is also described in the National Comprehensive Cancer Network guideline (9), and it has been approved in more than 41 countries. This article reviews the efficacy and current problems of bevacizumab therapy against GBM and other brain tumors.

RECURRENT GBM

Bevacizumab is a standard therapeutic agent for recurrent GBM or WHO grade III malignant gliomas after treatment with RT plus TMZ, and no other effective therapy is available. Single-agent bevacizumab after the failure of initial treatment with mainly TMZ for malignant gliomas has a reported objective response rate (ORR), progression-free survival (PFS), 6-month PFS rate and overall survival (OS) of 20.9–42.6%, 1.0–4.2 months, 20.9–42.6% and 7.1–12 months, respectively, as calculated from the initiation of bevacizumab treatment (10–14) (Table 1).

Bevacizumab alone or in combination with irinotecan was similarly effective for recurrent GBM in the BRAIN study (11). The PFS times were 4.2 and 5.6 months in the bevacizumab alone (n = 85) and bevacizumab plus irinotecan (n = 87) groups, respectively, and the OS times were 9.2 and 8.7 months, respectively, in the two groups. The 6-month PFS rates for bevacizumab alone and bevacizumab plus irinotecan were 42.6 and 50.3%, respectively, and the ORRs were 28.2 and 37.8%, respectively, for the two treatments. Based on these results, the US Food and Drug Administration (FDA) first granted bevacizumab accelerated approval for the treatment of recurrent GBM in 2009 (15).

The JO22506 study in Japan also revealed that single-agent bevacizumab was effective for recurrent malignant gliomas (n = 31) (14). The PFS and OS were 3.3 and 10.5 months, respectively, for this treatment. Additionally, the 6-month PFS rate, ORR and disease control rate were 33.9, 27.6, and 79.3%, respectively, and these findings were comparable with those of the BRAIN study. Approximately 70% of patients who received corticosteroids before treatment were able to reduce their dose or discontinue corticosteroid therapy after bevacizumab treatment, and >70% of patients displayed a lower tumor volume on magnetic resonance imaging (MRI) 6 weeks after treatment in this study.

Combination therapy of bevacizumab and irinotecan (11,12,16–18), carboplatin (19–21), erlotinib (22), etoposide (23) and dose-intense daily TMZ (24,25) for malignant gliomas was reported, and the treatment results were similar to that of single-agent bevacizumab therapy.

Generally, the 6-month PFS rate and OS of recurrent GBM are 10–20% and 6–9 months, respectively (26–28). Thus, single-agent bevacizumab has become the most promising second-line agent for recurrent GBM in adult. However, there are a few reports about the use of bevacizumab to treat recurrent pediatric high-grade gliomas or brainstem gliomas, and the radiological response rate, response duration and survival of children appeared to be inferior to those of adult cases (29–32).

Marked decreases in enhancing lesions and surrounding cerebral edema have been observed after the initiation of therapy, and patients exhibited improvements in clinical symptoms. Approximately 30–70% of patients who received bevacizumab could reduce their steroid doses (14,33). Steroids have been used to treat patients with brain tumors to control brain edema, and bevacizumab is occasionally considered an ‘expensive super steroid’. Thus, patients treated with bevacizumab display improved quality of life due to improvements in clinical symptoms and reductions of steroid doses, even if for a short time.

Wong et al. performed a meta-analysis of bevacizumab for recurrent GBM in 548 patients from 15 studies and reported that the 6-month PFS rate and OS were 45% and 9.3 months, respectively. The treatment doses of bevacizumab in most clinical trials were 10 mg/kg every 2 weeks, but they reported no difference in the bevacizumab dose response benefit between doses of 5 mg/kg and 10–15 mg/kg (34). The efficacy of superselective intra-arterial cerebral infusion of bevacizumab to increase the local concentration of the drug around the tumor has been reported (35).

MRI FINDINGS AFTER BEVACIZUMAB TREATMENT

Bevacizumab exhibited a dramatic and rapid reducing effect on enhancing lesions on MRI (36,37), and >70% patients

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**Table 1. Efficacy of single-agent bevacizumab for malignant gliomas**

<table>
<thead>
<tr>
<th>Study</th>
<th>ORR (%)</th>
<th>PFS</th>
<th>6-month PFS rate (%)</th>
<th>OS from bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAIN, 2009</td>
<td>28.2</td>
<td>4.2</td>
<td>42.6</td>
<td>9.2</td>
</tr>
<tr>
<td>JO22506, 2012</td>
<td>27.6</td>
<td>3.3</td>
<td>33.9</td>
<td>10.5</td>
</tr>
<tr>
<td>Kreisl, 2009</td>
<td>35</td>
<td>3.7</td>
<td>29</td>
<td>7.1</td>
</tr>
<tr>
<td>Chamberlain, 2010</td>
<td>42</td>
<td>1.0</td>
<td>42</td>
<td>8.5</td>
</tr>
<tr>
<td>Kreisl, 2010</td>
<td>43</td>
<td>2.9</td>
<td>20.9</td>
<td>12</td>
</tr>
</tbody>
</table>

ORR, overall response rate; PFS, progression-free survival; OS, overall survival.
displayed smaller enhancing lesions 6 weeks after the initiation of treatment (14). However, this effect is not caused by the antitumor effect of bevacizumab, but is attributable to the normalization of abnormally permeable tumor vessels or regional cerebral blood volume (38). Non-enhancing lesions on T2 or fluid-attenuated inversion recovery MRI are often detected without enhancing lesions, which are indicative of progressive infiltrative tumors. Iwamoto et al. reported that 46% of patients had larger enhancing lesions at the initial tumor site, 16% had a new enhancing lesion outside the initial site, and 35% had progression of predominantly non-enhancing tumors at the time of bevacizumab discontinuation for recurrent GBM (36).

The Macdonald criteria have been used for response assessment in glioma (39). These criteria are based on the two-dimensional WHO response criteria, and they use the enhancing tumor area on computed tomography (CT) or MRI as the primary measure while considering the use of steroids and changes in the neurologic status. However, these criteria cannot evaluate the enlargement of the non-enhancing area upon bevacizumab treatment or a pseudoresponse, which is often visualized as a transient increase in the enhancing lesion in patients receiving TMZ treatment. Thus, the Response Assessment in Neuro-Oncology Working Group developed new standardized response criteria for clinical trials of brain tumor treatment to evaluate the clinical response to recent treatment including antiangiogenic therapy (40).

REBOUND PHENOMENON AND BEVACIZUMAB CONTINUATION BEYOND PROGRESSION

No effective agent other than TMZ or bevacizumab is available to treat malignant gliomas, and TMZ or bevacizumab therapy, with or without other chemotherapeutic agents, often continues after progressive disease (PD) is observed. Increased doses of TMZ were reported to be beneficial for some patients (41–44). It is unclear whether continued bevacizumab treatment is effective in patients after PD is detected.

Two large observation studies showed that bevacizumab continuation beyond the initial diagnosis of PD improved the OS of patients with metastatic colorectal cancer (45,46). In the BRiTE study, patients with metastatic colorectal cancer receiving first-line bevacizumab with or without chemotherapy received further treatment after the first observation of PD as directed by a physician, and they were observed thereafter. The OS times beyond the first instance of PD for the no post-PD treatment (n = 253), post-PD treatment without bevacizumab (n = 531) and post-PD treatment with bevacizumab (n = 642) groups were 12.6, 19.9 and 31.8 months, respectively. Multivariate analyses demonstrated that the continuation of bevacizumab therapy was strongly and independently associated with improved survival after PD [hazard ratio (HR) = 0.48, P < 0.001] (45). Similar results were obtained in the ARIES study (46).

Reardon et al. analyzed the outcomes of patients who received subsequent therapy after PD to evaluate the efficacy of bevacizumab regimens against recurrent GBM in five studies (47). In the studies, bevacizumab was used in combination with irinotecan, daily TMZ, etoposide, bortezomib and erlotinib. The OS times of patients in the no post-PD treatment (n = 41), post-PD treatment without bevacizumab (n = 44) and post-PD treatment with bevacizumab (n = 55) groups were 1.5, 4.0 and 5.9 months, respectively (HR = 0.64, P = 0.04). The PFS times of patients in the post-PD treatment without bevacizumab (n = 44) and post-PD treatment with bevacizumab (n = 55) groups were 1.6 and 2.8 months, respectively (HR = 0.64, P < 0.0001). They concluded that bevacizumab continuation beyond the initial detection of PD modestly improves OS compared with available non-bevacizumab therapy for recurrent GBM.

Zuniga et al. (48) reported a rebound phenomenon after the discontinuation of bevacizumab in patients with malignant gliomas. Rebound PD was defined as an increase in the largest cross-sectional area of enhancement on MRI of at least 50% compared with that at the time of bevacizumab failure. Among 40 patients who did not respond to bevacizumab therapy, 11 patients (27.5%) displayed rebound PD, and they had poor prognoses with an OS of 6.8 weeks. Of three patients who were restarted on bevacizumab treatment after rebound PD, two exhibited a partial response, and the OS was extended to 21.3 weeks. Clark et al. (49) analyzed the survival of patients who underwent reoperation and reported that patients who received bevacizumab preoperatively had a worse postoperative OS (HR = 3.1, P < 0.001) and PFS than patients who did not receive bevacizumab.

Abrupt discontinuation of bevacizumab after PD may lead to a rebound phenomenon and increased tumor-associated cerebral edema, and therefore, continuation or slow tapering of the bevacizumab dose after PD might be necessary to prevent rebound PD.

NEWLY DIAGNOSED GBM

RT plus TMZ plus bevacizumab was applied for newly diagnosed GBM, and the OS and PFS times were 19.6–23 and 13–13.6 months, respectively (50,51). The efficacy of this combination therapy was superior to that of RT plus TMZ (OS = 14.6 months; PFS = 6.9 months) (1).

A Phase III trial of RT plus TMZ plus placebo vs. RT plus TMZ plus bevacizumab was conducted for 921 patients with newly diagnosed GBMs from 26 countries (52,53). The primary endpoints were PFS and OS, and the final PFS and interim OS results were presented at a Society of Neuro-Oncology meeting at the end of 2012. The PFS times of the placebo (n = 463) and bevacizumab groups (n = 458) were 4.3 and 8.4 months (P < 0.0001, HR = 0.61), respectively, and the addition of bevacizumab to RT plus TMZ significantly extended PFS. The median lengths of time for which patients maintained a Karnofsky performance status
score of $\geq 70$ in the placebo and bevacizumab groups were 6 and 9 months, respectively. The bevacizumab group exhibited a significantly prolonged median duration of stability or improvement from baseline for health-related quality of life (HRQoL) as assessed by the EORTC QLQ-C30 and BN20 scores for global health status, physical functioning, social functioning, motor functioning and communication deficit compared with the placebo group. Considering that bevacizumab in addition to TMZ improves PFS and HRQoL in patients with newly diagnosed GBM, it is possible that RT plus TMZ plus bevacizumab will be a new standard therapy for a newly diagnosed GBM. The final results including OS will be presented in 2013.

**BRAIN METASTASES**

The standard therapy for brain metastases is RT or surgery plus RT depending on the size and number of tumors (54). The role of chemotherapy in the treatment of brain metastases has not been established. Because bevacizumab is believed to induce ICH in patients with brain metastases (55), patients with brain metastases have previously been excluded from clinical trials of bevacizumab. The PASSPORT study of patients with non-small lung cell carcinoma (NSCLC) and nonprogressive brain metastases after RT demonstrated that bevacizumab in addition to chemotherapy agents or erlotinib did not induce $\geq$ grade 2 ICH and that bevacizumab can be safely used in patients with brain metastases (56).

A small series of patients with progressive brain metastases who failed on RT or surgery plus RT and received treatment with bevacizumab with or without chemotherapeutic agents were reported for breast cancer (57,58), NSCLC (59) and colorectal cancer (60). The ORR of the studies was 33–100%, and the PFS and OS of patients with breast cancer and brain metastases were 2.8–9 and 7.8 months, respectively. No $\geq$ grade 2 ICH was reported in these studies. These studies were very small, but they suggest that bevacizumab can be effective in patients who fail to respond to RT. No effective chemotherapy for patients with radiation-naïve brain metastases is available, and further investigation of bevacizumab-based therapies is necessary.

**SCHWANNOMA AND MENINGIOMA**

Surgery is the first choice for WHO grade I benign brain tumors such as schwannomas and meningiomas, and no chemotherapeutic agent is available for these tumors. These benign tumors occasionally recur, and repeated surgery is necessary, resulting in the deterioration of patient health. Recent reports demonstrated that bevacizumab is effective against these tumors. Neurofibromatosis type 2 (NF2) is an autosomal-dominant syndrome characterized by bilateral vestibular schwannomas, meningiomas and gliomas. The effective treatment options include surgery and stereotactic radiosurgery, and these patients often lose hearing activity. Bevacizumab was reported to be effective for schwannomas in NF2 (61–65). Plotkin et al. reviewed 31 cases of vestibular schwannomas in NF2 and reported that the ORR was 55% and that 88% of patients had stable or decreased tumor size after 1 year (63). Ninety percent of patients had stable or improved hearing activity after 1 year of bevacizumab treatment, and hearing was stable or improved in 61% of patients after 3 years.

Most of meningiomas, the most common benign primary brain tumors, are WHO grade I, but some of them are aggressive WHO grade II or III malignant tumors. Some patients with WHO grade I meningioma in the skull base recur at the same tumor site, and repeated surgery or radiotherapy is often performed. The VEGF is highly expressed in meningiomas, and it plays a role in tumor angiogenesis and peritumoral edema (66). Bevacizumab with or without chemotherapeutic agents was reported to control recurrent meningioma (67–70). Lou et al. (68) reviewed 14 cases of grade I–III progressive/recurrent meningioma and reported that 1 patient had a partial response and 11 patients had stable disease, and the PFS was 17.9 months. In their study, bevacizumab was administered as a single agent to 4 patients, and 10 patients received bevacizumab with chemotherapy with etoposide or TMZ.

Bevacizumab is also reported to be effective for hemangiopericytoma and malignant solitary fibrous tumors that often arise in the brain and are highly angiogenic. Park et al. reviewed 14 patients with these tumors including 6 brain tumors who were treated with bevacizumab and TMZ and reported that the ORR and PFS were 79% and 9.7 months, respectively (71).

**RADIATION NECROSIS AND RE-IRRADIATION THERAPY**

Radiation necrosis is the most severe delayed toxicity associated with RT. The standard therapy for radiation necrosis includes steroids, anticoagulation and the removal of necrotic tissues. The pathophysiological mechanism of radiation necrosis is RT-induced endothelial dysfunction with elevated levels of cytokines such as VEGF, resulting in increased capillary permeability of the blood brain barrier, subsequent extracellular edema, loss of the myelin covering of neurons, and finally hypoxia and necrosis (72,73). Thus, the VEGF is a target in the treatment of radiation necrosis, and bevacizumab was demonstrated to be effective for radiation necrosis via restoration of the blood brain barrier (74–80).

A Phase III study of patients with radiation necrosis and progressive neurological symptoms was conducted (81). All patients who received bevacizumab treatment ($n = 7$) at a dose of 7.5 mg/kg every 3 weeks showed a decreased volume of radiation necrotic lesions on FLAIR and T1-weighted gadolinium-enhanced MRI and improved neurological symptoms at 6 weeks after treatment; however,
patients in the placebo group (saline treatment; n = 7) exhibited no improvements. Five (71%) patients in the placebo group experienced worsening of neurological symptoms, and the other two patients showed progression on MRI. Bevacizumab at a dose of 7.5 mg/kg every 3 weeks for 12 weeks can stop the progression of radiation necrosis in most patients for at least 10 months after treatment. Levin et al. concluded that the study provided class I evidence for the efficacy of bevacizumab in the treatment of radiation necrosis secondary to the treatment of head-and-neck cancer and brain tumor.

Approximately 80% of patients with GBM have local recurrence at the original tumor site (82,83), and re-irradiation is a salvage treatment option, although it is limited by the radiation tolerance of surrounding normal brain tissue. Re-irradiation with hypofractionated stereotactic RT (HFSRT) at a dose of 20–36 Gy appears to be effective with acceptable toxicity (84–88). The OS after re-irradiation was reported to range between 3 and 10 months. Because bevacizumab is effective for recurrent high-grade gliomas and reduces the toxicity associated with RT, re-irradiation with HFSRT or radiosurgery combined with bevacizumab has been attempted for recurrent high-grade gliomas (88–90). OS after re-irradiation was reported to be 7.2–18 months in this series, compared with 3.3–12 months in the absence of bevacizumab as per historical data. Re-irradiation with bevacizumab is a promising therapeutic option, but further randomized clinical trials are needed.

**ADVERSE EVENTS**

Major adverse events associated with treatment with bevacizumab alone for recurrent gliomas include hypertension (HT), venous thromboembolism (VTE), proteinuria, and wound-healing complications, and the proportions of these events that were all grades/grade 3 (according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0: NCI-CTCAE) were 12.6–35.7%/4.2–16% (HT), 0–3%/0% (ICH), 3.2–16.0%/2.0–12.6% (VTE), 2.1–41.9%/0–3.2% (proteinuria), and 0–6.0%/0–2.4% (wound-healing complications), respectively (10–14) (Table 2). The rates of various types of hemorrhage including ICH, epistaxis, gingival bleeding, conjunctival hemorrhage and infusion site hemorrhage and the presence of blood urine were reported to range as high as 30% in previous studies (11,14). Arterial thromboembolism was also reported (11), but gastrointestinal perforation is a rare complication in the treatment for gliomas (10–14).

HT, the most common adverse event in patients treated with bevacizumab, is a cause of ICH, cerebral ischemia, and myocardial infarction. A recent meta-analysis revealed that the incidences of all-grade and grade 3–4 HT in patients receiving bevacizumab were 23.6 and 7.9%, respectively, and that the relative risk (RR) of high-grade HT is 5.3 (P < 0.001) (91). The mechanisms of bevacizumab-induced HT are renal thrombotic microangiopathy, glomerular damage, and vascular effects. Bevacizumab decreases the production of nitric oxide in the wall of arterioles, which induces endothelial dysfunction and increases systemic vascular resistance (92). Several reports suggest that very early HT is associated with the tumor response to bevacizumab in patients with colorectal cancer and non-small lung carcinoma (93,94), but Wick et al. reported that there was no prognostic correlation between HT and bevacizumab treatment in patients with GBM (95).

Table 2. Major adverse events of single-agent bevacizumab for malignant gliomas (% All grades/grade 3)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Hypertension</th>
<th>Intracranial hemorrhage</th>
<th>Venous thromboembolic events</th>
<th>Proteinuria</th>
<th>Wound-healing complications</th>
<th>Gastrointestinal perforation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAIN, 2009</td>
<td>85</td>
<td>35.7/8.3</td>
<td>32.3/9.7</td>
<td>3.6/3.6</td>
<td>4.8/0</td>
<td>6.0/2.4</td>
<td>0/0</td>
</tr>
<tr>
<td>JO22506, 2012</td>
<td>31</td>
<td>32.3/9.7</td>
<td>32.0/16.0</td>
<td>3.2/0</td>
<td>41.9/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Kreisl, 2009</td>
<td>48</td>
<td>12.6/6.4</td>
<td>12.6/12.6</td>
<td>12.6/12.6</td>
<td>21.0/0</td>
<td>0/0</td>
<td>2.1/0/2.1</td>
</tr>
<tr>
<td>Kreisl, 2010</td>
<td>31</td>
<td>32.0/16.0</td>
<td>6.4/6.4</td>
<td>32.0/16.0</td>
<td>28.8/3.2</td>
<td>3.2/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Chamberlain, 2010</td>
<td>50</td>
<td>14.0/6.0</td>
<td>8.0/2.0</td>
<td>10.0/2.0</td>
<td>4.0/2.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Proteinuria is a characteristic adverse event of VEGF inhibitors that may lead to renal failure, HT, and cardiovascular complications. One of the mechanisms of proteinuria is the injury of glomerular endothelium due to VEGF inhibition mediated by bevacizumab (96). A recent meta-analysis revealed that the incidence of grade 3–4 proteinuria in patients treated with bevacizumab was 2.2%, and its RR was 4.8 (97). High-dose (5.0 mg·kg⁻¹·week⁻¹) and low-dose (2.5 mg·kg⁻¹·week⁻¹) bevacizumab treatment is associated with increased risk of proteinuria, with RRs of 2.2 and 1.4, respectively (98). Close monitoring of blood pressure, blood pressure examination and urine tests are necessary because patients who require dialysis or who have been diagnosed with persistent nephrotic syndrome even after bevacizumab discontinuation were reported. When grade 3–4 proteinuria is observed, the dose of bevacizumab should be reduced or discontinued.

ICH can be a life-threatening event for patients with malignant brain tumors. ICH occurs primarily via intratumoral bleeding. Vlander reviewed the incidence of ICH in patients with cancer and reported that its incidence is as high as 10% (99). ICH occurs in all cancers, and GBM, oligodendrogial tumors, lung cancer, breast cancer, melanoma, renal cell carcinoma, hepatocellular carcinoma, chorionicarcinoma and thyroid cancer are the common malignancies in which ICH occurs as part of the natural history of the lesion. Since the
occurrence of fatal ICH in a patient in an early phase I study of hepatocellular carcinoma, bevacizumab has been contraindicated in Japan and Europe for use in patients with brain metastases from systemic cancers. Besse et al. analyzed the incidence of ICH in various clinical studies and reported that its incidence was 0.8–3.3 or 1.0% in patients with brain cancer who were treated with bevacizumab or were not treated with bevacizumab, respectively (100). Khasraw et al. (101) also reported that there was no difference in the incidence of ICH between patients with malignant brain tumors including GBM and brain metastases receiving bevacizumab (3.7%) and those not receiving bevacizumab (3.6%). Based on these findings, bevacizumab does not appear to increase the incidence of ICH compared with its natural incidence in gliomas or brain metastases, and bevacizumab is not contraindicated for malignant brain tumors.

Bevacizumab is reported to increase the risk of arterial thromboembolic events including myocardial infarction and angina with an RR of 2.1 (102) or a HR of 2.0 (103). Whether it increases the risk of cerebral stroke is controversial (102). Cerebral stroke is often observed in patients with brain tumors. Kreisler et al. reported that the majority of strokes are caused by surgery or RT and that the median latency from RT to stroke was 3.2 years (104). Fraum et al. reported that ischemic stroke occurred in 1.9 and 1.7% of patients who were treated with and without bevacizumab, respectively (105).

Patients treated with bevacizumab were reported to have a significantly increased risk of VTE with an RR of 1.3 compared with controls, and the risk was not different between patients receiving bevacizumab doses of 2.5 and 5.0 mg·kg⁻¹·week⁻¹ (106). However, GBM and malignant gliomas themselves are risk factors for VTE. The 2-year cumulative incidence of VTE was reported to be 7.5% in patients with malignant gliomas, and 55% of these patients were diagnosed within 2 months after surgery (107). Risk factors for VTE include older age (HR = 2.6), GBM histology (HR = 1.7), and chronic comorbidities (HR = 3.5) (107). Another study showed that the cumulative incidence of VTE was 21% at 3 months and 26% at 12 months after surgery and that residual tumors represented a risk factor (HR = 3.6) (108). Thus, VTE is often observed in patients with malignant glioma; however, and importantly, anticoagulation does not appear to increase the risk of ICH, and therapeutic anticoagulation for patients with malignant brain tumors and arterial or venous thromboembolism should be recommended (99). Treatment with bevacizumab concomitant with anticoagulation for VTE possibly increases the risk of ICH; however, these treatments did not necessarily cause severe hemorrhages with clinical symptoms, and patients treated with bevacizumab should be given low-molecular-weight heparin or warfarin with close monitoring of blood test examination whenever needed (109,110).

Posterior reversible encephalopathy syndrome (PRES) is a syndrome clinically characterized by HT, headache, confusion, visual disturbances and seizures. The causes of PRES are severe HT, eclampsia, cerebrovascular events, immunosuppressive agents and chemotherapeutic agents, and PRES was reported as an adverse effect of bevacizumab in the treatment of systemic cancers (111–113). Most patients who develop PRES during bevacizumab treatment had an increase in blood pressure from baseline, and PRES resolved after prompt withdrawal of bevacizumab and normalized control of blood pressure (113).

VEGF plays an important role in the healing of surgical wounds, and the preoperative and postoperative use of bevacizumab may increase the risk of wound-healing complications. Because the half-life of bevacizumab is approximately 3 weeks (20 days), patients should wait at least 6–8 weeks to have surgery after the cessation of bevacizumab treatment (114). Postoperative initiation of bevacizumab should be delayed by 4 weeks to prevent an increased risk of wound-healing complications. Clark et al. (115) analyzed 209 patients who underwent a second or third craniotomy and showed that patients receiving preoperative bevacizumab therapy developed wound-healing complications more commonly than those not receiving bevacizumab therapy (35 vs. 10.0%, P = 0.004). Patients with an interval of <28 days between the last dose of bevacizumab and surgery tended to have an increased risk of this complication compared with those with an interval of ≥28 days (odds ratio = 6.5, P = 0.07), albeit without significance. In total, 1 of 18 patients (6%) with a median of 43 days (range 22–65 days) between surgery and postoperative bevacizumab initiation had wound-healing complications, a rate that was not significantly different from that for controls not receiving bevacizumab treatment. The authors recommend performing repeated craniotomy more than 28 days after the last administered dose of bevacizumab whenever possible.

CONCLUSIONS

Single-agent bevacizumab is effective for recurrent GBM and improves the quality of life of patients. HT and proteinuria are characteristic adverse events associated with bevacizumab treatment. Many fatal adverse events such as ICH and VTE are reported in patients with gliomas. However, these events are also associated with glioma itself, and these events should receive due attention. Bevacizumab is used to treat various diseases including brain tumors and radiation necrosis, but further clinical trials are necessary.

Conflict of interest statement

None declared.

References

Bevacizumab for brain tumors


