Table 3 Number of patients who experienced adverse events according to CCTAE grade

Toxicity	Grade 2	Grade 3	Total
Anemia	1	0	1
Lymphopenia	3	3	6
Platepenia	2	0	2
Hypoalbuminiemia	1	0	1
Constipation	5	0	5
Total	12	3	15

CCTAE: Common Terminology Criteria for Adverse Events

subjects were patients with second recurrence of glioblastoma in our analysis. This is compatible with previous reports that the PFS-6 and ORR were numerically higher in patients experiencing first relapse compared to those experiencing second relapse.[4,8]

The phase II study to evaluate effect of bevacizumab-alone and bevacizumab-plus-irinotecan for recurrent glioblastoma demonstrated no significant difference of survival endpoints, median OS times were 9.2 months and 8.7 months, respectively. However, our analysis showed that in two patients (Cases 2 and 3) who received more than 8 cycles of ICE, bevacizumab improved their disease progressions refractory to ICE chemotherapy. Many previous reports also have implied that bevacizumab may have potential to affect tumor in combination with another chemotherapeutic agent.[7,18,19] A possible mechanism is that antiangiogenic therapy affects tumor vascular structure and blood perfusion. The study to assess tumor blood perfusion in recurrent glioblastoma treated with cediranib, a pan-VEGF receptor tyrosine kinase inhibitor, demonstrated that tumor blood perfusion increased in 7 of 30 patients. Increase of tumor blood perfusion was associated with longer survival. Antiangiogenic therapy induced-vascular normalization probably changes the efficacy of the combination drugs.[15]

Recently, two phase III studies, AVAglio and RTOG 0825, to evaluate the addition of bevacizumab to standard temozolomide management in patients with newly diagnosed glioblastoma were performed.[2,5] These studies showed that the addition of bevacizumab did not improve OS but did improve PFS. Based on these results, it is a controversial matter whether bevacizumab is combined with the standard temozolomide management as the initial treatment. And there are clinical questions to resolve. First, what is the factor to bring effect of bevacizumab? Bevacizumab-plus-irinotecan also resulted in high ORR and an increased PFS-6 value, but showed no improvement in OS. Some patients with recurrent glioblastoma and well respond to bevacizumab have survived significantly longer than non-responders.[19] In our analysis, salvage effects of additional bevacizumab tend to be prominent in ICE responders. Second, how do we use bevacizumab to be more effective and less harmful, for example, continuation or short-period administration similar to steroid? The retrospective study demonstrated that bevacizumab continuation beyond initial progression was associated with modestly improved outcome compared with non-bevacizumab therapy.[13] Third, no difference was seen in bevacizumab dose-response benefit between 5 mg/kg and 10 mg/kg to 15 mg/kg. The lack of a dose-response effect would require confirmation in a prospectively conducted clinical trial. A model for the potential therapeutic benefits of low-dose antiangiogenic therapy was introduced.[22] Antiangiogenic therapy is perspective tool in association with tumor vascularity and drug delivery.

There is no established standard salvage chemotherapy for recurrent glioblastoma after the failure of standard management with temozolomide. Phase II studies of ICE chemotherapy in patients with recurrent glioblastoma showed clinical benefit with a PFS-6 of 35%.[1] In our hospital, we use dose-reduction regimen of ICE as second-line chemotherapy for first relapsing glioblastoma. A Germany retrospective study, which was reported by Schäfer et al., showed that ICE was not effective in patients with recurrent high-grade glioma if applied at second or third relapse.[14] In our analysis, PFS-6 was 37.5% in patients treated with ICE chemotherapy at the first relapse of glioblastoma. Retrospective studies of chemotherapy containing bevacizumab and carboplatin have also shown favorable effect that PFS-6 rates were 22–50% in recurrent glioblastoma.[3,7,11,12] These suppose that the regimen containing carboplatin has potency to be active in malignant glioma, and that the efficacy of regimen combined with bevacizumab and ICE in patients with first relapse of glioblastoma should be addressed.

In conclusion, we consider that the combination of bevacizumab and ICE is well tolerated and may derive some clinical benefits in recurrent glioblastoma patients, in spite of the limitations of our analysis. Bevacizumab seems to be more active with in patients with first recurrence of glioblastoma compared those with its second recurrence. The dose intensity and schedule of bevacizumab and ICE need be optimized in future studies.

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Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in the article. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members. This manuscript has no COI that should be disclosed.

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

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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).

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

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

ORR; overall response rate, PFS; progression-free survival, OS; overall survival.

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 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

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 ≥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 chemotherapeutic agents or erlotinib did not induce ≥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 ≥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 radiosurgery 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 least at 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), ICH, 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

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

Study	BRAIN, 2009	JO22506, 2012	Kreisl, 2009	Kreisl, 2010	Chamberlain, 2010
Number of patients	85	31	48	31	50
Hypertension	35.7/8.3	32.3/9.7	12.6/4.2	32.0/16.0	14.0/6.0
Intracranial hemorrhage	2.4/0	3.2/0	0/0	0/0	4.0/0
Venous thromboembolic events	3.6/3.6	3.2/3.2	12.6/12.6	6.4/6.4	8.0/2.0
Proteinuria	4.8/0	41.9/0	2.1/0	28.8/3.2	10.0/2.0
Wound-healing complications	6.0/2.4	0/0	0/0	3.2/0	4.0/2.0
Gastrointestinal perforation	0/0	0/0	2.1/2.1	0/0	0/0

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).

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 ($5.0\ mg \cdot kg^{-1} week^{-1}$) and low-dose ($2.5\ mg \cdot kg^{-1} week^{-1}$) 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. Velander 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, oligodendroglial tumors, lung cancer, breast cancer, melanoma, renal cell carcinoma, hepatocellular carcinoma, choriocarcinoma 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. Kreisl 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 $mg \cdot kg^{-1} week^{-1}$ (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.

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特 集 脳腫瘍に対する治療の現状と展望

転移性脳腫瘍の集学的治療

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Multidisciplinary Approach to Management of Patients with Brain Metastases: Yusuke Tabei[*1], Shingo Miyamoto[*2] and Ichiro Suzuki[*1] ([*1]*Dept. of Neurosurgery, and* [*2]*Dept. of Clinical Oncology and Chemotherapy, Japanese Red Cross Medical Center*)

Summary

The incidence of brain metastases has increased over time as a consequence of an increase in the overall survival of patients with various types of cancer and the improved detection by magnetic resonance imaging (MRI). In this study, the guidelines and evidence for the radiotherapeutic, surgical, and chemotherapeutic management of patients newly diagnosed with brain metastases have been reviewed. For patients with good prognosis (expected survival, ≥3 months) and single brain metastases (>3-4 cm) in whom safe complete resection is possible, whole brain radiotherapy (WBRT) and surgery (level 1) should be considered. Another alternative is surgery and radiation boost to the resection cavity (level 3). For single brain metastases (<3-4 cm) that are not resectable, WBRT and radiosurgery, or radiosurgery alone should be considered (level 1). For selected patients with a limited number of multiple brain metastases (all<3-4 cm) and good prognosis (expected survival, ≥3 months), radiosurgery alone, WBRT and radiosurgery, or WBRT alone should be considered (level 1). However, data from recent clinical trials have shown that adjuvant WBRT after radiosurgery or surgery for a limited number of brain metastases reduces intracranial relapses and neurologic deaths but fails to improve the duration of functional independence and overall survival. Many clinical studies have reported the effectiveness of molecular targeted therapies for brain metastases. Gefitinib or erlotinib should be considered for the treatment of asymptomatic patients harboring activating epidermal growth factor receptor (EGFR) mutations. Lapatinib should also be considered for the treatment of patients with brain metastases from human epidermal growth factor receptor (HER)-2-overexpressing metastatic breast cancer. In Japan, the intravenous administration of bevacizumab is currently being used for the treatment of symptomatic radiation necrosis of the brain. Key words: Brain metastases, Radiotherapy, Radiosurgery, Molecular targeted therapy, Corresponding author: Yusuke Tabei, Department of Neurosurgery, Japanese Red Cross Medical Center, 4-1-22 Hiroo, Shibuya-ku, Tokyo 150-8935, Japan

要旨 近年の切除不能進行癌に対する化学療法の進歩，分子標的薬の導入による進行癌患者の予後の改善とMRIをはじめとする画像診断の進歩により，転移性脳腫瘍の発見頻度は増加していると考えられる。本稿では，転移性脳腫瘍に対する放射線治療，手術，化学療法に関するガイドラインとエビデンスを概説する。単発脳転移で3か月以上の予後が想定される場合，3～4 cm以上の場合は手術＋全脳照射（level 1）あるいは摘出腔のブースト照射（level 3）を，3～4 cm未満の場合は定位放射線治療単独あるいは全脳照射＋定位放射線治療を考慮する（level 1）。多発転移に対しては，3か月以上の予後が予想される場合，少数個の転移で3～4 cm未満の場合は，定位放射線治療単独あるいは定位放射線治療＋全脳照射，全脳照射単独のいずれかを考慮する。ただし近年の臨床試験で，手術および定位放射線治療後の全脳照射の追加により頭蓋内制御は改善するものの，生存期間だけでなくPSが低下するまでの期間も差がないことが明らかになった。脳転移に対する分子標的薬の有効性が多く報告されている。無症候性の非小細胞肺癌でEGFR変異陽性の患者に対してはgefitinibまたはerlotinibを，またHER2陽性の乳癌の患者に対してはlapatinibの使用を考慮すべきである。現在，症候性放射線壊死に対するbevacizumab静脈内投与の臨床試験がわが国で進行中である。

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はじめに

厚生労働省「平成23年度人口動態統計」[1]の悪性新生物による死亡者数は約35万7千人で，癌患者の20～40%が脳転移を合併し，その60～75%が症候性となるとの報告[2]から転移性脳腫瘍をもつ患者数は5～10万人と推定され，成人の頭蓋内腫瘍のなかで最も頻度が高い腫瘍となっている。近年の切除不能進行癌に対する化学療法の進歩，分子標的薬の導入による進行癌患者の予後の改善とMRIをはじめとする画像診断の進歩により，発症数，発見頻度は増加していると考えられる。わが国の全国脳腫瘍統計（第12版1984～2000）[3]に登録された13,393例の転移性脳腫瘍の内訳は，肺癌51.9%，乳癌9.3%，直腸癌5.7%，腎/膀胱癌5.3%，胃癌4.8%，大腸4.7%，頭頸部癌3.2%，肝2.1%，子宮癌1.7%，その他11.3%で，肺癌が約半数を占める。1年および5年生存率は，単発47.6%，16.2%，多発で21.9%，4.6%と未だに治療困難な病態に変わりはない。本稿では，転移性脳腫瘍に対する放射線治療，手術，化学療法に関するガイドラインとエビデンスを概説する。

Ⅰ．治療ガイドラインと予後因子

1．転移性脳腫瘍に対する治療ガイドライン

National Comprehensive Cancer Network（NCCN）中枢神経悪性腫瘍ガイドライン2013では，1～3個までの限定的な脳転移に関しては，全身制御が良好あるいはその後の全身化学療法の選択肢がある場合，切除可能な病変については，①腫瘍摘出術＋全脳照射（whole brain radiotherapy: WBRT）あるいは定位放射線治療（stereotactic radiosurgery: SRS），②WBRT＋SRS，③SRS単独のいずれかを選択し，切除不能な病変に対しては，①WBRT±SRSを推奨している[4]。4か所以上の多発脳転移に対しては，WBRTあるいはSRS[5]を推奨している。治療後は3か月おきの1年間のMRIフォローアップを行い，局所再発に対しては摘出術・WBRT・SRSの既往に応じて，摘出術・SRSあるいは分割SRS・WBRT・化学療法を，新規病変に対しては3個までは上記と同様，4個以上はWBRTあるいは化学療法を推奨している。全身疾患の増悪，performance status（PS）の低下を認める場合は，WBRTの既往がなければWBRTあるいは緩和ケアを，WBRTの既往がある場合はBSCあるいは放射線に感受性がある場合はWBRT（再照射）を考慮としている。ASTROガイドライン2012では，表1のとおり単発と多発に分けて，予後予測と治療目的（生存，局所制御，遠隔頭蓋内制御，神経機能保護）に沿って病変のサイズ別の治療指針を示している[6]。

2．転移性脳腫瘍の予後因子と予後予測

転移性脳腫瘍の予後因子に関して，Gasparらは1979～1993年までのRadiation Therapy Oncology Group（RTOG）の臨床試験に登録された1,200症例を検討し，生命予後に寄与する因子を解析しrecursive partitioning analysis（RPA）class 1～3に分類した[7]。最も生命予後良好なRPA class 1は，65歳未満，Karnofsky performance status（KPS）70以上，原発巣が制御されており，脳転移以外の転移病巣が存在しない症例で生存期間中央値は7.1か月であった。最も予後不良なKPS 70未満のRPA class 3は2.3か月で，その中間のRPA class 2は4.2か月であった。RTOG RPA分類は，現在も治療方針を決定する上で重要な指標であるが，癌腫別の予後を予測していない。近年，より有効な全身化学療法が使用されるようになった最近の世代（1985～2007年）のデータも含めて診断ごとの予後因子をスコアリング化したdiagnosis-specific graded prognostic assessment（DS-GPA）分類（表2，文献[8]より改変）が提唱され，ASTROガイドラインでも予後予測の指標として使用されている[8]。

3．転移性脳腫瘍に対する治療法

以下，ガイドラインの根拠となる転移性脳腫瘍に対する治療法を比較した近年の重要なランダム化比較試験（randomized control trial: RCT）を中心に解説する。

1998年Patchellらは，単発脳転移に対して摘出術を行いMRI上全摘が得られた症例に対する術後のWBRTが生存期間に有意差はないものの，脳転移の制御を有意に改善することを報告した[9]。PS 0-2の1～3個の脳転移症例に対して，SRSまたは全摘出術後のWBRT（30 Gy/10 Fr）の有無によるPS 3以上に増悪するまでの期間を比較したEuropean Organisation for Research and Treatment of Cancer（EORTC）22952-26001（登録期間1996～2007年）の結果が2011年に報告された[10]。

術後経過観察と術後WBRTの比較では，手術部位の局所再発率は59%と27%（$p<0.001$），新規病変発生率は42%と23%（$p=0.008$）で，WBRTにより頭蓋内制御が改善し神経学的死亡も減少した。SRSも含むデータだが，生存期間は10.9か月と10.7か月で差はなく，Patchellらの報告と同様の結果となった。しかし，主評価項目であるPS 3以上に増悪するまでの期間が10か月と9.5か月（$p=0.71$，HR=0.96）で差がなかったことから，WBRTは頭蓋内再発と神経学的死亡を減少させるが機能的な自立や生存率の改善は認められず，画像フォローを行えば控えることが可能で，手術後は局所再発リスクを減らすため摘出腔のブースト照射[11,12]を検討すべきと述べている。摘出腔に対するブースト照射（局

表 1 初発脳転移に対する ASTRO ガイドライン 2012（radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline）

(頭蓋外)予後区分[a]	他の要因	治療選択（evidence grade）	Clinical benefit S	LC	WB control	認知機能
単発脳転移　初期治療						
予後良好（予後3か月以上）	全摘可能	脳転移病変が3～4 cm 以下[b]				
		・手術＋全脳照射（level 1）	○	○	○	
		・定位放射線治療＋全脳照射（level 1）	○	○	○	
		・定位放射線治療単独（level 1）		○		○
		・手術＋定位放射線治療/摘出腔へのブースト照射±全脳照射（level 3）[b]		○	○（＋全脳照射）	
		脳転移病変が3～4 cm 以上				
		・手術＋全脳照射（level 1）	○	○	○	
		・手術＋定位放射線治療/摘出腔へのブースト照射±全脳照射（level 3）[b]		○	○（＋全脳照射）	
予後良好（予後3か月以上）	摘出不能	脳転移病変が3～4 cm 以下				
		・定位放射線治療＋全脳照射（level 1）	○	○	○	
		・定位放射線治療単独（level 1）		○		○
		脳転移病変が3～4 cm 以上				
		・全脳照射（level 3），原発不明の場合生検術を考慮	○	○	○	
予後不良（予後3か月未満）		・全脳照射（level 3）		○	○	
		・全脳照射なしの緩和ケア（level 3）				
多発脳転移　初期治療						
予後良好（予後3か月以上）	Mass effect なし	すべての脳転移病変が3～4 cm 以下[b]				
		・定位放射線治療＋全脳照射（level 1）		○	○	
		・定位放射線治療単独（level 1）		○		○
		・全脳照射（level 1）		○	○	
予後良好（予後3か月以上）	Mass effect あり	脳転移病変による神経症状あり[c]				
		・Mass effect のある病変の安全な摘出および術後全脳照射（level 3）[b]		○	○	
		・全脳照射（level 3）	○	○	○	
予後不良（予後3か月未満）		・全脳照射（level 3）		○	○	
		・全脳照射なしの緩和ケア（level 3）				

Level 1: 少なくとも一つの適切にデザインされ，RCT から得られたエビデンス
Level 2-1: ランダム化されていない，よくデザインされた前向き臨床試験から得られたエビデンス
Level 2-2: よくデザインされたコホートまたは患者対照研究（後方視解析）から得られたエビデンス
Level 2-3: 介入の有無を問わず，複数の時系列から得られたエビデンス
Level 3: 臨床経験，記述的研究あるいは専門委員会の報告に基づく権威ある専門家の意見
KPS: Karnofsky performance status，LC: local control，S: survival，WB: whole brain
診断が確定していない（たとえば，原発不明癌あるいは癌の既往から経過が離れており明らかな頭蓋外転位を認めない）場合には手術が薦められる。
[a]: 予後区分は既知の予後因子に基づく（表2を参照）。
[b]: 放射線感受性の病理（たとえば小細胞肺癌，白血病，リンパ腫，胚細胞腫瘍）を除く。RTOG9508 では 6～9% が肺小細胞癌であった[14]。
[c]: 定位放射線治療（あるいは手術）で治療されるべき最良の脳転移の最大数あるいは腫瘍体積は不明。定位放射線治療の使用を検証した無作為比較試験[15]では，4個までの転移の患者が選定されたが，4個以上の脳転移に対する定位放射線治療の使用を記録した後方視解析の報告もある[18,19]。

所照射）について，今のところ全脳照射と局所照射との RCT はないが，国立がん研究センターでの術後局所照射と術後全脳照射の後方視解析では，生存期間（13.9か月，16.7か月），局所再発率（9.4%，12.1%），新規病変発生率（42.2%，33.3%），神経学的死亡（35.6%，36.7%）のいずれも有意差はなかった[13]。Stanford 大学よりサイバーナイフによる術後摘出腔への定位低分割照射の報告があり，1年局所制御率，頭蓋内制御率は 79%，47%，生存期間 15.1 か月で[12]で今後の RCT が期待される。

2004 年に報告された RTOG9508 は，4 cm 以下の 1～3 個の脳転移を対象に WBRT 単独 164 例と WBRT＋SRS 167 例を比較した[14]。単発転移の場合，生存期間は 4.9 か月と 6.5 か月（p=0.039）で有意に WBRT＋SRS が勝っていたが，多発脳転移（2～3 個）の場合は 6.7 か月

表2　DS-GPAスコア基準と生存期間中央値（MST）（文献[8]より改変）

	DS-GPAスコア基準					DS-GPAスコア	MST（月）	患者数（%）
非小細胞肺癌								
予後因子		0	0.5	1.0		0～1.0	3.02	254（14%）
年齢（歳）		>60	50～60	<50		1.5～2.0	5.49	705（38%）
KPS		<70	70～80	90～100		2.5～3.0	9.43	713（40%）
頭蓋外転移		あり	—	なし		3.5～4.0	14.78	161（9%）
脳転移個数		>3	2～3	1		Over all	7.00	1,833（全体）
乳癌								
予後因子	0	0.5	1.0	1.5	2.0	0～1.0	3.35	23（6%）
KPS	≦50	60	70～80	90～100	—	1.5～2.0	7.70	104（26%）
ER/PR/HER2 Subtype	Triple Negative	—	ER/PR+ HER2−	ER/PR− HER2+	Triple Positive	2.5～3.0	15.07	140（35%）
年齢（歳）	≧60	<60	—	—	—	3.5～4.0	25.30	133（33%）
						Over all	13.80	400（全体）
消化器癌								
予後因子	0	0.5	1.0	1.5	2	0～1.0	3.13	76（36%）
KPS	<70	70	80	90	100	1.5～2.0	4.40	65（31%）
						2.5～3.0	6.87	50（24%）
						3.5～4.0	13.54	18（9%）
						Over all	5.36	209（全体）

と5.8か月で有意差はなかった。ただし，6か月後のKPSとステロイドの減量はWBRT+SRSが勝っていた。

日本放射線腫瘍学研究グループ（Japanese Radiation Oncology Study Group: JROSG）は，JROSG 99-1として1999～2003年に1～4個までの脳転移病変のすべてが3 cm以下，KPS 70以上の症例を対象にSRS単独61例とWBRT+SRS 59例とのRCTを行った[15]。その結果，生存期間は8.0か月と7.5か月で有意差はなく（p=0.42），神経学的死亡，1年後にKPS 70以上である割合，1年以上生存した症例でのMini-Mental State Examination（MMSE）にも有意差がなかった。頭蓋内制御は76.4%と46.8%（p<0.001）で有意にSRS単独が劣り，追加治療を要した症例も多かった。この結果よりSRS単独でWBRTを行わなければ有意に頭蓋内再発率は上がり追加治療の必要性は高くなるが，定期的なフォローを行うならSRS単独も治療選択の一つとしている。本試験では，MMSEが低下するまでの期間が，WBRT+SRSが16.5か月に対して，SRS単独が7.6か月と優位に早く（p=0.05），脳転移の再発が認知機能に影響していると推測している[16]。単施設ではあるが3 cm以下1～3個の脳転移に対してSRS単独30例とSRS+WBRT 28例で高次機能を比較したRCTは，4か月後の学習および記憶機能（Hopkins Verbal Learning Test-Revised: HVLT-R）の低下率が29%と52%でSRS+WBRTのリスクが高すぎるとして早期中止され，SRS単独と緊密な経過観察を推奨している[17]。EORTC22952-26001のSRSに関しては，1個の病変では最大径が35 mmまで，2～3個の病変では最大径25 mmまでの199例を対象にSRS後経過観察100例とSRS+WBRT 99例を比較した。2年後の局所再発率は経過観察31%に対してSRS+WBRT 19%（p=0.040），2年後の新規病変発生率は48%が33%（p=0.023）へとWBRTの追加により有意に減少した。ただし，先述のとおり主評価項目であるPS 3以上に増悪するまでの期間も生存期間も差がなかった[10]。

予後良好な4，5個以上の多発脳転移に対してはWBRTが標準治療で，今のところSRS単独について推奨し得る十分なエビデンスは存在しない。しかしながら，わが国ではガンマナイフ，サイバーナイフなどのSRS機器の普及により多発病変に対してもSRSが行われる傾向がある[5]。Pittsburgh大学からの報告でも，4個以上の病変に対するSRS（46%はWBRT+SRS）の結果，生存期間8か月，1年局所制御71%，頭蓋内無再発期間9か月，RPA分類Ⅰ，Ⅱ，Ⅲ別の生存期間は，18か月，9か月，3か月であった[18]。多変量解析では，総腫瘍体積，RPA分類および辺縁線量が有意な予後因子で，転移個数は差がなかった。Serizawaらは，1,030例，10,163か所のガンマナイフ治療症例を後方視解析し[19]，1年頭蓋内再発率は1～4個の転移病変で42.8%，5～10個で65.8%，10個以上で67.1%と5個以上の転移病変で有意に再発率が高く，多変量解析でも5個以上の病変が予後不良因子であることを報告している。現在10個以下，3 cm未満の転移性脳腫瘍に対するガンマナイフ単独での前向き試験（JLGK0901）が進行中で，結果が待たれる[20]。

Ⅱ．転移性脳腫瘍に対する化学療法

転移性脳腫瘍に対する化学療法は，明らかな有効性を示すデータは得られていない。2012年版肺癌診療ガイドラインでは，脳転移の項で症候性の脳転移を有する場合は，全身療法としての化学療法の適応ではあるが，化学療法の脳転移に対する奏効率は20～40%と低く，症状の緩解が高率(70～90%)に得られる放射線治療を推奨している[21]。無症候性脳転移を有する非小細胞肺癌に関しては，プラチナ製剤を含む化学療法と放射線治療併用とのRCTがある[22]。頭蓋内奏効率（27%と33%，p=0.12），6か月生存率（46%と40%），生存期間（24週と21週，p=0.21）で差はなく，放射線治療のタイミングは先行（early）でも，無効あるいは増悪時（delay）でも生存に影響しなかったことから化学療法先行も考慮の余地がある。また近年，葉酸代謝拮抗薬pemetrexedが脳転移に対し有効な報告がある[23,24]。Ortuzarらの報告でも進行非小細胞肺癌の初回再発部位として脳転移の発生頻度がpemetrexedを含む治療群で有意に低く(3.2% vs 6.6%)，脳転移のリスクを減少できる可能性が期待されている[25]。

Ⅲ．転移性脳腫瘍に対する分子標的薬

上皮成長因子受容体（epidermal growth factor receptor: EGFR）のチロシンキナーゼ阻害剤（thyrosin kinase inhibitor: TKI）であるgefitinib（イレッサ®），erlotinib（タルセバ®）について，わが国の後方視解析では，gefitinibの脳転移に対する効果は42～60%に認められる[26-28]。中国のWuらは，肺腺癌の脳転移40例にgefitinibの前向き試験を行い，奏効率32%，病勢制御率72%，無増悪生存期間9か月，生存期間15か月と報告している[29]。最近，4 cm以下，1～3個の脳転移を有する非小細胞肺癌126例に対してWBRT+SRSにTMZあるいはerlotinibの上乗せ効果を検証するRCT（RTOG 0320）の結果が報告された[30]。WBRT+SRSと，WBRT+SRS+TMZ，WBRT+SRS+erlotinibの生存期間は13.4か月，6.3か月，6.1か月と，薬物治療併用での有害事象の増加により成績が低下した可能性が示唆された。他方，EGFR遺伝子変異陽性例ではWBRTとerlotinibの併用で生存期間19.1か月との報告もあり[31]，EGFR遺伝子変異陽性例で無症候性脳転移を有する場合に一次治療でEGFR-TKIを使用するべきか，放射線治療を先行あるいは併用するべきか結論はでていない。

乳癌に対するtrastuzumabをはじめとする化学療法の進歩により進行乳癌の予後は改善したが，HER2陽性進行乳癌でtrastuzumab治療を受けた患者の25～34%に脳転移を発症し，治療開始から脳転移の診断までの期間は4～24か月といわれる[32]。HER1とHER2の双方を阻害するTKIで，trastuzumabより低分子量のlapatinibは血液脳関門を通過すると考えられており，脳転移に対する効果が期待されている。脳転移を有するtrastuzumab治療後のHER2陽性進行乳癌に対する第Ⅱ相試験で，lapatinib単剤による無増悪生存期間2.7か月，全生存期間は9.6か月であった。また20%以上の脳転移の縮小はlapatinib単剤21%，lapatinib+capecitabineで40%の症例に認められた[33]。最近報告されたlapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer（LANDSCAPE）の結果では，65.9%に50%以上の脳転移の縮小が認められ，無増悪生存期間は5.5か月，評価可能な症例での生存期間は17.0か月と良好な成績を認めた[34]。

Ⅳ．症候性脳放射線壊死に対するbevacizumab療法

わが国ではbevacizumabは，大腸癌，肺癌，乳癌に対して適応があり，2013年6月より悪性神経膠腫にも適応拡大となった。当初は転移性脳腫瘍がある症例では，重篤な脳出血を認めた症例があったことから禁忌とされていたが，その後の報告で脳出血の発症頻度に有意差はないことが報告され，現在は慎重投与に変わっている[35,36]。近年，SRS後などの症候性脳放射線壊死に対して有効な報告がある[37]。宮武により2010年4月から，高度医療による多施設臨床試験「症候性脳放射線壊死に対する核医学的診断とベバシズマブの静脈内投与」が行われている[38]。転移性脳腫瘍を原疾患とした症候性脳放射線壊死をも対象とした世界初の臨床試験であり，有効性が証明されれば公知申請により薬事承認の可能性がある。

おわりに

全身化学療法の進歩により転移性脳腫瘍症例は増加傾向にあると予想される。脳転移に対する治療もかつてのWBRT単独から，手術，SRS，WBRT，さらには分子標的薬をはじめとする化学療法による臨床試験のエビデンスが蓄積され治療の選択肢が広がりつつある。これらのエビデンスと個々の患者背景，全身状態や神経所見，全身予後などに基づいて腫瘍内科医，放射線治療医，脳神経外科医が協調し最適な治療方針を決定することが重要であると考える。

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