Systemic Management of Central Nervous System Tumors

Highlights of a Clinical Investigator Think Tank

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Systemic Management of Central Nervous System Tumors
A Continuing Medical Education Program

Overview of Activity
The incidence of central nervous system tumors has been increasing during the past 25 years, especially among the elderly. Astrocytic tumors account for more than 50 percent of primary brain cancer cases and include the most frequently diagnosed gliomas in North America: the WHO Grade III anaplastic astrocytoma and the WHO Grade IV glioblastoma multiforme (GBM). In addition, approximately 20 to 40 percent of patients with other forms of cancer may develop central nervous system (CNS) complications: intracranial metastasis, leptomeningeal involvement and spinal cord compression. Primary and metastatic brain cancer comprise a heterogeneous group of diseases with diverse treatment approaches and outcomes.

Current management of CNS cancer involves an interdisciplinary approach, integrating the knowledge and expertise of neurosurgeons, radiation oncologists, neurologists and medical oncologists. To bridge the gap between research and patient care, this program features a roundtable discussion with leading investigators to assist clinicians in formulating up-to-date clinical management strategies for patients with CNS cancer.

Learning Objectives
• Use biomarkers to identify patients with high-grade gliomas who may be more likely to experience response or resistance to alkylating agents.
• Explain the concept of pseudoprogression, and identify strategies to distinguish between true disease progression and pseudoprogression in patients with previously treated brain tumors.
• Apply emerging research results to develop evidence-based clinical management strategies for newly diagnosed or recurrent high-grade gliomas.
• Recall the rationale for use and the clinical outcomes associated with integrin- or VEGF-targeted therapies for GBM.
• Counsel patients with CNS metastases about the risks and benefits associated with available local and systemic treatment modalities.
• Incorporate best-practice supportive care measures into the management of high-grade gliomas.
• Enroll or refer eligible patients with high-grade gliomas for participation in ongoing clinical trials.

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PROGNOSTIC AND PREDICTIVE ROLE OF MGMT

DR LOVE: Tracy, would you review the clinical relevance of O\(^6\)-methylguanine-DNA methyltransferase (MGMT) methylation status in patients with gliomas?

DR BATCHELOR: The MGMT gene produces a protein that mediates resistance to alkylating drugs. If the gene is active and the protein is present, it mediates resistance to temozolomide and, potentially, other alkylators. The first paper about this demonstrated that patients with an inactivated or methylated MGMT promoter had much better outcomes and responses to carmustine (Esteller 2000). This was then validated in a large, randomized Phase III trial with temozolomide (Hegi 2005; [1.1]).

Clinical investigators routinely use MGMT status of patients who undergo resections. I have introduced the topic into the discussion with patients because it has some prognostic implications. If MGMT is inactivated, then patients have a better prognosis. They have a median overall survival of almost two years compared to about one year if it isn’t inactivated (Stupp 2009).

### Table 1.1

<table>
<thead>
<tr>
<th></th>
<th>Temozolomide + radiation therapy</th>
<th>Radiation therapy alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Median progression-free survival</td>
<td>10.3 months</td>
<td>5.9 months</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>21.7 months</td>
<td>15.3 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Temozolomide + radiation therapy</th>
<th>Radiation therapy alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>60</td>
<td>54</td>
</tr>
<tr>
<td>Median progression-free survival</td>
<td>5.3 months</td>
<td>4.4 months</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>12.7 months</td>
<td>11.8 months</td>
</tr>
</tbody>
</table>

“Our data suggest that the methylation status of the MGMT promoter may have prognostic value and, in addition, may be a clinically relevant predictor of benefit from temozolomide chemotherapy. Despite the survival benefit associated with temozolomide among patients with a methylated MGMT promoter, the overall survival curves for temozolomide and radiotherapy and for radiotherapy alone remain similar for the first nine months of follow-up. This suggests that MGMT methylation, though important, is not the sole factor determining outcome.”

DR LOVE: Patrick, would you discuss pseudoprogression in patients with glioblastoma?

DR WEN: Four weeks after radiation therapy and temozolomide, in approximately 40 to 50 percent of the cases, lesions may appear worse on MRI, and a key clinical issue is whether this is true tumor progression or pseudoprogression due to radiation therapy. Probably 50 percent of the time it is real tumor progression and 50 percent of the time it is pseudoprogression (Brandsma 2008; [1.2]).

MGMT status may be helpful in differentiating between the two. A study has suggested that in pseudoprogression, the patient is much more likely to have a methylated MGMT promoter, and in real tumor progression, the patient will likely have an unmethylated MGMT promoter (Brandes 2008). So to some extent MGMT methylation status helps you decide whether it’s real tumor progression or pseudoprogression.

DR LOVE: What’s the pathophysiology behind pseudoprogression?

DR WEN: It may be that radiation therapy makes the blood vessels more leaky. So when a contrasting agent is administered, enhancement is increased for a period of time. It is maximal in the first three months but can persist for six months or more.

DR LOVE: Any other clinical clues that can help in distinguishing between the two?

DR WEN: Usually, if it’s pseudoprogression, patients generally fare better and are not as symptomatic. However, that’s not a perfect way to differentiate.

1.2 Pseudoprogression in Glioblastoma

“Since the introduction of chemoradiotherapy with temozolomide as the new standard of care for patients with glioblastoma, there has been an increasing awareness of progressive and enhancing lesions on MRI, noted immediately after the end of treatment, which are not related to tumour progression, but which are a treatment effect. This so-called pseudoprogression can occur in up to 20% of patients who have been treated with temozolomide chemoradiotherapy, and can explain about half of all cases of increasing lesions after the end of this treatment.”


USE OF CARMUSTINE (GLIADEL®) WAFER

DR LOVE: Jon, would you discuss the implantable carmustine or Gliadel wafer?

DR WEINGART: For the implantable carmustine wafer to potentially affect the natural history of a patient’s disease, using it up front makes the most sense. As with any treatment, the best opportunity to have an effect on the disease is probably at initial therapy.

I don’t believe these are used as much as they could be. Potentially only a small proportion of those patients
who are eligible to have them implanted — based on their anatomy and what can be achieved at surgery — actually do. A patient eligible for an implantable carmustine wafer must have a tumor that the surgeon, before surgery, believes can be grossly resected.

Another consideration, to use a simple analogy, is that the resection cavity should be more like an “ice cream scoop” rather than a vase, where you have a tiny channel to a large cavity. If the wafer is placed and the cavity collapses, then often you will observe a significant tissue reaction as the drug is released, similar to pseudoprogression with brain edema. It’s best when the cavity is close to the surface and a complete resection can be performed.

**SELECT PUBLICATIONS**


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**EMERGING DATA ON BEVACIZUMAB FOR GBM**

**DR LOVE:** Would you review the clinical trials that have been conducted with bevacizumab for patients with high-grade gliomas?

**DR PEEREBOOM:** The first trials included patients with recurrent high-grade gliomas. After the initial report with bevacizumab and irinotecan (Stark-Vance 2005), reports by Dr Vredenburgh documented response rates up to 60 percent and 40 to 50 percent six-month progression-free survival (Vredenburgh 2007a, 2007b). This was certainly impressive, given that our historical response rates were typically 10 percent or less.

This led to a number of other trials, including a Phase II randomized trial comparing single-agent bevacizumab to bevacizumab with irinotecan. Those data demonstrated a little better response rate and progression-free survival with the combination, but no overall survival benefit was observed (Friedman 2009; [2.1]).

**DR LOVE:** Which off-protocol options would you recommend for a patient with a recurrent high-grade glioma?

**DR VREDENBURGH:** I believe chemotherapy and bevacizumab would be the treatment of choice.
DR LOVE: Which chemotherapy?

DR VREDENBURGH: Either etoposide or irinotecan.

DR LOVE: What about bevacizumab without chemotherapy?

DR VREDENBURGH: I believe that’s a reasonable option. Our community has been somewhat misled by the trial demonstrating that chemotherapy with bevacizumab had a higher response rate and median progression-free survival but equivalent overall survival compared to bevacizumab alone (Friedman 2009; [2.1]).

The reason this occurred was that the patients who were receiving bevacizumab alone continued on bevacizumab and had chemotherapy added when their disease progressed. So I believe the lesson from that trial is to continue bevacizumab. Chemotherapy appears to add some value to bevacizumab compared to bevacizumab alone.

DR LOVE: Tracy, if you use bevacizumab for recurrent disease outside of a protocol setting, will you generally use it with irinotecan or will you use it alone at times?

DR BATCHELOR: We use both approaches. For older, fragile patients, often we use bevacizumab alone.

DR MIKKELSEN: Our approach is to use the combination of bevacizumab with irinotecan. Our perception is that we see better long-term responses in the patients we treat with the combination. A number of other strategies are used besides removing irinotecan completely from the regimen. In the setting of asthenia, one strategy is to alter the interval of treatment. Rather than administering it every two weeks, we do it every four weeks. This strategy can maintain some patients with good sustained responses.

DR LOVE: What other data sets do we have with bevacizumab?

| Phase II Randomized Trial of Bevacizumab (BV) with or without Irinotecan for Recurrent Glioblastoma |
|---------------------------------------------------------------|---------------------------|
| Bevacizumab alone (n = 85)                                      | Bevacizumab + irinotecan (n = 82) |
| Objective response rate                                        | 28.2%                     | 37.8%                     |
| Six-month PFS rate                                             | 42.6%                     | 50.3%                     |
| Median PFS                                                     | 4.2 months                | 5.6 months                |
| Median OS                                                      | 9.2 months                | 8.7 months                |

PFS = progression-free survival; OS = overall survival

“The results demonstrated notable antitumor activity of single-agent BV and BV in combination with CPT-11 [irinotecan] in pretreated patients with glioblastoma in first or second relapse. The majority of patients experienced tumor shrinkage during the treatment period, and ORs [objective responses] were durable.”

Given the promising data for patients with recurrent disease (Vredenburgh 2007a, 2007b), several studies have reported early data with bevacizumab in the up-front setting (Lai 2008; Narayana 2008). A number of ongoing studies have added bevacizumab to the standard backbone of radiation therapy/temozolomide.

One trial, reported by Dr Vredenburgh, has produced interesting early data and proved that the combination is feasible. The group at Duke has extended that to a study evaluating radiation therapy with temozolomide/bevacizumab followed by temozolomide with both bevacizumab and irinotecan after chemoradiation therapy (Vredenburgh 2009; Kirkpatrick 2008). That trial has shown that the combination is feasible. No obvious unexpected toxicities occurred with the combination of these drugs.

Among the concerns that have arisen regarding the use of bevacizumab in this setting is wound healing. These patients have undergone surgery, may be receiving steroids and have received radiation therapy. If this combination is used in the up-front setting — and I don’t believe it should be used off study — it will be important for community-based physicians to visually verify that the wounds are intact. Even then, late wound dehiscence can occur, which is an important factor to consider.

Jon, we hear about waiting six weeks between surgery and administering bevacizumab in other cancer types. Is that how you approach it?

Yes, at least six weeks.

What about bowel perforations and intracranial bleeding?

Bowel perforations occur occasionally, less than five percent of the time. Intracranial hemorrhages also occur a small percent of the time. Frequently, we see petechial hemorrhages that are visible on MRI but are not symptomatic. A small subgroup of patients with intracranial hemorrhages actually have symptoms.

Bleeding can occur without treatment, so do you have any sense of how much of the bleeding is related to bevacizumab?

It appears that the incidence is similar with or without bevacizumab. So I believe that this toxicity, observed in multiple clinical trials, would not be considered a deal breaker in terms of offering bevacizumab to these patients.

What has been observed with bevacizumab in terms of proteinuria and hypertension?

We monitor the patient’s blood pressure. Hypertension is often the major side effect and requires some intervention. Proteinuria has been reported, but, frankly, we don’t routinely check for it. We have not seen any patients who have experienced nephrotic syndrome. It occurs, but it’s much less of a day-to-day consideration.

Jim, can you discuss the Phase III clinical trials evaluating bevacizumab for patients with newly diagnosed GBM?
DR VREDENBURGH: Two large Phase III trials recently started, and I believe they are the most important trials in our field. Both of them are randomized, placebo-controlled trials with more than 500 patients. RTOG-0825 is using a gene profile and MGMT status to stratify for risk groups.

In RTOG-0825 (2.2), patients are enrolled within three to five weeks of a partial or complete resection. They receive radiation therapy and concurrent temozolomide. Four weeks after the completion of chemoradiation therapy, they continue temozolomide for a year. Beginning in week four of chemoradiation therapy, either bevacizumab or placebo is administered and is continued with the reintroduction of temozolomide.

DR LOVE: How long is the bevacizumab continued?

DR VREDENBURGH: In RTOG-0825, temozolomide and either bevacizumab or placebo are continued for 12 months after radiation therapy.

DR LOVE: Can you review the other study?

DR VREDENBURGH: It’s also a placebo-controlled study. Those patients will begin bevacizumab earlier, ideally at the time radiation therapy is initiated. They will receive

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### RTOG-0825: Phase III Randomized Trial of Concurrent Chemoradiation Therapy and Adjuvant Temozolomide with or without Bevacizumab for Newly Diagnosed Glioblastoma or Gliosarcoma

**Protocol ID:** RTOG-0825; **Target Accrual:** 720 (Open)

*Initial 3wk of chemoradiation treatment + temozolomide qd x 21d*

*Final 3wk of chemoradiation therapy:*
- Radiation therapy + temozolomide + [placebo q2wk (continues without stop)]

*Final 3wk of chemoradiation therapy:*
- Radiation therapy + temozolomide + [bevacizumab q2wk (continues without stop)]

*4wk after completion of chemoradiation therapy:*
- Temozolomide d1-5 of q28d + placebo q2wk x 12mo

**Stratification**
- MGMT methylated vs unmethylated vs invalid
- Favorable vs unfavorable vs undetermined

**Eligibility**
- Grade IV disease
- Partial or complete resection within the past three to five weeks

**SOURCE:** [www.rtog.org](http://www.rtog.org), October 2009.
only six months of temozolomide after radiation therapy and continue with placebo or bevacizumab indefi-

SELECT PUBLICATIONS


Kirkpatrick JP et al. Radiotherapy, temozolomide, and bevacizumab followed by irino-
tecan, temozolomide and bevacizumab in newly diagnosed glioblastoma multiforme: Preliminary results from an ongoing phase II trial. Proc ASTRO 2008; Abstract 2089.


Narayana A et al. Feasibility of using bevacizumab with radiation therapy and temozololo-


Vredenburgh JJ et al. Safety and efficacy of the addition of bevacizumab (BV) to temozolomide (TMZ) and radiation therapy (RT) followed by BV, TMZ, and irino-


NEW SYSTEMIC AGENTS FOR GBM

CILENGITIDE

DR LOVE: What is the mechanism of action for cilengitide?

DR BATCHELOR: Cilengitide targets two specific families of integrins that are expressed on endothelial cells. It might have direct antiendothelial and antimigratory effects on these cells.

Integrins are receptors that mediate the interaction between the cell and the extracellular matrix. Interacting with the matrix or binding to matrix proteins is one of the ways in which endothelial cells can migrate and spread in the brain (Oliveira-Ferrer 2008). The integrins are on the cell surface, so they interact directly with matrix proteins and thus enable the cell to infiltrate or crawl along the brain parenchyma. Cilengitide acts as a substrate for two of these key receptors. It then prevents the cell/matrix interaction and, in theory, prevents migration of these cells. It might also have some direct apoptotic effects on the cells when it binds to these receptors.

DR LOVE: Would you bring us up to date on the clinical research with cilengitide?
DR BATCHELOR: Cilengitide has been the subject of trials for pediatric and adult gliomas. In the adult setting, it’s been studied both for recurrent and newly diagnosed glioblastoma. I’d say the results are not overwhelming, at least in the recurrent setting. Radiographic responses were recorded in approximately 10 percent of the patients, and the proportion of patients who were free of disease progression at six months was about 15 percent (Reardon 2008). It certainly was not a home run, but a few patients did respond.

Cilengitide was then studied in patients with newly diagnosed glioblastoma in terms of safety, feasibility and the correct dose to use in combination with radiation therapy and temozolomide. These data confirmed that cilengitide was safe and feasible to use with radiation therapy and temozolomide for newly diagnosed glioblastoma. The median overall survival was good (Nabors 2009; [3.1]), but the overall survival in the control arms of some other trials was also good, so it’s hard to read much significance into that.

A Phase III randomized trial for newly diagnosed glioblastoma, EORTC-26071-22072, is adding cilengitide to the backbone of temozolomide and radiation therapy in a subpopulation of patients with methylated MGMT.

CEDIRANIB

DR BATCHELOR: Cediranib is an oral tyrosine kinase inhibitor (TKI). It’s a pan-VEGF inhibitor that also has some activity against other tyrosine kinases, including platelet-derived growth factor and c-Kit.

DR LOVE: Which side effects and toxicities are associated with cediranib?

DR BATCHELOR: With the oral TKIs, some of the side effects are hypertension, diarrhea and fatigue. More than half of the patients in our trial of cediranib were treated for hypertension (Batchelor 2007), which can be effectively treated. An algorithm exists, and most of the patients end up receiving an antihypertensive medication.

3.1 NABTT-0306: A Phase II Randomized Trial of Two Doses of Cilengitide in Combination with Concurrent and Adjuvant Temozolomide (TMZ) and Radiation Therapy (RT) for Newly Diagnosed GBM

<table>
<thead>
<tr>
<th></th>
<th>N = 112</th>
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<tbody>
<tr>
<td>Median overall survival</td>
<td>18.9 months</td>
</tr>
<tr>
<td>Overall survival rate at 12 months</td>
<td>79.5%</td>
</tr>
</tbody>
</table>

“EMD 121974 (cilengitide) is well tolerated when combined with standard chemoradiation (TMZ + RT) and may improve survival for patients newly diagnosed with GBM given the substantial differences between the estimated median survival and that seen in the EORTC study.”

**DR LOVE:** What about bowel perforation and proteinuria?

**DR BATCHELOR:** Proteinuria can occur. Bowel perforation appears to be a low risk, probably even lower than with bevacizumab.

**DR LOVE:** Would you discuss the clinical research data for cediranib?

**DR BATCHELOR:** The initial trial with cediranib was for patients with recurrent glioblastoma, and we saw response rates that were similar to those obtained with bevacizumab.

About 50 percent of the patients had radiographic responses, and the proportion with a six-month progression-free survival was about 28 percent (Batchelor 2008, 2007; [3.2]), which was better than historical controls.

That trial led to a number of other ongoing studies. By spring 2010 we should have results on progression-free survival from an international randomized trial for recurrent glioblastoma that includes three arms — cediranib monotherapy, cediranib/lomustine and lomustine/placebo.

As with cilengitide and bevacizumab, we’ve moved cediranib to the up-front setting by combining it with temozolomide and radiation therapy in a Phase II trial.

### 3.2 Phase II Trial of Cediranib for Recurrent Glioblastoma

<table>
<thead>
<tr>
<th>Radiographic partial response rate (n = 16)</th>
<th>56%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients alive and progression free at six months (n = 30)</td>
<td>27.6%</td>
</tr>
<tr>
<td>Median progression-free survival</td>
<td>111 days</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>226 days</td>
</tr>
</tbody>
</table>

“AZD2171 [cediranib] has activity in patients with recurrent glioblastoma. Combination studies of AZD2171 with radiation and chemotherapy are planned.”


### SELECT PUBLICATIONS


**DR LOVE:** What are the current treatment approaches for patients with a solitary brain metastasis from non-small cell lung cancer?

**DR WEN:** Two randomized trials have demonstrated that for patients with a single brain metastasis, surgical removal in combination with radiation therapy improves survival, performance status and local control compared to radiation therapy alone (Vecht 1993; Patchell 1990; [4.1]). In theory, stereotactic radiosurgery might achieve the same result, but no trials have compared stereotactic radiosurgery to surgical resection.

**DR WEINGART:** The size of the lesion plays a role in the consideration of radiosurgery versus surgery for a single lesion. If a lesion is notably small, radiosurgery is most appropriate. If the lesion is larger and the patient has symptoms, then we tend to favor surgery. The cases in between, of course, are what cause debate. Additionally, the amount of brain edema and the proximity of the lesion to the surface of the brain play a role in that decision.

**DR WEN:** For patients who undergo surgical resection of a solitary brain metastasis, the issue then becomes whether they should receive whole brain radiation therapy.

**DR MEHTA:** Much controversy is associated with the issue of whole brain radiation, and with good reasons. Categorical evidence suggests that the use of whole brain radiation therapy dramatically decreases the incidence of further relapse in the brain (Patchell 1998; [4.2]). However,

### 4.1 Randomized Trial of Radiation Therapy with or without Surgical Resection for a Single Brain Metastasis

“We conclude that patients with cancer and a single metastasis to the brain who receive treatment with surgical resection plus radiotherapy live longer, have fewer recurrences of cancer in the brain, and have a better quality of life than similar patients treated with radiotherapy alone.”


### 4.2 Randomized Trial of Surgical Resection with or without Postoperative Radiation Therapy for a Single Brain Metastasis

“This prospective, randomized trial shows that postoperative radiotherapy given after a complete surgical resection of a single brain metastasis results in substantially better control of disease in the brain and a reduction in the number of deaths due to neurologic causes. We infer from these results that radiotherapy was successful at eradicating microscopic metastases that were undetected at the time of treatment.”

Concern exists about whole brain radiation therapy inducing neurocognitive side effects. Data support these benefits and concerns, and the real question is the balance.

Progression of disease in the brain will induce neurocognitive decline, and whole brain radiation therapy has the ability to induce neurocognitive decline. Where does the balance lie for each patient? In the vast majority of cases, the neurocognitive decline induced by recurrence is greater than the neurocognitive decline induced by whole brain radiation therapy.

Specific subsets of patients experience more neurotoxicity from whole brain radiation therapy. These are generally the older patients or those with underlying disease of the microvasculature — for example, diabetes, hypertension and so forth. For a 75-year-old patient with diabetes and hypertension, I’d be more concerned about neurocognitive decline related to whole brain radiation therapy. If the patient were healthy and otherwise had good vasculature, I would be less concerned.

SAFETY OF BEVACIZUMAB FOR PATIENTS WITH CNS METASTASES

Dr Love: Would you discuss the presentation at ASCO 2009 evaluating the use of bevacizumab for patients with brain metastases?

Dr Cloughesy: It was a retrospective analysis of prior studies with bevacizumab, in which some of the patients who were believed not to have had brain metastases actually had them. I believe the main take-home message was that bevacizumab was tolerable in terms of cerebral hemorrhages. No new toxicity signal was seen for patients with brain metastases (Rohr 2009; [4.3]).

However, we don’t want to be trapped into assuming that because we observe a benefit in glioblastoma with single-agent bevacizumab we will somehow have a benefit from single-agent bevacizumab in patients with brain metastases. The molecular biology is completely different. I don’t believe we will achieve a response without the appropriate chemotherapy or other therapy that is effective for the primary disease.

Dr Love: Tracy?

Dr Batchelor: I want to go back to the ASCO abstract about the safety of bevacizumab in patients with brain metastases (Rohr 2009; [4.3]). It may be absolutely right, but I would exercise some caution. I don’t believe the message should be that because the study retrospectively evaluated patients who had occult brain metastases, which are usually small, single lesions, it’s safe to use bevacizumab in patients with brain metastases.

Keep in mind that certain histologies may have a higher likelihood of bleeding, like squamous cell carcinoma of the lung, melanoma and other examples.

In some of the cases in the retrospective analysis, the patients were known to have had brain metastases, and they were treated with bevacizumab. However, the overwhelming majority of these patients had undetected brain metastases when they received bevacizumab. I believe we need a prospective trial to demonstrate that bevacizumab is safe in patients with symptomatic brain metastases.
TEMZOLOMIDE FOR CNS METASTASES

DR LOVE: David, do you believe that the use of temozolomide for brain metastases is a reasonable strategy?

DR PEEREBOOM: Long ago in *The New England Journal of Medicine* a case was reported of a tremendous response to temozolomide alone without radiation therapy for multiple brain metastases from melanoma (Biasco 2001).

Such responses are rare. In non-small cell lung cancer, temozolomide has some efficacy, but it’s minimal (Giorgio 2005). In breast cancer, it did essentially nothing (Trudeau 2006). I believe temozolomide may be an option for recurrent brain metastases, but its efficacy is not impressive.

Clinical trials have been performed evaluating radiation therapy with concurrent temozolomide for brain metastases, mainly in Europe (Addeo 2008, 2007; Kouvaris 2007; Antonadou 2002).

They’ve reported good response rates, but they have never been confirmed in a Phase III trial. So I believe that off study, temozolomide is certainly not the answer for brain metastases. We need further research into more active drugs.

### 4.3 Retrospective Analysis of the Safety of Bevacizumab (BV) in Three Data Sets from Patients with CNS Metastases

<table>
<thead>
<tr>
<th>Data set</th>
<th>Number of patients with CNS metastases</th>
<th>Rates of CNS hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A¹</td>
<td>91 (bevacizumab) 96 (no bevacizumab)</td>
<td>Bevacizumab: 3.29%  No bevacizumab: 1.04%</td>
</tr>
<tr>
<td>B²</td>
<td>321</td>
<td>Bevacizumab: 0.93%  No bevacizumab: —</td>
</tr>
<tr>
<td>C³</td>
<td>131</td>
<td>Bevacizumab: 0.80%  No bevacizumab: —</td>
</tr>
</tbody>
</table>

¹ Data from 13 randomized controlled trials in which patients with known CNS metastases at baseline were excluded; CNS metastases were identified after randomization
² Data from two open-label, single-arm safety trials (ATHENA and SAiL) in which patients with known CNS metastases at baseline were excluded; CNS metastases were identified after randomization
³ Data from two trials (PASSPORT and ATLAS) in which patients with treated CNS metastases were included.

“In this retrospective review, the rates of CH [CNS hemorrhage] in BV-treated patients with CNS metastases is low, and appears consistent with historical rates of CH in these patient populations. Ongoing trials are expected to provide additional data regarding the risk of CH in patients with primary and metastatic CNS tumors.”


**SELECT PUBLICATIONS**


SUPPORTIVE CARE FOR PATIENTS WITH CNS TUMORS

USE OF CORTICOSTEROIDS AND EFFECTS OF ANTI-ANGIOGENIC AGENTS ON EDEMA

DR LOVE: Jim, what are some of the important supportive care issues in the management of patients with GBM?

DR VREDENBURGH: I’ve been impressed that neuro-oncologists focus on quality of life.

When I take care of these patients, perhaps 20 percent of the time is spent on treatment and survival, and 80 percent is spent on living with the disease.

DR LOVE: Which palliative care issues could we improve on? I’d be particularly interested in corticosteroid management.

DR MIKKELSEN: Jim stated it well: We have to put into context how patients and families are managing with the disease. This includes not only the nuts and bolts of going through the specific experimental therapy, but also the complementary therapies. Corticosteroids significantly affect quality of life for patients.

Some efforts have been made to minimize steroid use, but they
are not well disseminated in the community. Patients still come to us receiving horrendous doses of steroids and experience tremendous long-term complications. One of our major jobs is always to minimize the steroid doses (Batchelor 2006; [5.1]).

DR MEHTA: They are a huge problem. We see patients chronically administered high doses of steroids without attention to their sequelae. I believe one of the major benefits of the anti-angiogenic agents is that we can take patients off of the steroids quickly.

DR LOVE: David, what do we know about the effects of anti-angiogenic agents on the ability to reduce steroid doses or edema?

DR PEEREBOOM: Most of the clinical trials evaluating bevacizumab (Friedman 2009; [5.2]) and other anti-VEGF agents have shown that the majority of patients can reduce their doses of steroids, which is a tremendous quality-of-life benefit.

DR LOVE: Do you believe it’s a mechanical or an antitumor effect?

DR PEEREBOOM: I believe it’s probably a mechanical effect related to a decrease in vascular permeability. We see it in the fluid attenuation inversion recovery changes on MRI, which occur as soon as a day after starting therapy. This suggests it is primarily related to vascular permeability in terms of edema and the ability to discontinue steroids.

DR LOVE: Do you have patients who experience a rapid improvement in functionality when you introduce an anti-angiogenic agent such as bevacizumab?

DR PEEREBOOM: It does occur early on. It’s exciting because I believe this

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5.1 Use of Corticosteroids for Patients with Brain Tumors

“Steroids can cause adverse side effects and induce metabolism of other drugs. The risks of steroids in patients who have asymptomatic brain edema thus generally outweigh any potential benefit. Alternatively, patients who have symptomatic brain edema typically respond and therefore usually benefit from steroid use. The patient should be maintained on the lowest dose that controls neurologic symptoms to avoid the development of adverse effects.”


5.2 Effect of Treatment with Bevacizumab or Bevacizumab/Irinotecan on Corticosteroid Doses in Patients with Recurrent Glioblastoma

“...There was a trend for patients who were taking corticosteroids at baseline to take stable or decreasing doses over time. No formal comparisons of average corticosteroid dose at different time points were made because of differences in the size of the patient population across time. However, similar trends of stable or decreasing corticosteroid dose were observed in patients for whom data were available up to 36 weeks.”

is the first antitumor agent for CNS tumors that produces a clinically relevant improvement in symptoms and neurologic function.

**USE OF ANTICONVULSANTS**

istrator: David, what about the use of anticonvulsants for these patients?

**DR PEEREBOOM:** We frequently see patients who have never had a seizure but are receiving anticonvulsants. Many of the anticonvulsants can bring toxicities and a major effect on quality of life. For a patient who’s never had a seizure, no benefit exists to being on an anticonvulsant after probably two or three weeks postoperatively. I believe this is an important practical point for oncologists: If the patient hasn’t had a seizure, his or her anticonvulsants should be discontinued (Glantz 2000; [5.3]).

**DR LOVE:** What is considered the standard first- or second-line anticonvulsant therapy?

**DR PEEREBOOM:** A group of anticonvulsants induces hepatic enzyme production, and some anticonvulsants have no or minimal impact on hepatic metabolism. I believe that as a neuro-oncology community, we prefer the latter group. With several drugs in that class, we don’t have to worry about the dosing of drugs such as irinotecan.

It also seems that the group of drugs that has less impact on hepatic metabolism generally has less toxicity. Many of the anticonvulsants that induce hepatic enzyme production, like phenytoin and carbamazepine, cause a fair amount of neurocognitive depression. Patients tell us they’re fatigued, and quality of life is significantly affected.

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5.3

**American Academy of Neurology Recommendations on the Use of Anticonvulsants as Prophylaxis for Newly Diagnosed Brain Tumors**

“In patients with newly diagnosed brain tumors, anticonvulsant medications are not effective in preventing first seizures. Because of their lack of efficacy and their potential side effects, prophylactic anticonvulsants should not be used routinely in patients with newly diagnosed brain tumors (standard). In patients with brain tumors who have not had a seizure, tapering and discontinuing anticonvulsants after the first postoperative week is appropriate, particularly in those patients who are medically stable and who are experiencing anticonvulsant-related side effects (guideline).”


**SELECT PUBLICATIONS**


QUESTIONS (PLEASE CIRCLE ANSWER):

1. Methylation status of the MGMT promoter might predict benefit from temozolomide in patients with newly diagnosed glioblastoma.
   a. True
   b. False

2. Pseudoprogression can occur after radiation therapy and temozolomide for newly diagnosed glioblastoma, and MGMT status might help in differentiating it from tumor progression.
   a. True
   b. False

3. In a Phase II randomized trial, patients with recurrent glioblastoma who received bevacizumab/irinotecan had a better ________ than those who received bevacizumab alone.
   a. Response rate
   b. Median progression-free survival
   c. Median overall survival
   d. Both a and b

4. Which of the following side effects/complications has been associated with bevacizumab?
   a. Bowel perforation
   b. Hypertension
   c. Proteinuria
   d. All of the above

5. A Phase III randomized trial, RTOG-0825, is evaluating the combination of ________ with adjuvant radiation therapy and temozolomide for newly diagnosed glioblastoma that has been resected.
   a. Cediranib
   b. Cilengitide
   c. Bevacizumab
   d. None of the above

6. Which of the following agents is an integrin inhibitor?
   a. Cediranib
   b. Cilengitide
   c. Bevacizumab
   d. None of the above

7. Which of the following agents is an oral VEGF tyrosine kinase inhibitor?
   a. Cediranib
   b. Cilengitide
   c. Bevacizumab
   d. None of the above

8. Which of the following side effects has been associated with cediranib?
   a. Diarrhea
   b. Hypertension
   c. Fatigue
   d. All of the above

9. A Phase III randomized trial, EORTC-26071-22072, is evaluating the combination of ________ with adjuvant radiation therapy and temozolomide for newly diagnosed glioblastoma that has been resected.
   a. Cediranib
   b. Cilengitide
   c. Bevacizumab
   d. None of the above

10. Randomized clinical trials have demonstrated that the surgical resection of a solitary brain metastasis followed by radiation therapy improves ________ compared to radiation therapy alone.
    a. Overall survival
    b. Performance status
    c. Local control
    d. All of the above

11. In a retrospective analysis of prior studies, bevacizumab was tolerable in terms of cerebral hemorrhages for patients who were assumed not to have had brain metastases but actually had them.
    a. True
    b. False

Post-test answer key: 1a, 2a, 3d, 4d, 5c, 6b, 7a, 8d, 9b, 10d, 11a
Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

**PART ONE — Please tell us about your experience with this educational activity**

How would you characterize your level of knowledge on the following topics?

<table>
<thead>
<tr>
<th>Topic</th>
<th>BEFORE</th>
<th>AFTER</th>
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</thead>
<tbody>
<tr>
<td>Pseudoprogression after radiation therapy and temozolomide in GBM</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
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<tr>
<td>MGMT promoter methylation status and resistance to temozolomide</td>
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<td>Selection of patients for the use of implantable carmustine wafers</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
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<tr>
<td>Efficacy and safety of bevacizumab alone or in combination with irinotecan for patients with recurrent GBM</td>
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<tr>
<td>Safety of bevacizumab in combination with radiation therapy and temozolomide for patients with newly diagnosed GBM</td>
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<tr>
<td>Mechanisms of action of cilengitide and cediranib</td>
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<td>4 3 2 1</td>
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<tr>
<td>Effect of the surgical removal of a single brain metastasis on survival</td>
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<td>4 3 2 1</td>
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<tr>
<td>Duration of anticonvulsant therapy for patients with gliomas</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
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</tbody>
</table>

Was the activity evidence based, fair, balanced and free from commercial bias?

- ☐ Yes
- ☐ No
- ☐ Not applicable

Will this activity help you improve patient care?

- ☐ Yes
- ☐ No
- ☐ Not applicable

Did the activity meet your educational needs and expectations?

- ☐ Yes
- ☐ No
- ☐ Not applicable

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

<table>
<thead>
<tr>
<th>LO</th>
<th>4 = Yes</th>
<th>3 = Will consider</th>
<th>2 = No</th>
<th>1 = Already doing</th>
<th>N/M = LO not met</th>
<th>N/A = Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use biomarkers to identify patients with high-grade gliomas who may be more likely to experience response or resistance to alkylating agents</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
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<tr>
<td>Explain the concept of pseudoprogression, and identify strategies to distinguish between true disease progression and pseudoprogression in patients with previously treated brain tumors</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
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<tr>
<td>Apply emerging research results to develop evidence-based clinical management strategies for newly diagnosed or recurrent high-grade gliomas</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
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<tr>
<td>Recall the rationale for use and the clinical outcomes associated with integrin- or VEGF-targeted therapies for GBM</td>
<td>4 3 2 1</td>
<td>N/M</td>
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<tr>
<td>Counsel patients with CNS metastases about the risks and benefits associated with available local and systemic treatment modalities</td>
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<td>Incorporate best-practice supportive care measures into the management of high-grade gliomas</td>
<td>4 3 2 1</td>
<td>N/M</td>
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<tr>
<td>Enroll or refer eligible patients with high-grade gliomas for participation in ongoing clinical trials</td>
<td>4 3 2 1</td>
<td>N/M</td>
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EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

What other practice changes will you make or consider making as a result of this activity?

What additional information or training do you need on the activity topics or other oncology-related topics?

Additional comments about this activity:

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

☐ Yes, I am willing to participate in a follow-up survey.
☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty and moderator for this educational activity

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Knowledge of subject matter</th>
<th>Effectiveness as an educator</th>
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</thead>
<tbody>
<tr>
<td>Tracy Batchelor, MD, MPH</td>
<td>4 3 2 1</td>
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<tr>
<td>Timothy F Cloughesy, MD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
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<tr>
<td>Minesh P Mehta, MD</td>
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<tr>
<td>Tom Mikkelsen, MD</td>
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<tr>
<td>David M Peereboom, MD</td>
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<tr>
<td>James J Vredenburgh, MD</td>
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<tr>
<td>Jon D Weingart, MD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
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<tr>
<td>Patrick Y Wen, MD</td>
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</table>

<table>
<thead>
<tr>
<th>Moderator</th>
<th>Knowledge of subject matter</th>
<th>Effectiveness as an educator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neil Love, MD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
</tbody>
</table>

Please recommend additional faculty for future activities:

Other comments about the faculty and moderator for this activity:

REQUEST FOR CREDIT — Please print clearly

Name: ........................................ Specialty: ........................................
Professional Designation: ☐ MD ☐ DO ☐ PharmD ☐ NP ☐ RN ☐ PA ☐ Other ..............................
Medical License/ME Number: ........................................ Last 4 Digits of SSN (required): ...........
Street Address: ........................................ Box/Suite: ..............................
City, State, Zip: ........................................
Telephone: ........................................ Fax: ........................................
Email: ........................................

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I certify my actual time spent to complete this educational activity to be _________ hour(s).

Signature: ........................................ Date: ........................................

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at CME.ResearchToPractice.com.
Systemic Management of Central Nervous System Tumors

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