

Brain Tumors



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Bevacizumab Plus Irinotecan Stalls Recurrent Gliomas

Progression-free survival at 6 months was 43% in patients with grade 4 disease.

The combination of bevacizumab and irinotecan continues to show significant activity against recurrent malignant gliomas, judging from phase II trial results.

Dr. James J. Vredenburgh, the lead investigator, reported 15 of 35 (43%) patients with grade 4 (glioblastoma multiforme) and 20 of 33 patients (61%) with grade 3 disease were progression free at 6 months. Median progression-free survival was 23 weeks and 42 weeks, respectively.

At 12 months, 13 of the grade 4 patients (37%) and 19 of the grade 3 patients (58%) were still alive. Median overall survival was 40 weeks and 60 weeks, respectively. All told, 59% (40 of 68) of patients in the single-arm study had at least a partial response.

Historically, chemotherapy response rates run about 10% in advanced glioma, according to Dr. Vredenburgh of the Pre-

endothelial growth factor (VEGF).

“Malignant gliomas have high concentrations of VEGF. The higher the concentration of VEGF, the poorer the prognosis,” Dr. Vredenburgh said. Bevacizumab, he also noted, is synergistic with chemotherapy in colorectal, breast, and lung cancers.

Irinotecan (Camptosar), a topoisomerase 1 inhibitor approved for treatment of metastatic colorectal cancer, has excellent penetration through the blood brain barrier, Dr. Vredenburgh continued. It has shown some activity against recurrent glioblastoma, he noted, citing response rates of 0%-15% and 6-month progression-free survival approaching 20%. “Clearly, it is the bevacizumab making a difference. It’s not the irinotecan,” he said.

Dr. Vredenburgh listed four mechanisms by which bevacizumab achieves its efficacy: a direct antitumor effect, an antiangiogenic effect, normalization of tumor vasculature with reduced interstitial pressure leading to improvement in hypoxia, and an antitumor stem cell effect.

The trial enrolled glioma patients with measurable disease in two successive cohorts of 32 and 36 patients. About two-thirds of both cohorts were men; nearly half were on enzyme-inducing antiepileptic drugs (EIAEDs). Median age was 49 and 46 years, respectively. More patients in the first cohort had grade 4 gliomas (23 vs. 9 with grade 3 gliomas), whereas patients with grade 3 gliomas predominated in the second group (24 vs. 12 patients with grade 4 gliomas).

The first 32 patients received 125 mg/m² of intravenous irinotecan over 90 minutes every 2 weeks if they were not taking any EIAEDs. If patients were taking phenytoin, carbamazepine, oxcarbazepine, or phenobarbital, the dose was increased to 340 mg/m² on the same schedule. After irinotecan, patients received 10 mg/kg of intravenous bevacizumab over 30-90 minutes.

After seeing acceptable safety results with the first cohort, the investigators changed the regimen. Depending on use of EIAEDs, the second group received 125 mg/m² or 350 mg/m² of irinotecan intravenously over 90 minutes on days

1, 8, 22, and 29. On days 1 and 22, they also received 15 mg/kg of intravenous bevacizumab after irinotecan.

A total of 14 patients (7 in each cohort) finished a year of therapy. Dr. Vredenburgh described the toxicity as man-

deep venous thrombosis (one), and grade 2 proteinuria (two), which required the patients to come off study. Another three patients came off study because they required surgery, and two patients who complained of fatigue opted for palliative care.

In the second cohort, Dr. Vredenburgh reported 10 patients came off study because of toxicity during the first three cycles. Another six patients required a reduction of their irinotecan dose, and one patient (who started enoxaparin after developing a deep vein thrombosis) had a grade 2 CNS hemorrhage during the ninth treatment cycle. Venous thromboembolism was more common in the second group, which had four cases (11%) and the same number of gastrointestinal toxicities.

Dr. Vredenburgh said the investigators will look for confirmation of safety and efficacy in a recently completed phase II trial comparing bevacizumab to bevacizumab and irinotecan in recurrent glioblastoma. They also hope to include bevacizumab early in the treatment of malignant gliomas, he said. ■

Goli K.J. et al. Phase II trial of bevacizumab and irinotecan in the treatment of malignant gliomas. Abstract 2003.

Bevacizumab achieves its efficacy via a direct antitumor effect, an antiangiogenic effect, normalization of tumor vasculature with reduced interstitial pressure leading to improvement in hypoxia, and an antitumor stem cell effect.

ageable, but concluded that giving irinotecan every 2 weeks was optimal.

In the first group, one patient developed an asymptomatic central nervous system hemorrhage after 10 cycles and was taken off therapy. Other adverse events included an arterial thrombotic stroke (one), pulmonary emboli (two),

identified to date in patients with recurrent malignant glioma.

A series of other studies that have been completed or are in progress will help provide important initial information. One example is a recently completed randomized phase II study of patients with first- or second-relapse glioblastoma multiforme who were treated with bevacizumab or bevacizumab plus irinotecan.

Studies such as these will help us try to understand the biological reasons for the marked activity of this treatment, and allow for rational translation into phase III trials in patients with newly diagnosed disease.

— Henry S. Friedman, M.D.



‘Clearly, it is the bevacizumab making a difference. It’s not the irinotecan.’

Dr. Vredenburgh

ston Robert Tisch Brain Tumor Center at Duke University in Durham, N.C.

Without comment on the implications, he reported that investigators took 12 patients off treatment after positron emission tomography (PET) scans showed their tumors to be hypometabolic. “They had a cold PET scan,” he explained afterward in an interview. “Given the toxicity and the risk involved, we thought that was a reasonable time to stop their treatment. There was no evidence of active tumor.”

Five of these patients, he added, have not progressed in more than a year. One young woman was able to return to graduate school.

The trial reported research support from Genentech, the developer of bevacizumab (Avastin), a humanized monoclonal antibody that acts as an antiangiogenesis agent targeting vascular

VEGF Inhibitor Cediranib Active in Recurrent Glioblastoma

The investigational agent cediranib demonstrated considerable activity in recurrent glioblastoma in preliminary results from a phase II trial, further strengthening evidence for suppression of angiogenesis as a strategy against brain tumors.

Dr. Tracy T. Batchelor reported the 6-month progression-free survival rate was 26% for 30 patients given cediranib (AZD2171, Recentin). All but two patients had progressed by the time of his presentation, but median progression-free survival reached 117 days and median overall survival reached 221 days.

Radiographic data on the first 16 consecutive patients showed 9 (56%) had partial responses to cediranib as reported by Dr. Batchelor, executive director of the Stephen E. & Catherine Pappas Center for Neuro-Oncology at the Massachusetts General Hospital Cancer Center in Boston. A preliminary analysis of the full population suggests the final rate will be 50%-60%, he said. While the results are encouraging, they come from "a small nonrandomized study and remain to be validated."

AstraZeneca, developer of cediranib, provided support to the trial, which was sponsored by the National Cancer Institute. An oral agent, cediranib targets all three receptors of the vascular endothelial growth factor (VEGF).

Bevacizumab (Avastin), an antian-

giogenic agent that inhibits VEGF also produced unprecedented response and progression-free survival rates in a phase II trial reported at the same meeting.

Findings from that earlier phase II trial showed 15 of 35 grade IV patients (43%) and 20 of 33 with grade III disease (61%) were progression free at 6 months. All told, 59% (40 of 68 patients) had a partial response. Bevacizumab is approved in combination with chemotherapy for metastatic colorectal cancer and unresectable locally advanced, recurrent, or metastatic non-squamous non-small cell lung cancer.

In a discussion, Dr. Timothy Cloughesy said both studies raise important questions about the role of VEGF in brain tumors and how best to use anti-VEGF therapies. Also, cediranib and bevacizumab seem to have antitumor effects that go beyond VEGF inhibition, noted Dr. Cloughesy, director of the neuro-oncology program at the University of California, Los Angeles, and member of the scientific advisory board of Genentech, maker of bevacizumab.

Dr. Batchelor made extensive use of monthly magnetic resonance imaging (MRI) in the cediranib study, from which data on normalization of tumor vessels and inhibition of edema was published earlier this year (*Cancer Cell* 2007;11:83-95). "The vascular network is dilated, disorganized, and leaky," he

said, showing images of significant, but temporary, decline in vessel diameters. Cediranib also reduced permeability, which in turn controlled edema, as documented by MRI and clinical data.

Dr. Batchelor reported that five patients never went on steroids before or during the trial. Of 11 patients who required steroids at some point, 8 had their dose reduced and 3 stopped steroids. All patients who progressed and stopped taking cediranib required steroids immediately after stopping.

Serial biomarker assessments showed levels of bFGF, SDF1a, and circulating

endothelial cells rose before tumors progressed and cediranib was halted.

At a daily dose of 45 mg, most patients needed antihypertension therapy and occasional drug holidays, but no one had an intracerebral hemorrhage, which has been a concern with antiangiogenesis agents. Of the first 16 patients, 10 had dose-limiting toxicity. ■

Batchelor T. et al. A phase II trial of AZD2171 (cediranib), an oral pan-VEGF receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma. Abstract 2001.

Commentary

AZD2171, a potent, oral pan-VEGF-receptor tyrosine kinase inhibitor, represents another approach to antiangiogenic therapy in patients with malignant glioma. This phase II study reports on 30 patients with recurrent glioblastoma multiforme. Of note, 6-month progression-free survival was 28% with AZD2171, and 9 of the first 16 evaluable patients had partial responses. This data is provocative. It will be interesting to see additional studies of this agent in combination with chemotherapy, which may be an even better approach.

Interestingly, tumors that fail therapy with one antiangiogenic regimen responded to an alternative one. These agents do not work in the same way, and mechanisms of resistance to one may not affect a second agent with a different mechanism of action. This report and the abstract by Goli et al. make clear that the potential benefits of antiangiogenic therapy extend to malignant glioma. We need to learn whether these agents can be used in newly diagnosed patients to have an impact on survival.

— Henry S. Friedman, M.D.

Motexafin Gadolinium Delays Progression in NSCLC Brain Metastases

The addition of motexafin gadolinium to whole brain radiation therapy significantly prolongs time to neurologic progression in non-small cell lung cancer patients with brain metastases, according to pooled data from two randomized phase III trials.

Time to neurologic progression was 15.4 months compared with 9 months for those given radiation alone, said Dr. William R. Shapiro of the Barrow Neurological Institute, Phoenix.

Motexafin gadolinium (Xcytrin, Pharmacyclics Inc) selectively localizes in tumors and induces apoptosis by inhibiting thioredoxin reductase. The agent is in development for treating brain metastases in patients with non-small cell lung cancer (NSCLC), and a new drug application was filed with the U.S. Food and Drug Administration in April 2007 by the manufacturer, which sponsored the analysis.

The pooled data were derived from the phase III PCI-P120-9801 trial of patients with brain metastases from any solid tumor, and from the Study of Neurologic Progression with Motexafin Gadolinium And Radiation Therapy (SMART) trial of patients with brain

metastases from NSCLC, and comprised a total of 805 patients. The PCI-P120-9801 was sponsored by Schering Plough, and SMART was sponsored by Pharmacyclics, which also sponsored the pooled data analysis.

Pooling data was necessary to derive statistical power. "Trials in brain metastases pose challenges because survival is short and a large percentage of patients die from systemic disease or medical complications," Dr. Shapiro said.

The primary end point was time to neurologic progression or death with evidence of neurologic progression, as determined by a blinded, centralized events review committee. Secondary end points were time to neurologic progression and time to neurocognitive progression.

Patients received whole brain radiation therapy of 30 Gy delivered in 10 fractions with or without motexafin gadolinium 5 mg/kg per day for 10 days.

Time to neurologic progression improved as determined by the review committee and by individual investigator, with *P* values of .016 and .015.

Time to neurocognitive progression also improved with motexafin gadolinium, with a *P* value equal to .02.

Skin discoloration occurred in 74%. "Patients turned a nice olive green, but this usually went away after 24 hours," Dr. Shapiro said. Other adverse effects were urine discoloration (41%), nausea and vomiting (32%), fatigue (30%), and hypertension (23%). For most, adverse events were grade 1 and 2.

Importantly, Dr. Shapiro added, motexafin gadolinium did not interfere with whole brain radiation therapy. Most patients (93%) received the full 10 days of motexafin gadolinium, and 99% received full radiation treatments.

However, there was no overall survival benefit. Dr. Shapiro observed that in the study of metastatic brain tumors, survival is not a good end point because lung cancer patients often die before they deteriorate neurologically. ■

Shapiro W.R. et al. Motexafin gadolinium (MGd) combined with whole brain radiation therapy prolongs time to neurologic progression in non-small cell lung cancer (NSCLC) patients with brain metastases: Pooled analysis of two randomized phase III trials. Abstract 2010.

Commentary

Treatment of patients with brain metastases has been based on a foundation of surgery and radiotherapy. Additional interventions such as chemotherapy have not been particularly effective. Motexafin gadolinium (MGd), a radiosensitizer, has prolonged time to neurologic progression in two randomized phase III trials for patients with non-small cell lung cancer metastatic to the brain.

This pooled analysis makes clear that time to neurologic progression and neurocognitive progression are significantly prolonged with MGd and whole-brain radiotherapy in patients with NSCLC metastatic to the brain. Other studies will be needed to determine if similar benefits are noted in patients with brain metastases and other histologies such as breast cancer and melanoma.

— Henry S. Friedman, M.D.

Dendritic Cell Vaccine Shows Promise in Glioblastoma

Combining dendritic cell vaccination with imiquimod for the treatment of glioblastoma more than doubled survival in a small intervention group during a phase I trial.

Two-year survival—the primary clinical end point—for 19 patients treated with the dendritic cell vaccines was 68%, and 3-year survival was 43%. In comparison, only 26% of conventionally treated patients at the University of California, Los Angeles, survived to 2 years, and only 20% survived to 3 years.

Median progression-free survival and median overall survival in the vaccinated group were 18 months and 34 months, respectively. This compared with 7 months and 15 months, respectively, for patients in the published literature.

Dr. Linda Liau, a neurosurgeon at UCLA, and her colleagues presented immunologic response data for 13 patients with newly diagnosed glioblastoma multiforme (GBM). Patients underwent resection, followed by a 6-week course of radiation and chemotherapy with temozolomide.

The vaccines consisted of autologous dendritic cells pulsed with lysates from GBM tumor cells. Each patient initially received three vaccinations at 2-week intervals. Four patients received 1 million dendritic cells per immunization; four others received 5 million dendritic cells per immunization, and the remaining five received 10 million den-

dritic cells per immunization.

Patients without tumor progression subsequently received booster injections every 3 months combined with topical administration of imiquimod, which is a toll-like receptor-7 agonist that enhances both the innate and acquired immune response. Imiquimod (Aldara) is indicated for the treatment of actinic keratosis, superficial basal

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cell carcinoma, and external genital and perianal warts.

The control group consisted of 191 patients with GBM at UCLA, who received standard treatment. The average age in the vaccinated and control groups was 51 and 49 years, respectively.

It appears that vaccination approaches in general are very successful,” said Dr. Albert Wong of Stanford (Calif.) University, who reviewed the poster.

Nearly all patients had de novo infiltration of T lymphocytes into CNS tumors. In addition, CNS tumors were found to express known tumor-associ-

ated antigens. Five patients also had an increase in tumor antigen-specific CD8-positive T cells following vaccination.

The relationship between response and patient survival was disappointing though. “In my opinion, there was not a strong correlation between the response to these defined tumor antigens and patient response,” Dr. Wong said.

No grade 3 or 4 adverse events were reported. The most frequent adverse events were low-grade fever, injection-site itching and pain, and arthralgia and myalgia. Seizures also occurred that were possibly related to the vaccines; however, seizures are also typical in GBM patients.

An important next step is to identify what the true tumor antigens are, in order to better refine the vaccine. Dr. Wong likened the current generation of dendritic cell vaccines to using foxglove to treat “x,” when it would really be better to extract and use the active component, digitalis.

The study was sponsored in part by Northwest Biotherapeutics Inc., which is developing the technology behind the vaccines. A phase II clinical trial, sponsored by Northwest Biotherapeutics Inc., is underway. ■

Liau L.M. et al. Dendritic cell vaccination in combination with TLR-7 agonist, imiquimod, following radio-chemotherapy for newly diagnosed glioblastoma. Abstract 2021.

Commentary

In this report of a phase I study, tumor lysate-pulsed dendritic cell therapy plus topical imiquimod, a TLR-7 agonist, was nontoxic and generated specific immunologic responses in brain tumor patients. In combination with the abstract by Sampson et al., this study makes clear that vaccine strategies represent a potential therapeutic approach for patients with malignant brain tumors.

Hopefully, further studies of vaccine strategies in combination with chemotherapy agents such as temozolomide as well as radiotherapy will demonstrate a role for a vaccine. Many issues still need to be resolved, however, including the optimal antigen to target, the presentation of this antigen (i.e. either using it with or without dendritic cell presentation), and the timing of vaccine strategies relative to surgery, radiation, and chemotherapy.

Presumably, vaccine strategies will be most effective at a time of minimal residual disease, i.e., in patients whose MRIs show no obvious gross residual tumor after initial intervention. There is less likelihood of results in patients with bulky disease.

— Henry S. Friedman, M.D.

Temozolomide and Vaccination Can Work Together to Treat GBM

Temozolomide may not be incompatible with immunologic approaches for the treatment of glioblastoma, based on data from an analysis of patients from two ongoing trials.

‘The important fact here is that temozolomide is not contraindicated in immunotherapy and may be beneficial in some of these immune responses.’

Vaccination with dendritic cells and either acid-eluted peptides or an antigen-specific peptide has shown promising results in extending survival of patients who have glioblastoma multiforme (GBM). Likewise, temozolomide (Temodar) has been shown to prolong survival in these patients and is part of a

standard treatment regimen. Temozolomide, however, often induces a profound and long-lasting lymphopenia that could limit immunotherapeutic approaches.

“This preliminary experience suggests that sequential administration of chemotherapy and immunotherapy may not be deleterious,” wrote Dr. John H. Sampson of Duke University in Chapel Hill, N.C., and his colleagues.

The analysis involved patients from two ongoing trials. All were newly diagnosed with GBM, positive for epidermal growth factor receptor variant III (EGFRvIII), and had complete resection.

In the ACTIVATE trial, patients received radiation (approximately 60 Gy) and concurrent temozolomide (50-75 mg/m² per day), followed by vaccination with EGFRvIII-specific peptide. In the ACT II trial, patients received the same radiation and temozolomide regimen. Vaccination was on day 21 of 28-day temozolomide cycles.

Grade 2 lymphopenia was induced in all patients receiving temozolomide after the first cycle. Grade 3 lymphope-

nia was induced in 70% of patients after the first cycle of temozolomide. However, lymphocyte counts returned to normal after treatment was stopped. “Standard dose temozolomide induces transient but profound lymphodepletion in the majority of patients with GBM,” the researchers wrote.

Regulatory T cells increased from 5.2% to 11.8% after temozolomide and radiation. Temozolomide cycles did not appear to have diminished EGFRvIII-specific CD3-positive/CD8-positive T cells producing interferon-gamma.

Commentary

This report clearly details that temozolomide can be used in patients receiving vaccine therapy without an adverse effect on the immune system. Indeed, this provocative abstract makes clear that the use of temozolomide, although inducing transient lymphopenia, produces an enhanced

Further, EGFRvIII-specific IgG responses were induced and maintained during treatment with temozolomide.

“The important fact here is that temozolomide is not contraindicated in immunotherapy and may be beneficial in some of these immune responses,” said Dr. Victor A. Levin, a professor of neuro-oncology at the University of Texas M.D. Anderson Cancer Center in Houston, who viewed the data. ■

Sampson J.H. et al. Temozolomide as a vaccine adjuvant in GBM. Abstract 2020.

specific immune response following recovery from this agent. Accordingly, temozolomide can be used in conjunction with vaccination strategies. Use of this active methylating agent in the treatment of the tumor only increases the potential merit of vaccines that are employed as well.

— Henry S. Friedman, M.D.