

Brain Cancer



Commentary by

Henry S. Friedman, MD

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Peritumoral administration best way to deliver IL13PE

Adequate catheter positioning important determinant of drug distribution and survival outcome

Peritumoral administration appears to optimize the delivery of IL13PE in patients undergoing tumor resection.

— Michael Prados

Convection-enhanced delivery (CED) of the recombinant cytotoxin IL13-PE38QQR (IL13PE) has shown a favorable risk/benefit profile in patients undergoing tumor resection for recurrent malignant glioma, Michael Prados, MD, University of California, San Francisco, announced at the 41st Annual Meeting of the American Society of Clinical Oncology.

CED uses positive pressure infusion to achieve locoregional delivery of therapeutic agents via intracerebral catheters, Dr. Prados explained. “One of the biggest problems we have is actually getting the drug to our targets. It’s a huge issue because of the blood-brain barrier and the inability of drugs to get to all of the tumor target. Local strategies that can overcome these variables are hugely attractive and may improve survival,” he said.

Because of the infiltrative nature of malignant glioma, Dr. Prados and colleagues investigated two different ways of delivering IL13PE with CED: intratumorally before resection in 23 patients and peritumorally after resection in 53 patients.

“The intratumoral technique places the intracerebral catheters directly into

the solid tumor mass and the drug is convected into the mass, while the peritumoral approach enters the region at risk around the surgical margin,” Dr. Prados explained.

Overall, the most frequent adverse event was headache. Drug distribution turned out to be a problem for the intratumoral catheter placements. There was limited delivery of the drug to the regions at risk when this particular toxin (IL13PE) was placed directly into the tumor. On the other hand, there was more benefit seen with PT infusion (median overall survival 44 weeks with peritumoral vs 37.1 weeks with intratumoral), Dr. Prados noted.

“Peritumoral administration appears to optimize the delivery of IL13PE in patients undergoing tumor resection. Post-operative catheter placement appears to result in more accurate positioning to get the drug to the target and improve survival outcome. CED of IL13PE, at least preliminarily, has a reasonable benefit/risk profile for treatment of patients with GBM [glioblastoma multiforme],”

Dr. Prados concluded.

These findings have been used to support the study design and catheter positioning guidelines for the ongoing phase III pivotal PRECISE trial, he added.

In a discussion after Dr. Prados’s presentation, Joon Uhm, MD, Mayo Medical School, Rochester, MN, commented that optimum catheter placement is indeed a challenge, particularly with regard to optimizing the depth of tissue distribution and minimizing the loss through back-flow or preventing inadvertent leakage through CSF channels. “As a result of this study, strict criteria have been developed for catheter placement that is being implemented in the PRECISE trial,” he said.

Prados M, Kunwar S, Lang FF, et al. Final results of phase I/II studies of IL13-PE38QQR administered intratumorally (IT) and/or peritumorally (PT) via convection-enhanced delivery (CED) in patients undergoing tumor resection for recurrent malignant glioma. Paper presented at the 41st Annual Meeting of the American Society of Clinical Oncology; May 13–17, 2005; Orlando, Fla. Abstract 1506.

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— Joon Uhm

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Comment

Not surprisingly, better results were seen in patients with two or more catheters placed at optimal locations. Of note, a randomized phase III trial of patients with first relapse glioblastoma is now being conducted with a standard arm of Gliadel Wafer placement and an experimental arm of convection-enhanced delivery using this toxin conjugate. This study is particularly important because it represents a strategy that may be meaningful in addressing the most pressing problem in patients with malignant glioma—specifically, management of patients with elevated AGT in their tumors. Tumors that contain AGT (also known as MGMT) do not respond favorably to temozolomide (Temodar) or indeed nitrosoureas. Accordingly, new treatments are necessary for this patient population. This current strategy utilizing CED may be such an approach for these patients.

— Henry S. Friedman, MD

NATIONAL COMPREHENSIVE CANCER NETWORK

New NCCN guidelines for CNS cancer reflect progress in this once bleak field

There is some light at the end of the tunnel

The updated National Comprehensive Cancer Network (NCCN) guidelines reflect multifaceted progress in the field of central nervous system (CNS) cancers, Steven S. Brem, MD, H. Lee Moffitt Cancer Center, University of South Florida, Tampa, said at the 10th annual NCCN conference.

“Brain cancer is no longer a bleak corner. It’s becoming a fertile and exciting area for all of oncology,” Dr. Brem told NCCN delegates. Thanks to reports such as the one published by Roger Stupp et al in the *New England Journal of Medicine* (Stupp R. *N Engl J Med* 2005;352:987–996) earlier this year, “there is some light at the end of the tunnel” for patients with glioblastomas.

In that safety and efficacy study, Stupp and others randomized 573 patients from 85 centers with newly diagnosed glioblastoma to radiotherapy alone or radiotherapy plus temozolomide (Temozor) given concomitantly with and after radiotherapy. At a median follow-up of 28 months, the median survival was 14.6 months with radiotherapy plus temozolomide, and 12.1 months with radiotherapy alone. The 2-year survival rate was 26.5% with radiotherapy plus temozolomide and 10.4% with radiotherapy alone. Toxicity was minimal.

“This is level 1A evidence for the benefit of temozolomide in glioblastoma,” commented Dr. Brem. The FDA

approved temozolomide for this indication in March 2005.

A companion study found a marker that predicted benefit from temozolomide treatment. Monika Hegi et al (*Hegi ME. N Engl J Med* 2005;352:997–1003) reported that patients whose glioblastoma contained a methylated MBMT promoter benefited from temozolomide treatment, while patients without that promoter did not. “This study launches a new era of selecting patients who will benefit from chemotherapy and those who will not,” Dr. Brem commented.

The guidelines also endorse the use of Gliadel Wafer in the adjuvant treatment of patients with newly diagnosed anaplastic astrocytoma, anaplastic oligodendroglioma, and glioblastoma. These wafers, tucked in the surgical cavity created by the removal of the tumor, have been proven to confer statistically significant survival benefits, Dr. Brem said. Unlike the evidence for temozolomide, however, this recommendation is a level 2B, he said. “It’s an option, there’s no consensus.”

Also new is a section on the treatment of spinal metastases. While there are no specific recommendations, the NCCN is at least taking a look at these patients, Dr. Brem noted.

“Up until now, patients with spinal me-

tastases were treated very conservatively, with steroids and radiation. This has produced poor outcomes. But new surgical techniques are yielding good results and even restoring ambulation,” he said.

He cited colleague Frank D. Vrionis, MD, PhD, also from H. Lee Moffitt Cancer Center, who is using instrumentation, including cages, plates, and pedicle screws, to rebuild the spine.

In an interview with *The Oncology Report*, Dr. Brem commented: “Central nervous system surgery was once very hazardous. Today with image guidance, safety has increased dramatically—we are able to do *tumor* surgery rather than *brain* surgery. The benefits exceed the risk instead of vice versa and we can offer the patients some really exciting developments post-operatively. Metastases from the brain were once invariably fatal but now they are often treatable. Chemotherapy used to be ineffective; now it’s often effective. There is still clearly a problem of blood-brain barrier drug resistance but even that is being tackled. At least now, there’s a shred of hope.”

Brem S. New NCCN guidelines for central nervous system cancer reflect continuing progress in this once bleak field. Paper presented at the 10th Annual Conference of the National Comprehensive Cancer Network, March 16–20, 2005; Hollywood, Fla.



Brain cancer is no longer a bleak corner. It’s becoming a fertile and exciting area for all of oncology.

—Steven S. Brem

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Enzastaurin (LY317615) promising in recurrent malignant gliomas

Continues to show antitumoral activity in these difficult-to-treat patients

The antiangiogenic agent enzastaurin (LY317615) is continuing to show antitumoral activity in patients with recurrent high-grade gliomas and is also well tolerated by these difficult-to-treat patients, Lyndon J. Kim, MD, Center for Cancer Research, National Cancer Institute, Bethesda, MD, said at the 41st Annual Meeting of the American Society of Clinical Oncology.

Dr. Kim presented phase II data on

behalf of Dr. Howard Alan Fine, Neuro-Oncology Branch, NIH, NINDS, on 87 patients, updated from the original 32 patients reported at last year’s meeting. “The results with enzastaurin continue to be promising,” he said in a poster presentation.

Patients were stratified into two groups—those who were not taking enzyme-inducing antiepileptic drugs (EIAEDs) (group A) and

those who were taking EIAEDs (group B). Group A patients received enzastaurin orally on a 6-week cycle at a fixed dose of 500 mg once daily. Group B patients received escalating doses of enzastaurin, starting at 525 mg and progressing to 700 mg, and then 900 mg once daily.

“These were heavily pretreated patients,” Dr. Kim noted.

Of the 87 patients, 20 had objective radiographic responses and 6 had

Enzastaurin exposures are significantly lower in the presence of EIAEDs.

—Lyndon J. Kim

stable disease. Progression-free survival for these patients was about 5 months, Dr. Kim said.

Enzastaurin exposures were significantly lower in the presence of EIAEDs, he added.

“The toxicity profile was extremely good. We saw some consistent throm-

bocytopenia, perhaps because these patients were heavily treated with chemotherapy in the past, but these were reversible. There was also some intratumoral hemorrhage,” Dr. Kim noted.

A new phase I study of enzastaurin is being conducted to establish the maximal tolerated dose and determine

if higher exposure levels can be maintained by patients, Dr. Kim concluded.

Fine HA, Kim L, Royce C, et al. Results from phase II trial of enzastaurin (LY317615) in patients with recurrent high grade gliomas. Paper presented at the 41st Annual Meeting of the American Society of Clinical Oncology; May 13–17, 2005; Orlando, Florida. Abstract 1504.

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Can PFS predict overall survival?

Stay tuned, concludes a study finding moderate agreement between the end points

In phase II trials of therapies for glioblastoma multiforme (GBM), progression-free survival at 6 months may be a reasonable surrogate for overall survival at 12 months, researchers said at the 41st Annual Meeting of the American Society of Clinical Oncology. However, they concluded, a definitive answer must await data from trials with positive results.

“Typically, we use the overall survival end point for newly diagnosed trials and the progression-free survival end point for recurrent trials,” said Karla V. Ballman, PhD, Mayo Clinic, Rochester, MN. “The advantage of an overall survival end point is that it is less noisy since it is easier

to ascertain, and independent of the trial evaluation schedule,” she explained. “Advantages of a progression-free survival end point are that it is not affected by subsequent treatment, which may potentially prolong survival when patients go off protocol due to progression, and there is a shorter time to the end point.”

To assess the relationship between the two end points, Dr. Ballman and her team used pooled data from all NCCTG GBM trials. Analyses were based on 12 trials (phase I–III) in 1,359 patients with newly diagnosed disease, and 16 trials (phase II and III) in 345 patients with recurrent disease. Of note, she said, all of the trials had negative results.

An initial plot of progression rate versus time showed differing patterns according to disease group. Specifically, in patients with recurrent disease, the progression rate peaked at 6 months and then dramatically fell off, whereas in patients with newly diagnosed disease, the progression rate was essentially constant from 4–12 months. Nonetheless, the majority of the former patients and a substantial proportion of the latter patients had a progression by 6 months and died by 12 months, Dr. Ballman said, a finding that suggests the 6-month end point is reasonable in both groups.

My personal opinion is that progression-free survival at 6 months should be used with caution.

— Karla V. Ballman

Comment

This study addresses the most appropriate way to evaluate end points in phase II trials of patients with glioblastoma multiforme (GBM), including 6-month progression-free survival and 12-month overall survival. Ballman and colleagues analyzed 12 NCCTG trials of newly diagnosed patients with GBM and 16 trials in patients with recurrent GBM with regard to these measures and discovered that there was only moderate concordance between these two parameters on a per patient and study arm basis. Their results suggested that overall survival of 12 months was a better end point for phase II clinical trials in newly diagnosed and recurrent GBM.

This is an important observation because it remains unclear as to what is the optimal measure to utilize for evaluating phase II trials in patients with GBM. The current finding suggesting that overall survival at 12 months is better is likely to remain true only as long as salvage therapy does not improve. If intervention for patients who have failed one therapy were to become more effective, then survival would be skewed by the introduction of this additional intervention. However, at the current time, such salvage therapy does not appear to be available and overall survival at 12 months appears to be the gold standard for these trials.

— Henry S. Friedman, MD

“Is it reasonable to use 6-month progression-free survival in place of 12-month overall survival? Unfortunately, the only definitive answer that could be reached based on these data would be a qualified no,” she said. “My personal opinion is that progression-free survival at 6 months should be used with caution. I do not believe we presented clear evidence that it is *not* reasonable to use progression-free survival at 6 months. However, this is not the same as saying it *should* be used,” she concluded.

Ballman KV, Jaeckle KA, Brown PD, et al. NCCTG N047D: Relationship between phase II end points of 12-month overall survival and 6-month progression-free survival for glioblastoma multiforme (GBM) phase II trials. Paper presented at the 41st Annual Meeting of the American Society of Clinical Oncology; May 13–17, 2005; Orlando, Florida. Abstract 1508.

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Thalidomide does not improve survival

No clear benefit, but toxicity evident when added to radiation therapy for brain metastases

A phase III study that compared conventional radiation therapy alone with conventional radiation plus thalidomide (Thalomid) in patients with multiple brain metastases found no advantage when thalidomide

was added to the regimen, Jonathan P.S. Knisely, MD, Yale University School of Medicine and Yale Cancer Center, said at the 41st Annual Meeting of the American Society of Clinical Oncology.

Whole brain radiation therapy

(WBRT) fails to control metastases in a “sizable percentage” of individuals. The Radiation Therapy Oncology Group (RTOG) 0118 investigators thought thalidomide might be beneficial as an adjunct to WBRT because of its potent

antiangiogenic and immunomodulatory activity. "It has a well-characterized toxicity profile, it can be taken orally, and most important to this patient population, it can be taken long term," Dr. Knisely explained.

Patients with multiple brain metastases or metastases that were ineligible for

radiosurgical treatment were randomized to receive 37.5 Gy in 15 fractions of WBRT with or without thalidomide, at an initial dose of 200 mg/d at bedtime, and then escalated as tolerated during and after WBRT. The investigators had hoped to enroll 332 patients, but only accrued 183 patients by June 2004,

when the study closed, Dr. Knisely said.

The intent was to treat for 2 years; however the majority of the patients (70%) were unable to tolerate thalidomide for more than 2 months, he reported. "Our patients stopped taking it because of toxicities, side effects, or complications. It doesn't seem to be as easy a drug to take as we'd hoped it would be," Dr. Knisely noted.

The median survival time in both arms was a little less than 4 months, Dr. Knisely concluded.

Knisely JP, Berkey BA, Chakravarti A, et al. RTOG 0118: A phase III study of conventional radiation therapy alone versus conventional radiation therapy plus thalidomide for multiple brain metastases. Paper presented at the 41st Annual Meeting of the American Society of Clinical Oncology; May 13-17, 2005; Orlando, Fla. Abstract 1500.



The median survival time in both arms was less than 4 months.

— Jonathan P.S. Knisely

Comment

This study demonstrates that thalidomide (Thalomid) does not improve survival for patients receiving whole brain radiotherapy for multiple brain metastases. The results are not surprising since it is clear that antiangiogenic therapies are most likely to work in patients who have small tumor burdens rather than patients with multiple brain metastases. Failure of thalidomide in this setting, although quite possibly related to a drug with only modest anti-angiogenic benefits, may also relate to a clinical setting in which anti-angiogenic agents are hard pressed to produce meaningful results.

— Henry S. Friedman, MD

AMERICAN ASSOCIATION FOR CANCER RESEARCH

Microdialysis offers a window on the brain

Straightforward technique detects presence and activity of drugs in the brain

A technique traditionally used to assess oxygenation after brain injuries and stroke can also be used to measure concentrations of chemotherapeutic agents within brain tumors, and thereby provide useful pharmacokinetic information, Jeffrey J. Olson, MD, Emory University, Atlanta, GA, said at the 96th Annual Meeting of the American Association for Cancer Research.

The technique, called microdialysis, is straightforward and offers a relatively easy way of determining whether or not a drug is actually getting into the brain, and just as importantly, whether it is active once there, Dr. Olson said.

Delivering potentially therapeutic concentrations of chemotherapy agents to brain tumors remains a major concern in the design and interpretation of clinical trials in neuro-oncology, he explained. "Emory and other institutions that participate in investigational trials for the National Cancer Institute are assessing drugs without ever really knowing if they get to the brain, or whether they do what they are supposed to do once they are there. What we have piloted here is a very straightforward way of getting that information," he told *The Oncology Report*.

Dr. Olson and colleagues used microdialysis to monitor local concen-

trations of high-dose methotrexate that were systemically administered in patients with recurrent and refractory glioblastoma multiforme following surgical biopsy or partial resection of their tumors. "We used methotrexate because it is a very standard and well-known drug and we already knew that it got into the brain. We just wanted to test our system," he explained.

A microdialysis catheter was placed within residual contrast enhancing tumor at the time of surgery or biopsy. Methotrexate was administered as a 4-hour IV infusion and plasma and microdialysate were collected at 30-minute intervals from 1 hour before dosing to 24 hours after completing the infusion. High performance liquid chromatography with mass spectrometric detection was used to measure high-dose methotrexate concentrations.

Reporting the results on the first patient to be tested, Dr. Olson noted that plasma concentrations of high-dose methotrexate showed expected results. The microdialysis assay showed that concentrations of high-dose methotrexate in extracellular fluid within the tumor rose rapidly to a maximum of 57 μ M and subsequently decayed in a monoexponential manner

with a half-life of 12.3 h. "As this was considerably slower than the loss of high-dose methotrexate from plasma, high-dose methotrexate concentrations in the perfusate actually exceeded the plasma levels beginning at 16 hours after the MTX [high-dose methotrexate] infusion ended," he observed.

This initial experience has demonstrated the ability to measure intratumoral concentrations of a chemotherapeutic agent in a brain cancer patient using microdialysis techniques, Dr. Olson concluded. "The analysis systems are all FDA approved. We're not inventing anything here. The only thing that is not being done is getting chemists to measure some novel agent in the extracellular fluid of the brain to see if it's really getting there. This approach could significantly impact the selection of drugs, dosing schedules, and routes of administration in clinical neuro-oncology trials."

Olson JJ, Supko JG, Phuphanich S, et al. Intratumoral pharmacokinetics determined with microdialysis in a patient with glioblastoma multiforme following systemic administration of high dose methotrexate. Paper presented at the 96th Annual Meeting of the American Association for Cancer Research; April 16-20, 2005; Anaheim, Calif. Abstract 3996.

Investigators are assessing drugs without ever really knowing if they get to the brain, or whether they do what they are supposed to do once they are there.

—Jeffrey J. Olson