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INSIDE

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Peer reviewer M. Flint Beal, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company having ties to this field of study.

A Promising New Treatment for Malignant Gliomas

ABSTRACT & COMMENTARY

By Andrew B. Lassman, MD

Assistant Attending Neurologist, Memorial Sloan-Kettering Cancer Center

Dr. Lassman reports no financial relationship relevant to this field of study.

Synopsis: *New combination chemotherapy protocol for malignant glioma improves 6-month progression-free survival for a dismal disease.*

Source: Vredenburgh JJ, et al., Phase II Trial of Bevacizumab and Irinotecan in Recurrent Malignant Glioma, *Clin Cancer Res*. 2007 Feb 15;13(4):1253-1259.

PATIENTS WITH RECURRENT MALIGNANT GLIOMAS (WORLD Health Organization grade III-IV tumors) were treated with the vascular endothelial growth factor (VEGF) inhibitor bevacizumab (Avastin; Genentech) and the topoisomerase 1 inhibitor irinotecan (CPT11) in a phase II prospective clinical trial. There were 32 patients, 9 with grade III gliomas (7 anaplastic astrocytoma (AA), 2 anaplastic oligodendroglioma (AO)) and 23 with grade IV gliomas (glioblastoma multiforme (GBM)). Responses (at least 50% decrease in cross-sectional area of contrast enhancing tumor on brain MRI) were seen in 63% of patients (61% for GBMs, 67% for AA/AO). The median progression-free survival (length of time patients were alive and without tumor growth) was 23 weeks (20 weeks for GBM, 30 weeks for AA/AO). Complications included thrombo-embolic events in 4 patients, including 3 with deep venous thromboses or pulmonary emboli and one with ischemic stroke. There were no central nervous system hemorrhages. Therefore, the combination is active in recurrent malignant glioma with acceptable toxicity.

COMMENTARY

Gliomas of WHO grade II-IV are diffusely infiltrative tumors that are not surgically curable and carry a dismal prognosis. GBMs are the most aggressive and most common subtype with a

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median survival of approximately 12 months despite aggressive surgery, radiotherapy, and chemotherapy. The most commonly used treatment strategy for newly diagnosed GBM is maximal surgical resection followed by concurrent radiotherapy and chemotherapy with the DNA alkylating agent temozolomide (Temodar; Schering-Plough) followed by at least 6 monthly cycles of adjuvant temozolomide (Stupp R et al., Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005 Mar 10;352(10):987-996.) However, essentially all patients eventually develop disease recurrence, for which prognosis is dismal.

The results of the phase II study of bevacizumab + irinotecan by Vredenburgh et al suggest that the treatment they employed is superior to any other presently available therapy. Most chemotherapy regimens for recurrent GBM are associated with response rates of 20% or less, where the authors here reported 61% response rate. Another commonly used outcome measure in recurrent GBM trials is the 6-month progression-free survival rate (6mPFS rate), defined as the percentage of patients who are alive and free of tumor growth 6 months after starting an experimental therapy. Use of the 6mPFS rate to measure efficacy helps to account for durability of response as well as tumor stabilization (neither tumor growth nor response). For patients with GBM, pooled results of 8 negative phase II trials generated a 6mPFS rate of 15% (Wong ET, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol*. 1999 Aug;17(8):2572-2578.). The 6mPFS rate observed here was 30% for patients with GBM, again suggesting the superior efficacy of this regimen.

However, it remains unclear whether the responses seen, and 6mPFS rate calculated, which depends on radiographic measurement of enhancing disease, is a true reflection of underlying tumor cell death or simply a masking of blood-brain barrier breakdown measured by gadolinium uptake. For example, contrast enhancement can shrink dramatically following treatment with corticosteroids (Watling CJ, et al. Corticosteroid-induced magnetic resonance imaging changes in patients with recurrent malignant glioma. *J Clin Oncol*. 1994 Sep;12(9):1886-1889.). although the underlying tumor has not significantly changed. It is possible that bevacizumab is having a similar effect, although the authors make strong arguments to the contrary. It also remains unclear whether the irinotecan contributes significantly to the responses, or whether the same results would be seen by bevacizumab alone. Finally, it should be noted that although the 6mPFS rate for patients with recurrent GBM reported here (30%) exceeded that of the Wong study (15%), the 95% confidence intervals overlapped (16%-57% vs 10%-19%), further emphasizing the need for the ongoing larger confirmatory multicenter study that is in progress to determine the level of significance to attach to these results. ■

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PLS or ALS?

ABSTRACT & COMMENTARY

By Michael Rubin, MD
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Dr. Rubin is on the speaker's bureau for Athena Diagnostics, and does research for Pfizer and Merck.

Synopsis: *The clinical presentation of PLS and ALS are similar, and it may be difficult to distinguish them early in the course.*

Sources: Tartaglia MC et al. Differentiation between primary lateral sclerosis and amyotrophic lateral sclerosis. *Arch Neurol.* 2007;64;232-236.

Mezzapesa DM, et al. Whole-brain and regional brain atrophy in amyotrophic lateral sclerosis. *AJNR Am J Neuroradiol.* 2007; 28:255-259.

CAN ONE, EARLY ON, DIFFERENTIATE PRIMARY LATeral sclerosis (PLS) from amyotrophic lateral sclerosis (ALS)? To address this question, retrospective

review of PLS (n = 43) and ALS (n = 661) patients seen at the Motor Neuron Disease Clinic at the University of Western Ontario, between 1990-2006, was undertaken. El Escorial and Pringle (Brain 1992;115;495-520) diagnostic criteria were used to classify ALS and PLS patients, respectively. All patients underwent nerve conduction studies and electromyography, and PLS was diagnosed only in the absence of lower motor neuron abnormalities on electrodiagnostic studies. Patients were evaluated for a myriad of symptoms and signs, including dysarthria, dysphagia, fasciculations, cramping, weakness, wasting, dementia, and parkinsonism. Concomitant illness was also assessed, including HIV, diabetes, epilepsy, malignancy, and cardiac, thyroid, rheumatologic, respiratory, and autoimmune disease. Statistical analysis included Mann-Whitney tests and logistic regression.

No significant gender difference was seen between the 2 groups. ALS onset was later than PLS, 59 vs 54 years, respectively ($P = 0.009$). At presentation, stiffness was the only symptom significantly ($P < 0.001$) more frequent in PLS (47%) compared to ALS (4%). At follow up, PLS patients rarely developed muscle wasting (2%), and their survival was significantly longer (11.2 vs 3.8 years, $P < 0.001$). Bulbar dysfunction was significantly more frequent in ALS than PLS (88% vs 74%, $P = 0.01$). Parkinsonism, cerebellar and sensory abnormalities were rare in both groups. Trauma was more often a historical feature of PLS than ALS, 19% vs 8% ($P < 0.05$), but the only medical condition significantly associated with either disease was autoimmune disorders, seen in 5 PLS vs 1 ALS patient ($P = 0.002$). Over 16 years of follow up, ALS survival was 33%, compared to 89% in PLS ($P < 0.001$). Less than 3% of motor neuron disease patients have PLS and spasticity is the only presenting sign significantly more common in PLS than ALS. If wasting has not developed in such patients by 3 years after onset, PLS rather than ALS is the likely diagnosis.

COMMENTARY

Although primary lateral sclerosis (PLS) and amyotrophic lateral sclerosis (ALS) are considered diseases of the motor neuron, there is evidence to suggest that the neuropathology of ALS extends beyond the motor system. Clinical, neuropsychological, and brain magnetic resonance (MR) studies, the latter using specific software to estimate brain atrophy and voxel-based morphometry to indicate selective volumetric loss, were performed on 16 patients who satisfied El Escorial criteria for ALS. None demonstrated clinically evident dementia, behavioral impairment, or personality change. All underwent cognitive evaluation including memory, language, and attention tests, encompassing concentration and processing speed as well. Depression was assessed using the Beck Depression Inventory. Nine healthy subjects served as controls. Statistical analysis included the Fisher Exact Test, nonparametric Mann-Whitney U test, and multivariate logistic regression.

None of the patients were depressed. Among the neuropsychological tests, only the Symbol Digit Modality test was significantly worse in ALS patients compared to healthy controls. Mini mental status testing was done, including Spinnler Prose Memory test, verbal fluency, and Brown-Peterson Interference tests were no different between the groups. MR whole brain measures were comparable between controls and ALS patients. Brain parenchymal fraction was slightly but significantly ($P = 0.012$) lower in the latter, correlating with the presence of cognitive impairment rather than ALS, with gray-matter volume-loss bilaterally in several frontal and temporal regions, slightly more on the right. In light of recent associations between ALS and fronto-temporal dementias (tauopathies), ALS may indeed be a neurodegenerative disease that is more extensive than previously thought.

Can Intractable Temporal Lobe Epilepsy be Determined Early in the Course of the Disease?

ABSTRACT & COMMENTARY

By Cynthia L. Harden, MD

Professor of Neurology and Neuroscience, Comprehensive Epilepsy Center, Weill Medical College of Cornell University

Synopsis: *The presence of hippocampal sclerosis, by itself, does not predict the clinical course of temporal lobe epilepsy.*

Source: Briellmann RS, et. al. Hippocampal sclerosis: MR prediction of seizure intractability. *Epilepsia*. 2007;48(2):315-323.

USING 3 TESLA MAGNETIC RESONANCE (MR) imaging, these investigators compared brain MR characteristics of 24 subjects with intractable tempo-

ral lobe epilepsy (TLE) with 17 subjects with mild TLE, and 60 normal controls. Specifically, the MR parameters studied were hippocampal volumes, T2 relaxometry in the hippocampus, amygdala, thalamus and white matter of the anterior temporal lobe (ATL) and frontal lobe, as well as proton MR spectroscopy (MRS) of the temporal lobe. The authors differentiated the intractable TLE from the mild TLE groups by seizure frequency; the intractable patients had an average of 3 complex partial seizures per week, while most of the mild TLE patients had no seizures for 3 months before the investigation, and the remainder had one mild complex partial seizure per month.

The rather surprising results showed no difference in hippocampal volumes or hippocampal T2 signal increase between the 2 epilepsy groups, and age at onset and duration of epilepsy were the same across the epilepsy groups. The MR characteristics that differentiated the high vs the low seizure frequency groups were T2 signal abnormality in the ATL white matter, and hippocampal N-acetylaspartate concentration determined by MRS in the temporal lobe ispilateral to the seizure focus; both were significantly more abnormal in the high seizure frequency group. The authors speculate that hippocampal T2 signal increase and decreased hippocampal volume, a complex known as hippocampal sclerosis (HS), and often present in temporal lobe epilepsy, is conferred by the presence of epilepsy but not by intractable epilepsy. However, abnormal T2 signal in the ATL white matter and abnormal MRS seizure-producing hippocampus are associated with intractable epilepsy, as defined by high complex partial seizure frequency.

COMMENTARY

These interesting results provide insight into how recurrent temporal lobe seizures affect brain structures, and perhaps provide a "surrogate marker" for intractable epilepsy. The findings would be useful for aiding in the decision to offer temporal lobe resection for persons with TLE; the presence of these markers may indicate ongoing temporal lobe injury and dysfunction in TLE whereas the findings associated with HS only support the diagnosis of TLE. It is now well appreciated that not all persons with HS have intractable epilepsy and may have only rare seizures throughout their lives. The ATL T2 increased signal and MRS information would also be potentially useful for managing patients who have difficulty reporting their seizure frequency since they may be amnestic for the events.

One limitation of this study is that data were obtained using a 3 Tesla MR scanner, which is not in widely available at this time. Further, although MRS N-acetylaspartate values are also not standardized, the findings suggest that reliable temporal lobe MRS N-acetylaspartate values as a fraction of normal control values may be useful in the MR evaluation of TLE patients and should further developed.

Although the authors make a clear case for how their intractable TLE patients were differentiated from their "mild" TLE group, the usefulness of self- and observer-reporting of seizure frequency can be questioned. The MR findings that differentiated these 2 groups really only differentiates between high and low seizure frequency reporting. It may be that these parameters do not differentiate between an intractable or nonintractable epileptic syndrome. This may be especially applicable to the MRS findings, which are known to be very dynamic in their representation of brain function. However, the ATL signal abnormality is likely a more reliable reflection of ongoing temporal lobe injury and intractable epilepsy itself.

Frontal Lobe Epilepsy Surgery — The Importance of Patient Selection

ABSTRACT & COMMENTARY

By Theodore H. Schwartz, MD, FACS

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Dr. Schwartz reports no financial relationship relevant to this field of study.

Synopsis: *Surgery for frontal lobe epilepsy can be very effective in patients with a localized ictal onset zone, focal MRI abnormalities, nocturnal epilepsy and complete resection of the epileptic zone and/or imaging abnormality.*

Sources: Jeha LE et. al. Surgical outcome and prognostic factors of frontal lobe epilepsy surgery. *Brain*. 2007;130:574-584.

Nobili L, et. al. Surgical treatment of drug-resistant nocturnal frontal lobe epilepsy. *Brain.* 2007;130:561-573.

As opposed to temporal lobe epilepsy, which has a well-documented 70%-80% rate of seizure-freedom following surgery in well-selected cases, frontal lobe epilepsy surgery is more controversial. Published reports indicate that anywhere from 13%-

80% of patients are seizure-free after surgery. Many of these reports are from the pre-MRI era and lump together patients with lesional and non-lesional epilepsy. Hence, there is little data on predictors of successful frontal lobe epilepsy.

Two recent articles in *Brain* address the question of outcome following frontal lobe epilepsy surgery. From the Cleveland Clinic, Jeha et al present 70 patients who underwent frontal lobe resections for intractable epilepsy. Overall, seizure-free rates started at 56% at one-year but decreased to 30% after 5 years. However, the authors were able to identify the most important factors that predicted a favorable outcome. Patients with MRI abnormalities limited to the frontal lobe, absence of generalized ictal EEG patterns, absence of early post-operative seizures and complete resection of the epileptic focus or imaging abnormality were more likely to be seizure-free after surgery. Patients with any one of these predictors had a 40% seizure-free rate at 5 years. Patients with all the indicators had an 85% chance of being seizure-free.

Nobili et al report from Milan on 21 patients with nocturnal frontal lobe epilepsy (NFLE). Patients with NFLE present with seizures that occur almost exclusively during sleep. Although NFLE is thought to be a benign medication-responsive type of epilepsy, ~30% of patients are resistant to medical treatment and suffer from, not only frequent seizures, but also excessive daytime sleepiness. Although half of the patients in this study had normal MRI scans, following surgery 76% were seizure-free after a mean follow-up of 42 months and 100% were improved (Engel I-III). Remarkably, all patients with excessive daytime sleepiness were relieved of this symptom, even if they were not cured of their seizures. The authors attribute their success to the high rate of patients with Taylor-type focal cortical dysplasia. Morbidity was quite low with only transient motor signs related to the proximity of the resections to the supplementary motor area.

COMMENTARY

Unlike the temporal lobe, the frontal lobe is a large region of relatively homogeneous-looking brain. The medial surface lies along the falx and the inferior surface along the base of the anterior fossa, both areas difficult to expose with a standard craniotomy. MR imaging in patients with frontal lobe epilepsy often reveals no obvious abnormality. Consequently, identification and adequate resection of topographically large and complex frontal lobe epileptogenic regions can be quite difficult. Migration abnormalities, which may involve widespread areas of brain, are common in the frontal lobe and the semiology of the seizures is often ambiguous. For this reason, some epileptologists are reluctant to pursue an aggressive surgical approach in patients with suspected frontal lobe epilepsy for fear that the risks of surgery may outweigh the perceived low therapeutic yield.

Both articles presented in this paper indicate that frontal lobe epilepsy surgery can be extremely successful and even approach the success rates for temporal lobe surgery. Not surprisingly, the more focal the EEG and imaging abnormalities, the more successful the surgery. The authors imply that with appropriate patient selection at a high volume center, following aggressive work-up (>75% of the patients required invasive subdural electrode monitoring), the outcome will be favorable enough to outweigh the risks. However, several questions remain unanswered. First, neither author actually presents the surgical risks in any detailed fashion. Jeha et al don't even mention any risks or adverse outcomes from surgery. Perhaps the authors felt that surgical risks were not the focus of the paper, yet these must be weighed closely against the chance of attaining seizure-freedom and are critical to the decision-making process. Second, it has been well-understood for years that the more focal the epileptogenic region, the more successful the surgery. For decades, papers have argued that epilepsy surgery should be performed at high volume centers to increase its efficacy since patient selection is so critical. Nevertheless, at the Cleveland Clinic, 25% of the patients with frontal lobe epilepsy who were selected for surgical resection had multifocal ictal onsets. Either the intent was palliative, in which case they should not be included in this paper on cure rates, or physicians at tertiary care epilepsy centers feel obliged to offer aggressive therapy even in cases with a low chance of cure. Once a patient is implanted with electrodes, it is difficult to remove them without offering a surgical resection that might improve their outcome, even if the chance of enduring cure is low. Hopefully, we can use the data from these articles to eliminate patients from consideration for surgery if their outcome will not likely be favorable. On the other hand, even a 15% cure-rate might be worth the risk in very severe cases.

Finally, it is most interesting to note that patients with NFLE and excessive daytime sleepiness observed resolution of this symptom after frontal lobe surgery, even if their seizures were only improved but not cured. It has long been a dictum in epilepsy surgery that patients' quality of life does not improve unless they are

completely seizure-free. Hopefully the authors will measure quality of life using a validated questionnaire in this group of patients to confirm this finding. ■

Cheynes-Stokes Respiration in Acute Stroke

ABSTRACT & COMMENTARY

By John J. Caronna, MD

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Dr. Caronna reports no financial relationship relevant to this field of study.

Synopsis: *Recent imaging studies reinforce the classical concept that periodic breathing in acute stroke indicates a large supratentorial infarct or hemorrhage.*

Source: Rowat AM, et al. Abnormal breathing patterns in stroke: relationship with location of acute stroke lesion and prior cerebrovascular disease. *J. Neurol Neurosurg Psychiatry*. 2007;78:277-279.

Periodic breathing (PB) is an abnormal pattern of respiration in which cyclic increases in the rate and depth of breathing alternate with a reduction or complete cessation of respiratory effort. Most clinicians use the term Cheynes-Stokes Respiration (CSR) to denote crescendo-decrescendo breathing. The causes of PB include pulmonary disease, cardiac failure, and neurogenic disturbances of respiratory control. In 1980, Plum and Posner[1] stated that CSR implied bilateral dysfunction of deep structures in the cerebral hemispheres and diencephalons. They observed, however, that in reports where CSR was associated with structural brain lesions, the sites of damage found at autopsy ranged widely from the forebrain to the rostral pons. In their experience, the emergence of CSR in patients with supratentorial mass lesions sometimes provided a valuable sign of incipient transtentorial herniation. More recent studies have failed to find any association between CSR and the location of brain lesions on imaging studies.[2]

Rowat and associates sought to determine in acute stroke patients whether PB is associated with acute involvement of any particular part of the brain or with the extent of total damage. In 134 patients with acute stroke, breathing pattern was recorded using portable continuous monitoring equipment. Patients underwent either CT or MRI scanning of the brain. A neuroradiologist blind to breathing patterns and clinical results classified the acute stroke lesions and prior cerebrovascular disease on brain images.

PB was identified in 31/134 (23%) of acute stroke patients. In these patients, there were 26 ischemic infarcts and 5 intracerebral hemorrhages. Twenty-eight acute lesions were supratentorial and 3 were infratentorial in location. There was no relationship between PB and either unilateral or bilateral lesions in any discrete brain location. PB was associated with large acute hemisphere strokes rather than small or medium-sized ones ($P = 0.01$) and with strokes causing severe rather than no or only mild mass effect ($P = 0.03$). There was no association between PB and severe prior cerebrovascular disease on brain imaging.

The authors concluded that PB is related to acute, not old, strokes, particularly to large acute hemisphere lesions with mass effect.

■ COMMENTARY

Breathing is a vital function that is integrated by nervous influences that arise from nearly every level of the brain and upper spinal cord. It is not surprising, therefore, that Rowat and associates found no specific PB-associated "respiratory center" in the brain. It should be noted that the present study was limited because it relied mainly on CT imaging and, therefore, it is possible that damage to small brain areas, especially those in the brainstem, was undetected.

That PB is associated with large supratentorial lesions that cause brain shift agrees with the pre-CT and pre-MRI era observations of Plum and Posner.[1] It may be in such cases that increased intracranial pressure or herniation stimulates efferent sympathetic vasoconstrictor pathways triggering pulmonary edema and cardiac failure that produce PB. If so, central or "neurogenic" PB would reflect cardiopulmonary dysfunction as well as brain damage.

The present study has not clarified the relationship of brain damage to CSR. It does, however, reaffirm the value of clinical observation of breathing pattern in acute stroke. ■

References:

1. Plum F, Posner JB. *The Diagnosis of Stupor and Coma*. 3rd Edition. FA Davis, Philadelphia 1980.35-36.
2. Nachtmann A, et al. *Neurology*. 1995; 45:820-821.

Anticoagulant Related Intracerebral Hemorrhage — Favorable Outcomes with Surgical Treatment

ABSTRACT & COMMENTARY

By Alan Z. Segal, MD

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Dr. Segal is on the speaker's bureau for Boehringer-Ingelheim.

Synopsis: *Selected patients with anticoagulation-associated intracerebral hemorrhage may benefit from surgical evacuation.*

Source: Rabinstein AA, Wijdicks EF. Determinants of outcome in anticoagulation-associated cerebral hematoma requiring emergency evacuation. *Arch Neurol.* 2007;64:203-206.

As the population ages, atrial fibrillation has become even more prevalent. In this setting, over the past decade, use of warfarin for stroke prophylaxis has approximately quadrupled. At the same time, the incidence of intracerebral hemorrhage (ICH) has increased over 10 fold, particularly among patients over the age of 80. This group is at particular risk for ICH, at least in part due to underlying cerebral amyloid angiopathy (CAA), which is typically unrecognized until after an often-major incident hemorrhage.

Warfarin associated ICH is associated with a more ominous prognosis than sporadic ICH, with significant risk of hematoma expansion over the initial 24 hours of hospitalization. Immediate reversal of anticoagulation with Vitamin K and fresh frozen plasma is crucial. Recombinant activated Favor VIIa is now an alternative standard of care for anti-coagulant associated ICH and we are awaiting Phase III data regarding efficacy in any ICH case.

Rabinstein reports on 17 consecutive patients at the Mayo Clinic who underwent craniotomy for evacuation of ICH between the years of between 1977 and 2004. Hypertension affected over 70% of patients. Since there is significant overlap between HTN and CAA in this population, neither could be specifically identified as causal in Rabinstein's series. Mean hematoma volume was 75cc, with shift of midline structures in all patients. Functional outcome at one year was favorable in 11 (65%) of the patients (mRS ≤ 3). Five of 6 patients, who failed to recover meaningfully, died; all of these developed serious medical complications. Among those who died, 3 of 5 awoke within the first day after surgery but later had systemic complications. There was no difference in outcomes based on incidence of HTN, indication for anticoagulation, INR level, time to surgery, depth of coma, size of hematoma, or degree of shift. Patients with unfavorable outcomes were significantly older. All patients with a heparin-associated bleed (n = 4) had a favorable outcome.

COMMENTARY

Despite multiple studies, there has been little data to support surgery for intracerebral hemorrhage. Surprisingly, in the current study of the most severe form of ICH, which associated with anticoagulants, surgical intervention produced a favorable outcome in a majority of cases. This was achieved despite huge hematoma volumes, well above the 60 ml cutoff associated with a poor prognosis in prior studies. Not surprisingly, advanced patient age was a negative prognostic factor and medical complications played a major role in mortality. With a lack of control patients, these data comprise a case series, rather than a comparative study. They do, however, indicate that an aggressive surgical approach, in concert with rapid reversal of coagulopathy, may be indicated for selected patients, who otherwise have a uniformly poor prognosis. ■

CME Questions

16. What is bevacizumab?

A) a tyrosine kinase inhibitor
B) a humanized monoclonal IgG anti-VEGF receptor antibody
C) a humanized monoclonal IgG anti-VEGF antibody
D) a topoisomerase inhibitor

17. What is irinotecan?

A) a tyrosine kinase inhibitor
B) a humanized monoclonal IgG anti-VEGF receptor antibody
C) a humanized monoclonal IgG anti-VEGF antibody
D) a topoisomerase inhibitor

18. Periodic breathing is associated with:

A) Unilateral lesions in the hypothalamus.
B) Bilateral lesions in the rostral pons.
C) Chronic ("old") infarcts, hemorrhages and periventricular white matter lesions
D) Hemispheric mass lesions causing brain shift
E) Small lesions in the cerebral hemispheres

19. Choose the correct statement

A) Trauma is more often a historical feature of ALS than PLS
B) PLS onset is usually later than ALS
C) At presentation, stiffness is the only symptom significantly more frequent in PLS compared to ALS
D) Bulbar dysfunction is significantly more frequent in PLS than ALS
E) Autoimmune disorders are more common in ALS than PLS

Answers: 16.(c) 17.(d) 18.(d) 19.(c)

CME Objectives

The objectives of *Neurology Alert* are:

• To present the current scientific data regarding diagnosis and treatment of neurological disease, including stroke, Alzheimer's disease, transient ischemic attack, and coma;

• To discuss the pathogenesis and treatment of pain;

• To present basic science lessons in brain function;

• To discuss information regarding new drugs for commonly diagnosed diseases and new uses for traditional drugs;

• To discuss nonclinical issues of importance to neurological, such as the right to die and the physician's legal obligation to patients with terminal illness. ■

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Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Which Inhaler Combination is Best for COPD Treatment?

Two recent large studies have looked at the effects of various inhaler combinations on outcomes in patients with COPD. In the first, published in the February 22 issue of the *New England Journal of Medicine*, researchers from the United Kingdom looked at over 6,000 patients with COPD in a randomized, double-blind trial comparing salmeterol plus fluticasone inhaler twice daily (in a single inhaler) vs salmeterol alone, fluticasone alone, or placebo for 3 years. The primary outcome was death from any cause, the frequency of exacerbations, health status, and spirometry values. The all-cause mortality was 12.6% in the combination therapy group, 13.5% in the salmeterol group, 16.0% in the fluticasone group and 15.2% in the placebo group. The hazard ratio for death in the combination therapy group was 0.825 vs placebo ($P = 0.052$), a level that did not reach statistical significance, but was associated with a 17.5% relative reduction in mortality. The mortality rate for salmeterol alone or fluticasone alone did not differ from placebo. Combination therapy was associated with a statistically significant lower rate of exacerbations ($P < 0.001$). The probability of having pneumonia was higher among patients receiving fluticasone alone or medications containing fluticasone (*N Engl J Med*. 2007;356:775-789). An accompanying editorial suggests that the findings show that monotherapy with fluticasone should not be recommended, monotherapy with a bronchodilator may be an option, and that combination therapy "offers statistically significant advantages for health status, frequency of exacerbations, use of oral steroids... and protection against a decline in lung function" (*N Engl J Med*. 2007;356:851-854).

In the second study, 449 patients with moderate or severe COPD were treated with the anticholinergic inhaler tiotropium plus placebo, tiotropium plus salmeterol, or tiotropium plus fluticasone/salmeterol. The primary endpoint was COPD exacerbation that required treatment with systemic steroids or antibiotics. After one year there was no difference in the rate of exacerbation between tiotropium alone (62.8%), tiotropium plus salmeterol (64.8%), or tiotropium plus fluticasone/salmeterol (60.0%). Tiotropium plus fluticasone/salmeterol improved lung function ($P = 0.049$), disease-specific quality of life ($P = 0.01$), and reduced the number of hospitalizations for COPD exacerbation and all-cause hospitalization compared with tiotropium plus placebo. The authors conclude that adding fluticasone/salmeterol to treatment with tiotropium did not influence rates of COPD exacerbation but did improve lung function, quality of life, and hospitalization rates (early release *Annals of Internal Medicine* 2/20/2007, print date 4/17/2007). So, what is the upshot of these papers? Combination inhalation therapy in patients with COPD works best, bronchodilator plus steroid inhalation therapy should continue to be the recommended regimen perhaps along with an anticholinergic inhaler.

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First Antihypertensive Drug Approved in Last 10 Years: Aliskiren

The FDA has approved the first of new class of antihypertensive drugs, and the first new antihypertensive medication to be approved in more than 10 years. Aliskiren is an oral renin inhibitor, inhibiting the renin-angiotensin system earlier in the cascade than angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. The drug is a once-a-day oral agent that is approved for use as monotherapy or in combination with other antihypertensives.

Aliskiren's effect is additive with hydrochlorothiazide, and seems to be well-tolerated with other cardiovascular agents. It will be available in 150 and 300 mg doses. The FDA approval was based on 6 placebo-controlled trials in more than 2,000 patients in which the blood- pressure-lowering effect was maintained for up to one year. The drug seems be effective across all age ranges, but is slightly less effective in African-American patients as compared to Caucasians and Asians, as is the case with ACEI's and ARBs. The primary side effect is diarrhea, which was seen in 2% of patients, usually on higher doses. Angioedema was also rarely noted. As with other drugs that affect the renin-angiotensin system, aliskiren should not be used during pregnancy. Aliskiren will be marketed by Novartis Pharmaceuticals, and will be marketed under the trade name Tekturna.

Alternate Treatment for Osteoporosis

Antiresorptive agents are standard therapy for osteoporosis. These drugs, which include the bisphosphonates (alendronate, risedronate, etc.) prevent bone breakdown, but they do not stimulate production of new bone. A new study looks at recombinant human parathyroid hormone (1-84) (PTH), a bone forming agent, as an alternative treatment for osteoporosis. In an 18 month, randomized, double-blind, placebo-controlled, parallel group study, 2,532 postmenopausal women with low bone mineral density at the hip or lumbar spine were randomized to receive 100 µg of PTH or placebo daily by subcutaneous injection. All received additional calcium 700 mg/d and vitamin D 400 U/d. The main outcome was new or worsened vertebral fractures, changes in bone mineral density as well as safety of the medication. PTH significantly reduced the risk for new or worsened vertebral fractures. The relative risk varied depending on the assumptions about women who did not complete the trial, but there was improvement in all subgroups. PTH also resulted in increased bone mineral density compared to placebo of 6.9% at the spine and 2.1% at the hip compared to placebo, but decreased bmd at the forearm. PTH also resulted in increased percentage of participants with hypercalciuria, hypercalcemia, and nausea by 24%, 23%, and 14% respectively compared to placebo. The authors conclude that parathyroid hormone (1-84) reduced the overall risk for new or worsened vertebral fractures in postmenopausal women with osteoporosis, and suggest that PTH provides an alternative therapy option for fracture prevention (*Ann Int Med.* 2006;146:326-339). This study adds a second option for anabolic (bone-forming) agents along with teriparatide.

Roche's Oseltamivir: Scrutiny, Bird Flu, and New Drug Applications

Roche's oseltamivir (Tamiflu) has come under scrutiny in Japan after 2 students who took the drug fell to their deaths in February. The drug has been associated with abnormal behavior in anecdotal reports including a Japanese boy who ran in front of a truck after taking the drug in 2004. Roche counters that influenza can cause abnormal behavior and denies a link between the medication and psychiatric problems. The drug has previously been associated with delirium, and the FDA has required labeling urging close monitoring for abnormal behavior since November 2006. Countries worldwide are stockpiling oseltamivir in case of avian influenza outbreak. Meanwhile Roche has filed a new drug application with the FDA for pediatric doses of the drug for children one year and older. The new capsules and a 30 milligram and 45 mg capsule would join the 75 mg adult strength capsule.

FDA Actions

The FDA has approved duloxetine (Cymbalta) for the treatment of generalized anxiety disorder. The drug is currently approved for the treatment of major depressive disorder in the management of diabetic peripheral neuropathic pain. The FDA approved duloxetine 60 mg once daily for the treatment of anxiety based on three randomized, double-blind placebo-controlled trials in 800 patients.

The FDA has approved lisdexamfetamine dimesylate capsules for the treatment of attention deficit/hyperactivity disorder in children age 6-12. Lisdexamfetamine is a pro-drug of dextroamphetamine that may be associated with less drug abuse than dextroamphetamine. The once-a-day drug will be available in 30, 50, and 70 mg strengths. Lisdexamfetamine is marketed by New River Pharmaceuticals under the trade name Vyvanase. ■