In all 3 medulloblastoma models, tumor growth was significantly slowed by MBZ treatment, whereas in untreated controls, tumors extended into the ventricles, resembling the human disease. Overall survival was prolonged by 150% in the SHH allograft model and by 100% in the SHH vismodegib-resistant allograft model. In the group 3 xenograft model, median survival was increased by a striking 129% from 21 to 48 days ($P < 1 \times 10^{-4}$; Figure). Tumors from MBZ-treated mice lacked the phenotype of hypervascularity and widespread hemorrhage seen at terminal stages in untreated mice. Microvascular density was greatly reduced within treated compared with untreated tumors. Notably, MBZ treatment did not alter the microvascular density within regions with no tumor involvement. Immunohistochemistry of MBZ-treated tumors revealed a marked absence of autophosphorylated VEGFR2 despite the presence of VEGF ligand, suggesting MBZ inhibition of VEGFR2 kinase activity. This inhibition was seen in the autophosphorylation assay with MBZ-treated human umbilical vein endothelial cells and in the cell-free VEGFR2 kinase assay.

MBZ prolonged survival in the SHH molecular subtype, a vismodegib-resistant SHH model, and a xenograft model of the group 3 subtype bearing the worst prognosis. This study shows encouraging antiangiogenic effects of MBZ that are limited to the tumor neovasculature and likely mediated through the inhibition of VEGFR2 kinase activity. These data add to the recognition of MBZ as an anticancer agent, including as an antiglioma therapy currently in clinical trials. Achieving adequate intracranial concentrations of other microtubule inhibitory chemotherapy agents such vincristine without neurocognitive sequelae remains challenging. The low-toxicity profile of MBZ, particularly in children, its additional role as an antiangiogenic agent, and the survival outcomes seen in this study further compel the initiation of clinical investigations into the use of this drug for medulloblastoma.

Imithri Bodhinayake, MD*
Marc Symons, PhD*
John A. Boockvar, MD*‡
**The Feinstein Institute for Medical Research*
Manhasset, New York
‡Lenox Hill Hospital
New York, New York

REFERENCE

1. Bai R, Staedtke V, Rudin CM, Bunz F, Riggins GJ. Effective treatment of diverse medulloblastoma models with mebendazole and its impact on tumor angiogenesis. *Neuro Oncol.* 2014. doi: 10.1093/neuonc/nou234. Available at: http://neuro-oncology.oxfordjournals.org/content/early/2014/09/24/neuonc.nou234.long.

Defining the Role of Epidural Steroid Injections in the Treatment of Radicular Pain From Degenerative Cervical Disk Disease

Upper-extremity pain caused by cervical radiculopathy is one of the most common complaints seen by spine surgeons in the clinic, and the prevalence of this condition is up to 3.5 per 1000 people.[1] Although 26% of patients undergo surgery,[2] usually in the form of anterior cervical diskectomy and fusion or posterior cervical foraminotomy, others are managed conservatively with physical therapy, pharmacotherapy, and epidural steroid injections (Figure). Although epidural steroid injections have been in use since the early 20th century and have become increasingly popular since the 1990s, there is currently little evidence to help clinicians understand whether this intervention works and which group of patients are most likely to experience an improvement in symptoms.[3] One recent randomized, multicenter study published in the *New England Journal of Medicine* by Friedly et al,[4] which was discussed in a previous issue of "Science Times," demonstrated that patients with leg pain resulting from lumbar stenosis did not experience any benefit from epidural glucocorticoid injections over patients who received epidural lidocaine only.[5] In a recent issue of *Anesthesiology*, Cohen et al[6] put forth a new multicenter, prospective, randomized, comparative-effectiveness trial to compare different nonsurgical therapies in the treatment of cervical radiculopathy. They found that patients who received epidural steroid

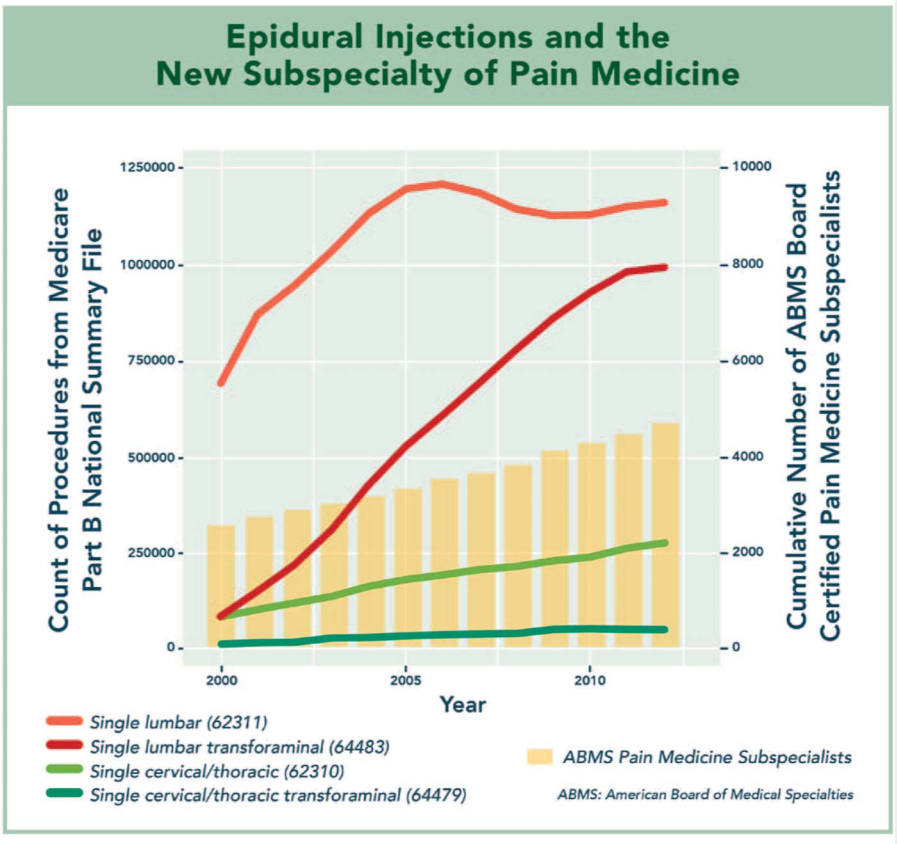

Figure. The number of epidural injections performed between 2000 and 2012 for Medicare patients, extracted from Centers for Medicare and Medicaid Services data. Reprinted with permission from Cohen et al.[6]

injections experienced a modest improvement in pain but that this was not significantly different from the improvement in patients who underwent physical therapy plus pharmacotherapy or patients who underwent a combination of physical therapy, pharmacotherapy, and epidural steroid injections over a 6-month period.

In this study, Cohen et al randomly assigned 169 consecutive subjects with cervical radiculopathy from 7 treatment facilities to 3 equal groups. The first group received cervical epidural steroid injections only; the second group underwent physical therapy plus pharmacotherapy; and the third group underwent a combination of physical therapy, pharmacotherapy, and epidural steroid injections. All patients were >18 years old, had a history of cervical radicular pain that was no less than 1 month and no more than 4 years, rated their arm or neck pain ≥4, and had magnetic resonance imaging demonstrating an anatomic correlate to their symptoms. Patients with myelopathy and patients who had undergone prior surgery were among those who were excluded. The patients in the epidural steroid group received an interlaminar injection of a 3-mL solution containing 60 mg depomethylprednisolone and normal saline at either the C6-7 or C7-T1 interspace under fluoroscopic guidance. The injection could then be repeated at 3 months and again at 6 months if the patient experienced only partial improvement or if symptoms initially resolved but later recurred. The patients in the pharmacotherapy plus physical therapy group were started on gabapentin and/or nortriptyline. The medication and dose were determined at the treating physician's discretion, and the doses were uptitrated over 16 to 24 days to reach a therapeutic range. Physical therapy began within 1 week of the initial evaluation, but patients who had previously tried and failed physical therapy could opt out of parts of the regimen that had not worked before or could even opt out of the entire regimen altogether. The patients who were in the third combination group received epidural steroid injections, pharmacotherapy with gabapentin and/or nortriptyline, and physical therapy according to the same standards as patients in the other 2 groups.[6]

The results of this study showed that all 3 groups experienced a modest reduction in both arm and neck pain. Although the largest improvements were seen in the combination group, the difference was not significant. The authors did find, however, that at 3 months patients in the combination therapy group were significantly more likely to have a positive "categorical outcome," meaning that the patient responded positively to a questionnaire about pain and satisfaction and had a 2-point improvement in arm pain. When this same outcome measure was taken again at 6 months, however, a significant difference was no longer appreciable.[6]

However, the authors speculate that perhaps their study was underpowered because the beneficial effect of combination therapy was less than expected during the design of the study. It seems more likely that there truly is not a statistical significance between the 3 treatment groups and that the nonsignificant trend toward subjectively better outcomes in the combination group may be explained simply by the placebo effect of receiving a shot. This is concordant with previous studies that have not shown a lasting benefit of epidural steroid injections over conservative treatment in the lumbar spine.[7,8] This study therefore suggests that the use of epidural steroid injections in the treatment of degenerative neck pain and cervical radiculopathy should be limited to a smaller group of patients who are also receiving physical therapy and pharmacotherapy. Additionally, given that there is no proven benefit to this procedure, which does carry risk, it may be that there is no role at all for epidural injections in the treatment of cervical radiculopathy. Rather than receiving multiple rounds of epidural injections, patients may benefit from referral to a spine surgeon for definitive decompression when conservative measures fail within the appropriate time period.

Viren Vasudeva, MD
John Chi, MD, MPH
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

REFERENCES

1. Salemi G, Savettieri G, Meneghini F, et al. Prevalence of cervical spondylotic radiculopathy: a door-to-door survey in a Sicilian municipality. *Acta Neurol Scand.* 1996;93(2-3):184-188.
2. Radhakrishnan K, Litchy WJ, O'Fallon WM, Kurland LT. Epidemiology of cervical radiculopathy: a population-based study from Rochester, Minnesota, 1976 through 1990. *Brain*. 1994;117(pt 2):325-335.
3. Rathmell JP. The proper role for epidural injection of corticosteroids. *Anesthesiology*. 2014;121(5):919-921.
4. Friedly JL, Comstock BA, Turner JA, et al. A randomized trial of epidural glucocorticoid injections for spinal stenosis. *N Engl J Med.* 2014;371(1):11-21.
5. Wang M, Serak J, Chi J. Epidural steroid injections for spinal stenosis. *Neurosurgery*. 2014;75(4):N16.
6. Cohen SP, Hayek S, Semenov Y, et al. Epidural steroid injections, conservative treatment, or combination treatment for cervical radicular pain: a multicenter, randomized, comparative-effectiveness study. *Anesthesiology*. 2014;121(5):1045-1055.
7. Koc Z, Ozcakir S, Sivrioglu K, Gurbet A, Kucukoglu S. Effectiveness of physical therapy and epidural steroid injections in lumbar spinal stenosis. *Spine (Phila Pa 1976).* 2009;34(10):985-989.
8. Laiq N, Khan MN, Iqbal MJ, Khan S. Comparison of epidural steroid injections with conservative management in patients with lumbar radiculopathy. *J Coll Physicians Surg Pak.* 2009;19(9):539-543.

Long-term Follow-up of the International Subarachnoid-Hemorrhage Aneurysm Trial

The International Subarachnoid Aneurysm Trial (ISAT) has been an ongoing landmark study that has firmly established endovascular coiling as an effective alternative therapy.

In 2002, investigators reported the initial results of 2143 subarachnoid hemorrhage (SAH) patients randomized to neurosurgical clipping (n = 1070) or endovascular treatment with detachable platinum coils (n = 1073). At the planned interim analysis, 23.7% of patients allocated to endovascular treatment were dependent or dead at 1 year compared with 30.6% allocated to neurosurgical treatment.[1] The risk of rebleeding from a ruptured aneurysm was higher in the coiled cohort. Results at 1 year were similar, with patients experiencing decreased death, dependence, and epilepsy in the endovascular cohort, but requiring an increased number of treatments and having an increased risk of rebleeding.[2] At a minimum of 6 years and a maximum of 14 years (mean follow-up, 9 years), rates of rebleeding were again higher in the endovascular group, but the risk of death was significantly lower in the coiled group. If the data are analyzed according to the primary outcome of the first two studies,[1,2] 241/867 (27.8%) in the endovascular group and 273/857 (31.9%) in the neurosurgical group had an mRS score of 3 to 6 at 5 years. The proportion of survivors at 5 years who were independent did not differ between the two groups: endovascular 83% (626 of 755) and neurosurgical 82% (584 of 713).

Recently, the authors report the results of 1644 patients in 22 UK neurosurgical centers with 10.0 to 18.5 years of follow-up (Figure).[3] The primary outcome could not definitively be ascertained, as death was assessed from the Office for National Statistics, and disability and outcome events were reported by questionnaire. At 10 years, 674 (83%) of 809 patients allocated to endovascular coiling and 657 (79%) of 835 patients allocated to neurosurgical