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Repurposing Mebendazole for the Treatment of Medulloblastoma

The current treatment for medulloblastoma—resection, radiation, and chemotherapy—negatively affects neurocognitive development and fails to ensure survival beyond 10 years for about 40% of children. Among the 4 molecular subtypes of this disease, the group 3 subtype has an especially poor prognosis. Recently, Bai and colleagues[1] demonstrated compelling preclinical evidence for using the microtubule inhibitory drug mebendazole (MBZ) to treat several molecular subtypes of medulloblastoma, including group 3. As a long-standing antihelminthic drug, MBZ has the advantage of a low-toxicity profile in children compared with other microtubule inhibitors such as vincristine and paclitaxel. As a lipophilic agent with a low molecular weight, MBZ has the additional advantage of blood-brain barrier permeability. Previous studies suggest that MBZ acts as an inhibitor of vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2), the primary receptor mediating the effects of VEGF. This study reveals the antiangiogenic effect of MBZ in medulloblastoma preclinical mouse models and its encouraging impact on overall survival.

The authors used 3 orthotopic models of medulloblastoma: a genetic model of the sonic hedgehog (SHH) molecular subtype consisting of allografts from spontaneous medulloblastomas in patched $(PTCH)^{+/-}$, $p53^{-/-}$ mice; a model of therapy-resistant SHH consisting of allografts from tumors resistant to the hedgehog pathway inhibitor vismodegib; and a xenograft model with human group 3 medulloblastoma cells, D425 MB, implanted into the cerebellum. Implanted cells were transduced with firefly luciferase–expressing lentivirus for in vivo bioluminescent imaging. Mice in the treatment group received daily oral gavage of MBZ (50 mg/kg) starting 5 days after tumor cell implantation. Tumor vasculature in brain tissue from treated animals was compared with that of phosphate-buffered saline–treated control animals by immunostaining for the endothelial marker CD31. The impact of MBZ on the kinase activity of VEGFR2 was assessed by Western blots for VEGFR2 autophosphorylation after VEGF stimulation of human umbilical vein endothelial cells and by a cell-free kinase assay.

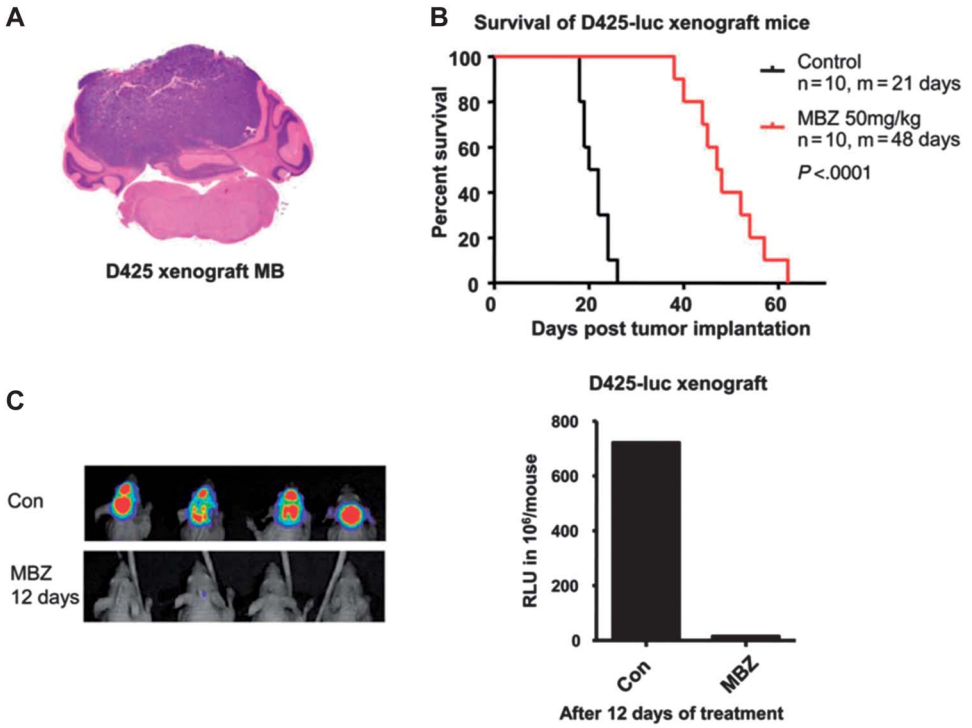

Figure. Mebendazole (MBZ) markedly extended the survival of D425 xenograft medulloblastoma (MB) of group 3. **A**, *D425 MB cells belong to group 3 of molecular classification and carry c-MYC and OTX2 genomic amplification. The cells were implanted into the right vermis of the cerebellum of nude mice. Hematoxylin and eosin staining demonstrated the fully grown cerebellar tumor.* **B**, *treatment by MBZ starting from day 5 of tumor implantation improved the median (m) survival from 21 to 48 days by 129%.* **C**, *xenogen scan demonstrated the inhibition of tumor growth after 12 days of MBZ treatment. The right graph shows the average xenogen counts without (Con) and with MBZ treatment.* Reprinted with permission from Bai et al.[1]

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.

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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

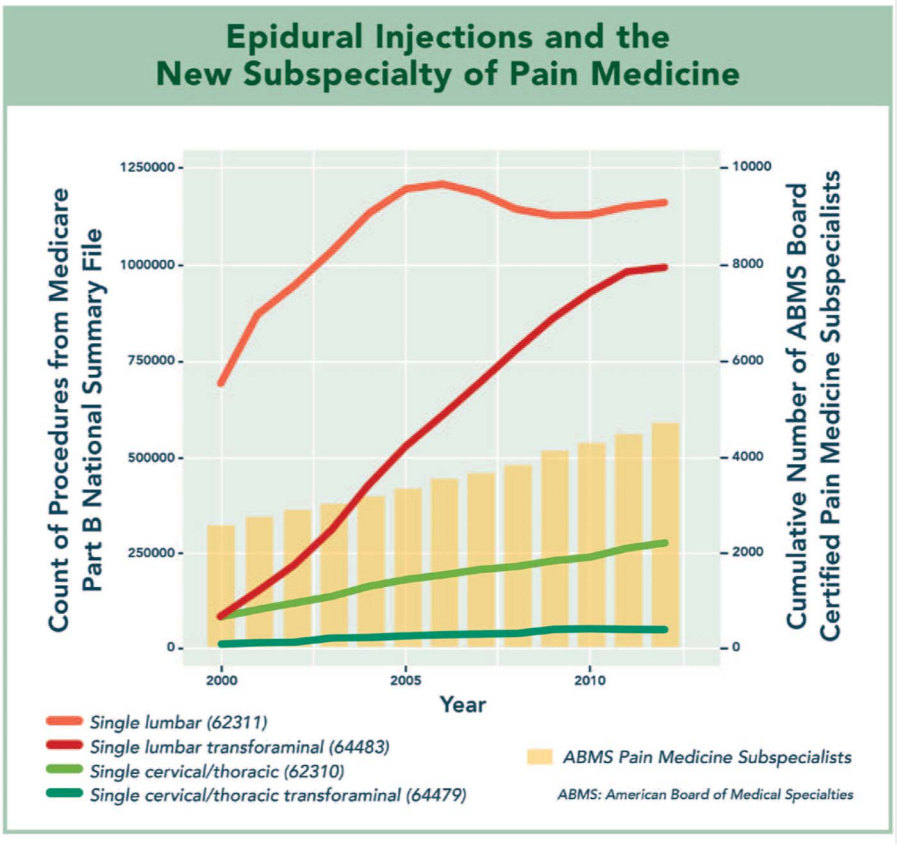

Figure. The number of epidural injections performed between 2000 and 2012 for Medicare patients, extracted from Centers for Medicare and Medicaid Services data. Reprinted with permission from Cohen et al.[6]