ATACH-2 trial. An estimated 41% of the participants in INTERACT2 underwent randomization ≥4 hours after symptom onset, whereas all participants in the ATACH-2 trial underwent randomization and were treated within 4.5 hours after symptom onset. Similarly, only a fraction of patients in INTERACT2 underwent randomization with an initial systolic blood pressure of ≥180 mm Hg vs all patients in the ATACH-2 trial. Additionally, treatment failure in the intensive cohorts was much more common in INTERACT2 (66%) vs ATACH-2 (12.2%). Mean systolic blood pressures in the first 2 hours after randomization were significantly lower in the ATACH-2 trial vs the INTERACT2 trial. Thus, the present trial does not support an aggressive protocol of systolic blood pressure lowering in the setting of ICH. A number of areas remain unclear, including the optimal targeting of blood pressure in these patients and the timing of achieving this goal. Furthermore, the results of this trial cannot be extended to patients with large ICHs, significant elevations in intracranial pressure, or altered cerebral perfusion pressure. Further studies are needed to define the best blood pressure management in these patients. Although the optimal goal is still a matter of debate and may need to be titrated on the basis of patient- and ICH-specific parameters, systolic blood pressures of 140 to 180 mm Hg would be a reasonable goal until we have firmer evidence.

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REFERENCES

“Tag Team” Glioblastoma Therapy: Results From a Phase 1 Trial of Toca 511 and 5-Fluorocytosine for Recurrent High-Grade Glioma

High-grade gliomas (HGGs), including glioblastoma multiforme (GBM), are not effectively treated with current therapies. Cloughesy et al recently reported the results of a phase 1 clinical trial treating patients with recurrent HGG with a novel combination of Toca 511 (vocimagene amiretrovvec) followed by Toca FC (extended release 5-fluorocytosine).

Toca 511 is an investigational nonlytic, retroviral replicating vector surgically injected into the walls of tumor resection cavities to deliver a yeast cytosine deaminase gene to replicating cells. Cytosine deaminase expresses an enzyme that converts the prodrug Toca FC (extended-release version of 5-fluorocytosine) to 5-fluorouracil (5-FU). Usually, 5-FU chemotherapy is inefficient at crossing the blood-brain barrier, but the combination of Toca 511 and Toca FC solves this problem because conversion to 5-FU occurs after 5-fluorocytosine has already crossed the blood-brain barrier into Toca 511-infected cells. Because this retroviral replicating vector was designed to depend on cell division for genome integration, it preferentially infects replicating cancer and nearby immune cells; in addition, systemic side effects are minimized because of the short 5-FU half-life and direct Toca 511 injection to infect tumor cells. To test safety and efficacy, Cloughesy et al administered increasing doses of Toca 511 to 45 subjects after surgical resection, followed by Toca FC administration for 7 days every 4 to 8 weeks until radiological tumor progression or clinical progression. These subjects were compared with an external control of subjects receiving standard therapy with lomustine for recurrent HGG. Subjects were divided into cohorts receiving either higher (cohorts 4-7a) or lower (cohorts 1-3) doses of Toca 511, with overall survival (OS) also compared between the 2 groups. There was a trend observed for dose response in OS of 14.4 months for the higher-dose cohort relative to the 11.8 months OS for the lower-dose cohort (Figure, A). Likewise, the OS of subjects receiving Toca 511 and Toca FC was 13.6 months compared with 7.1 months for the lomustine control (Figure, B). OS from initial diagnosis of patients with GBM at the first or second recurrence was 29.2 months compared with 21.3 months in the control group (Figure, C). Few adverse events were reported during the course of the study, and there were no treatment-related deaths. There were also fewer treatment-emergent grade ≥ 3 adverse events relative to the lomustine control, indicating that the Toca 511/Toca FC treatment course has a more favorable safety profile.

HGGs are molecularly heterogeneous, and the different subtypes may contribute to a variation in benefits of the Toca 511/Toca FC treatment. To test for this variability, Cloughesy et al profiled tumor mRNA expression by next-generation sequencing from frozen tissue biopsies taken immediately before Toca 511 administration. Many tumor samples from subjects who survived more than a year after the Toca 511/Toca FC therapy expressed mRNA involved in neuronal functions, called survival-related neuronal subtype. The survival-related neuronal subtype identified in these patients with recurrent GBM is similar to the TCGA neuronal subtype identified in newly diagnosed HGG tumors, although this subtype is not associated with better survival in newly diagnosed GBM.

In summary, the “tag team” therapy combination of Toca 511 and Toca FC treatment showed a favorable safety profile and better OS compared with an external lomustine control. Therefore, an international phase 2/3 trial in patients with recurrent HGG is underway to test this novel, surgically administered retroviral delivery of gene-mediated local tumor chemotherpay.

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Figure. Overall survival (OS) and comparison of Toca 511 and Toca FC to lomustine. A. OS Kaplan-Meier plot of subjects who have received higher (cohorts 4 to 7a [C4-7a]) vs lower (cohorts 1 to 3 [C1-3]) doses of Toca 511 and Toca FC. NR, not reached. B. OS Kaplan-Meier plot of subjects with GBM at first or second recurrence who received Toca 511 and Toca FC vs the lomustine external control. C. OS Kaplan-Meier plot from the initial diagnosis of subjects with GBM at first or second recurrence treated with Toca 511 and Toca FC vs lomustine external control. Tg 511-11-01 and Tg 11-01 are abbreviations for Toca 511 plus Toca FC treatment. From Cloughesy TF, Landolfi J, Hogan DJ, et al. Phase 1 trial of vocimagene amiretrorepvec and 5-fluorocytosine for recurrent high-grade glioma. Sci Transl Med. 2016;8(341):341ra75. Reprinted with permission from AAAS.
Abnormal Cerebrospinal Fluid Flow: A New Model of Idiopathic Scoliosis

As its name suggests, idiopathic scoliosis (IS) is a diagnosis made with unknown pathological factors that could give rise to observed scoliotic changes. It has been reported at rates of 3% to 5.2% in pediatric and adolescent populations and occurs more frequently in females than males (3:1). Disease progression and sequelae are largely a function of the location and severity of scoliotic curves, as well as the rate and manner in which these curves change over time. For example, curves in the thoracic spine have been reported as most vulnerable to progression and can cause cardiovascular or pulmonary pathology. Early detection has proven beneficial in patients treated conservatively (eg, bracing or casting) and surgically. However, as long as the cause of IS remains unknown, therapy can be initiated only after the scoliotic changes have begun, eliminating the opportunity for physicians to prevent these deformities from developing at all.

With a series of experiments, a joint team including researchers at Princeton University and the University of Toronto has recently identified a possible pathogenic mechanism for IS in zebrafish as a model for human spinal development. Their data show that mutations in protein tyrosine kinase-7 (ptk7, a signaling pathway regulator) impair the growth and function of ependymal cell (EC) cilia, preventing the proper flow of cerebrospinal fluid (CSF). Importantly, these mutations and CSF flow irregularities are directly associated with deformities in the developing spine that parallel the human manifestations of IS.

CSF flow during development is normally driven by the polarized beating of EC cilia. Therefore, the first step of any direction under scanning electron microscopy, comparing cells from zebrafish sibling pairs: 1 fish was a scoliotic ptk7 mutant (ptk7/ptk7), the other a ptk7-normal nonscoliotic control (ptk7+). Although the control group had a normal distribution and arrangement of EC cilia, ptk7 mutants generally lacked EC cilia, and the few present cilia were disorganized and lacked polarization. The mutants also showed signs of hydrocephalus, which is typically associated with impaired EC cilia function and CSF flow abnormalities (Figure).

Furthermore, by placing fluorescent microspheres across the EC surface, the team observed robust anterior-posterior flow in the ptk7-normal controls. In contrast, what little motion was observed in the ptk7 mutants was both erratic and significantly slower. In an attempt to show that IS develops directly from ptk7-related EC ciliary dysfunction, the team next used a transcription factor (foxJ1a) to restore ptk7 specifically in the midline structures of the brain and spinal cord in mutant lines. The mutants that were reintroduced ptk7 (ptk7+ Tg[foxJ1a::ptk7]) developed normal EC ciliary function, organized CSF flow, and no hydrocephalus. Furthermore, microcomputed tomography in these lines showed normal spine development with no scoliotic curves.

Having shown that IS was caused by ptk7 mutation, the consequent loss of EC motile cilia, and ultimately CSF flow defect, the team investigated other mutations that impair cilia development or function and so should in theory cause IS. However, these mutations generally cause death in the first 1 to 2 weeks of embryonic development, making their downstream effects on spinal development impossible to assess. To avoid early embryonic death, the

Figure. Scanning electron microscopy examination of ptk7 mutant (B) brain ventricles showed hydrocephalus (yellow line) compared with ptk7-normal control (A) and the mutants that were reintroduced ptk7 (C). A through C show the magnification of ciliary morphology from the green squares in A through C. The scoliotic spine curve seen in ptk7 mutant (D and D) and the normal curve seen in the mutants that were reintroduced ptk7 (E and E). From Grimes DT, Boswell CW, Morante NF, Henkelman RM, Bardine RD, Ciruna B. Zebrafish models of idiopathic scoliosis link cerebrospinal fluid flow defects to spine curvature. Science. 2016;352(6291):1341-1344. Reprinted with permission from AAAS.