Diffuse intrinsic pontine glioma case series

Somatic mutations in ACVR1 are found in a quarter of children with diffuse intrinsic pontine glioma (DIPG), however, there are no ACVR1 inhibitors licensed for the disease. Using an Artificial Intelligence-based platform to search for approved compounds for ACVR1-mutant DIPG, the combination of vandetanib and everolimus was identified as a possible therapeutic approach. Vandetanib, an inhibitor of VEGFR/RET/EGFR, was found to target ACVR1 (Kd=150nM) and reduce DIPG cell viability in vitro but has limited ability to cross the blood brain barrier. In addition to mTOR, everolimus inhibits ABCG2 (BCRP) and ABCB1 (P-gp) transporters and was synergistic in DIPG cells when combined with vandetanib in vitro. This combination is well-tolerated in vivo, and significantly extended survival and reduced tumor burden in an orthotopic ACVR1-mutant patient-derived DIPG xenograft model. Four patients with ACVR1-mutant DIPG were treated with vandetanib plus mTOR inhibitor, informing the dosing and toxicity profile of this combination for future clinical studies [1)].

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A retrospective observational study was performed enrolling pediatric patients affected by DIPG from 2008 to 2018. Clinical and radiological charts were reviewed to find patients' demographic, pathologic and radiologic features in hydrocephalic and non-hydrocephalic patients. In the hydrocephalus cohort, treatment strategy and its effectiveness and complications were analyzed.

Ninety-four pediatric patients were enrolled in the study. Patients who developed hydrocephalus showed significantly lesser maximum axial tumor areas than patients without hydrocephalus (respectively 6.5 cm2 vs 16.45 cm2, $p < 0.005$). Hydrocephalus developed in 33 patients (35%) with an onset interval of 5.24 ± 1.21 months (range 3.2-7.3). The majority of hydrocephalic patients (28 cases, 90%) were treated by a ventriculoperitoneal shunt, the remaining 3 patients being treated by endoscopic third ventriculostomy. The mean overall survival was 16.6 months $\pm$ 20 months without a significant difference between the groups.

The onset of hydrocephalus occurs in the first months of the disease story and found a negative correlation with tumor maximal axial diameter. Early treatment of hydrocephalus presents a very low complications rate with satisfying clinical outcome, as it allows the patients to continue the neurooncological therapies being a part of the treatment armamentarium instead of a palliative solution [2)].

As part of a trial using CED for diffuse intrinsic pontine glioma (DIPG), Bander et al. measured treatment-related volumetric alterations in the brainstem and ventricles.

Enrolled patients underwent a single infusion of radioimmunotherapy. Between 2012 and 2019, 23 patients with volumetric pre- and postoperative day 1 (POD1) and day 30 (POD30) MRI scans were analyzed using iPlan® Flow software for semiautomated volumetric measurements of the ventricles and pontine segment of the brainstem.

Children in the study had a mean age of 7.7 years (range 2-18 years). The mean infusion volume was 3.9 ± 1.7 ml (range 0.8-8.8 ml). Paired t-tests demonstrated a significant increase in pontine volume immediately following infusion ($p < 0.0001$), which trended back toward baseline by POD30 ($p =$

0.046; preoperative 27.6 ± 8.4 ml, POD1 30.2 ± 9.0 ml, POD30 29.5 ± 9.4 ml). Lateral ventricle volume increased (p = 0.02) and remained elevated on POD30 (p = 0.04; preoperative 23.5 ± 15.4 ml, POD1 26.3 ± 16.0, POD30 28.6 ± 21.2). Infusion volume had a weak, positive correlation with pontine and lateral ventricle volume change (r2 = 0.22 and 0.27, respectively). Four of the 23 patients had an increase in preoperative neurological deficits at POD30. No patients required shunt placement within 90 days.

CED infusion into the brainstem correlates with immediate but self-limited deformation changes in the pons. The persistence of increased ventricular volume and no need for CSF diversion post-CED are inconsistent with obstructive hydrocephalus. Defining the degree and time course of these deformational changes can assist in the interpretation of neuroimaging along the DIPG disease continuum when CED is incorporated into the treatment algorithm [3].

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