JOURNAL WATCH

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Our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of CNS oncology

Expert panel: Maura Massimino, Fondazione Istituto di Ricovero & Cura a Carattere Scientifico Istituto Nazionale dei Tumori, Milan, Italy; Larry Junck, University of Michigan Health System, MI, USA

Rohle D, Popovici-Muller J, Palaskas N et al. An inhibitor of mutant IDH1 delays growth and promotes differentiation of glioma cells. *Science* 340, 626–630 (2013).

The authors explored the role of mutant IDH1 (mIDH1) in transformed cells with endogenous *IDH1* mutations. By high-throughput screening, they identified a selective R132H-IDH1 inhibitor, AGI-5198, that blocks the production of R-2-hydroxyglutarate by mIDH1 in a dose-dependent manner. At a high dose that produces near-complete mIDH1 inhibition and partially inhibits tumor growth *in vivo*, the inhibitor decreased histone methylation and increased expression of genes associated with glial differentiation. These results suggest that mIDH1 restricts cellular differentiation and that this defect is reversed by blocking its enzymatic activity.

However, a lower dose of the inhibitor, which produced equivalent tumor growth inhibition, was associated with little or no histone demethylation or overexpression of genes associated with glial differentiation. Overall, the results suggest that mIDH1 promotes glioma growth through transcriptional and nontranscriptional mechanisms that are independent of its epigenetic effects. The discovery of the inhibitor provides an important new tool for further studies of the mechanisms by which mIDH1 contributes to gliomagenesis.

– Written by Larry Junck

Pallud J, Blonski M, Mandonnet E et al. Velocity of tumor spontaneous expansion predicts long-term outcomes for diffuse low-grade gliomas. *Neuro Oncol.* 15(5), 595–606 (2013).

The authors assessed whether the velocity of expansion of supratentorial diffuse low-grade gliomas can predict long-term outcomes. They studied 407 adults with newly diagnosed tumors. Tumor volume was assessed by manual segmentation on fluid-attenuated inversion-recovery MRI images. The mean velocity of diametric expansion prior to treatment was 5.8 ± 6.3 mm/year. During follow-up, which averaged 87 months, 209 patients had malignant transformation and 87 died. Comparing those with expansions <8 mm/year and ≥ 8 mm/year, significant differences were observed for survival free of malignant progression (103 vs 35 months, respectively) and overall survival (249 vs 91 months, respectively). In multivariate analysis accounting for several clinical and imaging variables, significant predictors were velocity of diametric expansion ≥ 8 mm (hazard ratio: 4.62; $p < 0.001$) and tumor volume >100 cc (hazard ratio: 2.92; $p = 0.001$). The authors concluded that measurement of the velocity of diametric expansion during the pretherapeutic period allows the identification of rapidly growing diffuse low-grade gliomas that have a higher risk of malignant transformation and death.

– Written by Larry Junck

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Nayak L, Fleisher M, Gonzalez-Espinoza R et al. Rare cell capture technology for the diagnosis of leptomeningeal metastasis in solid tumors. *Neurology* 80, 1598–1605 (2013).

The authors used rare cell capture technology (RCCT), a technique used to detect circulating tumor cells in blood, to analyze cerebrospinal fluid in patients with suspected leptomeningeal metastasis (LM). As applied, RCCT uses ferromagnetic particles coated with antibodies to EpCAM. Immunomagnetic technology is then used to isolate cells of interest. Cells that are positive for cytokeratins and DAPI (a nuclear marker), negative for CD45 (a leukocyte marker) and have morphologic features of tumor cells constitute a positive result. The authors studied 51 patients with solid tumors and a suspicion of LM. Fifteen met conventional criteria (cerebrospinal fluid or MRI) for LM; of these, cytopathology was positive in ten, but RCCT was positive in all 15 (sensitivity: 100%). Of the 36 patients who did not meet criteria for LM, one had a positive RCCT (specificity: 97%), but that patient met criteria for LM 6 months later. The authors concluded that RCCT is an accurate, novel method for detection of LM in patients with solid tumors.

– Written by Larry Junck

Reddy GD, Sen AN, Patel AJ, Bollo RJ, Jea A. Glioblastoma of the cerebellum in children: report of five cases and review of the literature. *Childs Nerv. Syst.* 29, 821–832 (2013).

The authors presented their experience with five patients whose tumor, diagnosed as malignant glioma, arose in the cerebellum, in four instances as a primary diagnosis and in one patient as a postradiation tumor after a first diagnosis of medulloblastoma. Although the authors grouped primary and secondary malignant gliomas and the patient follow-up was short and incomplete, the interest of the paper remains. The mean survival time does not seem to be better for the cases reported in this article and for cases from a literature

review compared with other high-grade glioma originating in the supratentorial areas or even these in adults [1–3]. Moreover, these tumors have no discernible features on imaging that can conclusively characterize their diagnosis and distinguish them from the more common pediatric tumors arising in the posterior fossa. Owing to the rarity of this entity and their supratentorial counterpart in children, they can be included in the same treatment protocols, keeping in mind that the prognosis is the same.

– Written by Maura Massimino

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Hargrave D, Georger B, Frappaz D et al. A Phase II single-arm study of irinotecan in combination with temozolomide (TEMIRI) in children with newly diagnosed high grade glioma: a joint ITCC and SIOPE-brain tumor study. *J. Neurooncol.* 113(1), 127–134 (2013).

This is the report of a Phase II trial whose primary end point was the response rate to a window phase constituted by temozolomide and irinotecan in children with newly diagnosed high-grade glioma. Only 17 patients were included as recruitment was stopped owing to no complete or partial responses during the two-cycle treatment window in the first ten patients. Five patients had stable disease and five progressed. Median survival was 9.4 months and 6-month overall survival was 71.4%. The authors also reported the difficulty in confirming diagnosis with over 17% pathological discordance and over 28% discordance between original and central radiological evaluation. Studies of the same regimen used in the same disease, but

in the adult context have been more successful [1,2]. This is a further confirmation of how difficult the management of high-grade glioma is in children.

– By Maura Massimino

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Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.