JOURNAL WATCH

For reprint orders, please contact: reprints@futuremedicine.com

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

Rubenstein JL, Hsi ED, Johnson JL *et al.* Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). *J. Clin. Oncol.* doi:10.1200/JCO.2012.46.9957 (2013) (Epub ahead of print).

In this single-arm multicenter trial, 44 patients with primary CNS lymphoma and an Eastern Cooperative Oncology Group performance status ≤ 2 were treated with methotrexate 8 g/m² every 2 weeks for eight cycles, rituximab 375 mg/m² weekly for 6 weeks and temozolomide 150 mg/m² for 5 days every 28 days for five cycles. This was followed by one consolidation cycle consisting of etoposide 40 mg/kg and cytarabine 16 g/m², both in divided doses over 4 days. Median progression-free survival was 2.4 years, and after a median follow-up of 4.9 years, median survival had not been reached. Initiation of treatment later than 30 days after diagnosis was associated with earlier progression. In a correlative study, high *BCL6* expression by immunohistochemistry correlated with shorter progression-free survival and survival. While the results of this treatment are quite promising, it must be kept in mind that this is a small study of patients with relatively favorable profiles. It is an odd treatment in that the greatest toxicity occurred during the consolidation phase, including most of the grade 4 neutropenia (81%) and thrombocytopenia (81%), and one toxic death.

– Written by Larry Junck

Leu S, von Felten S, Frank S *et al.* IDH/MGMT-driven molecular classification of low-grade glioma is a strong predictor for long-term survival. *Neuro Oncol.* 15(4), 469–479 (2013).

The authors screened 210 low-grade glioma tissue samples for mutations in *IDH1* and *IDH2* (*IDH*mut, found in 81%), *MGMT* gene promoter methylation (*MGMT*met, found in 70%), 1p/19q loss of heterozygosity (1p19qloh, 24%) and nuclear TP53 immunopositivity (TP53pos, >20% positive in 24%). *MGMT*met was strongly associated with *IDH*mut ($p < 0.001$). Multivariate analyses compared the molecular information with histopathologic subtype (astrocytoma: 44%; oligoastrocytoma: 30%; and oligodendroglioma: 25%). With 95 deaths (45%), TP53pos was the only molecular marker that was predictive of survival in isolation (negative predictor; hazard ratio [HR] = 1.02 per 1% of TP53 positivity; $p = 0.027$). However, the molecular markers in combination were better than histopathology as predictors of survival ($p < 0.001$). The triple combination *IDH*mut/*MGMT*met/1p19qloh was a very strong predictor of survival (HR = 0.18), but *IDH*mut/*MGMT*met was also a strong predictor (HR = 0.33). A different triple combination, *IDH*mut/*MGMT*met/TP53pos, was a strong predictor of malignant transformation (HR = 2.75). The results indicate that these four molecular markers in combination are better than histologic classification at predicting outcome for low-grade glioma.

– Written by Larry Junck

News & Views

News

Journal Watch

Conference Scene

Future
Medicine

part of
fsg

Chi AS, Batchelor TT, Yang D *et al.* *BRAF* V600E mutation identifies a subset of low-grade diffusely infiltrating gliomas in adults. *J. Clin. Oncol.* 31(14), e233–e236 (2013).

The authors, in routinely analyzing their gliomas for *BRAF* V600 mutations, identified five with *BRAF* V600E mutations (15%) among 33 grade II diffuse gliomas. The five patients were somewhat distinct in their clinical features (age range: 22–41; all presenting with definite or probable seizures) and tumor anatomy (four out of five in the temporal lobe, all small and discrete). Four were diffuse astrocytoma with distinct histologic features including well-demarcated borders, spindled cells and Rosenthal fibers; one was a fairly typical oligoastrocytoma. After resection, all patients were free of progression at 14–35 months without additional treatment. In addition, they identified two patients with *BRAF* V600E mutations in histologically typical glioblastoma. Both presented with seizures and had parietal lobe tumors, and they were free of progression at 19 and 36 months. These cases broaden the spectrum of gliomas with *BRAF* V600E mutations. Whether treatment directed at this target is beneficial in such patients remains unknown.

– Written by Larry Junck

Fouladi M, Stewart C, Blaney SM *et al.* A molecular biology Phase II trial of lapatinib in children with refractory malignancies: a pediatric brain tumor consortium study. *J. Neurooncol.* 114(2), 173–179 (2013).

This is a very interesting study affording both a molecular biology study *in vivo* and a Phase II trial with an ERBB inhibitor, lapatinib. High expression of ERBB2 has been reported in medulloblastoma and ependymoma, and EGFR is amplified and overexpressed in some brainstem gliomas. The subjects of the study were patients with recurrent medulloblastoma, ependymoma and high-grade glioma. A group of patients in the molecular biology study were administered lapatinib 7–10 days before resurgery to evaluate ERBB expression and pathway

activity after possible inhibition *in vivo*. While another group in the Phase II study was treated with oral lapatinib twice a day until progression. No intratumoral target inhibition was noted in any patients after pretreatment with lapatinib, while three children with medulloblastoma and four with ependymoma had stable disease for at least four systemic courses. The authors demonstrated that phospho-ERBB2 levels were highest in ependymomas. In the pharmacokinetics study, they also showed that lapatinib penetration reached 10–20% of the observed plasma concentration, which is probably too low to inhibit ERBB receptors. Even if the results are negative, this paper is interesting because it concerns the first report of intratumoral lapatinib concentrations *in vivo* in children with relapsing brain tumors.

– Written by Maura Massimino

Zeilhofer UB, Scheer I, Warmuth-Metz M *et al.* Natural history of a medulloblastoma: 30 months of wait and see in a child with a cerebellar incidentaloma. *Childs Nerv. Syst.* doi:10.1007/s00381-013-2077-9 (2013) (Epub ahead of print).

The authors present the very unusual case of a child radiologically diagnosed with a posterior fossa tumor 30 months before the final histological diagnosis of medulloblastoma. The story is an intriguing series of head traumas and surveillance MRIs that resulted in the final decision of surgery and the diagnosis of a malignant embryonal tumor, instead of a low-grade glioma, owing to the slow progression of the cerebellar nodule. Interest lies not only in the uniqueness of the case, but also in the fact that, as already shown by many papers, a precocious diagnosis is not the key to a cure for pediatric brain tumors. This patient had, in fact, not only a unique story, but also a rare subtype of medulloblastoma, which has nuclear immunoreactivity for β -catenin and the *CTNNB1* mutation that clearly correlates with good outcome. As the authors point out in their discussion, the timescale of the prediagnostic symptoms can provide some indirect evidence

regarding the kinetics of tumor growth. This case report gives us proof of how true this concept is.

– Written by Maura Massimino

Warren KE, Pouissant TY, Vezina G et al. Challenges with defining response to antitumor agents in pediatric neuro-oncology: a report from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. *Pediatr. Blood Cancer* 60(9), 1397–1401 (2013).

In neuro-oncology, determining the effectiveness of an agent is particularly complicated. Patients with brain tumors are followed with MRI scans to determine treatment response and the historically used McDonald criteria that takes into account clinical status, steroid use and change in 2D contrast enhancing tumor measurements on CT/MRI scans to define response/progression in supratentorial high-grade glioma are also applied to different tumors than supratentorial high-grade glioma. The Response Assessment in Neuro-Oncology (RANO) working group was established to address both the limitations in defining end points for clinical trials in adult neuro-oncology and to develop standardized response criteria for the same

trials. The Response Assessment in Pediatric Neuro-Oncology (RAPNO) parties, who wrote this paper, aim to specify the same issues in the pediatric neuro-oncology world. This is necessary because pediatric brain tumors represent a very heterogeneous population, with different histologies, locations and imaging characteristics. Even among the main cooperative groups, criteria used have not been homogeneous. There are also some particular issues that make pediatric brain tumor imaging quite different from that of adult tumors, including enhancement and the evolution of cysts in low-grade gliomas, the lack of correlation between tumor size reduction and survival in some histotypes and the interobserver variability.

– Written by Maura Massimino

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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

Journal Watch highlights some of the most important papers recently published in the field of CNS oncology and research. The editorial team welcomes recommendations for relevant papers for inclusion in future issues.

Please direct your suggestions to:

Tess O'Neill, Commissioning Editor, *CNS Oncology*
t.oneill@futuremedicine.com