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

CNS Oncology

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

Gilbert M, Dignam J, Armstrong T et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N. Engl. J. Med.* 370(8), 699-708 (2014).

This is a randomized, double-blind controlled trial of bevacizumab anti-angiogenic therapy for patients with newly diagnosed resected glioblastoma, given together with standard chemoradiation with temozolomide. In total, 637 patients were treated with bevacizumab (10 mg/kg every 2 weeks) or placebo starting in week 4 of chemoradiation, continued for up to 12 cycles of maintenance temozolomide treatment. At progression, patients who had received placebo were able to receive bevacizumab. Survival was similar in the two arms, 15.7 months with bevacizumab and 16.1 months with placebo. Progression-free survival was longer in the bevacizumab group (10.7 vs 7.3 months), but this result was not significant because the statistical design set a high threshold for this endpoint. An increased symptom burden, a worse quality of life, and a decline in neurocognitive function were more frequent in the bevacizumab group receiving bevacizumab. The results do not support early use of bevacizumab for patients with resected glioblastoma.

– Written by Larry Junck

Chinot O, Wolfgang W, Mason W et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N. Engl. J. Med.* 370(8), 709-722 (2014).

Patients with newly diagnosed glioblastoma were randomized to receive bevacizumab or placebo along with standard chemoradiation. Among 921 patients, progression-free survival was longer with bevacizumab than with placebo (median, 10.6 vs 6.2 months; stratified hazard ratio [HR], 0.64, $P < 0.001$), but overall survival did not differ (median, 16.8 vs 16.7 months; stratified HR, 0.88; not significant). Baseline health-related quality of life and performance status were maintained longer with bevacizumab, and the glucocorticoid requirement was lower. More patients in the bevacizumab group had grade 3 or higher adverse events (66.8 vs 51.3%). This trial had a similar design to that of Gilbert *et al.* [1] and yielded similar results for overall survival and progression-free survival. However, this study found better preservation of quality of life with bevacizumab, whereas the Gilbert study found worse quality of life; the reason for this difference is unclear. Neither study was designed to assess the potential benefit of bevacizumab in the patients who might benefit the most, those with large unresected tumor masses causing substantial ongoing neurological symptoms.

– Written by Larry Junck

Cairncross JG, Wang M, Jenkins RB et al. Benefit from procarbazine, lomustine, and vincristine in oligodendroglial tumors is associated with mutation of IDH. *J. Clin. Oncol.* 32, 783-791 (2014).

Previous results from the Radiation

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Therapy Oncology Group 9402 randomized trial showed that patients with 1p/19q codeleted anaplastic oligodendroglial tumors survive much longer after chemoradiotherapy (CRT) than after radiation therapy (RT) alone. In this article, the authors analyzed the outcome of 154 patients with *IDH* mutations among the 210 with evaluable tissue. Survival with CRT v RT was 14.7 v 6.8 years in 88 patients with codeletion and *IDH* mutation (hazard ratio [HR] 0.49, $P = 0.01$), 5.5 v 3.3 years in 66 patients with non-codeleted *IDH*-mutated tumors (HR 0.45, $P = 0.045$), and 1.0 v 1.3 years in 44 non-codeleted non-mutated tumors (HR 0.99, not significant). 10 patients with co-deleted non-mutated tumors had intermediate outcomes. In total, 76 patients with the germline allele rs55705857 (“G allele”) possibly benefited from CRT, and an exploratory analysis suggests that *ATRX* mutation, uniformly present in codeleted tumors, may be associated with benefit from CRT among 16 patients with non-codeleted *IDH*-mutated tumors. These results are from unplanned analyses and are unconfirmed, but they suggest that patients with non-codeleted *IDH*-mutated tumors benefit substantially from CRT.

– Written by Larry Junck

Ramaswamy V, Remke M, Shih D et al. Duration of the pre-diagnostic interval in medulloblastoma is subgroup dependent. *Pediatr. Blood Cancer* doi:10.1002/pbc.25002 (2014) (Epub ahead of print).

Previous studies on medulloblastoma have paradoxically suggested that a long pre-diagnostic interval is not associated with poor outcome; rather there is a complex relationship between shorter pre-diagnostic intervals and worse outcome. This study reports in fact that the early discovery of a medulloblastoma for its clinical manifestation is correlated with more aggressive subgroups that present peculiar genetics, transcriptomes and clinical outcomes. Specifically, in pediatric medulloblastoma, WNT and Group 4 tend to be more common in older children, while SHH and Group 3 occur more frequently in infants. Clinical outcomes are disparate across the four subgroups where WNT patients have an excellent outcome while Group 3 patients have a dismal outcome. Analyzing 126 medulloblastoma specimens and patients histories, they concluded that cases with WNT and Group 4

tumors showed significantly longer median pre-diagnostic intervals compared to those for SHH and Group 3 patients. Improved survival was significantly associated with a longer pre-diagnostic interval but was no longer significant when controlling for subgroups that therefore represented the true reason of the clinical heterogeneity in medulloblastoma.

– Written by Maura Massimino

Fąfara-Le A, Kwiatkowski S, Maryńczak L et al. Torticollis as a first sign of posterior fossa and cervical spinal cord tumors in children. *Childs Nerv. Syst.* 30, 425-430 (2014).

The authors give a description of the underestimation of acquired torticollis as early symptom of brain tumors. They analyzed the records of 54 patients with tumors arousing in the cervical cord or posterior fossa finding a symptom of torticollis in over 20% of them. The most commonly postulated justification was the XI cranial nerve pressure or the dura mother stretching causing pain and involuntary position of the head. Torticollis, despite this relatively frequent occurrence, is totally ignored and particularly in those tumors, if the first and single sign of manifestation, can be associated with significant tumor diagnosis delay. Sudden-onset, non-traumatic torticollis should therefore always raise a suspicion of spinal cord or posterior fossa tumors.

– Written by Maura Massimino

Di Giannatale A, Morana G, Rossi A et al. Natural history of cavernous malformations in children with brain tumors treated with radiotherapy and chemotherapy. *J. Neurooncol.* doi:10.1007/s11060-014-1390-9 (2014) (Epub ahead of print).

The authors examine their series of 34/108 patients treated for different brain tumors and thereafter developing cavernous malformations. The issue is quite important in pediatric neurooncology since this occurrence is quite common but we have no guidelines correlating follow-up, treatment and outcome. They underline the correlation with irradiation but also with the association of methotrexate. Location is significantly more common in cerebral hemispheres. Only three/34 needed treatment for

spontaneous and almost asymptomatic bleeding with around 20% of cavernous malformations growing over time. They recommend studying MRI with gradient echo T2-weighted images to better distinguish cavernous malformations that occurred at a median of 4.8 years after treatment and did not represent, in their experience, a major morbidity late-effect.

– Written by Maura Massimino

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Reference

- 1 Gilbert M, Dignam J, Armstrong T *et al.* A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N. Engl. J. Med.* 370(8), 699–708 (2014).

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