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: 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

Morris PG, Correa DD, Yahalom J et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. *J. Clin. Oncol.* 31, 3971–3979 (2013).

Fifty two patients with primary CNS lymphoma were entered into a single-arm multicenter Phase II study of rituximab, methotrexate, procarbazine and vincristine (R-MPV), followed by consolidation reduced-dose whole-brain radiotherapy (WBRT; 23.4 Gy) and cytarabine. Patients achieving a complete response on R-MPV were treated with reduced-dose WBRT, while those without a complete response received 45 Gy. The median age of the study group was 60 years and the median Karnofsky Performance Status was 70. Of the 43 patients evaluable for response, a complete response was achieved in 46.5% after five cycles, and an additional 32.5% after seven cycles. The primary end point, progression-free survival at 2 years for those with a complete response undergoing reduced-dose WBRT, was reached by 77%. Intent-to-treat analysis for the entire group showed a mean progression-free survival of 3.3 years and overall survival of 6.6 years. Cognitive assessment in 12 patients showed fairly good function after up to 4 years. This study shows that very good results can be achieved without high-dose WBRT in most patients. Additional studies are needed to assess long-term toxicity after reduced-dose

WBRT and to determine whether similar results can be achieved without radiation.

– Written by Larry Junck

Gilbert MR, Wang M, Aldape KD et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized Phase III clinical trial. *J. Clin. Oncol.* 31(32), 4085–4091 (2013).

Eight hundred and thirty three patients with newly diagnosed resected glioblastoma were treated with conformal radiotherapy and concomitant temozolomide. After completion of chemoradiation, patients were randomly assigned to treatment with cyclic temozolomide at a standard dose (150–200 mg/m²/day for 5 consecutive days every 28 days) or a dose-dense regimen (75–100 mg/m²/day for 21 consecutive days every 28 days). Median survival from randomization was 16.6 months with standard treatment and 14.9 months with dose-dense temozolomide (not significant). The group receiving dose-dense temozolomide had more grade 3 toxicities (53 vs 34%; $p < 0.001$), which were mostly fatigue and lymphopenia. Patients with methylation of *MGMT* had a better outcome (overall survival: 21.2 vs 14 months), but treatment efficacy did not differ with methylation status. The authors conclude that a dose-dense regimen of temozolomide after chemoradiation offers no increase in efficacy, but is more toxic compared with the standard treatment for glioblastoma.

– Written by Larry Junck

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Ask the Experts

Brennan CW, Verhaak RGW, McKenna A et al. The somatic genomic landscape of glioblastoma. *Cell* 155(2), 462–477 (2013).

New findings from The Cancer Genome Atlas Research Network (TCGA), based on over 500 glioblastomas, are described in this comprehensive catalog of alterations associated with glioblastoma. Results were constructed through whole-genome, exome and RNA sequencing, as well as copy-number, transcriptomic, epigenomic and targeted proteomic profiling. Findings indicate that the survival advantage of the proneural subtype is conferred by the CpG island methylator phenotype (G-CIMP). G-CIMP was found in all cases with *IDH1* mutation and in only seven cases without *IDH1* mutation. The predictive effect of *MGMT* DNA methylation may apply only in the classical subtype. Genomic rearrangements were common on chromosome 12q (11 out of 42 with whole-genome analysis). Receptor tyrosine kinase abnormalities were present in 67% (57% *EGFR*, 13% *PDGFRA*, 3.2% *FGFR2/3* and 1.6% *MET*). *PI3K* mutations were found in 25%, *p53* pathway alterations in 85% and the *BRAFV600E* sequence variant in 1.7%. These results constitute major advances in our understanding of the highly variable genetic make up of glioblastomas.

– Written by Larry Junck

McKean-Cowdin R, Razavi P, Barrington-Trimis J et al. Trends in childhood brain tumor incidence, 1973–2009. *J. Neurooncol.* 115(2), 153–160 (2013).

McKean-Cowdin and colleagues provide an update on the pattern of childhood brain tumor incidence in the USA over the past two decades, with commentary on the stabilization of the rate after the early 1990s. The increasing rates in the 1990s were largely restricted to brain stem and low-grade cerebral tumors, and were explained by improvements in imaging equipment [1].

The rates of childhood brain tumor were similar in males and females, but primitive

neuroectodermal tumors (PNETs)/medulloblastomas were more common in males. An interesting finding was the reduction in tumors simply called ‘astrocytoma’ owing to the more precise coding of pilocytic astrocytomas. For the same reason, that is a better identification of histological entities, there was an increase in PNET/medulloblastoma diagnosis due to the more accurate diagnosis of supratentorial PNET. The authors concluded that, despite the overall stable incidence pattern, there have been changes in the frequency of histologic subtypes, which has led to an apparent increase in some subsets (pilocytic astrocytomas and PNET/medulloblastoma) versus others (astrocytoma not otherwise specified).

– Written by Maura Massimino

Reference

- 1 Smith MA, Freidlin B, Ries LA, Simon R. Trends in reported incidence of primary malignant brain tumors in children in the United States. *J. Natl Cancer Inst.* 90, 1269–1277 (1998).

Phi JH, Kim SK, Lee YA et al. Latency of intracranial germ cell tumors and diagnosis delay. *Childs Nerv. Syst.* 29(10), 1871–1881 (2013).

Intracranial germ cell tumors (GCTs) represent approximately 10% of all pediatric brain tumors in east Asian countries; therefore, a Korean paper describing 181 patients, 17 of whom had a delayed diagnosis, is a very wide and informative study. The article provides a description of the diagnostic latency between first symptoms and diagnostic imaging, and its correlation with patients’ final outcomes. Intracranial GCTs, in fact, have a protracted course from symptom onset to the overt manifestation of disease because symptoms and signs vary, depending on the location and size of the tumors, and include headaches, visual disturbances and endocrinopathies. The delay can last several years. In their series of 17 patients, the authors have observed that, independent of tumor location and the presence of nongerminomatous cellular elements, the period between initial symptom onset

and the definitive intracranial GCT diagnosis correlates with final outcome if it is longer than 3 months. In contrast to what is commonly believed (i.e., that the final prognosis in GCTs is not correlated with the latency in diagnosis), this series shows that the overall survival was significantly shorter if a delay was present. The authors conclude that only clinical experience of these patients may enable clinicians to cope with ambiguous MRI properly and, therefore, these patients must be referred to highly specialized colleagues.

– Written by Maura Massimino

Perreault S, Lober RM, Carret AS et al. Relapse patterns in pediatric embryonal central nervous system tumors. *J. Neurooncol.* 115(2), 209–215 (2013).

Perreault *et al.* analyzed the pattern of relapse in 133 patients treated for medulloblastoma, supratentorial primitive neuroectodermal tumors and atypical teratoid/rhabdoid tumors in two neuro-oncologic centers over 10 years. Although there was a bias due to the different type of radiotherapy and chemotherapy schedules adopted over a few years that could have had an impact on the final outcome,

there was a clear distinction in site of relapse according to tumor types. None of the patients affected by supratentorial primitive neuroectodermal tumor had an isolated spinal relapse, all patients with pineoblastoma had dissemination and equally distributed relapses among local, distant and mixed sites were found for those with medulloblastoma. The authors do not mention radiotherapy quality control and, again, this is a significant issue. Apart from the methodological limitations, the paper provides good information on the natural history of the diseases and on the need, now that their different biological features have been outlined, to develop different treatment strategies at diagnosis.

– Written by Maura Massimino

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