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, Department of Neurology, 1914 Taubman Center, 1500 E. Medical Center Drive 5316, Ann Arbor, MI 48109-5316, USA; Maura Massimino, Pediatric Unit Fondazione IRCCS Istituto Nazionale dei Tumori Unit, Milan, 20133, Italy.

Couec ML, André N, Thebaud E et al. Bevacizumab and irinotecan in children with recurrent or refractory brain tumors: toxicity and efficacy trends. *Pediatr. Blood Cancer* 59, 34–38 (2012).

Bevacizumab specifically recognizes all isoforms of human VEGF: it may have a direct antiangiogenic effect by binding to and clearing VEGF from the tumor environment. In addition, bevacizumab could have an effect on vascular normalization, increasing the chemotherapy delivery to the tumor.

In this retrospective French series, major focus is put on the tolerability and efficacy trends of bevacizumab/irinotecan combination in relapsing brain tumors and efficacy trends. A total of 28 children were treated on a compassionate basis without major side effects. Notably, in two cases where grade 2 hypertension was already present and treated, no worsening was documented, therefore underlining that in this subset of patients, bevacizumab could also be given with no further harm.

Owing to the retrospective nature of this report, there were no data on long-term toxicity, in particular about normal growth of bone, heart and brain that require VEGF activity. In juvenile monkeys, it has been demonstrated that bevacizumab could disturb physal bone development. This should be noted because the authors did not find any response to bevacizumab-irinotecan combination except in six to seven low-grade tumors, which have a relatively good prognosis. Moreover, the

median age at treatment of this subgroup of patients is usually very young. As the authors wisely conclude, if this combination could become part of the armamentarium of first-line treatment in low-grade glioma, the long-term toxicity, including growth impairment (which is of particular concern in the youngest children), warrants appropriate and prolonged follow-up.

– Written by Maura Massimino

Li G, Mitra SS, Monje M et al. Expression of epidermal growth factor variant III (EGFRvIII) in pediatric diffuse intrinsic pontine gliomas. *J. Neurooncol.* 108, 395–401 (2012).

Despite numerous clinical trials over the past two decades, the overall survival for children diagnosed with diffuse intrinsic pontine glioma (DIPG) remains 9–10 months. Radiation therapy is the only treatment with proven effect and novel therapies are needed. In this paper, Li and colleagues brilliantly describe their findings, both through immunohistochemical staining and RT-PCR, of epidermal growth factor receptor variant III (EGFRvIII) expression in six/eleven DIPG cases. Another important finding in this paper, which confirms previous results published in *Proceedings of the National Academy of Sciences* by M Monje in 2011, is the possibility to obtain neurospheres from DIPG and the potential link between EGFRvIII and cancer stem cells in DIPG. Given that a peptide vaccine targeting EGFRvIII is currently

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undergoing investigation in Phase III clinical trials for the treatment of newly diagnosed glioblastoma, these data possibly suggest a target for DIPG patients, even if the authors prudently say that they do not know whether the expression levels are adequate for targeting.

– Written by Maura Massimino

Mallucci C, Pizer B, Blair J *et al.* Management of craniopharyngioma: the Liverpool experience following the introduction of the CCLG guidelines. Introducing a new risk assessment grading system. *Childs Nerv. Syst.* 28(8), 1181–1192 (2012).

Optimal management of craniopharyngioma is still a challenge for surgeons, oncologists and radiotherapists. In neurosurgery, the attitude has shifted in most centers from curative radical surgery ‘at all costs’ to a more tailored approach utilizing more conservative surgery when deemed too risky for quality of survival. The pediatric neuro-oncology group in Liverpool introduces a new risk assessment grading through the description of a relatively wide series of 20 children treated for craniopharyngioma between 2005 and 2011. Particular emphasis is given to their front-line approach, consisting of the endoscopic drainage of tumor cysts, when present, that allowed both the avoidance of ventricular shunt and the visualization of the third ventricular floor, thus preventing its injury, and the hypothalamus damage in the subsequent curative surgery. In their 20 patients they considered a score including hypothalamic syndrome, tumor size over 2 cm, hydrocephalus and breach of the third ventricle floor, but through their presurgical maneuver of cyst drainage, they could down-classify the risk in nine out of 20 patients. They concluded that the decompression of the cystic component

after endoscopy allowed a definitive reassessment of the hypothalamic involvement influencing definitive surgical strategy. Moreover, they argue that upfront radiotherapy could be avoided in cases of minimal residual disease (which is different from UK 2005 guidelines).

– Written by Maura Massimino

De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. *J. Clin. Oncol.* 30(20), 2559–2565 (2012).

Intraoperative stimulation mapping (ISM) has the potential to reduce neurological deficits with brain tumor resection and to facilitate more aggressive surgery. To evaluate its benefit, the authors performed a systematic review, identifying 90 reports between 1990 and 2010 of 8091 adults who underwent resection of supratentorial infiltrative glioma, with or without ISM. Severe early deficits were more common with ISM (36%) than without ISM (11.3%), but severe late deficits were significantly reduced with ISM (3.4%) versus without ISM (8.3%). For severe late deficits, the adjusted odds ratio was 0.39 (95% CI: 0.23–0.64). Radiologically confirmed gross total resections were achieved in 75% with ISM versus 58% without ISM. This meta-analysis provides valuable evidence supporting the use of ISM in appropriately selected patients, but it cannot exclude the possibility that other factors might partially account for the results, such as greater experience or skill of neurosurgeons, or a culture of aggressive management in centers that use more intraoperative stimulation.

– Written by Larry Junck

Ater JL, Zhou T, Holmes E *et al.* Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the children’s oncology group. *J. Clin. Oncol.* 30(21), 2641–2647 (2012).

Low-grade gliomas of children are sometimes curable by surgery, but for tumors that cannot be completely resected or that recur after surgery, there is no consensus on the optimal treatment. This is a randomized trial of the Children’s Oncology Group of 293 children younger than 10 years of age with low-grade gliomas of brain or optic chiasm. A total of 137 eligible patients were assigned to carboplatin and vincristine and 137 to thioguanine, procarbazine, lomustine and vincristine (TPCV). The 5-year event-free survival was 39% for carboplatin and vincristine and 52% for TPCV ($p = 0.10$ by stratified log-rank test). An unplanned ‘cure model’ analysis suggested superiority of TPCV ($p = 0.007$). Toxicity was considerable; notably grade 3–4 peripheral neuropathy in 19% of both arms as well as hematologic toxicity. While not establishing superiority, these results support TPCV as a treatment option for young children with low-grade gliomas. It must be kept in mind that this is a biologically heterogeneous group of tumors.

– Written by Larry Junck

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