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

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Sabel M, Fleischhack G, Tippelt S *et al.* SIOP-E Brain Tumour Group. Relapse patterns and outcome after relapse in standard risk medulloblastoma: a report from the HIT-SIOP-PNET4 study. *J. Neurooncol.* 129, 515–524 (2016).

After having published main HIT-SIOP-PNET4 trial results in 2012 [1], the SIOP-E brain tumor group describes here the long-term outcome after a median follow-up of 7.8 years, including detailed information on relapse and the treatment of relapse. The event-free survival (EFS) and overall survival at 10 years were 76 ± 2 and $78 \pm 2\%$ still maintaining no significant difference between the treatment arms. Isolated posterior fossa relapses were less frequent and occurred later than disseminated ones. Eight percent of relapses did occur after longer than 5 years. Despite the adoption of surgery, chemotherapy, also implying myeloablative courses, the 5-year survival after relapse was only $6.0 \pm 4\%$. The pattern of relapse did correlate with time to relapse, being local relapse more frequent in late relapsers. An important result in this paper is the consideration of the difference of survival among patients with symptomatic versus those with only radiological evidence of progression: the patients presenting with symptoms had a significantly shorter survival after relapse than those detected by surveillance MRI. This is a tribute to the consolidated use of having scheduled MRI after diagnoses instead of giving up to imaging

and waiting suspicious symptoms to drive the necessity of performing MRI. The awful outcome of relapsed patients however is very similar to all the other series published about re-treatment in already irradiated medulloblastoma, and no strategy so far used, including the very low number targeted compounds available, is winning this hard battle.

Written by M Massimino

Jakacki RI, Cohen KJ, Buxton A *et al.* Phase II study of concurrent radiotherapy and temozolomide followed by temozolomide and lomustine in the treatment of children with high-grade glioma: a report of the Children's Oncology Group ACNS0423 study. *Neuro Oncol.* 18, 1442–1450 (2016).

This study explored the possibility of improving the prognosis of children with high-grade glioma by the introduction of lomustine to the so-called standard of radiation and temozolomide. The study was designed as a Phase II but a comparison was done in this paper with a previous study utilizing the standard therapy called ACNS0126 [2] allowing to conclude that this new trial conferred better EFS and overall survival. A particular benefit was reported for children without gross total resection, glioblastoma and MGMT overexpression, in other words, those that have poor prognostic factors when treated with the standard chemo-radiotherapy schedule.

KEYWORDS

- magnetic resonance spectroscopy
- *MET* fusion genes
- *IDH* mutation
- pediatric glioblastoma

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The eligibility criteria as for site allowed also the inclusion of brainstem and spinal gliomas that are generally excluded. Even if this study does not bring to a clear progress in the field of pediatric malignant glioma treatment because the one-year EFS of 0.49 overlaps with one of the recent reports of the HERBY trial [3], there are important acquisitions. The authors in fact hypothesize that the dual alkylator regimen could help to overcome resistance by depleting MGMT, thus counteracting the impact of MGMT expression on treatment resistance in pediatric malignant glioma.

Written by M Massimino

Packer RJ, Pfister S, Bouffet E et al.
Pediatric low-grade gliomas: implications of the biologic era. *Neuro Oncol.*
doi:10.1093/neuonc/now209 (Epub ahead of print) (2016).

The conclusions and recommendations of a consensus conference held in 2015 on how best to integrate the growing body of molecular genetic information into tumor classifications, and, more importantly, for future treatment of pediatric low-grade glioma (LGG) are summarized here. The authors explore the molecular characterization and its therapeutic implications on a heterogeneous group of tumors, in a vast majority of cases seemingly driven by a single genetic hit, mostly in the MAPK pathway. Outside of the canonical MAPK pathway are alterations in the MYB and MYBL1 oncogenes. According to the necessity of having a molecular characterization coupled with histological diagnosis, the necessity of having a biopsy at diagnosis and at relapse to possibly orient therapy is recommended. While the outcome of children with LGGs with chemotherapy remains far from ideal, the outcomes in children treated with molecularly targeted therapies, in addition to 'standard' chemotherapy or in isolation, should be compared with chemotherapy-only trials in prospective trials. Any trial should include functional end points and radiographic end points must be more reproducible than what was done in the past to be also compared with the discovery and use of biomarkers. Far from being only an onward rush, the authors recommend that molecularly based therapy should be considered for newly diagnosed patients with LGGs, where tumors have been molecularly characterized and have rigorous indications for treatment in

institutional review board approved trials that will accurately report also on toxicities of old and new drugs.

Written by M Massimino

Bender S, Gronych J, Warnatz H-J et al.
Recurrent MET fusion genes represent a drug target in pediatric glioblastoma. *Nat. Med.* 22, 1314–1320 (2016).

The authors studied 53 pediatric glioblastomas with whole-genome sequencing of tumor and blood. Cell cycle regulation pathway alterations were found in 83%, including mutations in *TP53* and *PPM1D* and homozygous deletion of *CDKN2A/CDKN2B*. Genetic alterations likely to result in altered receptor signaling include activating mutations of genes coding receptor tyrosine kinases (e.g., *EGFR*) or downstream proteins (*NRAS*, *KRAS*, *BRAF* and *PIK3CA*) and high-level amplifications of *EGFR* or *PDGFR/KIT*. Other common features included chromothripsis, hypermutated tumors, and alterations in telomere maintenance. RNA sequencing revealed fusion transcripts resulting from structural rearrangements in 27 of 42 samples, often in known cancer-associated genes. Fusions involving *MET* were found in 6 patients. Transduction of *MET* fusion genes into cell lines led to transformed appearance that could be mitigated with foretinib or other *MET* inhibitors, and implantation into mice generated tumors that responded to foretinib. A child with a *MET*-fusion-expressing glioblastoma treated with the *MET*-inhibitor crizotinib had a transient response. The authors conclude that *MET* fusions are oncogenic in a fraction of pediatric glioblastomas and that *MET*-inhibitor therapy may play a role in these children.

Written by L Junck

Choi C, Raisanen JM, Ganji SK et al.
Prospective longitudinal analysis of 2-hydroxyglutarate magnetic resonance spectroscopy identifies broad clinical utility for the management of patients with IDH-mutant glioma. *J. Clin. Oncol.* 34(33), 4030–4039 (2016)

A total of 136 patients with grade II or III gliomas, including tumors with and without mutation in isocitrate dehydrogenase (IDH), underwent 511 research scans with single-voxel point-resolved proton magnetic resonance spectroscopy for the oncometabolite,

2-hydroxyglutarate (2HG). 2HG measurement was found to be reproducible. Concentrations were elevated in 30 of 34 patients with untreated IDH-mutant tumors (sensitivity, 88%) compared with a range established on eight patients with IDH wild-type tumors. Among patients with IDH-mutant tumors, concentrations in six anaplastic oligodendrogliomas with codeletions were significantly higher than in eight IDH-mutant anaplastic astrocytomas, while concentrations tended to be lowest among LGGs. Concentrations correlated directly with tumor cellularity as assessed histologically. 2HG concentrations were stable during indolent disease and increased with transformation to higher grade. In response to cytotoxic chemotherapy, concentrations decreased rapidly in 1p/19q

codeleted oligodendrogliomas but more slowly in astrocytomas and mixed gliomas. The findings suggest that 2HG concentrations can be useful for noninvasive diagnosis and monitoring of IDH-mutant tumors.

Written by L Junck

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