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

Massimino M, Biassoni V, Miceli R et al. Results of nimotuzumab and vinorelbine, radiation and re-irradiation for diffuse pontine glioma in childhood. *J. Neurooncol.* 18(2), 305–312 (2014).

This is a pilot Phase II study on pediatric patients affected by diffuse pontine glioma (DIPG) treated with an innovative association of nimotuzumab – a humanized anti-EGF receptor monoclonal antibody – and vinorelbine concomitant to radiation, and re-irradiation at relapse. This study demonstrates a significant survival improvement compared with any previously published series. DIPG is a deadly pediatric brain cancer showing 12 months of median overall survival in all series presented so far. Radiation is the only standard treatment for this awful disease since more than 30 years. During the last 20 years, there has been little or no improvement in clinical benefits. Recent molecular elucidation of DIPG genetic profiles, showing involvement of *EGFR*, *PDGFR* and *H3F3D* in different subsets of DIPGs [1,2] provided great promises, but these results were collected from post-mortem biopsies and patients not uniformly treated in clinical trials, limiting the translational impact of these data.

Although the number of patients enrolled and uniformly treated in this clinical protocol ($n = 25$) is consistent for such a rare disease, the absolute number is indeed limited. Still, the power of the study is appropriate to the primary end point and to our knowledge, no clinical study has been presented so far demonstrating a significant survival improvement, very limited toxicity and

elevated safety, with a median event-free survival of 8.5 months and a median overall survival of 15 months.

The survival benefit, which has to be validated in independent series, is most probably the combined result of the entire approach, while the exact contribution of individual agents is not dissectible. We would like also to underline that all imaging data, both at diagnosis and during treatment, were externally reviewed by a neuroradiologist (M Warmuth-Metz as co-author) devoted to pediatric brain cancer and blind to the patients status, at least partially overcoming the limitations of a mono-institutional study.

Biological correlations are prevented by the absence of surgery or biopsy specimen as the patients do not undergo routine surgical procedures. Nevertheless, on the opposite side, biological studies performed so far did not correlate with clinical data collected in a uniform trial.

– Written by Maura Massimino

Porkholm M, Valanne L, Lönnqvist T et al. Radiation therapy and concurrent topotecan followed by maintenance triple anti-angiogenic therapy with thalidomide, etoposide, and celecoxib for pediatric diffuse intrinsic pontine glioma. *Pediatr. Blood Cancer* doi:10.1002/pbc.25045 (2014) (Epub ahead of print).

The authors describe the results of an international study developed for diffuse pontine glioma (DIPG) in five European Nordic countries using a protocol called

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Angiocomb that used topotecan during radiation therapy followed by maintenance therapy, including an antiangiogenic component, with thalidomide, etoposide and celecoxib. The protocol was applied in 41 eligible patients whose results were compared with eight patients that were only irradiated. The median overall survival was 12 months and the treatment was quite well tolerated. The study has many bias because there was not a centralized radiological review, age of inclusion was brought up to 1 year of age, duration of symptoms before MRI was not an inclusion criteria, and response evaluation utilized an unusual method (i.e., a change >1 cm in the axial plane diameter). These limitations highlight the need for a common way of classifying and including these patients in trials, based on clinical grounds, as the International Society of Pediatric Oncology DIPG committee is trying to do through the creation of a DIPG registry. A credit to the authors is the effort of a quality of life report through the needs of daycare (time to use of wheelchair) and school attendance during the course of the disease as was never reported before.

– Written by Maura Massimino

Khatua S, Hou P, Bodiwala R et al.
Preliminary experience with diffusion tensor imaging before and after re-irradiation treatments in children with progressive diffuse pontine glioma.
Childs Nerv. Syst. 30(5), 925–930 (2014).

The authors introduce the use of diffusion tensor imaging tractography and fractional anisotropy (FA) of the pons in patients who received re-irradiation for progressive diffuse intrinsic glioma. They affirm that conventional MRI is not always able to differentiate radiation- and chemotherapy-induced changes from true tumor progression in diffuse pontine glioma. Diffusion tensor imaging is a MRI technique that is sensitive to directional mobility of water. This directionality can be quantified as FA, which varies from zero, when the diffusion is equal in all directions, to one, when the diffusion parallels a single axis. In the six patients evaluated, they demonstrated the restoration in FA values after re-irradiation, thus showing a sensitive measure of tract displacement by tumor and tract restoration after treatment.

– Written by Maura Massimino

Parker M, Mohankumar KM, Punchihewa C et al.
C11orf95–RELA fusions drive oncogenic NF-κB signalling in ependymoma.
Nature 506, 451–455 (2014).

Ependymomas generally lack the recurrent mutations that are characteristic of most cancers. The authors sequenced the whole genome of 41 ependymomas and RNA of 77 tumors. Most supratentorial ependymomas were found to have chromothripsis within chromosome 11q12.1–11q13.3 associated with fusion of two genes within this region, *C11orf95*, an uncharacterized gene, and *RELA*, the principal effector of NF-κB signaling. The *C11orf95–RELA* fusion protein was found to have accumulated predominantly in the nucleus and to have activated NF-κB signaling. The 29 of 41 (71%) supratentorial ependymomas with the *C11orf–RELA* translocation were in older patients (8.3 ± 0.9 years) than those without this translocation (3.5 ± 1.7 years). This translocation was not found in any infratentorial tumors. Using a retrovirus, the authors transduced transgenic mouse neural stem cells with the fusion gene. When implanted in nude mice, these formed lethal brain tumors with 100% efficiency, with pathology recapitulating ‘vascular variant’ human supratentorial ependymomas. These findings demonstrate that a specific intrachromosomal translocation is present in most supratentorial ependymomas and can cause tumors in a model system; its product is a candidate target for treatment.

– Written by Larry Junck

Mack SC, Witt H, Piro RM et al.
Epigenomic alterations define lethal CIMP-positive ependymomas of infancy.
Nature 506, 445–451 (2014).

Posterior fossa ependymomas are divided into group A (PFA), occurring mainly in infants with poor prognosis, and group B (PFB), in older children and adults with good prognosis. The authors sequenced the whole genome in five tumors and whole exome in 42 tumors. They found no somatic single-nucleotide variants with significant recurrence. They studied DNA methylation in 79 ependymomas and found a promoter CpG-island methylator phenotype (CIMP) in PFA tumors. The genes hypermethylated in PFA ependymoma overlapped with those silenced in embryonic stem cells by Polycomb repressive complex 2 (PRC2).

PRC2 trimethylates histone H3K27, leading to gene silencing. The findings suggest that hypermethylation of both DNA and of histone H3K27 may contribute to the pathogenesis of CIMP+ PFA ependymoma by silencing genes, perhaps including tumor suppressor genes. Decitabine, a DNA-demethylating agent, and 3-deazaneplanocin A, which prevents trimethylation of H3K27, demonstrate antineoplastic activity at nanomolar levels. The authors conclude that PKA ependymoma is genetically bland, is driven by hypermethylation, and may respond to drugs that target either DNA or H3K27 methylation.

– Written by Larry Junck

Nowosielski M1, Wiestler B, Goebel G et al. Progression types after antiangiogenic therapy are related to outcome in recurrent glioblastoma. *Neurology* 82, 1684–1692 (2014).

The authors retrospectively analyzed patterns of progression on MRI in 83 patients with glioblastoma treated with bevacizumab. Progression was categorized into four types: T2-diffuse, with decreased enhancement and increasing T2 abnormality with mass effect and indistinct borders; cT1 flare-up, with initial decrease in gadolinium enhancement, followed by a later increase at tumor progression; primary nonresponder, with no initial decrease in enhancement; and T2-circumscribed, with persisting decrease in enhancement but emergence of a bulky inhomogeneous T2-hyperintense mass

with distinct borders. Survival from starting bevacizumab for the four groups was T2-diffuse (18% of patients), 18 months; cT1 flare-up (42%), 10 months; primary nonresponder (19%), 5 months; and T2-circumscribed (20%), 5 months. While the T2-diffuse group might partially reflect after-effects of radiation, the T2-circumscribed group may have unfavorable biological characteristics leading to distinctly unfavorable outcome. These results may be informative about mechanisms of bevacizumab resistance and selection of patients for new treatment strategies.

– Written by Larry Junck

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References

- 1 Wu G, Broniscer A, McEachron TA et al. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. *Nat. Genet.* 44(3), 251–253 (2012).
- 2 Warren KE, Killian K, Suuriniemi M et al. Genomic aberrations in pediatric diffuse intrinsic pontine gliomas. *Neuro. Oncol.* 14(3), 326–332 (2012).