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

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Happold C, Gorlia T, Chinot O *et al.* Does valproic acid or levetiracetam improve survival in glioblastoma? A pooled analysis of prospective clinical trials in newly diagnosed glioblastoma. *J. Clin. Oncol.* 34(7), 731–739 (2016)

The interest on histone deacetylase (HDAC) inhibition as adjuvant treatment in several oncology fields has been raised since several years. Valproic acid, mostly used with its first indication, that is, antiepileptic drug, has been frequently added to standard therapies, also outside of GCP trial after the report that it could enhance radiosensitivity due to its HDAC properties. This paper analyzed the survival after the association of standard therapy for newly diagnosed glioblastoma with the use of antiepileptic drugs, namely valproic acid and levetiracetam. In this data harvest of four different randomized trials on 1869 patients, the authors succeeded in acquiring very precious information, useful to all those clinicians treating glioblastoma at any patient age, that is the uninfluenced outcome after both antiepileptic drugs on patients outcome, when given at the beginning of treatment or after the chemoradiotherapy phase. This does not mean the end of the research on this particular histone deacetylases inhibitor's use, but that only controlled clinical trials, able to put a formal question whose answer is reasonable and possible to be answered, have to incorporate valproic acid's use that is not a standard, apart from its antiepileptic activity.

– Written by Maura Massimino

Ares C, Albertini F, Frei-Welte M *et al.* Pencil beam scanning proton therapy for pediatric intracranial ependymoma. *J. Neurooncol.* doi:10.1007/s11060-016-2090-4 (2016) (Epub ahead of print)

This paper reports on the results of 50 patients treated for ependymoma with pencil beam scanning proton therapy (PT) between 2004 and 2013. After a median follow-up of <4 years, 5-year local control was 78% and overall survival 84%. One patient (2% of the series) experienced fatal brain stem necrosis. While the authors conclude that the results in local control are encouraging and the procedure is safe, some issues can be raised to criticize their statements. The best so far reported results by Merchant in St. Jude's Hospital have given an incidence of local failure of 12.6% and 7-year local control and overall survival of over 88 and 85%, respectively [1]. These previous results, in the context of a much bigger patient number, with not selected patients like those going to the PSI in Switzerland from different oncologic centers, seemed more positive. Also the case of fatal brain stem necrosis seems worrisome even if in the context of multiple resection and vascular accident before PT that could have obviously had a role in the outcome of the child. The whole report of late side effects is moreover not so distant by reports on the use of photons in the same disease, therefore, too optimistic messages on PT in childhood ependymoma treatment seem not so well justified so far.

– Written by Maura Massimino

**Ceccarelli M, Barthel FP, Malta TM *et al.*
Molecular profiling reveals biologically
discrete subsets and pathways of
progression in diffuse glioma. *Cell* 164,
550–563 (2016)**

In this study from The Cancer Genome Atlas Research Network, 1122 diffuse gliomas of grade II–IV were classified using whole genome sequencing and DNA methylation profiles. Seven groups were defined, three IDH mutant, four wild-type. Among IDH mutant tumors, those with 1p/19q codeletion (18%) had the best prognosis. Other IDH mutant tumors, mostly of grade II–III, tended to occur in younger adults and to have *ATRX* mutation; they were divided into a group with a high methylation profile (25%) and a relatively good prognosis and a group with low methylation profile (3%) and a poor prognosis. Among IDH wild-type tumors, most were older adults with glioblastomas, divided by methylation profiles into ‘classic-like’ (18%) and ‘mesenchymal-like’ (27%) groups, both with a very poor prognosis; most had *TERT* upregulation and *EGFR* amplification. The LGM6 group, defined by methylation profile, included glioblastomas (10%), with a poor prognosis; however, it also included grade II–III gliomas (3%), largely occurring in young adults, labeled ‘PA-like’ because their genomic features were similar to those of pilocytic astrocytoma, with a moderately favorable prognosis. This article advances our understanding of gliomas by highlighting the importance of DNA methylation profiles, by defining groups of IDH mutant tumors with high and low methylation profiles and by characterizing the PA-like group of IDH-wild-type tumors.

– Written by Larry Junck

**Flavahan WA, Drier Y, Liau BB *et al.*
Insulator dysfunction and oncogene
activation in IDH mutant gliomas. *Nature*
529, 110–114 (2016)**

Gene expression in normal brain normally correlates strongly for genes within the same chromosomal domain but not for genes in different domains. The authors studied 230 IDH mutant and 45 wild-type gliomas of grade II–III and showed that IDH mutant gliomas exhibit hypermethylation at cohesin and CCCTC-binding factor (CTCF)-binding sites.

They identified 203 domain boundaries, across which genes in IDH mutant tumors had

increased correlation of expression, and they postulated that loss of the insulating effect of these boundaries might lead to activation of oncogenes. In IDH mutant tumors, they found higher expression of *PDGFRA* ($p < 10^{-21}$), an established glioma oncogene, and of other candidate regulators of gliomagenesis. *PDGFRA* expression correlated with expression of *FIP1L1* expression in IDH mutant tumors, and the *PDGFRA* promoter was shown to interact more strongly with the *FIP1L1* enhancer, consistent with an effect caused by breakdown of the intervening boundary. Treatment of IDH mutant gliomaspheres with a demethylating agent partially restored insulator function and downregulated *PDGFRA*. The authors suggest that disruption of chromosomal topology by hypermethylation of CTCF-binding sites, in addition to causing overexpression of *PDGFRA*, probably deregulates oncogene expression more widely, providing a potential mechanism for gliomagenesis by mutant IDH.

– Written by Larry Junck

**Stupp R, Taillibert S, Kanner AA *et al.*
Maintenance therapy with tumor-
treating fields plus temozolomide vs
temozolomide alone for glioblastoma:
a randomized clinical trial. *JAMA* 314,
2535–2543 (2015)**

Low-intensity 200 kHz alternating electric fields have been shown to interfere with mitosis. This is the preliminary report of a randomized trial of such fields, tumor-treating fields (TTF), delivered by transducer arrays worn on the scalp. In adults with glioblastoma, TTF treatment was started after completion of standard radiotherapy with concomitant temozolomide; cyclic temozolomide followed. Trial enrollment was terminated slightly early due to a positive pre-specified interim analysis, reported here. From the date of enrollment, progression-free survival in the intent-to-treat population was superior in the 210 TTF patients (7.1 months median) than in 105 control subjects (4 months). Overall survival, analyzed in the per-protocol population, was also superior (median: 20.5 vs 15.6 months). Treatment was well-tolerated with minimal toxicity, but it must be kept in mind that patients had to shave their head, wear visible transducer pads and to be connected for over 18 h per day to a power source.

– Written by Larry Junck

Financial & competing interests disclosure

L Junck served on a single occasion in December 2014 on an Advisory Board for Novocure, Inc., the Company that developed and markets Optune Tumor Treating Fields, the treatment described in Stupp's article. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Reference

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