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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Bennett J, Ashmawy R, Ramaswamy V et al. The clinical significance of equivocal findings on spinal MRI in children with medulloblastoma. *Pediatr. Blood Cancer* doi:10.1002/pbc.26472 (2017) (Epub ahead of print).

As clinicians, we are always challenged by MRI images and their reports when final medical decision implies patient prognosis and survival quality outcome as in the case of pediatric medulloblastoma. The authors report their 15-year experience on the revision of 100 patients MRI with data about initial staging, subsequent treatment and follow-up. They reviewed 37 patients with normal spine MRI, 15 with surely spinal metastatic disease and 48 whose images were uncertain or as they define, 'equivocal'. Surprisingly, in the last cohort, more patients with sonic hedgehog subgroup medulloblastoma were represented. Sixty percent of these 48 patients received standard risk treatment without showing any different outcomes from those that were directly classified as not having spinal disease. The others had more clinical risk factors apart from spinal MRI uncertainties, therefore high-risk treatment choice depended on more than spinal suspicions. These equivocal findings, moreover, were not correlated to cephalospinal fluid cytologic positivity and could be an inflammatory reaction or secondary to pressure change after tumor presence and its removal. The conclusions of this paper are toward a more pragmatic and multidisciplinary way of

making final staging diagnosis to skip from more intensive and unnecessary treatments that can injure patients without need.

– Written by Maura Massimino

Veldhuijzen van Zanten SE, Baugh J, Chaney B et al. Development of the SIOPE DIPG network, registry and imaging repository: a collaborative effort to optimize research into a rare and lethal disease. *J. Neurooncol.* 132(2), 255–266 (2017).

Among the many efforts that all the pediatric neuro-oncology community is doing to ameliorate the dismal prognosis of children with DIPG, two registries were created. One was mostly USA, Australia and Canada based, the other European, but probably soon Turkey and Mexico patients were also be included. The registration does not mean only the inclusion of demographic data, but also imaging, treatment, histopathological and biological analyses, when available, in a retrospective and prospective modality. These registries will be able to put more light on this ominous disease through the grouping of patients with similar/different features, protocol and outcome. Biometric models will be applied. The registries will be maintained during time mainly with charities foundation. This paper reports the story of the birth of the SIOPE registry that is now also extended to Russia, Turkey and Mexico with the presence of an executive committee, a group

of scientific advisors, national coordinators and members. The collection of data is web based and there are already some international studies done and published and some others are in the pipeline, like that of long-term survivors to be compared with all the other patients. At the moment of the paper publication, data on nearly 700 patients have been already put in the SIOPE registry.

– Written by Maura Massimino

Łastowska M, Trubicka J, Niemira M et al. ALK expression is a novel marker for the WNT-activated type of pediatric medulloblastoma and an indicator of good prognosis for patients. *Am. J. Surg. Pathol.* doi:10.1097/PAS.0000000000000847 (2017) (Epub ahead of print).

This paper discusses the meaning of *ALK* gene expression in medulloblastoma, studied as RNA expression and immunohistochemistry positivity in 116 samples of pediatric patients affected by classic medulloblastoma (#71), large cell anaplastic medulloblastoma (#27) and desmoplastic/nodular, with extensive nodularity or nonspecified in the remaining 18 cases. The samples were also studied to determine the molecular subtypes according to the literature procedure [1] and the authors found out that *ALK* expression was significantly associated with subgroup WNT with a high score that they had previously defined. Moreover, through their analysis compared with clinical data, they found that *ALK* expression correlated with good prognosis in patients homogeneously treated over 3 years of age. The good prognosis was demonstrated also for non-WNT tumors whose favorable outcome is well known. The function of *ALK* gene is therefore different from that of other pediatric tumors where a worse prognosis is found when *ALK* expression is present, like rhabdomyosarcoma and neuroblastoma. These data need confirmation on other series.

– Written by Maura Massimino

Sulkowski PL, Corso CD, Robinson ND et al. 2-Hydroxyglutarate produced by neomorphic *IDH* mutations suppresses homologous recombination and induces PARP inhibitor sensitivity. *Sci. Transl. Med.* 9(375), pii:eaal2463 (2017).

2-Hydroxyglutarate (2HG) occurs as two enantiomers. (R)-2HG is known as an oncometabolite

induced by mutations in *IDH1* and *IDH2* occurring in gliomas and other tumors, while (S)-2HG is produced under conditions such as hypoxia. Both enantiomers are known to exert effects by inhibiting α -ketoglutarate-dependent dioxygenases. The authors report in two cell lines that *IDH1/2* mutant cells are deficient in DNA double-strand break (DSB) repair by homologous recombination. They found a synthetic lethal interaction between mutant *IDH* and poly(adenosine 5'-diphosphate-ribose) polymerase (PARP) activity, demonstrated using four different inhibitors of PARP including two drugs approved for cancer treatment. In this regard, the *IDH*-mutant cells resemble tumor cells deficient in BRCA, and the authors showed that they, like BRCA-deficient cells, manifest synergistic response to PARP inhibitors and cisplatin. The occurrence of DSBs due to homologous recombination deficiency could be reproduced by exposure to 2HG in the absence of *IDH* mutation. This effect could also be induced by another inhibitor of specific dioxygenases. DSB repairs defect and PARP sensitivity could be reversed by known inhibitors of mutant *IDH*. Patient-derived gliomas were found to show *IDH1* mutation associated and 2HG-mediated homologous recombination suppression and PARP inhibitor sensitivity. These findings elucidate the mechanisms of tumorigenesis resulting from *IDH* mutation and identify PARP inhibitors as therapeutic candidates.

– Written by Larry Junck

Perry JR, Laperriere N, O'Callaghan CJ et al. Short-course radiation plus temozolomide in elderly patients with glioblastoma. *N. Engl. J. Med.* 376(11), 1027–1037 (2017).

Evidence-supported treatments for glioblastoma include 6 weeks of radiotherapy (RT) with concomitant temozolomide (TMZ) for patients aged up to 70 and a 3-week course of RT for persons aged 65 and above. In this study, the authors randomly assigned 562 glioblastoma patients of 65 years of age and above to receive either RT alone (40 Gy in 3 weeks) or RT with concomitant TMZ followed by up to 12 cycles of TMZ. The overall survival was longer with RT + TMZ (median: 9.3 vs 7.6 months, HR: 0.67, 95% CI: 0.56–0.80). Progression-free survival was also longer (median: 5.3 vs 3.9 months, HR:

0.50, 95% CI: 0.41–0.60). There was a strong trend toward greater benefit in 165 patients with methylated O⁶-methylguanine methyltransferase (*MGMT*) status (median survival: 13.5 vs 7.7 months, HR: 0.53) than in 189 with unmethylated status (median survival: 10.0 vs 7.9 months, HR: 0.75). These results establish a new standard for best treatment for elderly persons with glioblastoma. However, it must be kept in mind that the benefit of TMZ was fairly small, especially for O⁶-methylguanine methyltransferase-negative patients.

– Written by Larry Junck

Tomasetti C, Li L, Vogelstein B. Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science* 355(6331), 1330–1334 (2017).

The authors report that the incidence of 17 cancer types, determined for 69 countries from the Cancer Research UK database, correlates with the estimated lifetime number of stem cell divisions in the organs of origin. The median Pearson correlation coefficient is 0.80 (range: 0.67–0.84), with significant correlations in all the countries. They argue that this is an evidence for a major role for random replicative errors giving rise to driver mutations as a cause of cancer. They developed a mathematical model to study the relationship between DNA sequencing data

from The Cancer Genome Atlas with cancer incidence. Among 32 cancer types, they estimate that 29% of mutations in cancer are due to environment, 5% due to heredity and 66% due to replicative errors. Their models fit well with estimates that 42% of these cancers could be prevented by avoiding known risk factors. Their results identify brain cancer as a prototype for cancer due almost entirely to replicative errors with extremely low contribution from environment and heredity.

– Written by Larry Junck

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Reference

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