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, MI, USA; Maura Massimino, Fondazione Istituto di Ricovero & Cura a Carattere Scientifico Istituto Nazionale dei Tumori, Milan, Italy

Frattini V, Trifonov V, Chan JW *et al.*
The integrated landscape of driver genomic alterations in glioblastoma.
Nat. Genet. 45, 1141–1154 (2013).

The authors analyzed samples from 139 glioblastomas by whole-exome sequencing and 469 glioblastomas by microarray for single copy number variations, using samples from The Cancer Genome Atlas. A total of 18 new driver mutations were identified with confirmation in an independent panel. *LTZR1* was found to have nonsynonymous mutations in 4.4% and deletions in 22%. Frequent co-occurrence of mutations and deletions suggested two hits in a tumor-suppressor gene. Introduction of *LTZR1* into glioblastoma sphere cultures inhibited sphere formation and expression of stem cell markers. *CTNND2*, which codes for δ -catenin in normal brain, was found to have frequent loss-of-function mutations associated with the aggressive mesenchymal phenotype. Introduction of δ -catenin inhibited glioma sphere formation *in vitro* and tumor growth *in vivo*. In-frame fusions involving *EGFR* were found in 7.6%, most commonly with *SEPT14*, and this fusion gene was found to confer sensitivity to lapatinib. These findings provide insights into the pathogenesis of glioblastoma and potential targets for treatment.

– Written by Larry Junck

Johnson BE, Mazor T, Hong C *et al.*
Mutational analysis reveals the

origin and therapy-driven evolution of recurrent glioma. *Science* 343(6167), 189–193 (2014).

To study genomic alterations in recurrent glioma, the authors sequenced the exomes of 23 initial low-grade gliomas and recurrent tumors resected from the same patients. In 43%, at least half the mutations in the initial tumor were undetected at recurrence, including driver mutations in *TP53*, *ATRX*, *SMARCA4* and *BRAF*. This suggests that recurrent tumors are often seeded by cells derived from the initial tumor at a very early stage of their evolution. The only mutation always shared between initial and recurrent tumor was in *IDH1*, implicating *IDH1* mutation as an initiating event. Tumors from six of ten patients treated with temozolomide (TMZ) followed an alternative evolutionary path to high-grade glioma. At recurrence, these tumors were hypermutated and harbored driver mutations in the *RB* and *Akt-mTOR* pathways, attributed to TMZ-induced mutagenesis. These findings indicate that recurrences of low-grade glioma may derive from clones that branch off early in the process of tumorigenesis, and mutagenesis from TMZ may contribute to transformation to hypermutated high-grade gliomas.

– Written by Larry Junck

Krull KR, Brinkman TM, Li C *et al.*
Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: a report

**from the St Jude lifetime cohort study.
J. Clin. Oncol. 35, 4407–4415 (2013).**

Detailed neurocognitive testing was performed on 567 survivors of average age 33 years, treated for acute lymphoblastic leukemia an average of 26 years earlier. Mean age was 33 years; mean time since diagnosis was 26 years. Impairment rates across neurocognitive domains ranged from 28.6 to 58.9%. Those treated with chemotherapy only demonstrated impairment in all domains, but impairment was worse in those receiving cranial radiotherapy. The impact of radiotherapy was related to young age at diagnosis for intelligence, academic and memory. In multivariate analysis, domains with the most impairment after radiotherapy were intelligence (after 24, but not 18 Gy), memory (after 24, but not 18 Gy) and academic (both doses). Intravenous methotrexate exposure was related to slow processing speed in a dose-dependent manner, and dexamethasone exposure was related to impaired attention and executive function. Despite frequent impairments, overall the educational attainment and employment status was similar to population norms.

– Written by Larry Junck

**Bautista F, Paci S, Minard-Colin V *et al.*
Vemurafenib in pediatric patients with
BRAF V600-mutated high-grade gliomas.
Pediatr. Blood Cancer doi:10.1002/
pbc.24891 (2013) (Epub ahead of print).**

BRAF gene is a member of the RAS–RAF–MEK–ERK pathway and its mutation affects cell proliferation, differentiation and survival. *BRAF* mutations have been detected in melanoma and papillary thyroid carcinoma among adults cancers and in childhood in grade 1 and anaplastic gliomas, in gangliogliomas and pleomorphic xanthoastrocytoma. Three pediatric patients were treated with vemurafenib because of *BRAF* V600E-mutated malignant gliomas at the Institut Gustave Roussy, obtaining significant durable responses in two cases despite relapse after previous heavy treatments. The interest of this report lies, of course, in the clinical outcome of the children, but also in some other consideration. Vemurafenib has similar activity in children and in adults despite the opening of the capsules that can be necessary for small patients, which happened in one of the three described, and the biological activity of the drug is also present in

different tumors compared with adult tumors. Targeting *BRAF*-mutated tumors can therefore benefit selected patients and this is an important message for the pediatric community.

– Written by Maura Massimino

**Nageswara Rao AA, Wallace DJ, Billups C,
Boyett JM, Gajjar A, Packer RJ. Cumulative
cisplatin dose is not associated with
event-free or overall survival in children
with newly diagnosed average-risk
medulloblastoma treated with cisplatin
based adjuvant chemotherapy: report
from the Children's Oncology Group.
Pediatr. Blood Cancer 61(1), 102–106
(2014).**

This is the review of cisplatin doses in the 379 patients enrolled in the CCG/POG A9961 trial for average-risk medulloblastoma whose cumulative dose of cisplatin should have been 600 mg/m². Due to the sensorineural hearing toxicity of cisplatin, doses were frequently reduced with less than 20% of children receiving the whole scheduled treatment. The authors in this paper categorized children according to the cumulative cisplatin doses received into four subgroups from a minimum of 75 mg/m² to the total dose of 600 mg/m² and did not observe any correlation of event-free survival and overall survival with the cumulative doses of cisplatin received. This is a very important issue since cisplatin causes dose-dependent cochlear damage that is higher in younger children. Moreover, the long-term impact of hearing loss is greater in younger children whose language is still not completely developed. The real dose of cisplatin required in the treatment of medulloblastoma is not known and this is the first study that has been realized to evaluate the association between cumulative cisplatin dose and event-free survival/overall survival in newly diagnosed patients, thus demonstrating that the cumulative dose of cisplatin needed to cure medulloblastoma can be lowered thus reducing acute and long-term toxicity.

– Written by Maura Massimino

**Canpolat M, Per H, Gumus H *et al.*
Rapamycin has a beneficial effect on
controlling epilepsy in children with
tuberous sclerosis complex: results of**

7 children from a cohort of 86. *Childs Nerv. Syst.* doi:10.1007/s00381-013-2185-6 (2013) (Epub ahead of print).

The authors report their experience with the diagnosis and follow-up of a big series of pediatric patients with tuberous sclerosis, with particular reference to the management of drug resistant seizures. They have experienced the possibility of a complete control of epilepsy in seven patients within 6 months of treatment using rapamycin that works by dissociating mTORC1 from its co-factor, Raptor. In the mutations shown by tuberous sclerosis, the source of inhibition of mTOR is absent. This generates a wrong regulation of synthesis and turnover of glutamate receptors of neurons with altered morphology of dendritic spines, crucial for epileptogenesis, learning, memory and consciousness. The authors used a single oral dose at 1.5 mg/m²/day and had success in

all their seven patients, thus allowing tapering of some antiepileptic concomitant drugs. Seizures are the most common cause of morbidity in these patients, leading to developmental delays and autism. Apart from controlling seizures, rapamycin also induced remission of facial angiofibromas, renal angiomyolipomas and subependymal giant cell astrocytoma.

– Written by Maura Massimino

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Natasha Leeson, Commissioning Editor, *CNS Oncology*
n.leeson@futuremedicine.com