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

Schumacher T, Bunse L, Pusch S et al. A vaccine targeting mutant IDH1 induces antitumour immunity. *Nature* 512 324–327 (2014)

The authors vaccinated MHC-humanized transgenic mice with a p123–142 peptide from the R132H variant of IDH1. They demonstrated both a T-cell response and anti-IDH1 antibodies. These responses were not induced after vaccination with a similar peptide from wild-type IDH1. Vaccination using the same peptide given to mice with previously transplanted or subsequently transplanted IDH1(R132H)-expressing sarcomas suppressed growth of the sarcomas. Among mice with subsequently transplanted sarcomas, the sarcomas that resisted the vaccination displayed reduced IDH1(R132H) expression. Additionally, among patients with gliomas expressing IDH1(R132H), the authors found IDH1(R132H)-specific T cells in four out of 25 patients and IDH1(R132H)-specific antibodies in four out of 42; similar responses were not found in patients with gliomas lacking IDH1(R132H). These results demonstrate that vaccination of mice with a peptide derived from IDH1(R132H) generates a robust T-cell- and antibody-mediated response that can suppress tumor growth; a small minority of patients bearing gliomas with IDH1(R132H) have a demonstrable immune response against IDH1(R132H).

– Written by Larry Junck

Kaley TJ, Wen P, Schiff D et al. Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. *Neuro Oncol.* doi:10.1093/Neuroonc/nou148 (2014) (Epub ahead of print).

Sunitinib maleate is an orally administered tyrosine kinase inhibitor targeting the VEGF receptor,

which is upregulated in meningioma, and PDGF receptor, thought to drive proliferation in meningioma. The authors treated 36 patients with multiply recurrent high-grade meningioma (30 atypical and six anaplastic) with sunitinib 50 mg daily for 28 of 42 days. Progression-free survival (PFS) at 6 months was 42%, meeting the study end point. Median PFS was 5.2 months, and the median survival was 24.6 months. Median PFS was 1.4 months in three patients whose tumors lacked VEGF receptor progression and 6.4 months in 25 with expression ($p < 0.005$). An additional 13 patients with other CNS tumor types were evaluable for toxicity. The most important toxicity among all patients was intratumoral or CNS hemorrhage in four patients (8%), including one death. This may be the first trial strongly suggesting benefit of drug treatment for high-grade meningiomas, but the benefit was short lived, and toxicity was high.

– Written by Larry Junck

Holdhoff M, Ambady P, Abdelaziz A et al. High-dose methotrexate with or without rituximab in newly diagnosed primary CNS lymphoma. *Neurology* 83, 235–239 (2014).

This retrospective study presents results of 54 patients with primary CNS lymphoma treated between 1995 and 2008 with high-dose methotrexate monotherapy 8 g/m² (HD-MTX) initially every 2 weeks, then, after complete response, continued monthly through 12 cycles, compared with 27 treated between 2008 and 2012 with the same regimen plus rituximab 375 mg/m² added to each methotrexate treatment (HD-MTX/R). Complete response was achieved in 36% with HD-MTX and 73% with HD-MTX/R; complete or partial response

was achieved in 60 and 89%, respectively. Progression-free survival was 4.5 months with HD-MTX and 26.7 months with HD-MTX/R ($p = 0.003$); overall survival was 16.3 months with HD-MTX and has not been reached in the HD-MTX/R cohort ($p = 0.01$). This study has a number of limitations including retrospective nature, nonconcurrent treatment and patients lost to follow-up. It adds to the growing evidence that multidrug chemotherapy yields better results than HD-MTX monotherapy.

– Written by Larry Junck

Letarte N, Gabay MP, Bressler LR, Long KE, Stachnik I, Villano JL. Analyzing temozolomide medication errors: potentially fatal. *J. Neuro Oncol.* 120, 111–115 (2014).

This paper describes the risks correlated to the ‘easy’ prescription of oral temozolomide in the last ten years after the EORTC study published by Stupp in 2005 showing an amelioration in overall survival of patients affected by glioblastoma by adding temozolomide to radiation and post-radiation treatment [1]. A total of 45 medical errors were reported from 1997 to 2012 either prescribing or dispensing or assuming the drug. In 18% of cases, these mistakes led to death for toxicity. Oral chemotherapy is at major risk of mistakes in addition to prescribing and dispensing drugs. Many risks in temozolomide dispensing are due to the homogeneity of the labels despite the different dosing of the tablets, and more recently mistakes are mostly due to the different colors in labels between the original brand and the generic temozolomide. The need to combine different tablet dosages increase dosing mistakes. The authors propose to give the patients the exact amount of drug needed to avoid hyperdosage. Maybe a further step could be giving the daily dosages in separate parcels.

– Written by Maura Massimino

Salaroli R, Ronchi A, Buttarelli FR et al. Wnt activation affects proliferation, invasiveness and radiosensitivity in medulloblastoma. *J. Neurooncol.* doi:10.1007/s11060-014-1621-0 (2014) (Epub ahead of print).

Among the four molecularly characterized medulloblastoma subtypes, the Wnt one is correlated to the best prognosis, but there are no clues

to understand whether the outcome is correlated to a minor invasiveness, or to a better treatment response. By analyzing the biological behavior of a medulloblastoma cell line, stably transfected with human beta-catenin cDNA encoding a nondegradable form of β -catenin, the authors were able to outline these issues. The growth of the nuclear β -catenin cell line decreased when cultured in standard conditions compared to the vector control line. Also the cells mortality rate after irradiation was greater when Wnt alteration was present, and their invasiveness was reduced with respect to controls. Comparing medulloblastoma samples, containing or not containing cells with nuclear accumulation of β -catenin, the authors observed a reduced Ki-67 labeling index in the first group. Therefore, in medulloblastoma, the accumulation of β -catenin in nuclei reduces cell proliferation, enhances cell sensitivity to radiation and inhibits invasion capability of cells.

– Written by Maura Massimino

Vallero SG, Lijoi S, Bertin D et al. End-of-life care in pediatric neuro-oncology. *Pediatr. Blood Cancer* 61, 2004–2011 (2014).

The authors describe the last disease phase in a subgroup of their patients, namely those 39 affected by CNS tumors dying between 2005 and 2011. They illustrate the modality of assistance for pediatric oncology in Piedmont region that is based on a hub-spokes model with one main center responsible for diagnosis, therapeutic decisions and palliation organization, and nine spoke centers that are educated and available for continuing treatment in any phase of the disease history. The paper describes how the decision of stopping specific treatment was taken by the medical staff and communicated to families during a dedicated meeting with the participation of the physician in charge of the patient and the psychologist. It is to be outlined that, despite the impossibility to cure the patient, six of 39 were still receiving chemotherapy in the last month for delaying the end of life or, more frequently, to comply with parents and patients desire to continue some specific treatment. In total, 56% of patients died in hospital, either in the hub or in the spokes centers. This quite high percentage is the expression not only of the complexity of the disease, but also of the efforts made by the specialists to assure the best possible support, also including neuromotor

rehabilitation, psychological treatment, anti-infectious therapies, apart from analgesics, sedation, anti-epileptic support that are quite obvious in this last phase of disease.

– Written by Maura Massimino

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Reference

- 1 Stupp R, Mason WP, van den Bent MJ *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N. Engl. J. Med.* 352, 987–996 (2005).