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Soffietti R

European Association of NeuroOncology Magazine 2014; 4 (2) 92-93

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Hotspots in Neuro-Oncology

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IDH-1 Mutant Malignant Astrocytomas Are More Amenable to Surgical Resection and Have a Survival Benefit Associated with Maximal Surgical Resection

Beiko J, et al. Neuro-Oncology 2014; 16: 81–91.

Large retrospective series on malignant gliomas have provided compelling evidence that more extensive resections are associated with better outcomes. So far, no data have been available on the relationship between the impact of surgery and molecular alterations. In the January issue, Beiko et al analysed in a retrospective cohort of 335 malignant astrocytomas (WHO grade III or IV) the correlations between the extent of surgery (based on tumour volumetry) and IDH-1 status (based on immunohistochemistry and sequencing). Interestingly, they found that IDH-1 mutation was an independent predictor of the success of obtaining complete resection of the enhancing tumour. Moreover, patients with IDH-1 wild-type tumours derived a benefit from complete resection of the enhancing tumour, but no further benefit from the resection of the non-enhancing one. Conversely, patients with IDH-1-mutant tumours derived maximum benefit when both enhancing and non-enhancing tumours were completely removed. To date, the most important implication of this study, whose results need to be further confirmed, is that future prospective studies on the impact of the extent of surgery on survival will need to include the IDH-1 status as a covariate.

Investigation of the Diffusion Abnormality Index as a New Imaging Biomarker for Early Assessment of Brain Tumor Response to Radiation Therapy

Farjam R, et al. Neuro-Oncology 2014; 16: 131–9.

Diffusion-weighted (DW) MRI has the potential to be a biomarker for early assessment of tumour response to therapies, but can be confounded by oedema and necrosis in or near brain tumours. In the present study, Farjam et al have developed a new diffusion abnormality index (DAI) based upon diffusion-weighted MRI: specifically, the DAI weighs the abnormal ADC contributions from high cellularity and oedema differently for prediction of tumour response. The authors evaluated the performance of DAI in patients with brain metastases who received WBRT, alone or associated with bortezomib as a radiosensitizer. Compared to other ADC metrics published previously and conventional metrics, the DAI showed a greater potential to predict the volumetric response of brain metastases to radiotherapy. Moreover, diffusion-related physiological changes in the tumour tended to occur earlier than morphological changes. These results need to be validated using independent datasets. In the future, it would be interesting to investigate the DAI in malignant gliomas for an early response assessment to radiotherapy or other experimental drugs (ie, antiangiogenic agents, etc).

Phase II Study of Everolimus in Children and Adults with Neurofibromatosis Type 2 and Progressive Vestibular Schwannomas

Karajannis MA, et al. Neuro-Oncology 2014; 16: 292–7.

Preclinical studies have suggested that the activation of the mammalian target of rapamycin (mTOR) signalling pathway could be a key driver of tumour growth in Merlin- (NF2-) deficient tumours, being a potential target for therapy. In the February issue, Karajannis et al conducted a single-institution pivotal phase-II trial to evaluate the response rate to everolimus, a rapamycin analogue, in neurofibromatosis type 2 (NF2) patients with progressive vestibular schwannomas (VS). Unfortunately, none of the 9 evaluable patients experienced a ≥ 15-% decrease in VS volume (primary endpoint) or had significant hearing improvement (secondary endpoint). Interestingly, the largest volumetric decrease (14 %) was observed in a cervical nerve root tumour, raising the possibility that everolimus might be more effective in treating non-VS tumours in NF2 patients. Two phase-II studies of everolimus for NF2 patients with a very similar trial design are ongoing in the US and will better define the role of this drug. So far, bevacizumab and lapatinib remain the sole compounds that have been demonstrated to lead to significant MRI and hearing improvements in VS of NF2.

Targeting Wee1 for the Treatment of Pediatric High Grade Gliomas

Mueller J, et al. Neuro-Oncology 2014; 16: 352–60.

Despite surgery, radiotherapy, and chemotherapy, paediatric high-grade gliomas (HGG) have a dismal prognosis with the vast majority of patients dying within 5 years. Wee1 is a potential specific molecular target for therapy: in fact, when activated, it causes inhibitory phosphorylation of CdC2, preventing G2-M cell cycle progression. In this preclinical study, Mueller et al investigated the expression of Wee1 in a series of 38 paediatric gliomas and evaluated the efficacy of MK-1775, a selective Wee1 kinase inhibitor, in potentiating radiation effectiveness. The authors showed that Wee1 is over-expressed in paediatric HGGs with increasing expression positively correlated with grade of malignancy, and the expression is markedly high in DIPGs (diffuse intrinsic pontine gliomas). Furthermore, combination treatment of MK-1775 and radiation reduced clonogenic survival to a greater extent than achieved

by radiation. Finally, combined MK-1775 and radiation conferred greater survival benefit to mice bearing engrafted, orthotopic HGG and DIPG tumours compared with radiation alone. In conclusion, this preclinical study provides a strong rationale for future clinical trials exploring the combination of MK-1775 with radiotherapy in children with newly diagnosed HGGs, in particular DLPG.

Clinical Value of Chromosome Arms 19q and 11p Losses in Low Grade Gliomas

Alentorn A, et al. Neuro-Oncology 2014; 16: 400–8.

Low-grade gliomas (LGG) are a complex subgroup of glial tumours with a heterogeneous prognosis. 1p/19q co-deletion, which is associated with IDH-1 mutation, is associated with a favourable prognosis, while non-co-deleted tumours display a worse outcome. In this study, Alentorn et al focused on the latter subgroup to better characterise the driving molecular alterations. They showed in a retrospective series of 126 LGGs that non-1p/19q-co-deleted tumours can be divided into 5 main genomic subgroups: 11p loss, 19q loss, 7 gain, 19 gain, and unclassified. Interestingly, 11p loss was associated with astrocytoma phenotype and had an independent negative prognostic value, and 19q loss diminished the favourable prognostic value of IDH-1 mutation. All these findings were validated in an independent cohort of 98 LGGs. This study demonstrates that genomic changes commonly associated with the pathogenesis of LGGs may help to stratify these tumours regarding prognosis and, in the future, may facilitate the individualisation of treatment. Prospective studies are needed to confirm these findings.

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