Hotspots in Neuro-Oncology

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Combined Analysis of O6-Methylguanine-DNA Methyltransferase Protein Expression and Promoter Methylation Provides Optimized Prognostication of Glioblastoma Outcome


Methylation of the promoter region of the O6-methylguanine-DNA methyltransferase (MGMT) gene is a predictive biomarker for benefit from alkylating-agent chemotherapy in glioblastoma. The MGMT status is commonly determined by methylation-specific PCR. In the March issue, Lalezari et al challenged the notion that immunohistochemical assessment of MGMT in tumour tissue is of no prognostic or predictive value. These authors compared MGMT test results obtained by genetic testing and immunohistochemical assessment, trying to make sure that the MGMT signal on immunohistochemistry was obtained from tumour cells and not from tumour-infiltrating host cells. They conclude that combined MGMT testing using methylation-specific PCR and immunohistochemistry is superior to methylation-specific PCR alone because high MGMT protein levels were associated with poor outcome irrespective of genetic MGMT status, whereas low protein was not associated with a favourable outcome in the absence of MGMT promoter methylation. Although these observations are interesting and enhance our understanding of the significance of MGMT in the outcome of glioblastoma, this study argues for supplementing genetic testing with protein testing, not for replacing it.

A Multi-Disciplinary Consensus Statement Concerning Surgical Approaches to Low-Grade, High-Grade Astrocytomas and Diffuse Intrinsic Pontine Gliomas in Childhood (CPN Paris 2011) Using the Delphi Method


Defining widely accepted standards of care for rare brain tumours has been notoriously difficult. Most national or international guidelines do not include such tumours. In the April issue, Walker et al, on behalf of the Consensus Conference on Paediatric Neurosurgery, Paris, France, 2011, published a multidisciplinary consensus statement on surgical approaches to low- and high-grade astrocytomas and diffuse intrinsic pontine gliomas in childhood. They used the Delphi method, that is, they drafted statements which were then subjected to an online voting procedure. A 70%-agreement was looked for, statements achieving lower agreement were modified and re-evaluated. The consensus group comes up with 27 statements which should be very helpful, especially for sites or countries where no large cooperative networks are available to standardize approaches to these tumours in childhood. The approach pursued can be realized with a reasonable effort and may be applied successfully to other areas of controversy in clinical neuro-oncology.

Glutamine Synthetase Expression as a Valuable Marker of Epilepsy and Longer Survival in Newly Diagnosed Glioblastoma Multiforme


The biological determinants of symptomatic epilepsy in intrinsic brain tumours including glioblastoma remain controversial. Expression of glutamine synthetase has previously been linked to inferior outcome, but decreased risk of epilepsy. Glutamine synthetase is an enzyme expressed by astrocytes which catalyzes the conversion of glutamate and ammonia to glutamine. In the May issue, Rosati et al from Italy expand on this topic by performing a retrospective study of glutamine synthetase expression in a series of 83 consecutive patients with newly diagnosed glioblastoma. Staining intensity and homogeneity of this distribution for glutamine synthetase was inversely correlated with epilepsy. Moreover, absent or low intensity of glutamine synthetase expression was associated with prolonged survival on uni- and multivariate analyses. This interesting study appears to confirm a link between glutamine synthetase, risk of epilepsy, and outcome and provides an explanation for the association of tumour-associated symptomatic epilepsy with better outcome in glioblastoma.

Patterns of Care and Outcome for Patients with Glioblastoma Diagnosed During 2008–2010 in Spain


Several efforts have recently been made to assess the changing management and outcome patterns in patients with glioblastoma on a population-based level, based on the assumption that the introduction of concomitant and adjuvant temozolomide in 2005 resulted in an overall improvement of outcome. In the June issue, Graus et al from Spain report the results of a retrospective analysis of such data collected via questionnaires, covering patient files from 19 Spanish hospitals. A total of 834 patients were studied. One quarter of the patients was older than 17 and 1/3 of the patients was initially managed by biopsy rather than resection. One quarter received no further treatment beyond surgery. Three quarters of the patients who were treated after surgery received radiotherapy plus temozolomide. Age was confirmed as an impor-
tant prognostic factor. Surgery-associated morbidity was identified as a significant factor linked to cessation of further treatment measures in patients with newly diagnosed glioblastoma, notably in the elderly. Median overall survival was 11.8 months which conforms to other larger contemporary studies, overall suggesting a moderate improvement in survival since the introduction of temozolomide. Yet, similar to other studies, also this series is not truly population-based, rendering it very likely that a fraction of poor-prognosis patients was not captured in this survey.

**Phase 2 Study of Dose-Intense Temozolomide in Recurrent Glioblastoma**


Dose-intense temozolomide regimens are among the most commonly used treatment regimens for recurrent glioblastoma in many countries in Europe, notably where bevacizumab is not available. Moreover, the repertoire of nitrosourea compounds has been reduced over the last years, mostly to CCNU (lomustine), which is available in most countries. In the July issue, Norden et al reported results from a phase-II study of dose-intense temozolomide at 21 out of 28 days in patients with glioblastoma at first relapse. 58 patients were enrolled, 65% of assessed patients had MGMT promoter methylation. The partial response rate was 13%, and progression-free survival at 6 months was disappointingly low with 11%. This figure is lower than with CCNU in recent randomized trials or continuous dosing of temozolomide according to the “rescue” regimen. Although this is a small study, it increases the series of publications questioning the overall strategy of dose-intense temozolomide in newly diagnosed or recurrent glioblastoma. Data from the randomized DIRECTOR trial comparing the 21-out-of-28 and 7-out-of-14 days regimens will soon be available and may allow for a more definitive conclusion on the future of this regimen for patients with recurrent glioblastoma.

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