Medulloblastoma: selecting children for reduced treatment

A major challenge in paediatric neuro-oncology is to accurately predict the outcome for an individual patient. Particularly, so those patients with a good prognosis can avoid life-long complications of intensive treatment. In a paper in this issue of the journal, Goschzik and colleagues investigate the best way to do this in medulloblastoma, the commonest malignant brain tumour in children [1].

Survival rates for children with medulloblastoma are impressive compared with many malignant brain tumours but complications of treatment are frequent and the children carry the burden of this disability, potentially for the many years of their adult life [2–5]. For example, one study found significant impairment on neuropsychological testing in more than 50% of medulloblastoma survivors [5]. Therefore, there is a pressing need to be able to identify children for whom treatment might be reduced without increasing the risk of tumour relapse.

David Ellison, Steve Clifford and colleagues first showed in a trial cohort that activation of the WNT signalling pathway could be used to identify a subgroup of paediatric medulloblastoma with an excellent prognosis [6]. They found that patients with WNT activation had a 5-year overall survival of 92.3%, compared with 65.2% in patients without WNT activation. This result has subsequently been replicated in several studies [7–11]. However, at present, it is unclear which of these, if any, represent the best way to identify a WNT-group tumour for clinical diagnosis or for trial design. For example, WNT-tumours have been reported without monosomy 6 or CTNNB1 mutations [6,16]. A particular problem with staining for nuclear β-catenin is determining the percentage threshold of positive cells at which a diagnosis of WNT subtype is made, an issue confounded by variability in staining protocols and the subjective nature of interpretation.

In this issue, Goschzik et al. have addressed these uncertainties by comparing three standard approaches: immunohistochemistry for nuclear β-catenin, sequencing of CTNNB1 and chromosome 6 copy number analysis. In addition, they undertook tumour subtyping on methylation arrays. In a large cohort of 186 cases, they found that immunohistochemistry for nuclear β-catenin (at a threshold of 5% of the cells) identified all the WNT-group tumours (when compared with the other tests), suggesting that this a very sensitive screening test for WNT-group tumours. However, their data suggest that immunohistochemistry cannot be used definitively in isolation. In particular, they found that 3 of the 21 tumours that were positive for nuclear β-catenin belonged to non-WNT subgroups as judged by methylation profiling. Interestingly, all three of these cases had β-catenin staining that was close to the 5% threshold. The authors found that all of the remaining 18 cases with >5% nuclear β-catenin positivity had mutations in CTNNB1 but in contrast, monosomy 6 was only present in 15 of the cases. On the basis of this data, the authors recommend that patients are
Patients with nuclear β-catenin positivity in >5% of cells and mutant CTNNB1 are classed as low risk. Those with MYC/MYCN amplification or anaplastic/large cell change are considered high risk. Cases not matching criteria for either category and without high-risk clinical features (e.g. metastatic disease) are considered standard risk.

While not seen in this study, previous investigations suggest that some true WNT-group medulloblastomas would be excluded by this approach because they are negative for a CTNNB1 mutation [19]. However, the approach taken by Goschzik et al. avoids the danger of undertreating children with non-WNT-group tumours and therefore risking relapse. The techniques employed are conducive to large cohorts and can be undertaken in real time in diagnostic practice in many labs. Therefore, the suggested protocol provides a practical way to introduce stratification into trials and clinical practice (Figure 1).

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