Medulloblastoma in infants: the never-ending challenge

Despite substantial improvements in overall survival, management of infants and young children with medulloblastoma remains a major challenge. In this age group, which is loosely defined as from birth to 6 years of age depending on protocol eligibility criteria, treatment is different from that for older children, because of the higher risk of radiation-related injury to the developing brain.1 There is a fine line between success (complete remission with reintegration [reinstatement of regular life], neurological integrity, and few or no side-effects) and catastrophic success (complete remission with poor or no reintegration, and neurological, intellectual, and endocrinological deficits), a difference that is not reflected in crude overall survival results. However, despite innovative treatment approaches used in infants and young children with medulloblastoma, overall survival remains disappointing compared with that of older children treated with craniospinal radiotherapy.2–4 Nodular or desmoplastic medulloblastoma histology in infants is associated with improved outcomes compared with classic medulloblastoma histology.1 However, until now, whether this prognosis difference was also driven by biological characteristics was unclear. Since the publication of a consensus paper in 2012,5 medulloblastoma has been accepted worldwide to comprise four biologically and clinically distinct subgroups: WNT, sonic hedgehog (SHH), group 3, and group 4. However, even within these defined subgroups, there is molecular heterogeneity.6

In The Lancet Oncology, Giles Robinson and colleagues7 report the results of the phase 2, multicentre, SJYCO7 trial of risk-adapted therapy in 81 infants and young children (aged <5 years) with medulloblastoma. Patients were stratified postoperatively according to clinical and histological criteria into three treatment groups: low-risk, intermediate-risk, and high-risk. All patients received chemotherapy, with the intensity of the regimen adapted by risk, and intermediate-risk patients also received focal radiation to the tumour bed. Subsequently, all patients received oral maintenance chemotherapy. Although the trial did not meet its coprimary therapeutic endpoint and cannot be regarded as a success, with a disappointing 5-year event-free survival for the entire cohort of 31.3% (95% CI 19.3–43.3), the molecular findings improve our current understanding of infant medulloblastoma. First, focal radiation does not seem to be the solution to improve outcomes in young patients with medulloblastoma, as shown by the low 5-year event-free survival for intermediate-risk patients (24.6%, 95% CI 3.6–45.6), and cannot replace craniospinal radiotherapy in older children eligible for this therapy. Second, the frequent occurrence of progression or relapse during maintenance did little to suggest remission could be maintained on oral chemotherapy. Finally, patients who do not receive radiotherapy as first-line treatment and have relapse or refractory disease are salvageable. Previous studies8 had shown that some children who do not respond to chemotherapy can be treated with craniospinal radiotherapy as a salvage option, but at what cost? Long-term neurocognitive follow-up studies should be mandatory in all trials using craniospinal radiotherapy to answer this question.

Also, the investigators assembled a large cohort of tumour samples for molecular diagnosis. As previously described,5 Robinson and colleagues found only three molecular medulloblastoma subgroups in infants and young children: SHH (83/190 [44%]), group 3 (68 [36%]); and group 4 (22 [25%]); no patients harboured WNT-activated tumours. The distribution of subgroups varied with age, with large differences between the under 3-years-old group and the 3–6-years-old group (SHH, 61/84 [73%] vs 22/106 [21%]; group 3, 21/84 [25%] vs 47/106 [44%]; and group 4, 2/84 [2%] vs 37/106 [35%]). The age limit, which was established by paediatric neuro-oncologists decades ago regarding the neurocognitive effects of radiotherapy in children younger than 3 years, seems to be strongly associated with these molecular findings.

Some trials have attempted to reduce the intensity of therapy to decrease toxicity in infants with medulloblastoma.9 One of the major findings of the current study is the identification of a good responder group among the SHH subtype, iSHH-II (n=11), that had improved progression-free survival in the absence of radiotherapy, intraventricular therapy, or high-dose chemotherapy. The 5-year progression-free survival of the clinically defined low-risk iSHH-II patients was 90.9% (95% CI 73.1–100.0) compared with 22.2% (0.1–44.3) for the iSHH-I subtype (n=12; HR 14.75, 95% CI 1.84–118.04; p=0.0007). These results need to be validated in other clinical trials as soon as possible to further refine the identification of good responders.
medulloblastoma subgrouping in young patients and adjust future protocols accordingly.

Most studies of medulloblastoma in infants have reported on small numbers of patients, limiting the accuracy of the results. Owing to these small numbers, international collaborative trials must be designed, addressing the most important questions identified in previous studies, such as the role of high-dose chemotherapy, intrathecal treatment, optimum management for patients with classic histology, and the need to offer separate treatment strategies for patients with SHH-I and SHH-II tumours. Indeed, the study by Robinson and colleagues along with other studies exploring medulloblastoma biology provide an important framework, and support the idea that risk stratification by molecular subclassification could be a robust alternative to stratification by clinical risk factors. Molecular subclassification is also likely to lead to personalised treatments and, most importantly when treating young patients, decrease the long-term toxicity associated with cancer treatments.

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I declare no competing interests.