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Medulloblastoma in adults: they're not just big kids

Alvaro Lassaletta and Vijay Ramaswamy

Division of Haematology/Oncology, Hospital for Sick Children, Toronto, Ontario, Canada (V.R., A.L.); Department of Pediatric Hematology/Oncology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain (A.L.)

Corresponding Author: Vijay Ramaswamy MD, PhD, FRCPC, Division of Haematology/Oncology, Labatt Brain Tumour Research Centre, Hospital for Sick Children, 555 University Avenue, Toronto, ON, M5G 1X8, Canada (vijay.ramaswamy@sickkids.ca).

See the article by Zhao et al., on pages 982–990.

Medulloblastoma is the most common malignant brain tumor of childhood, however, it is a rare entity in adults and accounts for only 1% of all CNS tumors.[1] Due to the relatively low incidence of medulloblastoma in adults, very few studies exist; only one prospective study has been published to date.[2] Conversely, childhood medulloblastoma is one of the most heavily studied neoplasms, but our knowledge of adult medulloblastoma stems primarily from the inclusion of adults in primarily pediatric analyses. Although molecular risk stratification of childhood medulloblastoma is maturing towards molecularly informed clinical trials, genomic events and clinical-genomic correlates specific to adult medulloblastoma are poorly described.3

There have been clues over the past decade that adult medulloblastoma might be biologically separate from childhood medulloblastoma. A previous study from Remke et al. has shown that adult medulloblastoma comprises 3 molecular variants rather than 4 and that the majority of tumors are SHH with smaller percentages comprising Wingless (WNT) and group 4.[4] Moreover, several genomic studies have suggested that adult SHH medulloblastoma is distinct from the pediatric entity, being enriched for *PTCH1* and *SMO* mutations and coupled with a near absence of *TP53* mutations.[5,6] Interestingly, the most common somatic nucleotide variant in adult SHH tumors is *TERT* promoter mutation, an event more commonly observed in adult high-grade glioma.[7] A major limitation in the interpretation of these biological studies is the lack of correlation with treatment. Indeed, almost all children over ages 3–5 years receive radiotherapy plus chemotherapy independently of the risk group at diagnosis, while adults with localized disease often receive 36 Gy of radiotherapy alone with chemotherapy occasionally being added when the diagnosis is high-risk.

In this issue of *Neuro-Oncology*, Zhao et al. assigned the molecular subgroup using gene expression analysis in 13 primary medulloblastomas and a large immunohistochemistry-based validation cohort of 201 primary samples. This comprises the largest cohort of adult medulloblastoma profiled genomically to date. As previously described by Remke et al., they confirmed only 3 subgroups of adult medulloblastoma: a predominance of SHH-activated tumors (62%) followed by group 4 tumors (28%) and WNT-activated tumors (10%).[4] No patients were classified as group 3. Similar to children, there is a female preponderance in WNT tumors but, unlike children, a male preponderance in SHH. Adult SHH tumors were lateral hemispheric, likely indicating granule cell precursors as a shared cell of origin with childhood SHH tumors.

The novelty of this study pertains to treatment correlates, in which the authors incorporate a multivariable analysis including treatment and subgroup as variables. Similar to the findings of the Remke et al. cohort,[4] group 4 tumors have a dismal prognosis—even when correcting for treatment—and metastatic dissemination compared with SHH and WNT, which is a clear difference from the pediatric disease. It has previously been suggested that adult WNT medulloblastomas are not low-risk; however, WNT tumors had a relatively favorable 5-year survival, with 2 late events after 5 years accounting for the 2 progression events. Other than group 4, metastatic status and anaplastic histology were also correlated with poor survival; however, adjuvant chemotherapy interestingly was not a prognostic factor.

Due to its rarity, most available studies on medulloblastoma in adults have been retrospective and limited in their scope (Fig. 1). As such, adults have been excluded from pediatric studies including ongoing trials from the Children's Oncology Group and SIOPe. The majority of adults treated at adult neuro-oncology centers are usually treated with craniospinal irradiation only, although substantial treatment variation exists.[8] The addition of chemotherapy in children has significantly reduced toxicity while improving survival, but the role of chemotherapy is unknown in adults. Adapting adult protocols to pediatric strategies is clearly advantageous in other cancers such as acute lymphoblastic leukemia.[9] Indeed, the higher incidence of extraneural relapses in adults is reminiscent of the high rate of extraneural relapses in children prior to the adoption of adjuvant chemotherapy.[10] Five-year survival of adults is favorable; however, late relapses are more common in adults and result in poor 10-year survivals, suggesting that longer follow-up is clearly required for this population.

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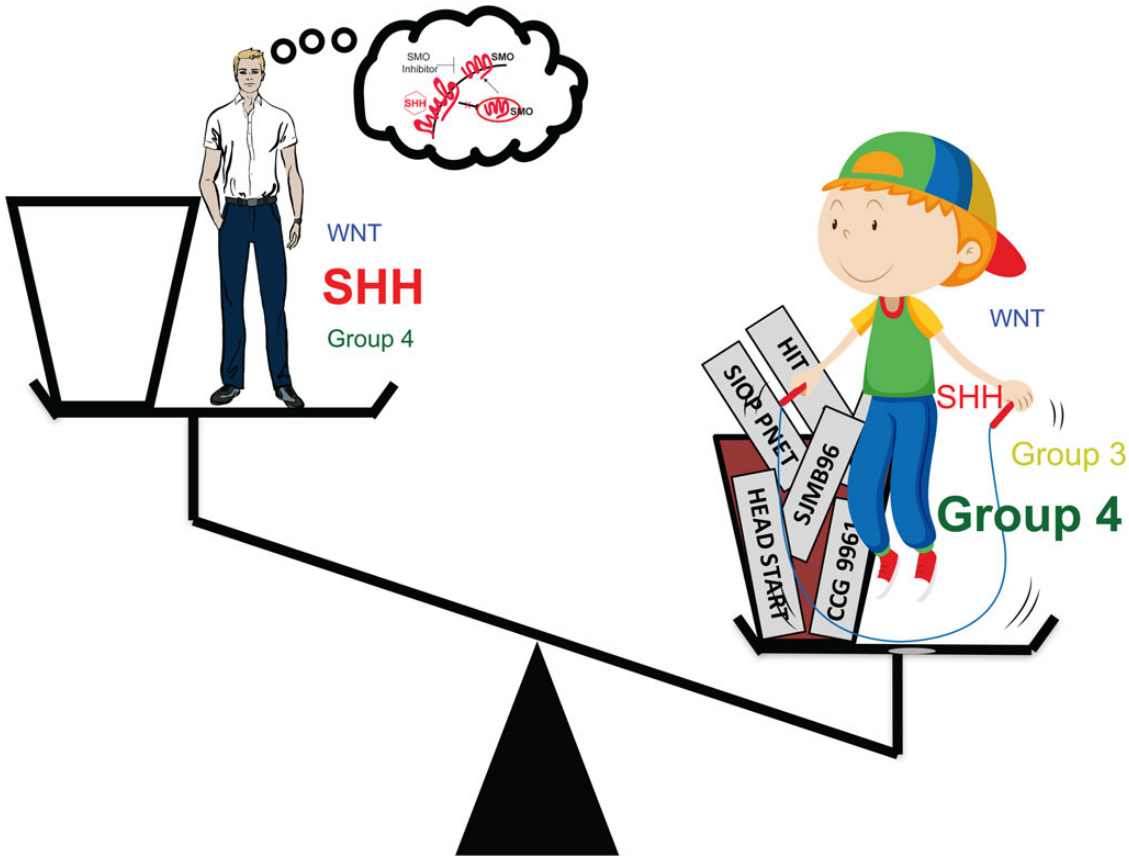

Fig. 1. The medulloblastoma age scale: Published clinical trial cohorts and molecular characterization of medulloblastoma in adults and children. (Figure elements from Shutterstock; used with permission).

An unknown question is the tolerability of adjuvant pediatric chemotherapy protocols in adults, particularly the use of high doses of platinum agents. One intriguing possibility to mitigate this barrier is the incorporation of SHH pathway inhibitors—specifically SMO inhibitors—into the upfront treatment of adult medulloblastoma. Two of these inhibitors have been recently approved, specifically vismodegib and sonidegib, which show activity in relapsed adult SHH medulloblastoma.[11,12] A sequencing study from Kool et al. also suggests that the mutational profile of adult SHH tumors predicts a favorable response to SMO inhibition, further supporting their use.[6] The major toxicity of SMO inhibition in children has been predicted to be inhibition of bone growth, which is an irreversible phenomenon in mice. This is certainly not a major consideration in adults and opens the possibility of incorporating targeted therapy into the upfront treatment alongside radiation and/or low dose conventional chemotherapy. Our current sporadic preclinical models of SHH medulloblastoma, specifically those with *PTCH1* and *SMO* mutations, likely recapitulate adult medulloblastoma and can serve as a robust platform for generating new and novel therapies.[13] However, the authors' observation of a dismal prognosis in adult group 4 medulloblastoma is in stark contrast to pediatric group 4 and warrants further efforts to both determine a possible biological explanation for this discrepancy and prioritize these patients for new and novel therapies.[14]

The first step in improving outcomes for adults would be the adoption of international collaborative trials, in which treatment can be uniform and standardized. Indeed, the current study from Zhao et al. and the previous study from Remke et al. provide a background and impetus for a molecularly informed study analogous to those proposed in childhood medulloblastoma while taking into account the clear differences of pediatric tumors such as late relapses and incorporation of targeted agents.[3] Adult medulloblastoma is an orphan disease with a limited number of patients. Therefore, a dedicated multicenter effort is essential for moving forward with improved outcomes for adults with medulloblastoma, specifically understanding their molecular and genetic bases, and ultimately developing optimal treatment regimens.

Conflict of interest statement. None declared.

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