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He is also the chair of the Children's Oncology Group frontline clinical trial for Wingless (WNT) subgroup medulloblastoma (ACNS1422; ClinicalTrials.gov identifier: NCT02724579). This study investigates therapy reduction to minimize long-term side effects experienced by patients with WNT subgroup medulloblastoma, who have excellent survival.

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"Coming Full Circle": Reintroduction of Radiotherapy Delaying Chemotherapy Followed by Craniospinal Radiotherapy for Infants With Medulloblastoma

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Medulloblastoma, the most common brain cancer in childhood, has a median age at diagnosis of 6 years, and approximately 40% of cases occur in children <5 years of age. In this issue, Bagchi et al[1] eloquently outline a comprehensive review of medulloblastoma in infants and young children (<6 years of age). Their review includes studies spanning different therapeutic eras, from the 1970s to recently reported completed clinical trials. The authors also performed a large retrospective cohort study and pooled data from 5 international genome-wide and epigenome-wide studies with 329 infants and young children with medulloblastoma.

Medulloblastoma has been shown to be a highly heterogenous disease, consisting of a collection of molecularly distinct diseases with 4 main molecular subgroups; Wingless type (WNT), Sonic hedgehog (SHH), Group 3 (G3), and Group 4 (G4). DNA methylation profiling has revealed further molecular heterogeneity within these 4 subgroups, resulting in a total of 13 subgroups. The SHH group is further divided into 4 subgroups (SHH-1, SHH-2, SHH-3, and SHH-4), and the non-WNT/non-SHH group is separated into 8 molecular subgroups (denoted G3/4-I to G3/4-VIII). Notably, each group has unique clinical and prognostic characteristics. In infants (<3 years of age), 2 molecular subgroups predominate—SHH (specifically SHH-1 and SHH-2) and G3 (specifically G3/4-III and G3/4-IV)—with a small proportion (~5%) of cases in the G4 group and none in the WNT group.[1]

Postoperative craniospinal irradiation (CSI) was introduced in the 1950s to prevent the inevitable metastatic relapses throughout the central nervous system (CNS) that many patients sustained, cementing this modality as the backbone of medulloblastoma therapy. For children aged >3 years, major strides in survival have been made using risk-stratified CSI. For patients classified as average-risk (children aged ≥3 years with <1.5 cm^2 of residual tumor and no metastatic disease), the 5-year overall survival is now 80% to 85% using 23.4 Gy CSI and adjuvant chemotherapy,[2,3] and approximately 70% for those with high-risk disease (children aged ≥3 years with ≥1.5 cm^2 of residual tumor and/or with metastatic disease) who receive a CSI dose of 36 Gy and adjuvant chemotherapy.[3,4]

To permit more precise risk-stratified therapy, medulloblastoma clinical trials are now embedding a molecular risk-adapted approach integrating traditional clinical and histologic criteria with molecular information (ClinicalTrials.gov identifiers: NCT01878617, NCT05535166, NCT02724579, NCT02066220). Given the ongoing concerns around the negative long-term consequences of CSI, to decrease morbidity, therapy reduction strategies are applied for patients with the lowest risk of relapse, such as those with average-risk WNT medulloblastoma (NCT02066220, NCT02724579, NCT01878617). In contrast, intensified and experimental therapies are used for high-risk groups, such as those with G3 *MYCC*-amplified medulloblastoma, to increase survival (NCT01878617).

Bagchi et al[1] conclude that after 4 decades of clinical trials applying a multitude of strategies trying to avoid CSI, a cure is achievable in the vast majority of infants and young children with the SHH group of medulloblastoma using chemotherapy

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alone. Notably, patients with the SHH-1 subtype of medulloblastoma have a worse outcome using lower-intensity chemotherapy than those with SHH-2, an effect that can be nullified using more-intensive chemotherapy strategies.[1] This highlights that even in the age of molecular characterization with integrated clinical and molecular risk stratification, the most important predictor of survival is therapy. Conversely and perturbingly, for infants with G3 medulloblastoma, a realistic chance of cure can only be obtained with the use of CSI. The authors cogently contend that infants with G3 medulloblastoma currently effectively undergo a "double whammy" of therapy, because high-intensity chemotherapy treatment approaches fail to prevent relapse and the inevitable subsequent use of salvage CSI, thereby multiplying toxicity and long-term morbidity.

These conclusions form the basis for their recently opened medulloblastoma study called SJiMB21 (ClinicalTrials.gov identifier: NCT05535166). This trial, exclusively for infants and young children with medulloblastoma, adopts a sophisticated stratification system combining established clinical risk factors with molecular characteristics to more precisely tailor therapy. Thus, patients with SHH medulloblastoma receive a chemotherapy-only strategy, risk stratified according to the underlying SHH subtype. Patients with SHH-1 disease receive more intensive intraventricular methotrexate–based chemotherapy. In contrast, patients with SHH-2 disease receive less-intense chemotherapy[1] in an attempt to minimize the long-term neurocognitive sequelae associated with intraventricular methotrexate. In stark contrast, for infants with G3 medulloblastoma, the study will reintroduce radiotherapy-delaying chemotherapy followed by risk-adapted CSI, with the dose of CSI varying from 18 to 36 Gy, in patients reaching 3 years of age. Some patients will also receive concurrent carboplatin during radiotherapy, because this therapy has recently been shown to significantly improve survival exclusively in G3 disease.[4] This approach is based on the reasonable but unproven premise that improved survival will be seen if CSI is given up-front rather than as salvage therapy after relapse for this population.

The treatment of infants with medulloblastoma has remained a major challenge. The initial application of CSI-based therapy in infants led to the confronting realization of the impacts of this approach on the especially vulnerable developing CNS of infants, with the resultant dire consequences on cognition, growth, and development. Fittingly, the "price for cure" was regarded as unacceptable, which led investigators to explore alternative therapeutic strategies. This highlights the balance between life and death, treatment and life-time harm is so finely balanced. Consequently, in the mid-1970s, a team at The University of Texas MD Anderson Cancer Center demonstrated that chemotherapy alone could effect cure in some infants with medulloblastoma and that these patients retained cognitive function.[5] This observation paved the way for a paradigm shift in the management of infants with medulloblastoma and heralded the era of radiotherapy-delaying studies in the mid-1980s. A notable example was the seminal Baby POG-1 study conducted by the Pediatric Oncology Group,[6] which aimed to delay radiotherapy to age 3 years with the administration of multidrug chemotherapy. For patients with no evidence of disease, the study planned to deliver reduced-dose radiotherapy on completion of planned chemotherapy. The trial experienced 2 significant issues. First, many children experienced progressive disease during therapy. Second, a significant proportion of patients who completed chemotherapy without evidence of disease did not receive the planned radiotherapy as intended due to parental concerns. These observations led to the generation of radiotherapy avoidance approaches with strategies centered on intensification of chemotherapy using high-dose chemotherapy with autologous stem cell rescue or intensive intraventricular methotrexate–based therapies.[1]

The review by Bagchi et al[1] and their recently opened SJiMB21 study illustrates that although our knowledge of the underlying biology has dramatically increased and now permits a much more refined stratification system, the unravelling of the medulloblastoma genome has not yet yielded the anticipated novel targeted therapies for the vast majority of patients with medulloblastoma. Inhibitors targeting upstream signalling pathway mutations in SHH-driven medulloblastoma initially generated optimism for replacing conventional therapies. However, short-lived effectiveness combined with the major complication of growth impairment has significantly restricted use to skeletally mature patients. Thus, with the exception of SHH-1 and SHH-2 medulloblastoma in infants and young children, the sobering reality is that radiotherapy remains the most potent therapy against medulloblastoma. This reality re-emphasizes that, ultimately, adequate treatment is the most powerful determinant of survival. This was recently highlighted in a pilot trial that attempted to completely omit radiotherapy for patients with WNT medulloblastoma, the most favorable medulloblastoma subgroup. The trial was terminated early because all patients (n=3) experienced rapid relapse.[7]

Bagchi et al's pragmatic but potentially controversial approach reveals how, given the absence of effective novel therapies, we have come full circle for some infants with medulloblastoma, with the reintroduction of radiotherapy-delaying strategies, as was done in first-generation infant medulloblastoma trials in the 1980s.[6] The success of this strategy will be predicated on 2 main factors: first, that the chosen preradiotherapy chemotherapy is adequate to prevent relapse/progression before patients reach 3 years of age; and second, that history does not repeat itself and parents (and/or physicians) accept the planned CSI when the time comes, especially for children stratified to receive high-dose CSI (36 Gy). Despite significant advancements in radiotherapy techniques, such as proton beam therapy, with early reports showing reduced CNS toxicity,[8] many parents and physicians may still see this approach as unpalatable.

Given the controversy around delivering CSI to young children, several radiotherapy-sparing medulloblastoma studies that use intensive high-dose chemotherapy strategies leave the decision to use CSI to the treating physician's (and ergo also the family's) discretion. This has inadvertently led to inadequately

collected radiotherapy-free survival data in some trials, hampering evaluation of the effectiveness of the strategies. This issue combined with the small numbers of patients included in these studies can therefore limit interpretation. However, although infants with G3 medulloblastoma have dismal survival rates, a proportion of patients do survive without radiotherapy. In particular, 2 recent reports (albeit one in abstract form only[9]) suggest more promising survival for this group of patients.[9,10] Both trials adopted the same high-dose chemotherapy backbone, but one trial also included high-dose methotrexate during induction.[9] Importantly, these studies have also reported the use of radiotherapy. The Pediatric Brain Tumor Consortium PBTC-026 trial on the feasibility of incorporating noncytotoxic therapy demonstrated a 5-year progression-free survival of 43%,[10] and the Children's Oncology Group ACNS0334 study reported a 5-year overall surival of 80% for the 10 infants with G3 disease who were randomized to high-dose methotrexate during induction.[9] Based on these encouraging results, the Children's Oncology Group will continue to adopt high-dose chemotherapy as the backbone for building new therapeutic strategies. Additionally, to significantly advance risk stratification, they will also adopt an integrated histologic, clinical, and molecular characterization in future studies in infants.[11] A pooled analysis of infants with G3 disease who experienced relapse after radiotherapy-sparing treatment identified CSI as an effective salvage therapy.[12] To try to develop predictors for the G3 infants that can be cured without radiotherapy, an analogous analysis to assess this group could yield important novel therapeutic insights, as well as additional molecular refinement.

Finally, this review and the SJiMB21 trial highlight the importance of ongoing preclinical research to identify novel therapies for these patients. The currently applied medulloblastoma therapy evolved from the empirical refinement of CSI in combination with multiagent chemotherapy. The extraordinary progress in unravelling the molecular pathogenesis of medulloblastoma achieved in the past decade provides an opportunity to develop novel therapeutic approaches tailored to each molecular subtype of medulloblastoma to improve survival while minimizing toxicities. Indeed, many more potential novel anti-cancer therapies exist now, which more precisely target molecular abnormalities in cancer cells that drive tumor growth, as well as immunotherapies. Consequently, preclinical modelling is a critical step that can direct the field to agents active in the CNS against specific medulloblastoma subgroups, and preclude the investigation of ineffective or minimally active agents in the clinic. We now have high-throughput drug screening platforms, tumor organoids, and an array of sophisticated medulloblastoma animal models, which more closely mimic the clinical characteristics of the disease in children than historic models. In addition, advanced preclinical radiotherapy platforms that precisely target tissues of interest while sparing normal healthy tissue permit the assessment of potential radiosensitizers. To assist the prioritization of therapies for clinical translation with the best chance of success, international clinical and preclinical consortia have developed consensus pediatric brain cancer preclinical testing guidelines.[13] These guidelines provide a collaborative framework for preclinical testing that supports validation in multiple different institutions to increase rigor and reproducibility. The hope is that novel more-targeted/subgroup-specific therapies will enable the reduction, or preferably omission, of CSI.

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