WNT Medulloblastoma Limbo: How Low Can We Go?

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SUMMARY

Survival rates for average-risk medulloblastoma exceed 80%; however, long-term sequelae are substantial. A study from Mumbai, India evaluated the role of omission of craniospinal irradiation. Albeit unsuccessful, this study raises the crucial question of how low therapy can be safely de-escalated with the intent of improving quality of survival.

See related article by Gupta et al., p. 4180

In this issue of *Clinical Cancer Research*, Gupta and colleagues report the final analysis of a clinical trial of focal radiotherapy for WNT (Wingless) activated medulloblastoma (WNT-MB; ref. 1). Over the past two decades, it has become clear that medulloblastoma is a highly heterogeneous entity, comprising at least four distinct molecular subgroups, with distinct demographics, cells of origin, genetics, transcriptomes, and outcomes (2, 3). The rationale for this clinical trial stems from the observation that of the four medulloblastoma subgroups, survival for WNT-MB exceeds 90% across many studies globally, with an increasing appreciation for the lifelong side effects of current therapy (4–8). This has prompted North American and European cooperative groups to explore subgroup specific deescalation of therapy as a potential option. A study of radiation avoidance was suspended early due to an unacceptable number of failures. However, three studies (ACNS1422, PNET5, SJMB12) are currently exploring reduced craniospinal irradiation (15–18 Gy), from the current standard of care of 23.4 Gy for carefully selected and molecularly confirmed WNT-MB.

A clinical trial conducted at Tata Memorial Centre in Mumbai, India was designed to evaluate focal radiotherapy of 54 Gy followed by six cycles of cisplatin, cyclophosphamide and vincristine therapy for average-risk WNT-MB. The study selected children aged 3–16 with WNT-MB using a previously validated gene expression and microRNA assay, and included a careful central review of imaging for any residual or metastatic disease (9). Although the study was designed to accrue 60 subjects, the trial was closed after 2 years since 3 of 7 children enrolled in this study had early disseminated relapses. Although one patient died of treatment-related toxicity, the remaining 6 children remain alive, including the 3 relapsed WNT-MB who went on to receive craniospinal irradiation with additional chemotherapy. Orthogonal molecular diagnoses for WNT-MB confirmed the presence of *CTNNB1* mutations and/or monosomy 6 to ensure that molecular misdiagnosis was not the cause of failure (10).

The rationale for this clinical study is the identification that late effects of radiotherapy in medulloblastoma are devastating, leading to significant long-term sequelae related to neurocognitive deficits, endocrine abnormalities, early cardiovascular events, radiation-induced malignancies and hearing loss (6, 11). Indeed, many survivors of medulloblastoma are unable to live an independent life, thus raising the conundrum of how much toxicity is acceptable in survivors (7). Considering the survival for average risk medulloblastoma has consistently been shown to exceed 80% with 23.4 Gy of craniospinal irradiation and boost to 54–55.8 Gy to the tumor bed, a substantial subset are likely overtreated. In particular, WNT-MB has an excellent survival of close to 100% in many recently completed studies, clearly justifying the need to reduce therapy in this group and potentially other low-risk groups. This study builds upon a closed North American study showing that chemotherapy without irradiation results in an unacceptable number of treatment failures, and clearly suggests that there is a role for craniospinal irradiation (12). The recently closed SJMB12 study evaluated 15 Gy of craniospinal irradiation followed by cisplatin, cyclophosphamide, and vincristine. This study may represent the global standard-of-care if it ultimately results in an overall-survival exceeding 90%. Subsequently, efforts to further reduce therapy to 12 Gy of craniospinal irradiation will most likely be evaluated in future clinical trials.

Although the results of this study are disappointing, several important observations can help design future studies. The metastatic pattern of relapse suggests that some form of craniospinal prophylaxis is required for WNT-MB (13). This is consistent with a previous report of 15 WNT-MB showing a predominantly metastatic pattern of relapse in the lateral ventricles. This observation is also important with respect to treatment of relapses, whereby salvage therapy requires 36 Gy of craniospinal irradiation, negating the benefits of reduced radiotherapy. Interestingly, all three failures seemed to have been successfully salvaged with high doses of craniospinal irradiation and additional chemotherapy. Previously, it has been suggested that the chemotherapy regimen is important in WNT-MB, including preclinical studies suggesting an exquisite sensitivity to chemotherapy particularly vincristine due to a leaky blood–brain barrier (14). The current study administered a cumulative dose of 12 g/m^2 of cyclophosphamide, which has been suggested to be required for optimal survival in this group when combined with radiotherapy (13). Indeed, this suggests that this particularly studied chemotherapy regimen is unlikely the predominant cause of relapse.

The obvious question now is whether there is still a role for further studies omitting craniospinal irradiation for WNT-MB. Although there have been isolated reports of high-dose chemotherapy using thiotepa-based conditioning with autologous stem cell support successfully used, the toxicity of this approach would need to be carefully weighed against the long-term sequelae of 15–18 Gy craniospinal

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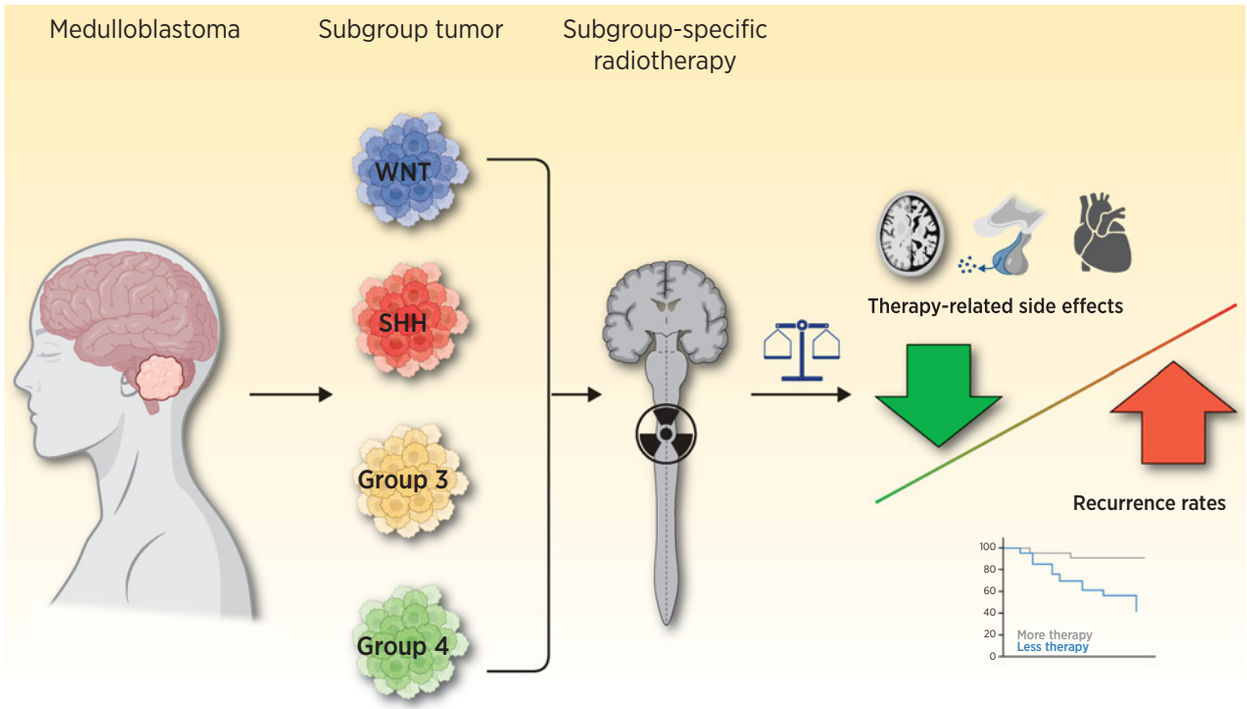

Figure 1.
A molecular-based approach to balancing quality of life with quality of survival in newly diagnosed patients with medulloblastoma. The balance between treatment-related cognitive deficits, endocrine dysfunction, and cardiac toxicity needs to be evaluated in the context of suboptimal survival with reduced radiotherapy. Adapted from an image created with BioRender.com.

irradiation (13, 15). The balance between therapy-related toxicity versus quality of life needs to be continually evaluated across all medulloblastoma subgroups.

It has been 39 years since the initiation of the pilot trial of the "Packer" protocol, which represented a dramatic reduction in therapy for nonmetastatic patients from 36 Gy to 23.4 Gy (16). Although subsequent efforts to reduce therapy in noninfant medulloblastoma have been mixed, the need to balance quality of survival with overall survival remains of crucial importance in the treatment of medulloblastoma (**Fig. 1**). This study was well conducted at an institution with remarkably high patient volume, which establishes a very important proof-of-principle that robust clinical trials in medulloblastoma are not restricted to high-income countries. The long-term benefits of reducing toxicity in low and middle income countries (LMIC) is arguably even more relevant, further supporting an urgent need to support these trial groups in conducting studies. Indeed, over a period of only 19 months, a single high-volume center in Mumbai, India was able to identify 17 WNT-MB, and enroll 7 patients, highlighting the possibility that multi-center studies in LMIC could complete trial accrual far more quickly than either the Children's Oncology Group or the European Society for Pediatric Oncology. Although the observation that focal radiotherapy is not sufficient for the treatment of WNT-MB is disappointing, the search for the optimal balance of quality of life and survival outcomes needs to continue across all subgroups of medulloblastoma. This study from Tata Memorial Centre in Mumbai, India clearly identifies a role for specialized centers in the developing world to help rapidly establish this balance.

Authors' Disclosures

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