



Different intellectual outcomes in molecular subgroups of medulloblastoma

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Comment on: Moxon-Emre I, Taylor MD, Bouffet E, *et al.* Intellectual Outcome in Molecular Subgroups of Medulloblastoma. *J Clin Oncol* 2016;34:4161-70.

Submitted Nov 02, 2016. Accepted for publication Nov 21, 2016.

doi: 10.21037/tcr.2016.12.65

View this article at: <http://dx.doi.org/10.21037/tcr.2016.12.65>

Medulloblastoma (MB) is one of the most common pediatric malignant brain tumors, representing up to 20% of newly diagnosed central nervous system tumors in children. Standard treatments for MB include surgical resection, craniospinal irradiation with a posterior fossa boost, and adjuvant chemotherapy (1). Although these strategies can increase the survival of 70–80% of MB patients, they are associated with serious treatment-induced morbidity, including a decline in neurocognitive function (2,3). Reports suggest that neurocognitive functions deteriorate after craniospinal irradiation for MB, and that most MB survivors require substantial care. Studies also indicate that decreasing the radiation dose can prevent this irradiation-associated cognitive decline (2,4,5).

With recent advances in genomic analysis, MB was found to consist of at least four distinct molecular subgroups: WNT, SHH, Group 3, and Group 4 (6). These subgroups have distinct demographic, transcriptional, genetic, and clinical features, and the prognosis of MB is associated with the subgroup classification. These findings have been reviewed in several articles (7-9).

The molecular classification system is an important prognostic tool with great potential for improving MB treatment (10). Of the subgroups, WNT MB has the best prognosis. SHH MB has an intermediate prognosis. Group 3 MB is frequently associated with metastasis and a poor prognosis. Group 4 is sometimes associated with metastasis and has an intermediate prognosis. A recent analysis suggests that a subset of Group 4 has a good prognosis, similar to that of WNT MB (11). Based on these subgroup-

specific prognosis, a new risk stratification proposed for MB patients (12) suggests that both the WNT subgroup and the Group 4 subgroup with chromosome 11 loss have a good prognosis and can be cured by current therapeutic strategies. Thus, MB patients classified into these molecular groups would be good candidates for prospective clinical trials using limited therapeutic protocols such as reduced radiation dosage and/or reduced chemotherapy.

The identification and characterization of MB subgroups has dramatically changed our perspective of MB over the past few years. However, current treatment protocols still stratify patients into high- and average-risk groups according to their age, their metastatic status, and the presence of residual tumors after resection (13,14), and do not consider the MB subgroup.

Recently, Moxon-Emre *et al.* examined the intellectual outcomes for MB patients according to MB subgroups for the first time, and found that baseline cognitive functions differ between the four subgroups (15). The authors report that reducing the radiation dosage and/or chemotherapy can prevent intellectual decline in MB patients, as expected. Of particular interest is their finding that reducing the radiation dosage is only beneficial to WNT and Group 4 MB patients, and not to Group 3 or SHH MB patients. This retrospective study found that reducing the radiation or chemotherapeutic regimen can prevent cognitive decline particularly for patients with WNT MB, which has the best prognosis, and for patients with a subset of Group 4 MB. These findings will undoubtedly lead to prospective clinical trials with reduced radiation or chemotherapeutic regimens

in these groups. Thus, in the near future, radiation dosage will be chosen according to the MB subgroup, and subgroup-specific therapeutic strategies will become the standard. These subgroup-specific therapies are expected to be more effective and significantly safer than current standard therapies.

Other reports that analyzed intellectual outcomes for MB patients were conducted before the MB subgroups were recognized. Moxon-Emre *et al.* were the first to compare intellectual outcomes by MB subgroup, and they found that each subgroup has distinct intellectual characteristics and outcomes. The authors suggest that the SHH MB subgroup in particular has unique characteristics of intellectual outcome, and that a biological mechanism other than demographic and medical features might contribute to this uniqueness. Each MB subgroup has distinct demographic characteristics. WNT MB develops from progenitor cells of the lower rhombic lip (16), and SHH MB from cerebellar granule neuron precursors (17). Group 3 MB is proposed to originate from neural stem cells. The cells of origin of Group 4 MB were long unknown, but a very recent study suggests that they are progenitors of the upper rhombic lip (uRL) (18). Another recent study reported characteristic MRI findings for each MB subgroup (19). WNT MB contacts the brain stem and expands into the fourth ventricle. SHH MB grows predominantly in the rostral cerebellar hemisphere. Most Group 3 and Group 4 tumors grow in the vermis and infiltrate the fourth ventricle. These locations may be related to the cells of origin of each MB subgroup. Thus, Moxon-Emre *et al.* suggest that the demographic differences between subgroups may also influence the intellectual function in MB patients.

An important finding in Moxon-Emre *et al.* is that reduced-dosage radiation therapy is only beneficial to WNT and Group 4 patients. Although reports published in the pre-subgroup era indicated that reducing radiation doses could minimize the intellectual decline in MB patients (20,21), it was not clear whether a reduced dosage would benefit all MB patients regardless of subgroup. Moxon-Emre *et al.* reported that WNT and Group 4 patients maintain intellectual function with a reduced radiation dosage, making patients in these subgroups good candidates for clinical trials of limited-dose radiation therapy. These trials are already underway, and should confirm the study's findings.

However, the Moxon-Emre *et al.*'s study has some limitations, and we need to be cautious about coming

to definite conclusions. Although the median follow-up time was about 5 years, some patients were followed for only about a year. One report suggests that the late effect on cognition occurs more than 5 years after the initial radiation therapy (22), so long-term follow-up data is necessary for a definite conclusion. Furthermore, Moxon-Emre *et al.* analyzed WNT and Group 4 patients together because of the small number of patients; ideally these two groups should be analyzed separately. We need data from more patients, and this effort will require worldwide collaboration, because even high-volume centers see only a small number of MB patients. In addition to intellectual outcomes, we also need to examine the effects of treatments and MB subgroup on endocrine function, academic function, and social function. Academic and social function are directly related to the patient's quality of life (4), and these analyses would complement an assessment of the overall late effects of therapeutic interventions.

Moxon-Emre *et al.* found that reduced-dose radiation did not influence the intellectual scores of SHH and Group 3 patients. This might have been because the prognosis of Group 3 patients is too poor to observe any benefit from reduced-dosage radiation therapy, in which case it would be necessary to improve the prognosis of Group 3 patients to improve their intellectual outcome. These findings also suggest that radiation therapy has only a limited effect on Group 3 patients, and that other therapies, including molecularly targeted therapies, are necessary to improve both the prognosis and the intellectual outcome of this subgroup. Some SHH patients can be cured with current treatment strategies, so it is not clear why reducing the dosage of radiation therapy does not benefit them. Moxon-Emre *et al.* suggest that some SHH patients may have a p53 or other germ-line mutation, such that a genetic factor could influence their resistance to radiation; more research is necessary to explore this possibility. If the intellectual outcome of SHH patients declines even with a minimum radiation dose, it might be possible to use molecularly targeted therapies to improve intellectual outcomes without compromising the prognosis. Recently, small-molecule SMO inhibitors were synthesized and studied extensively in SHH MB patients (23,24). The results from these studies indicate that SHH inhibition is a promising new strategy for treating SHH MB.

The findings of this study will further improve patient stratification and molecularly targeted treatment strategies, and will lead to safer and more effective treatments for MB.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Xian-Xin Qiu (Department of Neurosurgery, the Children's hospital of Medical College, Zhejiang University, Hangzhou, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2016.12.65>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Kijima N, Kanemura Y. Different intellectual outcomes in molecular subgroups of medulloblastoma. *Transl Cancer Res* 2016;5(Suppl 7):S1311-S1314. doi: 10.21037/tcr.2016.12.65