Helping Survivors of Medulloblastoma Learn From What We Learn

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The article by Palmer et al that accompanies this editorial investigates the neuropsychologic late effects arising from the treatment of pediatric medulloblastoma survivors treated on a single protocol across eight medical centers in North America and Australia between 2003 and 2011. The study population impressively includes 126 patients between the ages of 3 and 21 years at diagnosis (median, 9.8 years; standard deviation, 4.4), who were uniformly treated with risk-adapted therapy; 90 patients with average-risk disease received 23.4 Gy craniospinal irradiation (CSI) and 55.8 Gy conformal primary site boost, whereas 36 patients with high-risk disease received between 36.0 and 39.6 Gy CSI and 55.8 Gy conformal primary site boost, all followed by four cycles of high-dose chemotherapy with stem-cell support. The investigators prospectively used the Woodcock Johnson Tests of Cognitive Abilities–III, a well-validated assessment measure, for a total of 509 evaluations. The median number of three assessments per patient provides ample opportunity to identify change in functioning over time within the primary domains of processing speed, broad attention, and working memory.

As with the majority of neuropsychology follow-up studies, the rate of participation is commonly suboptimal and the sample evaluated in this study represents 40% of the 318 patients treated on this collaborative medical study. This always begs the question of whether the study sample includes a disproportionate amount of survivors doing well and therefore more likely to be able to participate or alternately a disproportionate amount of survivors who are not doing well and therefore in need of assistance. On closer review, 75 patients were excluded from this study as a result of having developed posterior fossa syndrome after surgery that understandably restricted their functioning at baseline; however, the inclusion of these patients, which represents almost 25% who developed cerebellar mutism, could possibly provide valuable scientific knowledge about a prominent and not well understood sequela of medical treatment. In addition, almost another quarter of the study sample either had one or no evaluations, which are presumed to result primarily from the lack of adequate access to psychologists at participating sites because patients not tested as a result of scheduling conflicts or parental refusal, were treated as separate categories for noninclusion. This common problem can be minimized for pediatric oncology programs that hire psychologists to work directly within their centers, which in conjunction with developing a training program for psychology fellows, interns, and externs, would enable significantly more patients to be seen for both assessments and therapy in a timely and consistent manner.

One of the main findings of this study identified processing speed as the lowest neuropsychologic domain at 5 years after diagnosis, particularly among younger patients and those with high-risk classification, who received higher doses of CSI. This important finding using a different assessment measure (Woodcock Johnson Tests of Cognitive Abilities–III) is consistent with previously published literature using the Wechsler scales and underscores the inherent challenges that survivors encounter to learn at a rate commensurate with their healthy classmates. Consequently, the majority of these survivors unfortunately fall progressively further behind their peers unless proactive accommodations and interventions are implemented immediately upon re-entry into the classroom for those in need based on the results of either clinical neuropsychological evaluations or a formal mechanism to provide written reports for research evaluations. The authors aptly point out that identifying which patients are at risk for deficits in key cognitive skills, and the time course they may manifest, would provide important information to implement proactive intervention programs. As an example of potentially important intervention programs, the authors reference a randomized computer-based reading intervention study that was available for a portion of this population, and we eagerly await these results, along with the data from their simultaneous administration of the Woodcock Johnson Tests of Academic Achievement–III, to better understand their academic functioning and rehabilitation. Previous efforts in developing and piloting interventions to alleviate cancer-related neurocognitive late effects have been described in the recently published Children’s Oncology Group (COG) 2013 Blueprint: Behavioral Science and include pharmacotherapy, clinic-based cognitive remediation, parent-directed approaches, academic prevention approaches, and computer-based cognitive training.

Interestingly, the authors have documented that patients with higher baseline processing speed, working memory, and broad attention display a higher rate of decline in these specific domains. This finding is not frequently acknowledged but is consistent with the statistical principle of regression toward the mean, where a group’s average will move in a direction toward the population’s average, or it might indicate that children of higher intellect are particularly sensitive to the developmental toxicity of irradiation. In the two cooperative group follow-up studies (Children’s Cancer Group 9892 and COG A9961), a salient pattern emerged in which the rate of decline was steeper for the higher baseline group; however, it is important to note that this group still maintained higher scores during the
follow-up period than those with lower baseline scores. This overall pattern for young children being treated with CSI and a boost to the primary site for medulloblastoma can be explained by the interaction between the opposing forces of brain reserve theory, referring to the brain’s ability to cope with increasing damage, and is indexed by anatomic measures (ie, total intracranial volume, ventricle to brain ratio, and so on) and cognitive reserve, which reflects differences in processing the relevant task and is indexed by cognitive and lifetime experience variables (socioeconomic status, patient and parent education, and so on).

Given the recent follow-up report of patients treated with reduced-dose CSI of 23.4 Gy with a 32.4 Gy boost to the posterior fossa for average-risk medulloblastoma still being associated with significant declines in intellectual and academic functioning over time, we eagerly await the long-term follow-up results from the COG 0331 consortium study where the experimental arm was lowered to 18.0 Gy of CSI, along with restricting the volume of the posterior fossa boost. Given the role of the connections between the cerebellum and the cerebral hemispheres (ie, frontal lobes), which regulate selective and sustained attention, as well as information processing speed, intelligence, language, and memory skills, alternate approaches to the treatment of medulloblastoma have included the use of proton beam radiotherapy, which is intended to provide better targeting of tumors than conventional photon beam radiotherapy while sparing surrounding healthy tissue. A follow-up study of survivors of pediatric brain tumors treated with proton beam radiotherapy revealed no decline in nearly all areas assessed, with the exception of a significant decrease in processing speed and reduced visuospatial organization.

Given the consistency of serial data that documents a decline in processing speed secondary to treatment with CSI plus a boost, alternate treatment approaches include myeloblative, high-dose chemotherapy, followed by autologous hematopoietic cell transplantation in which radiotherapy is only administered either for residual disease, at relapse, or for older children. A neuropsychology follow-up study based on this treatment approach noted that radiotherapy was avoided in two thirds of the survivors evaluated, whereas the remaining third received radiotherapy after a mean time of 17 months after diagnosis, and serial assessments indicated stable mean intelligence quotient scores during an approximate 3-year follow-up.

In summary, research articles such as the one by Palmer et al provide valuable opportunities to better understand the underlying mechanisms by which standard tumor therapies result in long-term progressive cognitive deficits. It is anticipated that the results from future medulloblastoma treatment regimens that further stratify treatment intensity on the basis of biologic analyses, such as molecular and genetic markers, will be able to successfully increase overall and event-free survival while minimizing late effects. Additionally, the development of early, sensitive biomarkers capable of predicting cognitive outcomes that arise from brain tumor treatments could identify those who are at significant risk for declining neuropsychological functioning. For example, promising techniques to study structural white matter connectivity include diffusion tensor imaging, retroviral tracing techniques, and resting state functional connectivity magnetic resonance imaging to grade the location, extent, and type of disruption in neural networks caused by the treatment of cerebellar tumors. Perhaps these data could allow for both the identification of patients at increased risk for neuropsychological late effects and in need of proactive remedial interventions, as well as to possibly establish a methodology for closely monitoring the effectiveness of these interventions during the recovery process in order to maximize clinical outcomes while minimizing cognitive deficits.

AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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REFERENCES


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