Medulloblastoma: Molecular Classifications and Prognostic Associations

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Of particular relevance for clinicians is the possible recommendation of omitting concurrent chemotherapy with CSI in adults, due to the lower marrow reserves and overall lack of data for clear efficacy of concurrent chemotherapy in adults. Additional refinement of these therapeutic regimens for adult medulloblastoma awaits further advances in both the molecular prognostic associations for these tumors and the potentially exciting development of targeted therapies for specific molecular subtypes.

As discussed by Shonka et al, adult medulloblastoma is a rare tumor, and the optimal postoperative treatment approach remains unclear. Since Cushing's time, radiotherapy has been the mainstay of postoperative therapy for medulloblastoma, in both pediatric and adult populations.[1] Craniospinal irradiation (CSI) to near tolerance doses followed by additional radiation to the primary site results in progression-free and overall survival of 60% and 80%, respectively, in adult patients.[2] Similar results are found in pediatric series.[3] Attempts to lower the dose of CSI in average-risk pediatric patients resulted in an excess of failures outside the primary site.[4] However, with the addition of chemotherapy—weekly vincristine during radiotherapy followed by adjuvant platinum-based chemotherapy—excellent event-free survival is achieved with CSI of 23.4 cGy.[5] It is important to emphasize that this lower dose of CSI is only appropriate in combination with the chemotherapy described and that the impetus for this approach is largely to reduce late effects that are specific to the pediatric population (neurocognitive and growth issues). Therefore this approach is unproven, and perhaps unwarranted, in the adult population. Postoperative radiotherapy consisting of 36 Gy CSI followed by a “boost” to the primary site to a total dose of 54 Gy should be considered a component of “standard” therapy in adult medulloblastoma, regardless of risk stratification.

In terms of prognostic associations and molecular classification, the current review nicely outlines some of the significant recent developments in the medulloblastoma field and some of the potential similarities and differences between adult and pediatric disease. For the clinical prognostic associations, one difference is the potential lower prognostic significance of extent of residual disease and M stage in adult medulloblastoma compared with pediatric patients. On the molecular front, several recent publications and international collaborations have significantly clarified the molecular classification and prognostic associations for pediatric medulloblastoma, with lesser clarity regarding the classification of adult medulloblastoma. While some of the recently identified molecular classifications and prognostic associations may also hold true for adult medulloblastoma, and provide potential insights for promising targeted therapies for specific subtypes, some uncertainties and potential differences compared with pediatric disease remain. First, the exact degree of similarity between molecular classification of adult vs pediatric medulloblastoma is still not entirely clear. Korshunov et al[6] highlighted some of these potential differences with the observation that adult medulloblastoma had much lower frequencies of MYC/MYCN amplification than pediatric tumors. The authors also found that while chromosome 6q deletions and β-catenin activation were observed in some adult tumors, a good prognostic association was not seen in the adult tumors as compared to pediatric ones. On the other hand, the most comprehensive profiling of adult medulloblastoma (28 tumors) by Remke et al[7] highlighted some potential similarities with the pediatric population. These authors found that adult medulloblastoma could be classified into three main subtypes, which roughly mapped to three of the four subtypes observed in pediatric medulloblastoma. The major difference between adult and pediatric subtypes in this analysis was the absence of the Group 3 (formerly subtype C) tumors that display MYC amplification. Over half of the adult tumors demonstrated activation of the sonic hedgehog (SHH) pathway and are similar to the SHH subgroup in pediatric medulloblastoma. The remainder of adult medulloblastomas fell into the Group 4 (formerly subtype D) or WNT subtypes.

These observations suggest significant molecular similarities between adult and pediatric
medulloblastoma and highlight the hope that current development of targeted therapies may have benefit in both groups. However, a note of caution is in order, as there are some indications that, despite the similarities on the gene expression level, adult medulloblastomas may be more heterogeneous than their pediatric counterparts. This is based on the observation that the pattern of other mutations and cytogenetic alterations in adult medulloblastoma did not always match the corresponding pediatric tumors, and that prognosis also was not necessarily matched. This was particularly evident in the adult WNT tumors, in which the excellent prognosis of pediatric WNT tumors was not reliably seen. Thus, while the growing body of data on pediatric medulloblastoma will almost certainly continue to inform our understanding of the biology of the less common adult tumors, these differences highlight the potential danger of simply extrapolating the pediatric results to adults. A consensus statement for the subclassification of pediatric tumors was recently published that addresses many of these issues; it will form the basis for future developments in this field.[8]

Shonka et al also provide a useful summary of current outcomes data regarding the chemotherapy options for adult medulloblastoma. Again, these data highlight potential similarities and differences with pediatric disease. The similarity in overall survival between the low-risk and high-risk groups reported in the update of the prospective trial by Brandes et al[9] highlights the possibility that the definition of high- and low-risk medulloblastoma may be different in adults, and that it may not be practical to attempt to achieve in adults the excellent outcomes observed in pediatric patients with lower-intensity treatment. Overall, the authors’ recommendations for chemotherapy after radiation in patients at high risk of recurrence, and consideration of chemotherapy after radiation even in patients considered “average” risk, are reasonable. Of particular relevance for clinicians is the possible recommendation of omitting concurrent chemotherapy with CSI in adults, due to the lower marrow reserves and overall lack of data for clear efficacy of concurrent chemotherapy in adults. Additional refinement of these therapeutic regimens for adult medulloblastoma awaits further advances in both the molecular prognostic associations for these tumors and the potentially exciting development of targeted therapies for specific molecular subtypes.

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**References:**


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