REVIEW

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Medulloblastoma: recurrence and metastasis

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Practice Points

- Medulloblastoma is the most common malignant brain tumor of childhood, with the rate of long-term survival or cure presently at 70–80%.
- There is a significant burden of complications in survivors, probably due to intense therapies.
- Currently there is a risk-adapted scheme for prognosis of medulloblastoma:
 - High risk: children <3 years of age with >1.5 cm² of residual disease and/or evidence of metastasis;
 - Low risk: children >3 years of age with minimal residual tumor and no metastases.
- Pathological stratification falls into five groups: classic, desmoplastic/nodular, extensively nodular, large cell and anaplastic. The large-cell and anaplastic variants carry poor prognoses and high frequencies of metastatic disease.
- Current genetic consensus classification involves four main subgroups (WNT, SHH, group 3 and 4):
 - WNT tumors generally have classic histology and very good long-term prognoses;
 - SHH tumor prognosis is intermediate between WNT and group 4 tumors;
 - Group 3 tumors are recognized by their transcriptional profile. There is a close association between group 3 tumors and high levels of *Myc* expression;
 - Group 4 tumors are also recognized by transcriptional profiling. Isochromosome 17q is most common in group 4. Group 4 tumors have an intermediate prognosis.
- Combined molecular/clinical grading may be more informative than either modality alone.
- Recent genome-wide association studies have identified many more potential molecular abnormalities than previously appreciated.
- Metastasis research indicates that primary and metastatic tumors may be phenotypically different.
- Owing to good prognosis, trials are contemplated for WNT tumors with reduced primary therapy. Preliminary reports for SHH pathway inhibitors show dramatic but short-lived shrinkage of advanced tumors. There are now several clinical trials with this class of agent to determine if long-term tumor control can be obtained.

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SUMMARY Medulloblastoma is the most common malignant brain tumor of childhood. Although there is now long-term survival or cure for the majority of children, the survivors bear a significant burden of complications due, at least in part, to the intense therapies given to ensure eradication of the tumor. Significant efforts have been made over the years to be able to distinguish between patients who do and do not need intensive therapies. This review summarizes the history and current state of clinical risk stratification, pathologic diagnosis and genetics. Recent developments in correlation between genetics and pathology, genome-wide association studies and the biology of medulloblastoma metastasis are discussed in detail. The current state of clinical treatment trials are reviewed and placed into the perspective of potential novel therapies in the near term.

Medulloblastoma: historical overview

Medulloblastoma is the most common malignant brain tumor of childhood. It is estimated that the annual incidence rate is 0.5 per 100,000 in children younger than 15 years of age [1]. There is a bimodal peak of incidence between ages 3–4 and 8–9 years [2]. Adult cases account for less than 1% of the total and rarely occur in individuals beyond the age of 40 years.

Prior to the 1970s, the 5-year survival for patients with this tumor was 30% with deaths due to tumor recurrence and leptomeningeal dissemination of tumor (across the surface of the brain and spinal cord) [3]. In the past 30 years, improvements in surgery, imaging, pathologic stratification, radiotherapy and chemotherapy have changed that dramatically. The rate of long-term survival or cure now stands at 70–80% for standard-risk older children. In infants, adults and high-risk cases the outcome is less favorable [4]. Patients with recurrent disease following initial therapy bear the worst prognosis: median survival of <6 months and 2-year survival of 9% [5].

Despite long-term survival for many patients, there is a significant burden of complications, including neurocognitive deficits, endocrine dysfunction and an increased incidence of secondary neoplasms [6]. These are probably due, at least in part, to the intense therapies, particularly craniospinal radiation, given to the developing nervous system of these children to ensure eradication of the tumor. Given this scenario, significant efforts have been made over the years to be able to distinguish patients at the outset who have the greatest chance of responding to standard therapies. More recently, there has been interest in further defining groups of patients who may respond to intensive therapies. At the same time, both basic and applied research has been directed to understanding the pathobiology of the medulloblastoma leptomeningeal metastasis,

and developing strategies for prediction and treatment of this complication.

Clinical risk stratification

The Chang Criteria represented the earliest clinical risk stratification to predict and treat disseminated medulloblastoma based on the surgeon's intraoperative observations [7]. Tumor staging ranged from T1 (tumor <3 cm in diameter and limited to the cerebellum) to T4 (tumor spreading through the aqueduct of Sylvius to involve the third ventricle or midbrain, or tumor extending to the upper cervical spinal cord). Metastasis staging ranged from M0 (no metastases) to M4 (tumor spread outside the neuraxis). Evaluating these criteria over 100 patients, the authors noted that "It is apparent that the prognosis is much better for patients with T1 or T2 lesions than for those with T3, or T4 lesions." Examination of their data also shows a parallel of the T and M stages, with the majority of T1 cases being M0 or M1, and T2 and T3 cases accounting for the M2 and M3 cases. Metastasis was detected in 14% of patients.

Since that report, changes in technology have replaced intraoperative evaluation with pre- and post-operative MRI of the brain and spinal cord with gadolinium. Other criteria that have proved to be prognostic include age [5,8] and residual tumor bulk postresection [5]. This has led to the current use of a risk-adapted scheme in which children >3 years of age, with the largest measurable surface greater than 1.5 cm² of residual disease and/or evidence of metastasis are considered high risk, whereas those >3 years of age, with minimal residual tumor and no metastases are low risk [4,5].

Pathology

Medulloblastomas are stratified pathologically into classic, desmoplastic/nodular, extensively nodular, anaplastic, large-cell, myogenic differentiation and melanocytic differentiation variants.

Of these, the anaplastic and large-cell variants carry poor prognoses [9–12] and are characterized by high frequencies of metastatic disease [9,10,13]. Owing to the shared poor prognosis and the recognition that the pathologic features of these two variants are often intermixed in the same tumor, it has been proposed that anaplastic and large-cell medulloblastomas are a continuum and should be combined into a large-cell/anaplastic category [9,12,14].

There is disagreement between studies as to whether the desmoplastic variant bears a better prognosis than the classic medulloblastoma [15–18]. It has been proposed that the variable results are due to the use of different diagnostic criteria for the two entities [18,19]. In infants, several studies have shown better survival for the group of patients with desmoplastic/nodular as well as extensively nodular medulloblastomas in comparison with the group with classic medulloblastomas [20,21].

Genetics

Since different morphological variants of medulloblastoma exist and, to some extent, these phenotypes can predict biological behavior and outcome, the idea that these represent different disease entities with diverging pathway perturbations and underlying mechanisms of tumorigenesis has long been suspected [22].

Traditional chromosomal analysis revealed that the most common cytogenetic abnormality in medulloblastomas is isochromosome 17q, which is present in 30–40% of tumors [23,24]. Isochromosome 17q results in loss of 17p and gain of 17q. The loss of 17p, which can also occur via interstitial deletion or monosomy of 17, occurs in as many as 50% of medulloblastomas and is associated with poor prognosis [11,25–28]. Loss of chromosome 6 is observed independently of isochromosome 7q and is associated with good prognosis. There are also abnormalities of chromosomes 7, 8, 9 and 11 [29], as well as double minutes. Although traditional cytogenetics has been progressively supplanted by comparative genomic hybridization, FISH, spectral karyotyping and high-throughput genomics, many of these early findings point the way toward our current understanding of genetic risk stratification in this disease.

The current consensus classification of medulloblastomas, based primarily on transcriptomic data recognizes four principal subgroups (WNT, SHH, group 3 and 4) [30].

The WNT pathway was initially recognized to be involved in medulloblastoma pathogenesis via the rare association with familial adenomatous polyposis in Turcot syndrome [31]. Germline mutations of the *APC* gene in that syndrome ablate the normal negative regulation of *APC* on the WNT pathway. Somatic *APC* mutations in sporadic medulloblastoma are relatively rare. Only 3–4% of tumors contain sequence changes [32,33]. In addition, while the *APC* mutations in familial adenomatous polyposis patients result in a truncated, nonfunctional protein, those in sporadic tumors are missense mutations of undetermined functional significance. A more common route of WNT involvement in medulloblastoma occurs via β -catenin mutations, which occur in 5–10% of tumors and activate WNT pathway signaling [32–35]. Using immunohistochemistry for β -catenin as a marker, between 18 and 25% of medulloblastomas show evidence of WNT activation [34,36,37]. This correlates fairly well with the results of transcriptomic studies [38]. Virtually all WNT tumors have classic histology. The promising long-term prognosis of this subgroup [36,38–44] correlates well with the observation that there is frequent deletion of chromosome 6. Recently, it has been recognized that experimental WNT medulloblastomas arise from a distinct subset of developing cells in the developing rhombic lip and dorsal midbrain. This accounts for the presentation of the human tumors in the dorsal midbrain. Both the cell of origin and the involvement of the WNT pathway are integral to the good long-term prognosis of these patients [45].

The SHH subgroup historically derives from the recognition that *PTCH*, the human homolog of the *Drosophila* segment polarity gene is involved in medulloblastoma pathogenesis. Located on chromosome 9, where allelic losses are found in 10–18% of medulloblastomas [46,47], *PTCH* is mutated in Gorlin's syndrome patients who develop nevi, basal cell cancers and desmoplastic medulloblastomas [46–48]. Inactivating *Ptch* mutations are also found in approximately 8% of sporadic medulloblastomas [49–53]. SHH signaling plays an important role in cerebellar development since SHH is a mitogen for cerebellar granule cell precursors, one of the putative sources of medulloblastoma [54]. Pathway activation involves the secretion of SHH by Purkinje cells, which binds to *Ptch* at the cerebellar granule cell membrane, releases the normal *Ptch* inhibition of SMO and activates GLI

transcription factors, resulting in granule cell proliferation [55]. Besides *Ptch* mutations, other events likely to activate the SHH pathway have been reported, including mutational activation of SHH [56] and SMO [57,58], amplification of *SHH* and *GLI* [59], as well as mutation of *SUFU*, another SHH pathway inhibitor [60]. Transcriptional profiling has been used to identify the majority of SHH-positive tumors [38,42,43,61,62], with the majority of mouse models of medulloblastoma belonging to this group of tumors [63]. Evidence, both from human tumors and these models, points to cerebellar granule cell precursors as the cells of origin of SHH medulloblastomas [64]. The majority of nodular/desmoplastic medulloblastomas are SHH. Of the entire SHH group, nodular desmoplastic tumors account for approximately 60% with the other 40% split between classic and large-cell anaplastic types [62]. There are two distinct peaks for age of incidence, infants (0–3 years) and adults (>16 years). The prognosis for recurrent disease after treatment in this subset is intermediate between WNT and group 4 tumors.

The group 3 tumors are recognized by their transcriptional profile [42,43,61]. There is a close association between group 3 tumors and high levels of *MYC* expression. In fact, almost all cases of *MYC* amplification are group 3. Amplification of *MYCC* or *MYCN* is associated with the aggressive large-cell tumor variant and with poor clinical outcome [47,65–67]; *OTX2* amplification/overexpression is limited to group 3 and 4 tumors. When subdivided, the 3 α subgroup includes almost all patients with *MYC* amplification and most of the high-risk patients. The 3 β subgroup may have a similar risk to group 4 tumors [61].

Group 4 tumors are also recognized by transcriptional profiling. *KCNA1* immunohistochemistry may be a good marker for group 4 [43,61]. Isochromosome 17q is more common in group 4 than 3 (66 vs 26%) [30,43]. Isolated 17p deletion is found only in groups 3 and 4 tumors. Group 4 tumors have an intermediate prognosis.

Genome-wide association studies

Four recent in-depth genome-wide association studies have enlarged on the theme of the associations between specific genetic events and molecular subgroups of medulloblastoma. These studies have characterized well over 1000 tumors. Specifically, they report on the somatic copy number aberrations in

1087 cases [68], whole-exome sequencing of 92 cases [69] and whole-genome sequencing of 162 cases [70,71]. These reports have brought to the fore a number of new mutations. Common to more than one study are mutations of the RNA helicase gene *DDX3X*, epigenetic modifiers, such as *KDM6A*, and chromatin-remodeling genes, including *SMARCA4*. Other mutations reported include nuclear corepressor complex genes *GPS2*, *BCOR* and *LDB1*; *CTDNEP1*, which may have a role in BMP signaling and is a good candidate for a 17p tumor suppressor; *SNCAIP*, normally associated with Parkinson's disease; *TBRI*, a transcription factor involved in grain development; and abnormalities in both the TGF- β and NF- κ B signaling pathways. These new mutations and aberrant pathways may provide us with a number of new viable therapeutic targets.

Combined molecular & clinical grading

Since both the current clinical and molecular schemes are imperfect, two recent studies have demonstrated the utility of combining molecular and clinical data for improved prediction of recurrence and survival [72,73]. They have demonstrated that combination of clinical data with targeted immunohistochemistries improves risk stratification for medulloblastoma. The second of these studies has constructed a Bayesian cumulative log-odds model of recurrence based on clinical data, expression profiles and DNA copy gains/losses [73]. The Bayesian model may outperform current clinical classification schemes.

Biology of leptomeningeal metastasis

Although leptomeningeal metastasis constitutes one of the poorest prognostic indicators in this disease, the mechanisms that drive metastasis have received less attention than other prognostic aspects of medulloblastoma. Better understanding of leptomeningeal metastasis would be a further step in the design of more effective therapies. Efforts to unravel the metastatic mechanisms have focused on several aspects of cancer cell behavior: the interaction of medulloblastoma with the extracellular matrix; the intracellular network of filaments that drives motility; growth factors and their receptors; miRNAs that organize a number of cellular pathways; and genomic characterization of primary versus metastatic tumors.

Perhaps the first cell surface protein to be associated with metastatic medulloblastoma was

PSA-NCAM. Normally expressed in migrating neurons during development, PSA-NCAM concentrations have also been associated with leptomeningeal metastasis of medulloblastoma [74]. Other proteins that have shown correlation with experimental and clinical metastatic behavior include the extracellular matrix protein tenascin-C in concert with the cell surface proteins $\alpha 9$ - and $\beta 1$ -integrin [75]. A link between *MYC* overexpression in medulloblastomas and extracellular matrix proteins has also been noted. High *MYC* expression stimulates medulloblastoma cell migration and invasion via inhibition of the extracellular matrix protein thrombospondin-1 [76].

There are many links between the cellular filamentous network and medulloblastoma metastasis. The basement membrane protein SPARC can decrease migration in medulloblastoma cells in culture through cytoskeleton disruption [77]. Independent of that, the CaMKK/CaMKI cascade regulates basal medulloblastoma cell migration via Rac1, in part by activation of the Rac GEF, β PIX [78]. The ezrin protein, which provides linkage between the cell membrane and cytoskeleton, is also implicated in medulloblastoma migration. The level of ezrin expression in cells in culture correlates with the formation of filopodia and *in vitro* invasion in these cells [79]. *In vitro* experiments in medulloblastoma cell lines showed a strong reduction of cell migration, increased adhesion and decreased proliferation upon LASP1 knockdown by siRNA-mediated silencing, further indicating a functional role for LASP1 in the progression and metastatic dissemination of medulloblastoma [80].

The PDGFR α and its downstream activation of the RAS–MAPK signaling pathway have been associated with medulloblastoma metastasis in several studies [81,82]. It has also been suggested that PDGF β may have similar effects through the Rac1–Pak1 motility pathway [83]. Other growth factor receptors associated with medulloblastoma invasion include ERBB2, IGF2 and MET [83–86]. Overexpression of molecules downstream from IGF2 results in metastatic medulloblastoma in animal models [87]. Inhibition of the HGF–Met pathway with both molecular and pharmacologic agents reduces the metastatic potential of these cells [88–90].

Three different miRNAs have been associated with medulloblastoma metastasis; *miR-21*, *miR-182* and *miR-183*. Aberrant expression of *miR-21* is linked to metastasis in a number of

cancers, including gliomas. It has been found to be upregulated both in human primary medulloblastomas and in cell lines. Knockdown of *miR-21* decreases medulloblastoma migration in culture [91]. *miR-182* is significantly overexpressed in metastatic medulloblastoma as compared with non-metastatic tumors. Overexpression of *miR-182* in non-SHH medulloblastoma increases and knockdown of *miR-182* decreases cell migration *in vitro* [92]. The *miR-183* cluster regulates multiple biological programs that converge to support the maintenance and metastatic potential of medulloblastoma. There is relative enrichment of pathways associated with migration, metastasis and epithelial-to-mesenchymal transition, as well as pathways associated with dysfunction of DNA repair in cells with preserved *miR-183* cluster expression [93].

A recent genomic screen of both murine and human medulloblastomas has shed new light on the relationship between the primary and metastatic tumors [85]. In individual cases the metastases were similar to each other but were different from the primary tumor. Clonal genetic events in the metastases were demonstrated in restricted subclones of the primary tumor, suggesting that only rare cells within the primary tumor generated viable metastases. The data led the authors to hypothesize that metastatic medulloblastoma is bicompartamental and that successful therapy would depend on better characterization of the metastases as well as the primary tumor.

New therapeutic approaches based on molecular data

For the SHH subtype, therapy with the new class of hedgehog inhibitors has shown promise [94], and several hedgehog inhibitor compounds, including GDC-0449, LDE225 and LY2940680, are in clinical trials [101]. Owing to patients with the WNT subgroup having an excellent prognosis, there are considerations of trials with a reduction of therapy [95]. Other targets for specific therapy include the large number of new mutations and pathway aberrations discovered through genome-wide association studies as noted above [68–71]. Despite enthusiasm, these trials should be viewed with caution since both the efficacy and side effects of these inhibitors are not well characterized. Nonetheless, there is reason to believe that a better understanding of the biologic processes driving tumor recurrence and metastasis will, in the future,

serve as the basis for the design of more discreet therapies with fewer side effects.

Future perspective

In medulloblastoma, improvements in staging and treatment in the past 50 years have resulted in significant advancements in patient survival. The current challenge is to improve the quality of life of the patients that survive. The recent emphasis on genomic characterization has provided us with distinct subclasses. Over the next decade, these data will fuel efforts to decrease therapies in good-prognosis patients and develop targeted, less toxic therapies for patients with aggressive tumors. We predict that more successful therapies for primary tumors will spur greater interest in understanding the process of, and

therapies specifically targeted to, leptomeningeal metastasis.

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■ Summarizes the classification that will be the standard for several years to come.

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