Evolving Biology and Therapy of WNT-Activated Medulloblastoma

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Abstract

WNT-activated medulloblastoma is one of the 4 molecularly defined subgroups of medulloblastoma and is characterized by distinct molecular, biological, and clinical features. These tumors originate from progenitor cells in the lower rhombic lip, leading to a characteristic anatomical location: midline, often involving the fourth ventricle and dorsal brainstem. This distinct location can help differentiate WNT-activated medulloblastomas from other subtypes on MRI. Although imaging may suggest WNT-activated medulloblastoma, a tissue diagnosis is required. WNT-activated medulloblastoma exhibits several unique histologic features that aid in diagnosis, and nearly all cases harbor either somatic *CTNNB1* mutations or germline *APC* mutations. Treatment of all medulloblastoma is multimodal and includes maximal safe resection, radiotherapy, and adjuvant therapy. However, perhaps the most notable feature of WNT-activated medulloblastoma is the excellent prognosis associated with these tumors under current therapeutic regimens. The vasculature of WNT-activated medulloblastoma is thought to contribute to these favorable outcomes, as it mimics peripheral vascular endothelium, functionally eliminating the blood–brain barrier and increasing tumor susceptibility to systemic therapies. However, this vascular feature poses some challenges during surgical resection, as WNT-activated medulloblastomas carry an increased risk of intratumoral hemorrhage. With 5-year progression-free and overall survival exceeding 90% for WNT-activated medulloblastoma, and given the significant morbidity and late effects of current treatments, several trials are evaluating de-escalation of both craniospinal radiotherapy and adjuvant chemotherapy. Results of these trials are pending, but preliminary findings suggest that dose reductions can decrease long-term side effects while maintaining comparable progression-free and overall survival.

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Medulloblastoma is a WHO grade 4 central nervous system (CNS) embryonal tumor that most commonly arises in the cerebellum in children. It is the second most common malignant brain tumor in children, accounting for approximately 20% of all pediatric primary CNS tumors.[1–3] The annual age-adjusted incidence ranges from 0.20 to 0.58 cases per 100,000 persons worldwide.[4] Diagnosis and management of patients with medulloblastoma has rapidly evolved with the identification and description of 4 molecularly defined groups: WNT-activated, SHH-activated, group 3, and group 4.[5,6] The focus of this review is WNT-activated medulloblastoma.

Epidemiology

WNT-activated medulloblastoma accounts for approximately 10% of all medulloblastomas, with an incidence of approximately 0.01 per 100,000 persons in the United States, making it the least common of the 4 molecular groups.[4,7] Although medulloblastomas are most common in children aged 4 to 9 years, WNT-activated tumors typically occur in older children, with a median age of 10.4 years.[7] They also account for approximately 20% of adult medulloblastomas.[8] WNT-activated medulloblastomas show a female predominance, with a female-to-male ratio of 2:1, in contrast to the male predominance observed in medulloblastomas overall.[9,10]

Cell of Origin and Tumor Microenvironment

Although most medulloblastomas are thought to arise from cerebellar progenitor cells, studies have suggested that WNT-activated medulloblastomas originate from progenitor cells in the lower rhombic lip (Figure 1A).[11–13] As such, these tumors are located midline, involving the fourth ventricle or cerebellopontine angle, and are commonly found to be adherent or infiltrative to the dorsal brainstem at the time of surgery (Figure 1B, C). Although most studies demonstrating this have been conducted in mouse models, one study used single-cell transcriptomic data from both mouse and human brainstem tissue and found that WNT-activated medulloblastomas transcriptionally matched cells from the lower rhombic lip, specifically from the mossy fiber neuron lineage.[14] The most common molecular alteration in WNT-activated medulloblastomas is a *CTNNB1* mutation. *CTNNB1* is thought to disrupt normal differentiation and migration of progenitor cells from the lower rhombic lip to the pontine gray nucleus, leading to the accumulation of aberrant cells in the dorsal brainstem that are susceptible to malignant transformation.[11]

In addition to their unique cell of origin, there is evidence that WNT-activated medulloblastoma contains aberrant, non-CNS vasculature. The vascular endothelium in these tumors contains more fenestrated pores, with disrupted endothelial tight junctions, and is more like peripheral vascular endothelium.[12] Although this has also primarily been studied in mouse models, clinical observations correlate with a tendency for intratumoral and peritumoral hemorrhage during surgical resection.[15,16] Therefore, it is hypothesized that WNT-activated medulloblastomas lack a functional blood–brain barrier, in turn allowing for improved penetration of systemic chemotherapies, which may contribute to the improved outcomes associated with this molecular group.

Risk Factors

Most WNT-activated medulloblastomas are sporadic, with no identifiable risk factors. However, 6% to 8% of patients are found

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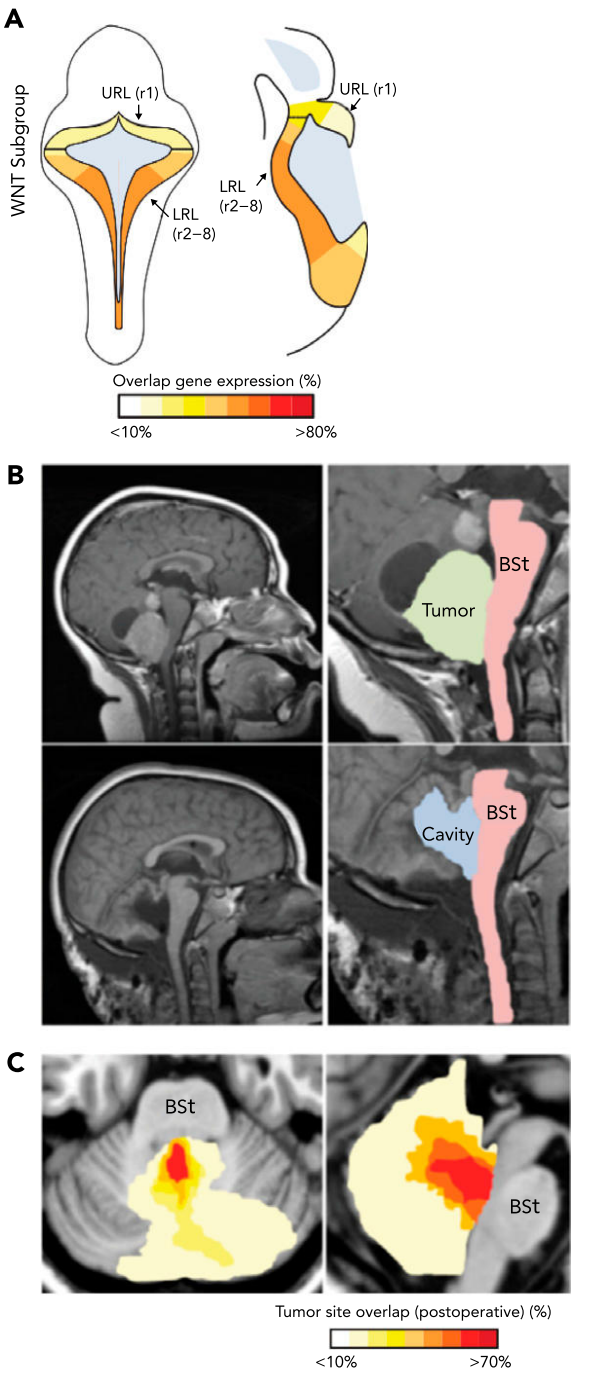

Figure 1. WNT-activated medulloblastomas originate from progenitor cells in the LRL, leading to midline tumors that often involve the fourth ventricle and dorsal brainstem. **(A)** Increased expression of WNT-activated medulloblastoma signature genes in the LRL at embryonic day 11.5 in mouse models. **(B)** Preoperative and postoperative MRI scans of an exemplary WNT-activated medulloblastoma with close-up views of the brainstem. **(C)** Frequency of postoperative tumor sites in mouse models of WNT-activated medulloblastoma.
Abbreviations: BSt, brainstem; LRL, lower rhombic lip; URL, upper rhombic lip.
Modified from Gibson P, Tong Y, Robinson G, et al. Subtypes of medulloblastoma have distinct developmental origins. Nature 2010;468:1096; with permission.

to have a heterozygous germline *APC* mutation, and therefore brain tumor polyposis syndrome, a variant of familial adenomatous polyposis (FAP).[17] Germline *APC* mutations are mutually exclusive with somatic *CTNNB1* mutations. Rates of *CTNNB1* wild-type WNT-activated medulloblastoma are higher in some ethnic populations.[18] Together, somatic *CTNNB1* mutations and germline *APC* mutations account for approximately 97% of WNT-activated medulloblastomas.[17,19] Therefore, testing for *APC* alterations should be considered in patients with WNT-activated medulloblastoma who lack *CTNNB1* mutations. For those with germline *APC* mutations, genetic counseling is essential due to their elevated risk for colon cancer and other malignancies. Other germline alterations associated with genetic predisposition to medulloblastoma, including *SUFU*, *PTCH1*, *TP53*, *PALB2*, *BRCA2*, and *ELP1*, have not been identified in WNT-activated medulloblastomas, and are instead associated with SHH-activated medulloblastoma.[17,20]

Clinical Presentation

Medulloblastoma, including WNT-activated medulloblastoma, commonly presents with signs and symptoms of increased intracranial pressure and cerebellar dysfunction. Symptoms include headaches and vomiting, which can be worse in the morning; visual disturbances; papilledema; ataxia; slurred speech; and nystagmus.[21,22] Symptom duration is variable, ranging from 1 to 12 weeks or longer. However, WNT-activated medulloblastomas have been associated with a longer prediagnostic interval, with a median of 8 weeks.[21]

Diagnosis and Staging

Imaging

Imaging is key in diagnosing medulloblastoma. The modality of choice is an MRI with and without contrast. WNT-activated medulloblastomas have MRI signal characteristics similar to the other medulloblastoma subtypes, with homogeneous, avid restricted diffusion, T1 hypointensity, T2 isointensity, and heterogeneous postcontrast enhancement.[23] However, WNT-activated medulloblastomas have a characteristic spatial orientation on MRI, which reflects their embryologic origin and can help differentiate them from other subtypes. A retrospective review of preoperative and postoperative MRIs in 16 WNT-activated medulloblastomas demonstrated that these tumors universally lateralized to the side of origin. Tumors in the fourth ventricle demonstrated subtle signs of lateralization, such as asymmetric extension into the foramen of Luschka (75%), and invasion of the dentate nucleus (69%) and/or the superior cerebellar peduncle (31%) on the side of origin (Figure 2A–F). The lateralization was confirmed by an iterative analysis of the preoperative and postoperative MRI, which demonstrated asymmetric surgical damage on the side of tumor invasion. On the other hand, extraventricular tumors were centered at the foramen of Luschka and demonstrated more obvious signs of lateralization, with extension into the cerebellopontine angle (Figure 2G–I). A small number of extraventricular tumors in this cohort (12%) were centered in the cisterna magna, and demonstrated asymmetric invasion of the dorsal brainstem and extension into foramen of Luschka on the side of origin.[24]

Histopathology and Molecular Pathology

Nearly all WNT-activated medulloblastomas exhibit classic histology (Figure 3A), characterized by sheets of densely packed, poorly differentiated, and monotonous tumor cells with apparent

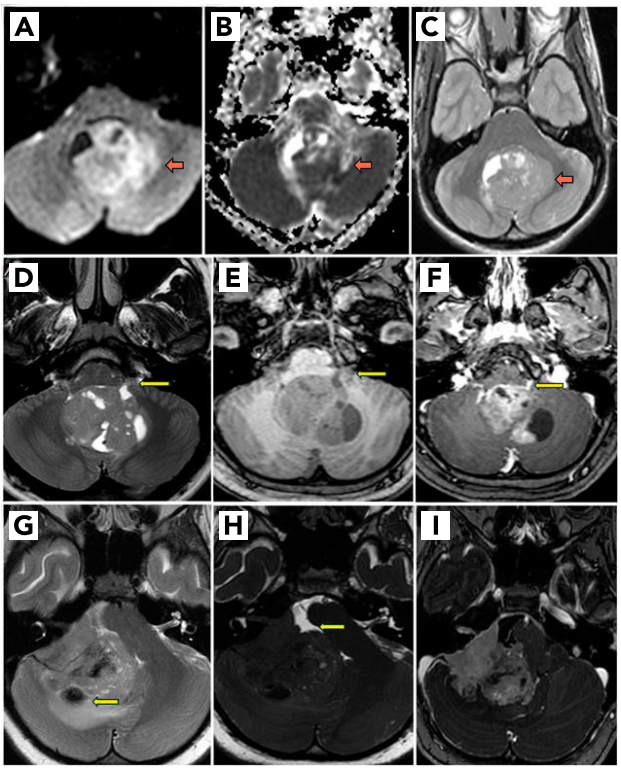

Figure 2. MRI examples of WNT-activated medulloblastoma. **(A-C)** 10-year-old female with a fourth ventricular tumor: **(A)** axial diffusion-weighted, **(B)** ADC map, and **(C)** T2-weighted images demonstrate invasion of the left dentate nucleus (arrow). **(D-F)** 10-year-old male with a fourth ventricular tumor: **(D)** axial T2-weighted, **(E)** precontrast T1-weighted, and **(F)** postcontrast T1-weighted images demonstrate extension into the left foramen of Luschka. **(G-I)** 9-year-old female with a right cerebellopontine angle tumor: **(G)** axial T2-weighted, **(H)** CISS, and **(I)** postcontrast T1-weighted images demonstrate a mass in the right CP angle. On T2 **(G)**, the internal hypointense signal represents intratumoral hemorrhage (arrow). On CISS **(H)**, note the CSF cleft between the tumor and the pons (arrow).
Abbreviations: ADC, apparent diffusion coefficient; CISS, constructive interference in steady state; CP, cerebellopontine; CSF, cerebrospinal fluid.

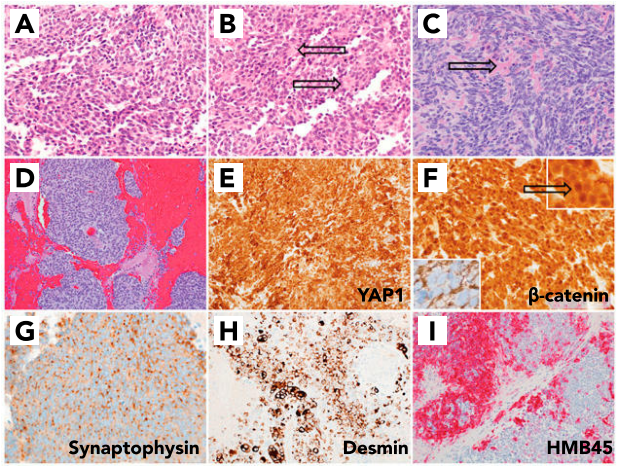

Figure 3. Histopathologic and immunohistochemical features of WNT-activated medulloblastomas. Nearly all WNT-activated medulloblastomas exhibit classic histology **(A)**, with prominent Homer Wright rosettes in some cases **(B)**. A hyalinized background is frequently observed **(C)**, whereas intratumoral hemorrhage is a distinctive feature of this subtype **(D)**. Immunohistochemistry demonstrates **(E)** characteristic YAP1 positivity and **(F)** WNT pathway activation, shown by universal or patchy β-catenin staining (right upper inset: high-magnification image showing nuclear β-catenin immunoreactivity; left lower inset: non-WNT/non-SHH medulloblastoma for comparison, showing absence of nuclear β-catenin). A dot-like synaptophysin immunostaining pattern is also commonly seen **(G)**. Rare WNT-activated medulloblastomas may exhibit myogenic differentiation, detected by desmin immunohistochemistry **(H)**, or melanocytic differentiation, identified by HMB45 staining **(I)**. Chromogens for immunohistochemistry: **(E-H)** diaminobenzidine (DAB; brown); **(I)** Fast Red.

mitotic activity, high nuclear-to-cytoplasmic ratios, and inconspicuous amounts of cytoplasm, producing a "small blue round cell" appearance on routine hematoxylin-eosin–stained sections. Necrosis is uncommon, unlike in high-grade gliomas or ependymomas that also occur in the posterior fossa. Homer Wright rosettes are a prominent feature in some WNT-activated medulloblastomas (Figure 3B), along with a hyalinized background (Figure 3C). Intratumoral hemorrhage is particularly associated with WNT-activated medulloblastomas (Figure 3D).[12] Once recognized by experienced neuropathologists, these histologic findings help narrow down the selection of confirmatory immunohistochemistry and molecular testing. Intratumoral desmoplasia of desmoplastic/nodular or medulloblastoma with extensive nodularity (MBEN) histology is absent in WNT-activated medulloblastomas, and features of large cell/anaplastic histology, such as marked nuclear pleomorphism, high apoptotic counts, nuclear molding, and prominent nucleoli, are exceedingly rare.

Apparent anaplasia or large cell histology should prompt consideration of alternative diagnoses, such as certain SHH or non-WNT/non-SHH (ie, group 3/4) medulloblastomas.[25] The multilayered rosettes and patches of neuropil seen in embryonal tumor with multilayered rosettes (ETMR), the rhabdoid cells seen in atypical teratoid/rhabdoid tumor (ATRT), and the glial differentiation seen in high-grade gliomas (HGGs) are not features of WNT-activated medulloblastomas.

Immunohistochemistry can be used to discriminate between WNT, SHH, and non-WNT/non-SHH medulloblastomas.[9] WNT-activated medulloblastomas are characteristically positive for YAP1 (Figure 3E) and negative for GAB1. Activation of the WNT pathway can be demonstrated by universal or patchy β-catenin (Figure 3F) and LEF1 immunoreactivity in tumor cell nuclei.[9,26,27] Medulloblastomas in other molecular groups show cytoplasmic expression of β-catenin. A dot-like synaptophysin immunostaining pattern is an interesting feature of WNT-activated medulloblastoma (Figure 3G). Rare WNT-activated medulloblastomas may exhibit myogenic and/or melanocytic differentiation (medullomyoblastoma or melanotic medullomyoblastoma), sometimes accompanied by large cell/anaplastic histology. These variants could be detected by desmin (Figure 3H) or HMB45 (Figure 3I) immunohistochemistry, respectively. It remains uncertain whether WNT-activated medullomyoblastoma or melanotic medullomyoblastoma behave similarly to tumors with classic histology.

It is worth noting that, aside from non-WNT/non-SHH medulloblastomas, tumors occurring in the posterior fossa, including ETMR (embryonal tumor with multilayered rosettes), ATRT (atypical teratoid/rhabdoid tumor), and HGG (high-grade glioma), are all positive for YAP1, and approximately 10% of ETMRs harbor *CTNNB1* mutations with β-catenin nuclear immunoreactivity.[28] β-catenin nuclear immunoreactivity can also be observed in CNS tumor with *BCOR* internal tandem duplication

(ITD).[29] In contrast to WNT-activated medulloblastoma, ETMR, ATRT, and CNS tumor with BCOR ITD preferentially arise in young children.

Nearly 90% of WNT-activated medulloblastomas harbor somatic mutations in exon 3 of *CTNNB1*.[17,30,31] Most WNT-activated medulloblastomas lacking somatic *CTNNB1* mutations arise in patients carrying pathogenic germline *APC* mutations.[17] It is worth noting that *CTNNB1* mutation is not specific to WNT-activated medulloblastoma and can be seen rarely in SHH-activated medulloblastomas.[32] Other somatic mutations in WNT-activated medulloblastomas include those encoding subunits of the SWI/SNF nucleosome-remodeling complex (*SMARCA4*, *ARID1A*, *ARID2*; ~30% of cases), *DDX3X* (~40%), *CSNK2B* (~15%), *TP53* (~15%), *KMT2D* (~15%), and *PIK3CA* (~10%).[31] Unlike *TP53* mutations in SHH-activated medulloblastomas, *TP53* mutations in WNT-activated medulloblastomas, which are all somatic and mostly heterozygous, are not thought to confer poor prognosis.[33] However, a subsequent study challenged this finding,[34] although prospective clinical trials did not demonstrate increased risk in TP53-altered WNT-activated medulloblastomas.[19,35,36]

Monosomy 6 on a background of a diploid genome is a characteristic feature of WNT-activated medulloblastoma and is observed in approximately 83% of cases.[7,31,37] High proportions of *CTNNB1*-mutated and *APC*-altered WNT-activated medulloblastomas harbor monosomy 6.[17]

DNA methylation profiling is considered the standard method for determining medulloblastoma group or subgroup status.[38,39] Two molecular subgroups of WNT-activated medulloblastoma have been proposed: WNT-α and WNT-β.[40] WNT-α tumors harbor monosomy 6 and preferentially arise in children, whereas WNT-β tumors commonly lack monosomy 6 and tend to occur in older children and young adults. The prognosis for children with WNT-activated medulloblastoma is excellent, with overall survival approaching 100%.[41,42] However, adult patients with WNT-activated medulloblastoma do not have such a favorable outcome.[43–45] Additionally, it remains uncertain whether rare embryonal tumors of the pineal or sellar regions, which share DNA methylation profiling and genetic characteristics of WNT-activated medulloblastomas, behave similarly to their posterior fossa counterparts.[46,47]

Staging

Although WNT-activated medulloblastomas rarely present with metastatic disease, staging evaluation is still required. MRI of the brain and spine with and without contrast, along with cerebrospinal fluid (CSF) sampling when safe, are required for appropriate medulloblastoma staging. Tumor size has no prognostic significance and is therefore not considered in staging.[48]

Management

Treatment of medulloblastoma is multimodal and requires maximal safe resection, radiotherapy, and adjuvant chemotherapy. With the combination of these therapies, prognosis for medulloblastoma has improved greatly. However, late effects are substantial and include neurocognitive deficits, endocrinopathies, hearing loss, secondary malignancies, and additional complications.[49–51] Compared with other groups, WNT-activated medulloblastoma has significantly improved outcomes, with 5-year overall survival >90%.[10,19,36,41,52] As a result of this excellent prognosis and the significant sequalae associated with current treatment regimens, many studies are exploring therapy deintensification to reduce late effects while maintaining high cure rates.[53]

Surgical Resection

Surgical resection remains the cornerstone of medulloblastoma treatment, achieving multiple critical objectives: histopathologic diagnosis, prognostic enhancement through gross total resection (GTR) or near-total resection (NTR), and re-establishment of CSF pathways to obviate the need for CSF diversion. Although it is common practice at many institutions to obtain GTR whenever feasible, sometimes requiring second-look surgery for small residual tumors, the necessity of achieving GTR or NTR is debated.[54] One retrospective analysis of 787 patients with medulloblastoma suggested that GTR did not confer additional benefit over subtotal resection (STR) in WNT, SHH, or group 3 subtypes, indicating limited utility for second-look surgeries in cases of residual disease for these groups.[55]

WNT-activated medulloblastomas are often associated with obstructive hydrocephalus due to their frequent localization within the fourth ventricle. The 2 most common surgical approaches to the lower part of the fourth ventricle are the transvermian and telovelar approaches. Both are inferior trajectories performed via midline suboccipital craniotomy with or without C1 laminectomy.[56] The supplementary C1 laminectomy helps provide an optimal angle of attack from an inferior trajectory rather than a straight transvermian approach. The transvermian approach involves transecting the vermis, whereas the telovelar approach entails dissection of the telovelar junction at the cerebellomedullary junction or at the intersection of the inferior medullary velum with the tela choroidea of the fourth ventricle. In cases with significant tonsillar ectopia secondary to tumor-induced pressure, tonsillar cautery or reduction should be considered to minimize cerebellar manipulation. Once the dura is opened and the brain is exposed, the medullotonsillar space and the uvulotonsillar space are dissected, manipulating the cerebellar tonsils up and laterally, which will spread and expose the tela choroidea. The tela will then be coagulated and incised from the foramen of Magendie. This wide opening using the telovelar approach is pivotal to prevent injury to critical structures such as the cerebellar hemispheres, tonsils, and vermis. Adequate telovelar opening allows for dynamic retraction, reducing the risk of surgeon-induced posterior fossa syndrome and cerebellar injury in general.[57] WNT-activated medulloblastomas have a higher propensity for dorsal brainstem infiltration than other subtypes, sometimes necessitating intraoperative neuromonitoring to map and preserve brainstem integrity.

It is important to recognize the high-risk anatomic locations for residual tumors. Patel et al[54] identified the roof of the fourth ventricle, specifically the superior medullary velum and fastigium, as the most common sites for residual tumor, followed by the foramina of Luschka and the lateral recess. These findings underscore the importance of a meticulous telovelar approach and thorough inspection to ensure complete resection.

A notable surgical challenge in WNT-activated medulloblastoma is significant intratumoral hemorrhage.[15,16] This reflects the anomalous vascularity and disrupted blood–brain barrier characteristic of this subgroup. It is crucial to achieve maximal resection during the initial surgery, because partial resection in the presence of substantial peritumoral hemorrhage

can exacerbate obstructive hydrocephalus and negatively impact outcomes. Careful inspection at the conclusion of surgery is essential to avoid leaving hemostatic agents, such as Surgicel or Gelfoam, which may complicate the identification of residual tumor during follow-up imaging and facilitate extensive scarring of the surgical bed.

Posterior Fossa Syndrome

Postoperative cerebellar mutism syndrome (poCMS) occurs in up to 40% of children undergoing medulloblastoma resection and represents a significant surgical complication rather than a presenting feature. Predictive models, such as the Rotterdam model, have been proposed to assess poCMS risk, with a score ≥100 suggesting a 66% likelihood of development.[58] However, the consistency of this model remains debated, with other studies failing to show these results.[59]

poCMS is characterized by mutism, cranial nerve palsies, involuntary movements, ataxia, and behavioral changes.[60] Although most symptoms resolve over time, persistent cognitive and physical impairments may persist beyond 1-year postsurgery.[61] Emerging evidence implicates injury to the deep cerebellar nuclei (fastigial and dentate), right paramedian cerebellum, and cerebellar outflow tracts as key contributors to poCMS pathophysiology. Consequently, surgical planning must prioritize maximal safe resection while avoiding injury to these critical structures.[62,63]

Radiotherapy

Radiotherapy is a backbone of medulloblastoma treatment. Standard treatment includes craniospinal irradiation (CSI) with a boost to the tumor bed or posterior fossa. Doses of CSI depend on several disease factors, including group, molecular features, and metastatic staging. WNT-activated medulloblastomas have historically been treated with 23.4 Gy CSI, a standard dose for average-risk medulloblastomas first established by COG A9961 and confirmed in several subsequent trials.[19,52,64] Following the identification of the 4 molecular groups and the superior outcomes of WNT-activated medulloblastomas, one study attempted to eliminate radiotherapy in patients with WNT-activated medulloblastoma, treating them with surgery and chemotherapy alone. This trial was terminated early after the first 2 patients developed recurrent disease. Ultimately, 3 of the 5 children who completed this regimen experienced recurrence, while the remaining 2 received radiation at the end of therapy to prevent recurrence.[65] Another study evaluated the use of focal radiotherapy without CSI followed by adjuvant chemotherapy in patients with nonmetastatic WNT-activated medulloblastoma. This study also closed early due to a high rate of recurrence within the neuroaxis.[66] These 2 trials demonstrate that CSI is an essential component in the successful treatment of WNT-activated medulloblastomas. Several prospective trials are currently evaluating reduced doses of CSI (Table 1). SIOP-PNET 5 MBLR (ClinicalTrials.gov identifier: NCT02066220) and COG ACNS1422 (NCT02724579) reduced the CSI dose to 18 Gy for patients with average-risk WNT-activated medulloblastoma. These trials are now closed to accrual with results pending. The St. Jude Children's Research Hospital SJMB12 trial (NCT01878617) reduced the dose to 15 Gy for patients with low-risk WNT-activated medulloblastoma and reported that they maintained progression-free and overall survival rates >90%. Final data have not yet been published, but preliminary observations suggest that reducing the CSI dose to 15 Gy will result in fewer endocrinopathies, low incidence of hearing loss, and improvement in neurocognitive outcomes.[67]

Chemotherapy

Adjuvant chemotherapy has been routinely used in the treatment of medulloblastoma for the past 3 decades.[68,69] Standard post–radiation therapy regimens have included either cisplatin, vincristine, and lomustine (CDDP/Vcr/CCNU), or vincristine, cisplatin, and cyclophosphamide (Vcr/CDDP/cyclophosphamide), delivered over 9 months. With recognition that patients with WNT-activated medulloblastoma have an excellent prognosis, several ongoing trials are evaluating reduced doses of adjuvant chemotherapy, in addition to lower doses of CSI. The SJMB12 trial reported comparable progression-free and overall survival rates >90% in patients with WNT-activated medulloblastoma who received reduced CSI and only 4 cycles of Vcr/CDDP/cyclophosphamide chemotherapy.[67] The SIOP-PNET 5 MBLR (ClinicalTrials.gov identifier: NCT02066220) and COG ACNS1422 (NCT02724579) trials also reduced chemotherapy,

Table 1. Dose-Reduction Studies in Standard-Risk WNT Medulloblastoma

	St. Jude Children's Research Hospital SJMB12[a]	SIOP-PNET 5 MBLR[b]	COG ACNS1422[c]	SKCCC Study[d]	Tata Memorial Hospital Study[e]
Cisplatin	300 mg/m^2	210 mg/m^2	300 mg/m^2	450 mg/m^2	225 mg/m^2
Vincristine	8 mg/m^2	18 mg/m^2	27 mg/m^2	45 mg/m^2	18 mg/m^2
Cyclophosphamide	12 g/m^2	6 g/m^2	6 g/m^2	6 g/m^2	6 g/m^2
Lomustine (CCNU)	N/A	225 mg/m^2	300 mg/m^2	450 mg/m^2	N/A
Radiotherapy	CSI: 15 Gy Boost: 51 Gy	CSI: 18 Gy Boost: 54 Gy	CSI: 18 Gy Boost: 54 Gy	None	No CSI Focal: 54 Gy
Study status	Closed (completed accrual)	Closed (completed accrual)	Closed (completed accrual)	Terminated early due to recurrent disease	Terminated early due to recurrent disease

Abbreviations: COG, Children's Oncology Group; CSI, craniospinal irradiation; N/A, not applicable; SIOP-PNET 5 MBLR, International Society of Paediatric Oncology-PNET 5 Medulloblastoma Low-Risk; SKCCC, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins.
[a] ClinicalTrials.gov identifier: NCT01878617.
[b] ClinicalTrials.gov identifier: NCT02066220.
[c] ClinicalTrials.gov identifier: NCT02724579.
[d] ClinicalTrials.gov identifier: NCT02212574.
[e] CTRI/2017/12/010767.
Modified from Gottardo NG, Gajjar A. Verschlimmbesserung: craniospinal radiotherapy is essential in WNT medulloblastoma patients. Clin Cancer Res 2023;29:4997; with permission.

although results are still pending.[53] The ultimate goal is to cure WNT-activated medulloblastoma while minimizing morbidity and long-term sequelae.

Conclusions

WNT-activated medulloblastoma differs markedly from the other 3 molecular subgroups, with distinct molecular and clinical features, a unique cell of origin, and a tumor microenvironment that enables an improved response to systemic therapies. Perhaps the most notable clinical feature of WNT-activated medulloblastomas is the excellent prognosis, which is now prompting the de-escalation of therapy. Several trials are attempting to reduce doses of CSI and adjuvant chemotherapy with a goal of minimizing long-term side effects while maintaining high progression-free and overall survival rates in patients with WNT-activated medulloblastoma.

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