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Immunotherapy and Medulloblastoma

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ABSTRACT

Medulloblastoma is one of the leading cancers in pediatric patients. It is an embryonal tumor that originates from the cerebellum or posterior fossa. It is one of the most common cancers in children, and 40% cases were diagnosed below the age of 5 years. Data analysis performed on surveillance, epidemiology and end-results (SEER) for 9 registries suggested that 1372 cases were diagnosed in the period 1973 to 2007. The associated risk factors for the development of medulloblastoma are unknown. Pathophysiology can be best understood with the help of cellular signaling pathways which includes signaling pathways like SHH Signaling, Wnt Signaling and Notch Signaling. Till date, no immune-oncology product has been approved by FDA for this indication. Some available immune-oncology products are under investigation in clinical trials phase I to III. The complete perspective of immunotherapy treatment has not been realized and utilized.

Keywords: Medulloblastoma, Sonic Hedgehog (SHH) signaling, Wnt signaling, ErbB signaling, C-myc signaling, IGF/PI3K signaling and nd notch signalling, Desmoplastic/nodular type, Medulloblastoma with extensive nodularity, Large-cell variant, Anaplastic medulloblastoma a, Environmental factors, Irradiation and radiation, Viral infection, Genetic alteration, Monoclonal antibodies (mAbs), SHH inhibitors, Tyrosine kinase autologous stem cell transplantation and autologous stem-cell rescue

Abbreviations: AHSCR: Autologous Stem-Cell Rescue; APC: Adenomatous Polyposis Coli; CBTRUS: Central Brain Tumor Registry of the United States, CSF: Cerebrospinal Fluid; EGFR: Epidermal Growth Factor; FDA: Food and Drug Administration; GSK3-β: Glycogen Synthase Kinase 3-β; HDCT-AHSCR: High-Dose Chemotherapy with Autologous Stem Cell Rescue; Hh: Hedgehog; IRS-1 Insulin Receptor Substrate-1; LRP: Lipoprotein Receptor-Related Protein; LEF: Lymphoid Enhancer Factor; mAbs: Monoclonal Antibodies; MAPK: Mitogen-Activated Protein Kinase; OSR: Overall Survival Rate; PDGFRB: Platelet-Derived Growth Factor Receptor B, PI3K: Phosphatidylinositol 3-Kinase; PKB: Protein Kinase B; PTCH1: Gene Patched 1; mTOR: Mammalian Target of Rapamycin, SEER: Surveillance, Epidemiology and End-Results; SHH: Sonic Hedgehog Signaling; TCF: Transcription Factors T-Cell Factor, US: United States

INTRODUCTION

Medulloblastoma is an embryonal tumor that originates from the cerebellum or posterior fossa [1]. Cerebrospinal fluid (CSF) plays an important role, in terms of metastasizing to different sites in the brain and spine. Infratentorial tumors are invasive and grow rapidly in comparison to other tumors [2].

Medulloblastoma is one of the most common cancers in children and 40% cases were diagnosed below the age of 5 years [3]. It accounts for less than 2% of adult brain tumors and approximately 18% of pediatric brain tumors. The median age for medulloblastoma is approximately 7 years in children and 25 years for adults [4].

Data analysis performed on surveillance, epidemiology and end-results (SEER) for 9 registries suggested that 1372 cases were diagnosed in the period 1973 to 2007. As per the CBTRUS statistical report in 2005-2009, 2,617 cases of embryonal tumors was identified [5].

Statistical representation of data in accordance to gender, race and Hispanic ethnicity

A study conducted by Padovani et al. [6] and similar studies in adults, stated that 5 years and 10 years overall survival rate (OSR) was 72% and 55% respectively, in 2004.

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There is predominance of male over female in respective ratio of 1.33:1, with higher incidence observed in between the age of 3 to 20 years [7] **(Table 1)**.

Table 1. Statistical representation of data in accordance to gender, race and Hispanic ethnicity.

Data in accordance to statistical variation		
Gender	Male=1,529	Female=1,088
Race	White=2,154	Black=294
Hispanic Ethnicity	Non-Hispanic=2,098	Hispanic=519

Etiology/predisposing factors

The associated risk factors for the development of medulloblastoma are unknown. Familial history can increase the chances of development of brain tumor.

Environmental factors: Diet and vitamins have shown some effects due to the key role of nitrosamines, oxidants and antioxidants. It is not clearly defined, but it might predispose to pediatric brain tumor [8]. Some studies show effects of exposure to carcinogens as a leading cause of pediatric brain tumor. Evidence revealed that the father getting exposed to carcinogens prior to conception and the mother at the time of maternity will damage DNA and predispose to cancer [9].

Irradiation and radiation: It has been observed that children who are constantly exposed to radiations have higher chances of developing childhood brain tumors. In a study, it was reported that the lesser exposure to strontium-90 after the nuclear power plants ceased to operate, led to lower incidences of brain tumor in children [10,11].

Viral infection: Few studies suggested a strong relationship between human neurotropic polyoma virus, i.e., JC virus and medulloblastoma. Viral protein plays an important role in the binding efficacy, interference to tumor suppressor activity and regulation of protein like p53 and Rb [12]. Exposure to measles immunization and SV40 shows link to the development of medulloblastoma [13].

Genetic alteration: Various genetic disorders act as important predisposing factor for the development of medulloblastoma. These syndromes along with their genes and chromosomal locations have been mentioned in **Table 2**.

Table 2. Various genetic syndromes associated with medulloblastoma with their gene and chromosomal location [14].

Genetic syndrome	Gene	Chromosomal location
Li-Fraumeni syndrome	*p53*	17p13.1
Gorlin's syndrome	*PTCH*	9q22.3
Turcot's syndrome A	*APC*	5q21-q22
Rubenstein-Taybi syndrome	*CBP*	16P13.3

Pathophysiology and molecular basis

Pathophysiology can be best understood with the help of cellular signaling pathways.

Figure 1 explains the various signaling pathways associated with the pathogenesis of medulloblastoma.

Sonic Hedgehog (SHH) signaling

Gene Patched 1 (PTCH1), a tumor suppressor, located on 9q22.3 chromosomal location encrypts for Hedgehog proteins' transmembrane surface receptor. This pathway is associated with the progression of external granular layer of the cerebellum. Purkinje cells produce SHH, which binds to PTCH1 receptor and makes the smoothened (SMO) free from inhibition by activating the proliferation of precursors of cerebellar granule cell. It also activates the Gli family of transcription factors. In medulloblastoma, BMI1 is over-expressed. This disrupts the normal regulation of signaling pathways like Rb and p53 [14].

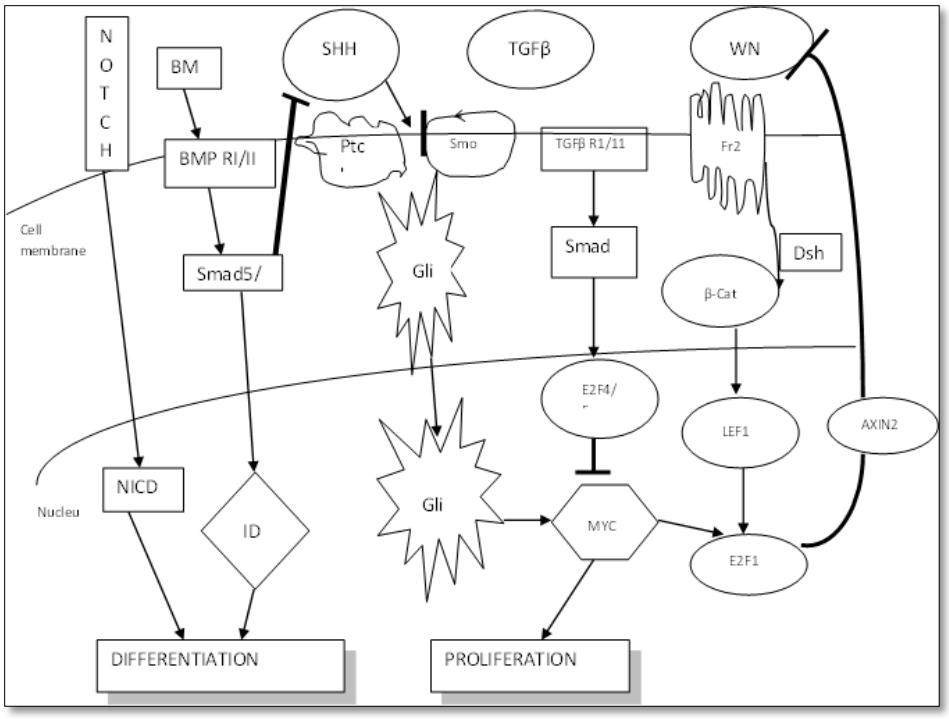

Figure 1. Signaling pathways associated with the pathogenesis of medulloblastoma.

Wnt signaling

A protein complex is formed by adenomatous polyposis coli (APC) in association with β-catenin (CTNNB1), axin 1 (AXIN1) and glycogen synthase kinase 3-β (GSK3-β). In case of Turcot's syndrome, APC is germ line mutated and is the predisposing factor for the development of medulloblastomas [15].

Wingless (WNT) ligand binds to a receptor complex, which includes seven transmembrane Frizzled (FZ), serpentine receptor and low density lipoprotein receptor-related protein (LRP). CTNNB1 is prevented from phosphorylation by glycogen synthase kinase-3β (GSK-3β) and is translocated to the nucleus. Upon activation, a downstream effect of β-catenin is observed and deprivation is followed by TCF (Transcription Factors T-cell Factor)/LEF (Lymphoid Enhancer Factor) interaction with activation of transcription of Wnt targets gene (c-Myc, cyclin D1 and AXIN2) [16].

Survivin, an apoptosis inhibitor is also over-expressed in the presence of activation of Wnt signaling pathway. SOX4 and SOX11 are over-expressed as well and are linked to medulloblastoma [15].

Notch signaling

In Human, 4 types of NOTCH receptor have been identified. Notch, heterodimeric receptor, is a single transmembrane protein. NOTCH 2 is overexpressed in case of medulloblastoma. Extracellular domain and cytoplasimc domain contains different binding efficacy. Cytoplasmic domain contains domain like RAM, a transcription transactivation, two nuclear localization signals, six CDC10 repeats and a PEST sequence. Extracellular binding helps in ligand binding and contains epidermal growth factor (EGFR) like repeats. In the absence of ligand binding, extracellular domain will impede signaling. Once NOTCH binds to ligands Jagged (JAG-1, JAG-2) and Delta-like (DLL-1, DLL-2, DLL-3) family members, release of Notch intracellular domain (NCI) and translocation to the nucleus takes place.[16] NCI interacts with DNA binding proteins (CBF1), which in turn activate the loop-helix transcription factors HES1 and HES5. HES1 forms transcriptional repressor complexes with FOXG1 which negatively regulates the differentiation of neural progenitor cells [15].

ErbB signaling

ErbB include four receptors (ErbB1-ErbB4) and a variety of ligands and neroregulins. They belong to tyrosine kinase family. ErbB4, CYT1 isoform, is over-expressed in tumor, which activates anti-apoptotic phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB)/AKT signaling. ErbB2 gene is located on 17q11.2-q12 chromosome and is regarded as a prospective medulloblastoma oncogene. The ErbB ligand, NRG1-β is expressed by ErbB2 and ErbB4 results in disease progression, while C-myc is the leading target.

C-myc signaling

C-myc is linked to the activation of the different signaling pathways like SHH and Wnt pathways, translocations, viral insertion, genomic amplification and activating mutations. C-myc binds to JPO2 protein, which can activate C-myc

transformation. It is related to metastatic medulloblastoma. N-Myc is linked to SHH signaling pathway. PI3K prevents the degradation of N-Myc and in turn, enhances the effects of IGF/PI3K signaling pathway. This process explains the development of medulloblastoma associated with SHH pathway.

IGF/PI3K signaling

IGF-1 receptor (IGF-1R) protein (e.g. insulin receptor substrate-1 (IRS-1), PI3K, AKT/PKB, Erk-1 and Erk-2) and activated phosphorylated form of IGF-1R are over-expressed, in case of medulloblastoma. Inhibition of dephosphorylation of GSK3-β and IGF-1R are important for the management of medulloblastoma by reducing tumor growth. IGF-1R signaling pathway can lead to the activation of AKT, PI3K, ras/MAPK (mitogen-activated protein kinase) signaling. In case of metastatic medulloblastoma, up-regulation of ras/MAPK pathway and platelet-derived growth factor receptor B (PDGFRB) are key factor [17].

CELLS OF ORIGIN

Activation of different signaling pathways in different medulloblastoma subtypes suggest that medulloblastomas have different origins. There are four types of medulloblastoma identified, based on the following molecular and genetic aspects as well as clinical and prognostic features.

1) Desmoplastic/nodular type
2) Medulloblastoma with extensive nodularity
3) Large-cell variant
4) Anaplastic medulloblastoma

IMMUNOTHERAPY

Monoclonal antibodies (mAbs)

Non-FDA approved monoclonal antibodies: There is no FDA approved monoclonal antibody as an immunotherapy for medulloblastoma. However, Bevacizumab is under clinical trials for the management of medulloblastoma as mentioned below in **Table 3**.

Table 3. Non-FDA approved monoclonal antibody [18].

Drug	NCT identifier	Phase	Study design	Target
Bevacizumab	NCT01217437	Phase II	Efficacy study, Open label	VEGFR

SHH inhibitors:

Non-FDA approved SHH inhibitor: Currently no SHH inhibitor is approved by FDA for medulloblastoma. However, some SHH inhibitors that are under clinical trials are mentioned in **Table 4**. The secreted SHH ligand generate the signal by smoothened (SMO) receptor and helps in the proliferation of neural precursor cells.

Table 4. Non-FDA approved SHH inhibitors [19-21].

SHH inhibitors	NCT identifier	Phase	Study design	Target
LDE225	NCT01708174	Phase II	Open Label, Single Group Assignment, safety and efficacy	Hh-pathway
Vismodegib	NCT01774253	Phase II	Open Label, Single Group Assignment, safety/efficacy	PTCH/SMO
Taladegib (LY2940680)	NCT01697514	PhaseI	Safety Study, Open Label	SMO

Tyrosine kinase inhibitors

Non-FDA approved tyrosine kinase inhibitors: Currently, no tyrosine kinase inhibitor is approved by FDA for medulloblastoma. However, the kinase inhibitors under clinical trials are mentioned in **Table 5**.

Table 5. Non-FDA approved tyrosine kinase inhibitor [22,23].

Tyrosine kinase inhibitor	Clinical trial identifier number	Phase	Study design	Target
Lapatinib	NCT00095940	PhaseI	Efficacy Study, Open Label	EGFR
Erlotinib	NCT00077454	PhaseI	Safety Study, Open Label	EGFR

Autologous stem cell transplantation

Autologous stem-cell rescue: The procedure of high-dose chemotherapy with autologous stem cell rescue (HDCT-AHSCR) has been one of the successful treatment modalities in medulloblastoma. AHSCR also restores the suppression of the process of hematopoiesis, which is limited by the dose of the chemotherapy [24].

A COG trial has been done using the combination of chemotherapy and peripheral stem cell transplant. This COG trial is open for children aged 3 years or younger, on being diagnosed with high-risk disease, which is defined as those with disseminated and/or sub-totally resected tumors or those younger than 8 months with otherwise standard-risk disease. Patients with cortical primitive neuroectodermal tumors or pineoblastomas are also eligible. This study is evaluating chemotherapy as given in the completed COG study COG-99703, which used multi-agent chemotherapy followed by thiotepa-based, higher-dose, marrow-ablative chemotherapy and peripheral stem cell rescue, and randomly assigns patients to treatment with or without intravenous high-dose methotrexate [25].

COX-2 inhibitors

Non-FDA approved COX-2 inhibitors: Currently, no COX-2 inhibitor is approved by FDA for medulloblastoma. However, the COX-2 inhibitors under clinical trials are mentioned in **Table 6**.

Table 6. Non-FDA approved COX-2 inhibitors [26].

COX-2 Inhibitor	NCT identifier	Phase	Study design	Target
Celecoxib	NCT01756989	Phase II	Open Label, single group assignment, safety/efficacy	MGMT

mTOR inhibitors

Non-FDA approved mTOR inhibitors: Currently, no mTOR inhibitor is approved by FDA for medulloblastoma. However, the mTOR inhibitors under clinical trials are mentioned in **Table 7**.

Table 7. Non-FDA approved mTOR inhibitors [26].

mTOR inhibitors	Clinical trial identifier number	Phase	Study design	Target
Sirolimus	NCT01331135	Phase I	Safety/Efficacy Study, Open Label	mTOR

CONCLUSION

Medulloblastoma is one of the leading cancers in pediatric patients. Pathophysiology includes signaling pathways like SHH Signaling, Wnt Signaling and Notch Signaling. Apart from that, chromosome 17, p53, 17p gene, RENKCTD11, MnT and duplication of genes on 17q are few leading causes for the pathogenesis of medulloblastoma. Till date, no immune-oncology product has been approved by FDA for this indication. Some available immune-oncology products are under investigation in clinical trials phase I to III. The complete perspective of immunotherapy treatment has not been realized and utilized. Proper pre-clinical and clinical designs are the important pillars in understanding the future of immunotherapy in treating cancer patients.

REFERENCES

1. http://www.williamdoolin.com/what-is-medulloblastoma.html
2. Okamoto Y, Shimizu K, Tamura K, Miyao Y, Yamada M, et al. (1988) An adoptive immunotherapy of patients with medulloblastoma by lymphokine-activated killer cells (LAK), ActaNeurochir (Wien) 94: 47-52.
3. http://wikitheme.warmachine.im/Medulloblastoma
4. Smoll NR, Drummond KJ (2012) The Incidence of medulloblastomas and primitive neuroectodermal tumors in adults and children. J Clin Neurosci 19: 1541-1544.
5. CBTRUS (2005-2009) Number of brain and central nervous system tumors by major histology groupings, histology, gender, race and Hispanic ethnicity. CBTRUS Statistical Report: NPCR and SEER.
6. Padovani L, Sunyach MP, Perol D, Mercier C, Alapetite C, et al. (2007) Common strategy for adult and pediatric medulloblastoma: A multicenter series of 253 adults. Int J Radiat Oncol Biol Phys 68: 433-440.
7. Farwell JR, Dohrmann GJ, Flannery JT (1984) Medulloblastoma in childhood: An epidemiological study. J Neurosurg 61: 657-664.
8. Wrensch M, Minn Y, Chew T, Bondy M, Berger MS (2002) Epidemiology of primary brain tumors: Current concepts and review of the literature. Neuro Oncol 4: 278-299.
9. Wrensch M, Lee M, Miike R, Newman B, Barger G, et al. (1997) Familial and personal medical history of cancer and nervous system conditions among adults with glioma and controls. Am J Epidemiol 145: 581-593.

10. Solomon G; Natural Resources Defense Council (2014). Brain and central nervous system tumors: The collaborative on health and the environment. Available from: http://www.healthandenvironment.org/brain_cancer/peer_reviewed
11. Mangano JJ, Gould JM, Sternglass EJ, Sherman JD, Brown J, et al. (2002) Infant death and childhood cancer reductions after nuclear plant closings in the United States. Arch Environ Health 57: 23-31.
12. Caracciolo V, Reiss K, Khalili K, De Falco G, Giordano A (2006) Role of the interaction between large T antigen and Rb family members in the oncogenicity of JC virus. Oncogene 25: 5294-5301.
13. Farwell JR, Dohrmann GJ, Flannery JT (1984) Medulloblastoma in childhood: An epidemiological study. J Neurosurg 61: 657-664.
14. de Bont JM, Packer RJ, Michiels EM, den Boer ML, Pieters R (2008) Biological background of pediatric medulloblastoma and ependymoma: A review from a translational research perspective. Neuro Oncol 10: 1040–1060.
15. Li KK, Lau KM, Ng HK (2013) Signaling pathway and molecular subgroups of medulloblastoma. Int J Clin Exp Pathol 6: 1211-1222.
16. Kim J, Rudin CM (2014) Hedgehog Signaling Pathway: Therapeutic abrogation of a fundamental developmental molecular pathway, molecular marker. ASCO Meetings. Available from: http://am.asco.org/hedgehog-signaling-pathway-therapeutic-abrogation-fundamental-developmental-molecular-pathway
17. National Cancer Institute (NCI) (2014) Emozolomide and irinotecan hydrochloride with or without bevacizumab in treating young patients with recurrent or refractory medulloblastoma or CNS primitive neuroectodermal tumors. In: ClinicalTrials.gov [Internet].
18. Novartis Pharmaceuticals (2014) A Phase II Study of Oral LDE225 in patients with hedgehog (Hh)-pathway activated relapsed medulloblastoma (MB). In: ClinicalTrials.gov [Internet].
19. Sholler G (2014) Spectrum Health Hospitals. Erivedge (Vismodegib) in the treatment of pediatric patients with refractory pontine glioma. In: ClinicalTrials.gov [Internet
20. Lilly E (2014) A study of LY2940680 in pediatric medulloblastoma or rhabdomyosarcoma. In: ClinicalTrials.gov [Internet].
21. National Cancer Institute (NCI) (2014) Lapatinib in treating young patients with recurrent or refractory central nervous system tumors. In: ClinicalTrials.gov [Internet].
22. National Cancer Institute (NCI) (2014) Erlotinib and temozolomide in treating young patients with recurrent or refractory solid tumors. In: ClinicalTrials.gov [Internet].
23. Panosyan EH, Ikeda AK, Chang VY, Laks DR, Reeb CL, et al. (2011) High dose chemotherapy with autologous hematopoietic stem-cell rescue for pediatric brain tumor patients: A single institution experience from UCLA. J Transplant 2011: 1-11.
24. Seoul National University Hospital, Seoul National University Hospital (2014) Tandem high dose chemotherapy and autologous stem cell rescue for high risk pediatric brain tumors. In: ClinicalTrials.gov [Internet].
25. Helsinki University Central Hospital (2014) ANGIOCOMB anti-angiogenic therapy for pediatric patients with diffuse brain stem and thalamic tumors. In: ClinicalTrials.gov [Internet].
26. Emory University; Children's Healthcare of Atlanta (2014) Aflac ST0901 CHOANOME - Sirolimus in solid tumors. In: ClinicalTrials.gov [Internet].