REVIEW WILEY

Immune cell landscape and immunotherapy of medulloblastoma

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ABSTRACT
Medulloblastoma is the most common primary pediatric malignancy of the central nervous system. Recurrent and refractory patients account for approximately 30% of them. Immune cells are an important component of the brain tumor microenvironment, including tumor-associated macrophages, T lymphocytes, natural killer cells, dendritic cells, neutrophils and B lymphocytes. Understanding how they behave and interact is important in the investigation of the onset and progression of medulloblastoma. Here, we overview the features and recent advances of each component of immune cells in medulloblastoma. Meanwhile, immunotherapy is a promising but also challenging treatment strategy for medulloblastoma. At present, there are a growing number of immunotherapeutic approaches under investigation including immune checkpoint inhibitors, oncolytic viruses, cancer vaccines, chimeric antigen receptor T cell therapies, and natural killer cells in recurrent and refractory medulloblastoma patients.

KEYWORDS
Medulloblastoma, Tumor microenvironment, Immune cells, Immunotherapy

Introduction

Medulloblastoma is the most common primary pediatric malignancy of the central nervous system. With advanced multidisciplinary therapy, the 5-year survival rate has been significantly improved.[1,2] However, approximately 30% of medulloblastoma patients with high risk stratification or recurrences remain incurable.[3,4]

In recent years, the role played by the tumor microenvironment (TME) in promoting or inhibiting tumor growth has attracted widespread attention.[5,6] Immune system cells are an important component of the brain TME. Tumorigenesis is a complex and dynamic process. Diverse immune cells establish complex interactions with each other and with tumor cells described as an intricate network. These interactions promote proliferation and invasion of the tumor by producing growth factors, chemokines and matrix-degrading enzymes.[7] Each of these immune cells contributes to brain tumor biology in unique ways. Understanding their functions and relationships is critical to understanding the biology of tumor initiation, progression, and metastasis. Despite the low expression of immune cells in medulloblastoma, there are specific variations among the different subgroups. Pham et al[8] adapted murine models of human Sonic Hedgehog (SHH)-driven and group 3 medulloblastomas for evaluation. They found that there were more dendritic cells, infiltrating lymphocytes, myeloid-derived suppressor cells, and tumor-associated macrophages in murine SHH medulloblastomas, and murine group 3 medulloblastomas had more $CD8^+$ T cells. Recently, Bockmayr et al[9] analyzed ten microenvironment cell populations in eight brain tumors including medulloblastoma. Eight immune cell populations were involved: T cells, $CD8^+$ T cells, cytotoxic lymphocytes, B lineage cells, natural killer (NK) cells, monocytic lineage cells, myeloid dendritic cells, and neutrophils. They discovered that medulloblastoma showed low expression of immune cells but with subgroup-specific infiltration. SHH-driven medulloblastomas had larger numbers of T cells, macrophages, and fibroblasts while group 3 and group 4 medulloblastomas had larger

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numbers of $CD8^+$ T cells and cytotoxic lymphocytes. Interestingly, they also identified two immune stromal patterns (macrophage and regulatory T cell [Treg]-mediated mechanisms vs. immunosuppressive cytokines and checkpoints), and they were accurately distributed to the known medulloblastoma subtypes, except for group 4 tumors.

The molecular characterization of medulloblastoma has been intensely researched, and many studies have been done to investigate the additional substructure within subgroups.[10-12] Typically, Cavalli et al[11] identified 12 different subtypes of medulloblastoma, and Northcott et al[10] discovered new subtypes enriched for specific genetic and transcriptional signatures, especially in Group 3 and Group 4. However, the contributions of the immune system to tumorigenesis, progression, response to treatment, and overall prognosis in medulloblastoma remain unclear. In addition, the immune system may provide additional approaches to therapeutic interventions. In this review, we mainly summarize the current knowledge on immune cells in medulloblastoma and immunotherapeutic strategies.

Immune cell landscape of medulloblastoma

Tumor-associated macrophages (TAMs)

TAMs are a key component of the TME that can promote tumor immune system evasion, inhibit T cell activity, and support tumor growth by promoting angiogenesis or suppressing tumor growth if they are pro-inflammatory.[13] They are the major immune cells within some brain tumors especially in glioma and medulloblastoma that are mainly composed of bone marrow-derived macrophages and brain-resident microglia.[14,15] Considerable data demonstrates that macrophage polarization plays an essential role in the growth and progression of brain tumors.[16] However, the role played by TAMs in medulloblastoma is still unclear.

Margol et al[17] first reported that infiltration of TAMs was significantly higher in SHH medulloblastomas compared with that in other medulloblastoma subgroups and that they contributed to the TME of medulloblastomas. They found that TAMs seen on immunohistochemistry (IHC) were of the M2 phenotype, which had been shown to promote tumor progression via a variety of mechanisms with increased expression of the TAM-related genes, *CD163* and *CSF1R*. However, the roles of TAMs and their activation phenotypes are inconclusive in SHH medulloblastomas. Another study suggested that high levels of M1 rather than M2 macrophages correlated with poor prognosis in SHH medulloblastoma patients, contrary to the common view of the M1 phenotype.[18] These studies suggest that the M1/M2 classification may be reversed and incomplete.

TAMs probably play an important role in leptomeningeal metastases. A recent study demonstrated that medulloblastoma cells can spread through the blood to the leptomeningeal space, resulting in leptomeningeal metastases.[19] Leptomeningeal metastases express high levels of monocyte chemotactic protein-1 (CCL2), which is responsible for macrophage recruitment. More interestingly, Maximov et al[15] demonstrated recently that TAMs played an active role in SHH medulloblastoma by inhibiting tumor growth, unlike in glioblastoma. This study indicated that TAMs were predominantly of myeloid origin recruited by CCL2 and that they could promote tumor cell death both *ex vivo* and *in vivo*. Furthermore, a reduction or repolarization of TAMs can result in accelerated tumor progression. Overall, whether TAMs promote or suppress tumor growth still remains controversial.

T Lymphocytes

T lymphocytes have two major subgroups: $CD4^+$ cells and $CD8^+$ cells. $CD4^+$ cells are considered as helper T lymphocytes (Th). $CD8^+$ cells are considered as an antitumor factor that leads to apoptosis. $CD4^+$ and $CD8^+$ T cell responses are part of the cancer-immunity cycle, and tumor growth is controlled by them.[20] In this context, Tregs are a cluster of cells with a $CD4^+ CD25^+ FOXP3^+$ phenotype regulating the body's immune response.[21] It has been reported that patients with medulloblastoma show overall reduced $CD4^+$ T cell counts at diagnosis, and Tregs increase during standard treatment but gradually decline after therapy.[22]

T lymphocytes consistently infiltrate medulloblastomas, and they are recruited to the TME only after the tumor cells have interacted with the tumor vascular endothelium. Macrophage migration inhibitory factor (MIF) is the pivotal chemokine molecule secreted by tumor cells that induces the tumor vascular endothelial cells to secrete potent T lymphocyte attractants.[23] Tumor-infiltrating lymphocytes (TILs) of medulloblastomas, which predominantly infiltrate into perivascular and intratumoral areas, are mainly $CD3^+ CD8^+$ T cells. Several studies have found that group 3 medulloblastomas have an increased number of $CD8^+$ T cells.[8,9] The relationship between TILs and the overall survival is unclear. A recent study showed no correlation between TILs and overall survival in medulloblastoma patients.[24] However, in another study, a reduction in TILs predicted a poor prognosis in medulloblastoma patients.[25]

Immune checkpoints are the important mechanism to escape T-cell mediated immune response. Blockade of immune checkpoints can enhance T cell responses.[26] The precise role of immune checkpoints is not known for multiple cancers. Programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1), as negative regulators of T cell immune function, are key immune checkpoints that decrease the cytotoxic activity of $CD8^+$ T cells towards the tumor.[27] Cyclin-dependent kinase 5

(CDK5) is a kinase required for PD-L1 upregulation that allows medulloblastomas to escape immune elimination. Disruption of CDK5 expression can attenuate tumor PD-L1 expression and promote antitumor immunity.[28] The PD-1/PD-L1 pathway has been shown to be inactive in pediatric cancers.[29,30] Vermeulen et al[24] found that there was a limited number of PD-1$^+$ T cells and a complete absence of PD-L1 in medulloblastoma.[24] This suggested that there would be a limited value for immunotherapy with PD1/PD-L1 blockers in medulloblastoma. Interestingly, Murata et al[25] observed high expression of PD-L1 in nine (56.3%) of 16 medulloblastoma samples. They showed that medulloblastoma patients with high expression of PD-L1 and a low infiltration of CD8$^+$ lymphocytes had a worse prognosis. In a recent study, it has been demonstrated that the gene expression levels of PD-L1 were not uniformly low, while single SHH and WNT medulloblastoma cases showed high PD-L1 expression, although it was still undetectable using IHC.[9] In murine models, PD-1 blockade appears to be more effective in group 3 compared with SHH medulloblastomas.[8]

Transforming growth factor β (TGF-β) plays a complex role in tumor initiation and progression. T cells are critical targets of TGF-β. TGF-β directly inhibits the activities of T cells by suppressing their proliferation, differentiation, and metabolism.[31] It also converts peripheral naive CD4$^+$ T cells into Tregs that are then recruited to the immunosuppressive TME.[32,33] Therefore, TGF-β may reveal itself to be a promising therapeutic target in medulloblastoma. In addition, induction of indoleamine 2,3-dioxygenase 1 (IDO1) can strongly promote the recruitment of Tregs to prevent an immune response against tumor cells.[34] IDO1 inhibitors may present a possible potential for new strategies in the treatment of medulloblastomas.

NK cells

NK cells are large granular lymphocytes that can directly kill tumor cells without specific immunization. They can also secrete various cytokines to initiate antitumor responses and recruit other immune cells into the antitumor response.[35,36] The TME can also affect the metabolism and function of NK cells. The TME contains large numbers of immunosuppressive cytokines and other soluble factors that affect the function of NK cells.[37,38]

NK cells can be found in medulloblastomas by using IHC, flow cytometric analysis, RNA sequencing, etc.[8,9,39] It has been confirmed that NK cells can exhibit cytolytic activity against medulloblastomas both *in vitro* and *in vivo*, and they can also migrate from a distal location to the tumor. In a xenograft mouse model, it was shown that NK cells can suppress medulloblastoma growth.[39] Major histocompatibility complex class I-related chain A (MICA) and UL16-binding protein 2 (ULBP2) are tumor cell surface ligands for the NK group 2, member D (NKG2D) activating receptor on NK cells, and they are prevalent in malignant brain tumors.[40] NKG2D/MICA-ULBP-2 interactions have been considered critical for NK cell cytotoxicity against tumor cells. It has been demonstrated that MICA and ULBP2 are overexpressed on medulloblastoma cells, and NK cell cytotoxicity decreases when NKG2D/NKG2DL interactions are blocked.[41]

Intracranial injection of *ex vivo* expanded human NK cells has therapeutic effects on medulloblastoma xenografts in mouse models. It suggests that patient-derived NK cells could be expanded *ex vivo* and be used for adoptive immunotherapy. In a phase I study, Khatua et al[42] demonstrated the feasibility and safety of intraventricular infusions of *ex vivo* expanded autologous NK cells in recurrent pediatric medulloblastoma patients.[42] It has also been reported that cord blood NK cells may be advantageous in TGF-β-rich medulloblastoma patients.[43]

To sum up, because of tumor heterogeneity, NK cells with non-antigen requirements have some advantages compared with other cells in this respect, especially in pediatric brain cancers.[44] Although studies on NK cells in medulloblastomas are relatively few, they have shown the unique potential as a novel opportunity for exploring new treatment strategies.

Dendritic cells (DCs)

DCs are myeloid-derived, potent antigen-presenting cells (APCs) that are divided into three major subsets: plasmacytoid DC (pDC), myeloid/conventional DC1 (cDC1), and myeloid/conventional DC2 (cDC2).[45,46] They play a critical role in the adaptive immune response by governing T cell immunity and tolerance with a specialized role of the cDC1 subset in CD8$^+$ T cell priming, cDC2 in CD4$^+$ T cell priming, and a role for pDCs in immune regulation.[47,48] DCs have been identified to impact disease progression in many malignancies. Infiltration by mature and active DCs into tumors increases immune activation and recruitment of immune effector cells and pathways.[49] More DCs are found in the murine SHH medulloblastoma model.[8]

The most potentially beneficial use of DCs is in the application as a DC vaccine in cancer therapy that may prolong survival in refractory patients. It is noteworthy that DCs are able to be efficiently loaded with a wide range of treatment agents which is a pivotal procedure in immunization strategies, without leading to undue toxicities in patients.[50-52] There have been a number of clinical trials examining the effectiveness of DC vaccination in malignant brain tumors, especially in gliomas. In a large phase III clinical trial of glioblastoma, the addition of an autologous tumor lysate-pulsed DC vaccine (DCVax-L) proved to be feasible and safe.[53] Nevertheless, reports on the application of DCs in medulloblastoma treatment are relatively few at present.

Nair et al[54] successfully generated DCs that met both phenotypic and functional requisites in 2 out of 5 (40%) patient samples. This study supports the feasibility of DC generation and DC-RNA-based vaccination in pediatric medulloblastoma patients. We can also use DCs pulsed with a tumor RNA transcriptome to expand polyclonal tumor-reactive T cells during adoptive T cell therapies in medulloblastoma.[55]

In general, DCs are the feasible option regarding the specific loading of treatment agents to achieve effective antitumor immunization, and further exploration of DCs in the immunotherapeutic treatment of medulloblastomas is warranted.

Neutrophils

Neutrophils account for approximately 70% of total leukocytes and are the first line of defense against pathogens. In the context of cancer, tumor-associated neutrophils (TANs) present an N1 (tumor-suppressive) or N2 (tumor-promoting) phenotype, with different characteristics of maturity, tumor cytotoxicity, and immune suppression.[56-59] Neutrophils can activate and regulate immune and inflammatory responses against tumor cells, and they are able to have both pro-tumor and antitumor effects on tumor development. It has been found that TANs play an antitumor role in the early stage of the tumor, but as the tumor progresses, TANs convert to a pro-tumor phenotype, while the antitumor ability decreases gradually.[60,61]

Multiple studies have suggested that the specific location of neutrophils within the tumor is related to prognosis. Neutrophils are often found deeper within the tumor during tumor progression and have an N2 phenotype to promote tumor growth.[57] Neutrophils are observed in medulloblastoma tissues using IHC, appearing with a low infiltration; meanwhile, the SHH group has lower numbers of neutrophils than tumors from other medulloblastoma subgroups.[9]

High counts of blood neutrophils are found in many patients with advanced-stage cancers, and the neutrophil-to-lymphocyte ratio (NLR) has been introduced as a prognostic factor for survival in many tumor types. It has been found that a higher pre-operative NLR correlates with a higher histological grade of tumor.[62] Several studies have investigated the significance of the NLR in medulloblastomas. Patel et al[63] observed statistically significantly elevated NLRs in medulloblastoma patients before treatment. They showed that the tumor-induced systemic immune suppression in medulloblastoma patients was already present at the time of diagnosis. In another study, methylation-derived (md)NLRs were measured in peripheral blood samples of pediatric medulloblastoma patients.[64] It has been reported that an elevated mdNLR was significantly associated with mortality in adjusted models. Subsequently, Li et al[65] proved that a high preoperative NLR predicted unfavorable survival in childhood medulloblastoma patients and that levels of preoperative NLRs in group 3 and 4 medulloblastomas were significantly higher than in other groups.

Neutrophils are also being used to indicate a response to treatment. It has been shown that a high peripheral neutrophil count before bevacizumab treatment correlated with a positive and beneficial response to therapy in glioblastoma patients.[66,67] However, no relevant data on medulloblastomas has yet been shown.

Until now, our knowledge of the functions of neutrophils in medulloblastoma patients remains limited. In light of the functional plasticity of neutrophils, there will be more studies focusing on this aspect in the future.

B Lymphocytes

B lymphocytes play a dual role in the TME.[68,69] They can have antitumor activities by recognizing tumor-specific antigens and producing antibodies, as well as APC function or direct killing of cancer cells. They can also display pro-tumor activities through activation of myeloid-derived suppression cells, production of pro-tumorigenic cytokines, or activation of immunosuppressive Tregs. Infiltrating B cells are associated with a positive or neutral prognosis in a variety of tumor types.[70,71]

The role of B lymphocytes in brain tumors has received little attention compared with that of T lymphocytes, which have been studied extensively. The specific role of B lymphocytes in the tumorigenesis and progression of brain tumors remains unclear. On this basis, current studies have been focusing more on their function in gliomas and meningiomas.[72-74] In a glioblastoma model, B cells were shown to act as APCs, playing a critical role in T cell-mediated antitumor immunity and brain tumor regression.[75] They are also involved in response to treatment. A potential mechanism of acquired drug resistance mediated by tumor-associated B cells has been described in melanoma.[76]

Actually, few studies are conducted in the associated field of medulloblastoma. Furthermore, B cells have been shown to minimally infiltrate into medulloblastomas.[9] Therefore, more studies are needed to analyze and explore their potential value in treating medulloblastoma patients and perhaps be used in the development of new treatment strategies.

Current immunotherapy for medulloblastoma

Medulloblastoma has a low number of infiltrating immune cells and little immunogenicity with minimal tumor mutational burden. Thus, it is challenging to design targets for immunotherapy.[77] Immunotherapy has proven to be a promising strategy in various preclinical research

studies. Nevertheless, no immunotherapeutic approach has revealed convincing clinical results in pediatric medulloblastoma. Still, it is a strategy worth pursuing. Current clinical trials evaluating immunotherapy in medulloblastoma patients are outlined in Table 1.

Current immunotherapy has focused predominantly on the following strategies:

Immune checkpoint inhibitors

As mentioned above, Overall levels of PD-1/PD-L1 in human medulloblastomas are low, but some single cases may present high expression of PD-L1.[8,30] It has been demonstrated that PD-1 blockade can result in a more effective outcome in group 3 than that in SHH medulloblastomas. Therefore, PD-1/PD-L1 blockers perhaps show limited value for immunotherapy in medulloblastoma patients and the antitumor efficacy may depend on the subtype of medulloblastoma. Nivolumab is well tolerated without dose limiting toxicities in pediatric brain tumors.[78] Nivolumab, pembrolizumab, and durvalumab are undergoing clinical trials separately, recruiting medulloblastoma patients and patients with other brain tumors. In addition, indoximod, an IDO pathway inhibitor, combined with radiation and temozolomide has been investigated in a first-in-children phase I trial.

Oncolytic viral therapy

Oncolytic measles virus (MV) has potent oncolytic efficacy against medulloblastoma *in vitro* and in mouse models. Intraventricular injection of a modified oncolytic MV into murine xenograft models is safe and can effectively clear medulloblastoma cells.[79-81] G207, a genetically engineered herpes simplex virus (HSV-1) is able to target the highly aggressive MYC-overexpressed group 3 murine medulloblastomas.[82] Poliovirus oncolytic immunotherapy is also a novel approach to treat pediatric brain tumors. The polio:rhinovirus recombinant, PVSRIPO, can significantly decrease cellular proliferation of medulloblastoma *in vitro*.[83] Other effective oncolytic viruses *in vivo* include myxoma virus, reovirus, and Seneca Valley Virus-001 (SVV-001).[84-86] Furthermore, they are currently being tested in clinical trials.

Vaccine therapy

The feasibility of vaccination has been verified in preclinical trials in pediatric medulloblastoma patients, as mentioned earlier.[54] But as yet, clinical trials evaluating vaccines have not reached a satisfactory outcome. A phase I/II trial tried to determine the safety of the combination of decitabine and a cancer vaccine for relapsed or refractory patients including medulloblastoma patients. Unfortunately, it was terminated after enrolling one patient. Another phase I study evaluated the safety and maximum tolerated dose of autologous DCs loaded with allogeneic brain tumor stem cells administered as a vaccination with recurrent brain tumors. Eight patients were involved, but the study was completed with no results posted. At present, several clinical trials on cancer vaccine therapy are underway in recurrent medulloblastoma patients.

Chimeric antigen receptor (CAR) T-cell therapy

CAR T cells were initially approved for hematological malignancies. However, CAR T cell therapy has recently begun to be used for brain tumors and has the potential to be integrated into treatment schema for aggressive pediatric malignant brain tumors in the future.[87] Many preclinical studies have shown efficacy for medulloblastomas. It has been reported that B7-H3 (CD276) CAR T cells can mediate significant antitumor activity *in vivo* and result in regression of medulloblastoma xenografts.[88] Regional and intravenous delivery of human epidermal growth factor receptor 2 (HER2)-CAR T cells causes durable regression *in vitro* and in murine medulloblastoma models, and their intraventricular delivery in non-human primates is feasible without systemic toxicity.[89] Recently, Donovan et al[90] identified three cell-surface targets, erythropoietin-producing hepatocellular receptor A2 (EPHA2), HER2, and interleukin 13 receptor α2 (IL13α2), expressed on medulloblastomas, and demonstrated that intrathecal delivery of the three CAR T cells was an effective treatment in group3 medulloblastoma xenografts in mouse models. This study also showed that intrathecal delivery appeared a superior therapeutic effect compared to intravenous delivery approach. Currently, several clinical trials are underway recruiting medulloblastoma patients.

Adoptive NK cell therapy

The side effects and appropriate dose of expanded NK cell infusions have been tested in children with recurrent pediatric medulloblastoma and ependymoma in a phase I clinical trial.[41] Nine patients received protocol therapy of up to three infusions weekly, in escalating doses from 3×10^6–3×10^8 NK cells/m^2 each infusion, for up to 3 cycles, without dose-limiting toxicities. The study demonstrated the feasibility and safety of intraventricular infusions of autologous NK cells. But the clinical efficacy was disappointing in view of the fact that all patients showed progressive disease, except one patient who had transient stable disease. However, further investigation of NK cell infusions are needed.

Radioimmunotherapy

In a phase II trial, compartmental radioimmunotherapy (cRIT) with intraventricular ^{131}I-3F8 proved to be safe and had clinical utility in maintaining remission in high-risk or recurrent medulloblastoma.[91]

Antigenic targets based immunotherapy

CD47 is a protein on the surface of many solid tumors including medulloblastoma, which has been considered

TABLE 1 Current immunotherapy clinical trials in medulloblastoma patients

Therapeutic ategory	Trial ID	Phase	Title	Treatment	Status	Enrollment	Sponsor
Immune checkpoint inhibitors	NCT02359565	I	Pembrolizumab in treating younger patients with recurrent, progressive, or refractory high-grade gliomas, diffuse intrinsic pontine gliomas, hypermutated brain tumors, ependymoma or medulloblastoma	Pembrolizumab	Recruiting	110	National Cancer Institute (NCI)
	NCT03173950	II	Immune checkpoint inhibitor nivolumab in people with select rare CNS cancers	Nivolumab	Recruiting	180	National Cancer Institute (NCI)
	NCT02793466	I	Durvalumab in pediatric and adolescent patients	Durvalumab	Recruiting	36	Children's Hospital Los Angeles
	NCT03130959	II	An investigational immuno-therapy study of nivolumab monotherapy and nivolumab in combination with ipilimumab in pediatric patients with high grade primary CNS, alignancies (CheckMate 908)	Nivolumab; Ipilimumab	Active, not recruiting	170	Bristol-Myers Squibb
	NCT02502708	I	Study of the IDO pathway inhibitor, indoximod, and temozolomide for pediatric patients with progressive primary malignant brain tumors	Indoximod; Temozolomide; Conformal Radiation; Cyclophosphamide; Etoposide	Completed	81	NewLink Genetics Corporation
	NCT04049669	II	Pediatric trial of indoximod with chemotherapy and radiation for relapsed brain tumors or newly diagnosed DIPG	Indoximod; Full-dose radiation; Temozolomide; Cyclophosphamide; Etoposide; Lomustine	Recruiting	140	Theodore S. Johnson
Oncolytic viral therapy	NCT03911388	I	HSV G207 in children with recurrent or refractory cerebellar brain tumors	G207	Recruiting	15	University of Alabama at Birmingham
	NCT03043391	I	Phase 1b study PVSRIPO for recurrent malignant glioma in children	PVSRIPO	Recruiting	12	Istari Oncology, Inc.
	NCT00314925	I	Safety study of Seneca Valley Virus in patients with solid tumors with neuroendocrine features	Seneca Valley Virus	Completed	60	Neotropix
	NCT02962167	I	Modified measles virus (MV-NIS) for children and young adults with recurrent medulloblastoma or recurrent ATRT	Modified measles virus; Modified measles virus Lumbar puncture	Recruiting	46	Sabine Mueller
	NCT02444546	I	Wild-type reovirus in combination with sargramostim in treating younger patients with high-grade relapsed or refractory brain tumors	Laboratory biomarker analysis; Sargramostim; Wild-type reovirus	Active, not recruiting	6	Mayo Clinic
Vaccine therapy	NCT02332889	I/II	Phase I/II: decitabine/vaccine therapy in relapsed/refractory pediatric high grade gliomas/ medulloblastomas/CNS PNETs	Vaccine (autologous dendritic cells); Decitabine and Hiltonol	Terminated	1	University of Louisville
	NCT01326104	I/II	Vaccine immunotherapy for recurrent medulloblastoma and primitive neuroectodermal tumor	TTRNA-xALT; TTRNA-DCs	Active, not recruiting	17	University of Florida
	NCT03299309	I	PEP-CMV in recurrent medulloblastoma/ malignant glioma (PRiME)	PEP-CMV	Recruiting	30	Gary Archer

(Continues)

TABLE 1 (Continued)

Therapeutic ategory	Trial ID	Phase	Title	Treatment	Status	Enrollment	Sponsor
	NCT03615404	I	Cytomegalovirus (CMV) RNA-pulsed dendritic cells for pediatric patients and young adults with WHO Grade IV glioma, recurrent malignant glioma, or recurrent medulloblastoma (ATTAC-P)	CMV-DCs; Td (tetanus toxoid)	Active, not recruiting	11	Gary Archer
	NCT01171469	I	Vaccination with dendritic cells loaded with brain tumor stem cells for progressive malignant brain tumor	Dendritic Cells; Imiquimod	Completed	8	Masonic Cancer Center, University of Minnesota
CAR T cell therapy	NCT04270461	I	NKG2D-based CAR T cells immunotherapy for patient with r/r NKG2DL+ solid tumors	NKG2D-based CAR T cells	Not yet recruiting	10	Jiujiang University Affiliated Hospital
	NCT03638167	I	EGFR806-specific CAR T cell locoregional immunotherapy for EGFR-positive recurrent or refractory pediatric CNS tumors	EGFR806-specific CAR T cell	Recruiting	36	Seattle Children's Hospital
	NCT03500991	I	HER2-specific CAR T cell locoregional immunotherapy for HER2-positive recurrent/refractory pediatric CNS tumors	HER2-specific CAR T cell	Recruiting	48	Seattle Children's Hospital
	NCT04185038	I	Study of B7-H3-Specific CAR T cell locoregional immunotherapy for diffuse intrinsic pontine glioma/diffuse midline glioma and recurrent or refractory pediatric CNS tumors	SCRI-CARB7H3(s); B7H3-specific CAR T cell	Recruiting	70	Seattle Children's Hospital
Adoptive NK cell therapy	NCT02271711	I	Expanded natural killer cell infusion in treating younger patients with recurrent/refractory brain tumors	Natural killer cell therapy	Active, not recruiting	12	M.D. Anderson Cancer Center
	NCT02100891	II	Phase 2 STIR Trial: Haploidentical Transplant and Donor Natural Killer Cells for Solid Tumors (STIR)	Allogeneic HCT; Donor NK cell infusion	Recruiting	20	Monica Thakar
Radioimmunotherapy	NCT00058370	II	Intrathecal radioimmunotherapy, radiation therapy, and chemotherapy after surgery in treating patients with medulloblastoma	Cisplatin; Lomustine; Vincristine sulfate; Adjuvant therapy; Iodine-I-131 monoclonal antibody 3F8; Radiation therapy	Completed	6	Memorial Sloan Kettering Cancer Center
Antigenic targets based immunotherapy	NCT03652545	I	Multi-antigen T cell infusion against neuro-oncologic disease (REMIND)	TAA-T	Recruiting	32	Catherine Bollard

IDO, indoleamine 2,3-dioxygenase; PVSRIPO, Polio/Rhinovirus Recombinant; DIPG, diffuse intrinsic pontine glioma; TTRNA, total tumor RNA; xALT, *ex vivo* expanded Autologous Lymphocyte Transfer; PEP-CMV, peptide vaccine derived from cytomegalovirus; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HCT, hematopoietic cell transplantation; TAA-T, tumor multi-antigen associated specific cytotoxic T lymphocytes.

as a viable antigenic target. A humanized anti-CD47 antibody, Hu5F9-G4 demonstrated therapeutic efficacy *in vitro* and *in vivo* in Group 3 medulloblastoma xenograft models.[92] Moreover, a recent study showed that PRAME (PReferentially expressed Antigen in MElanoma) was detectable in 82% of medulloblastoma tissues independent of molecular and histopathologic subgroups, and high PRAME expression was correlated with worse overall survival.[93] This study demonstrated that PRAME was a viable target for adoptive immunotherapy using genetically modified T cells with a PRAME-specific T-cell receptor in mouse models. A phase I research on multi-antigen T cell infusion against neuro-oncologic disease is being carried out.

Conclusion

In general, there is significant immunologic heterogeneity in different subgroups of medulloblastoma. Immune cell components have important roles in medulloblastoma development. Further studies are necessary to increase our understanding of their functions and interactions. Immunotherapy is a promising strategy to increase survival with less toxicity in recurrent and refractory medulloblastoma patients. More clinical trials are being explored with the expectation of a major breakthrough in the not too distant future.

CONFLICT OF INTEREST

None.

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