

Prognostic Indicators and Treatment Strategies for Diffuse Midline Glioma: a Systematic Review

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Abstract

Introduction

Diffuse Midline Gliomas (DMGs) are a class of grade IV gliomas associated with a very dismal prognosis. Despite many decades of research, a cure for DMG has yet to be found. In this paper, we will review the drugs and therapeutic techniques published in the scientific literature for DMG.

Methods

A comprehensive search of current literature was conducted in MEDLINE/PubMed. Relevant studies were identified among those in the English language published after 1990 to the present. The Medical Subject Headings (MeSH) search term consisted of the singular phrase “diffuse midline glioma”. Prior to completion of the full-text review, a total of 298 articles were identified as of 26 April 2021. For this systematic review, 20 studies were included after review.

Results

Recent genetic testing has identified a H3K27M mutation that is characteristic of DMGs. This finding has helped pave the way in developing new therapeutic agents and techniques for DMG. Although these newer drugs and therapeutic modalities have not been shown to cure DMG, some of them have been shown to increase overall survival and reduce symptom severity in select patients.

Conclusions

At this point in time, there is no best treatment agent/modality for patients with DMG; rather, the treatment plan should be tailored to the patient’s specific type of DMG. More research is needed to develop better therapeutics and provide improved outcomes to patients.

Introduction

Diffuse Midline Glioma H3 K27M-mutant was classified by the World Health Organization (WHO) as a distinct entity in 2016. This disease is characterized by a K27M mutation in the histone H3.3 H3F3A gene or less commonly the histone H3.1 HIST1H3B gene, both of which are located on chromosome 1q, as well as a midline location (such as the pons, thalamus, spinal cord), being a grade IV tumor, and a diffuse growth pattern [1]. The etiology can be traced back to the Polycomb Repressor Complex 2 (PCR2), which inhibits gene expression via methylation of Lysine 27 on histone H3 [2, 3]. PCR2 plays an important role in stem cell differentiation, X chromosome silencing, and DNA repair [4, 5]. The K27M mutation inhibits PCR2 catalytic function via interactions with the EZH2 domain, located within the catalytic subunit of PCR2. The lysine to methionine substitution leads to excessively strong binding of the nucleosome to PCR2, preventing it from carrying out its catalytic functions. This causes gene over-expression, poor stem cell differentiation, and failure of DNA repair mechanisms, leading to subsequent disease [6–9]. Other associated mutations include TP53, ATRX, and ACVR1 [10]. DMG is most common in children but can be

found in adults. Within the DMG K27M-mutant classification of tumors, there are other tumors found in children formerly known as Diffuse Intrinsic Pontine Glioma (DIPG), although only 80% of have the K27M mutation [1, 11, 12].

Following the onset of neurological symptoms, DMG is diagnosed via a combination of MRI and immunohistochemistry or in-house gene sequencing to identify the telltale K27M mutation [12–15]. Biopsy is less relied upon as a diagnostic tool due to the invasive nature of the disease and the sensitive anatomy it inhabits [16]. DMG prognosis is abysmal, with the H3 K27M-mutant having an even poorer prognosis with the median overall survival (OS) for DMG H3 K27M- mutant being about 1 year with radiotherapy, while the H3 K27M-wildtype OS is about 6 years. The mortality rate for patients afflicted with both the mutant and the wild-type tumors is nearly 100% [17]. Within the group of K27M mutants, mutations in the H3.3 H3F3A gene are associated with worse clinical outcomes than the H3.1 HIST1H3B gene, including less responsiveness to radiation therapy, earlier relapse times, and shorter OS [10, 18].

Dexamethasone can be used to manage neurological symptoms until radiotherapy is begun, and ventriculostomy can manage symptoms of hydrocephalus (HCP) [19]. Surgery is not an option due to the sensitive anatomy and diffuse growth pattern of the disease [16]. The current standard of care is radiotherapy [20], with conventional chemotherapeutic agents proving unsuccessful [12], and no significant progress being made in improving OS within living memory [21, 22]. However, the 2016 WHO reclassification of the DMG K27M-mutant has opened the door for targeted therapy of DMG, an exciting prospect for research and future therapy. In the present work, we aim to delineate the latest findings in DMG treatment research, as the recent 2016 WHO reclassification has already helped to produce a large body of knowledge that can have a significant impact on the lives of patient afflicted with this terrible disease.

Methods

Literature search strategy

A comprehensive search of the current literature was conducted in MEDLINE/PubMed as the selected database. The purpose of this was to identify relevant studies among those in the English language published after 1990 to the present, with the search results last updated in April 2021. The Medical Subject Headings (MeSH) search term consisted of the singular phrase “diffuse midline glioma”. All search results were initially exported as a text document, with all relevant articles later imported to an Excel document for organization and extraction.

Eligibility Criteria And Data Extraction

The eligibility criteria for the inclusion of studies included: (a) articles were written in English; (b) investigations were deemed to represent clinical studies with an emphasis on extracting randomized clinical trials when available; (c) articles were written after 1990; (d) review articles and meta-analyses

were marked as well for exploration of, and potential inclusion, of the references cited. The exclusion criteria included: (a) animal studies; (b) studies not representative or within the field of interest; (c) reviews, poster presentations. A team of four reviewers identified all relevant articles through implementation of the above criteria. The extracted data placed into an Excel document included all of the following: study title, author, publication date, study population, and a general summary.

Results

A total of 298 articles were identified until 26 April 2021. After completion of the full-text review, 20 studies were included for the purpose of this systematic review.

Numerous preclinical and clinical trials have been conducted for DMG. Here we summarize the results of the clinical trials available in the scientific literature as well as promising treatments that are in development. Table 1, found in Appendix A, presents a summary of past clinical trials and promising preclinical studies for DMG.

Park (2021)

This study demonstrated that a progression free survival at 6 months after radiotherapy significantly improved survival in adult patients with DMG while surgical extent did not improve survival, suggesting the important role of radiotherapy in patients with adult brain DMG [23].

Chi (2019)

ONC 201 is a selective dopamine D2 receptor antagonist that can cross the blood-brain barrier. This study was of 14 patients (7 adults and 7 children) with K27M mutant DMG or DIPG with prior radiotherapy. They were given adjuvant ONC201 therapy once weekly. The progression free survival rate was 14 weeks, and the overall survival was 17 weeks. 4 of the adults are continuing therapy. Clinical and radiographic improvements were appreciated [24].

Li (2020)

Retrospective institutional review between 1984 to 2019 of 108 patients with DMG, 62 of which need ventricular shunting for treatment of HCP. VAD (ventricular access device) placement was shown to adequately manage HCP in patients with DMG while also showing promise as a method of disease monitoring via CSF analysis [19].

ONC201

ONC201 is a selective DRD2 antagonist capable of crossing the blood brain barrier and exhibits p53-independent anti-cancer efficacy in preclinical models of high-grade glioma. Furthermore, ONC201 activates the integrated stress response (ISR) and inactivates Akt/ERK along with other pro-survival signaling pathways. In one case study, ONC201 was administered to a 10-year-old female following

unsuccessful radiotherapy. Treatment with ONC201 proved to be effective as it decreased tumor volume by 44% and significantly improved the patient's hearing and grade IV facial palsy. Another study with 18 patients aged 3 to 42 years also showed promising outcomes. The median overall survival for patients with recurrent disease (n=14) was 17 weeks. Some patients experienced a stabilization and subsequent reduction in tumor size with one adult patient even experiencing a full response after 10 months of treatment.^{2,4} While these results are promising, these studies did not account for prior therapies in some patients potentially confounding interpretation. More research will need to be conducted to evaluate the true effect of OCN201 on DMG [24, 25].

Olaparib in combination with Bevacizumab

Olaparib is a poly-adenosine diphosphate-ribose polymerase (PARP) inhibitor shown to inhibit gliomas in preclinical trials. Preliminary studies have demonstrated that PARP inhibitors elicit a therapeutic response independent of BRCA1/2 status or homologous recombination deficiency (HRD). Furthermore, olaparib is believed to be effective against tumors harboring TP53 mutations. Olaparib has been used in combination with bevacizumab for patients with advanced ovarian cancer and has resulted in favorable outcomes. One case study of a 37-year-old female treated with olaparib and bevacizumab reported the complete remission of DMG after approximately 7 months of treatment. Unfortunately, the patient relapsed the following month and died two months later resulting in an overall survival of 16 months. Though the patient passed, this case study demonstrated the potential to use olaparib and bevacizumab for the treatment of DMG. Clinical trials investigating the efficacy of Olaparib for tumors harboring TP53 mutations are currently being conducted [26].

Nimotuzumab

Nimotuzumab is a recombinant monoclonal antibody for the epidermal growth factor (EGF) receptor. 80 to 85% of pediatric high-grade gliomas overexpress the EGF receptor. Nimotuzumab mediates anti-neoplastic effects by antagonizing the intrinsic tyrosine kinase activity of the EGF receptor. A phase III clinical study with 42 patients aged 3 to 20-years-old administered nimotuzumab in combination with radiotherapy. The resulting median overall survival was 9.4 months. The longest overall survival period was 47.4 months. While this treatment method may not have favorable outcomes when compared with other treatments described in this paper, it is worth noting because of the low toxicity of the drug.

Ribociclib

Ribociclib is an orally bioavailable inhibitor of cyclin D-CDK4/6, which induces cell-cycle arrest by maintaining the tumor suppressor protein retinoblastoma (RB) in a hypophosphorylated, active state. In one study, ribociclib was administered to 10 RB+ patients, 9 diagnosed with diffuse intrinsic pontine glioma (DIPG) and 1 diagnosed with DMG, following their radiotherapy. The ages of the 10 patients ranged from 3.7 to 19.8 years old. The outcomes for the DIPG patients were a 1-year overall survival of 89% and a mean overall survival of 16.1 months with a range of 10–30 months. The overall survival for the DMG patient was 6 months. The results from this study have spurred additional clinical trials

investigating the efficacy of a combination study with everolimus, and a second study evaluating how effectively ribociclib reaches target tissues in pediatric brain tumors [28].

H3.3K27M-Specific Vaccines

The H3.3K27M mutation is seen in most patients with DMG and more than 70% of patients with DIPG. The H3.3K27M protein contains a 10 mer peptide sequence, spanning position 26–35, that can function as an HLA-A*02:01–restricted cytotoxic T lymphocyte (CTL) epitope. In one clinical trial, a synthetic H3.3K27M_{26–35} peptide vaccine was administered to 29 patients following completion of radiotherapy. 39% of patients developed an immunological response and generated sufficient levels of H3.3K27M-reactive CD8+ T cells. The median OS of immunological responders was 16.3 months compared with 9.9 months for nonresponders. This data suggests that patients who mount a sufficient immune response will have a better prognosis when treated with this vaccine. As such, concurrent administration of corticosteroids, such as dexamethasone, should be avoided when utilizing this treatment regimen [29].

Convection-Enhanced Delivery

One of the challenges of administering chemotherapeutic agents is the difficulty of crossing the blood brain barrier (BBB). Even drugs that cross the BBB may not be distributed in the desired manner. Convection-enhanced delivery (CED) is a new therapeutic strategy that allows for targeted release of a drug into a specific region via a cannula thereby bypassing the BBB. CED also allows for the continuous infusion of drugs at a steady rate over a prolonged period, which has been shown to be more effective than single dose administration systems.⁸ In a phase 1 clinical trial, omburtamab was administered via CED. Omburtamab is a monoclonal antibody that binds the membrane-bound protein CD276, an immune modulator, which is frequently overexpressed in DMG. Although the trial is still incomplete, the children treated at the time of the paper have a median overall survival of 17.5 months and a 1-year survival rate of 58.5%. There are currently other trials underway examining the efficacy of delivering other agents such as IL13-Pseudomonas toxin, Panobinostat, and DNX-2401 via CED [30, 31].

Role of Imaging and Treatment Outcomes in Pediatric DMG Patients

The association and role of metabolic imaging in relation to diagnosis and treatment within diffuse intrinsic pontine gliomas (DIPGs), a DMG subgroup, is not currently well understood. Investigation of 11C-methionine uptake intensity after baseline and post-treatment 11C-methionine PET/CT scans in a group of 22 pediatric patients with a diagnosis of DIPG was conducted. While the 11C-methionine uptake was correlated with an elevated risk of recurrence, no strong correlation was found between uptake and treatment outcomes among the pediatric patients in this study [32].

H3.3 K27M Mutation Impact on DMG Prognosis

The H3.3 K27M mutation is found in certain rare Diffuse Midline Gliomas (DMGs). The 2016 guidelines set by the World Health Organization (WHO) reclassified DMG H3.3 K27M mutants as grade IV spinal

cord gliomas, and as such the prognostic factors for this new classification were explored by analyzing data among 25 patients diagnosed with a grade IV spinal cord glioma. The H3.3 K27M mutation was found to not be a major poor prognostic factor among these patients [33].

DIPG Intratumoral Pharmacokinetics Investigation

An absence or lack of intratumoral penetration has been suspected in the failure of many systemic chemotherapy trials. Utilization of gemcitabine as a model agent for assessment of DIPG intratumoral pharmacokinetics in a small Phase 0 clinical trial among pediatric patients has shown otherwise. Models of orthotopic patient-derived xenograft (PDX) models of DIPG and H3K27M pediatric glioblastomas were shown to have comparable levels and clearance of gemcitabine. This finding supports the idea that orthotopic PDX models may be utilized to successfully model human DIPG [34].

Treatment and survival of DMG relapse

This is a discussion of DMG relapse and a comparison of factors influencing long and short-term survival. Receiving a second radiotherapy at the time of relapse improved survival. Additionally, Steroid-independent patients had better survival after relapse, potentially due to the relapse disease being lesser in severity. Majority of long survivors had a lansky play score above 50% [35].

Use of F-DOPA PET in predicting DMG treatment response

The role of F-DOPA PET and MRI in predicting treatment response of DMG was studied. It was found that a ratio of F-DOPA uptake of tumor/uptake of striatum greater than 1 showed an overall survival less than or equal to 1 year. This ratio also presented a smaller reduce in tumor volume following treatment [36].

Efficacy of biopsy in diagnosis and treatment decision

Analysis of seven pediatric patients undergoing biopsy for intrinsic brainstem lesions was conducted to clarify who would benefit from biopsy. Based on MRI findings, the cases analyzed were considered atypical for DMGs. Patients with intrinsic pontine lesions that expand beyond the pons or with localized enhancing portion benefit from the biopsy [37].

DMG Subclasses based on oncogenic pathways

The differences between DMG and supratentorial HGG and the two subgroups of DMG were examined. The study found different patterns of expression of HLH genes and upregulation of GAL3ST1, MAFB, OLIG2 and HOXA2, 3 and 4 in DMG compared to HGG.

DMG arises from two distinct oncogenic pathways. The first group of DMG exhibited an oligodendroglial phenotype associated with PDGFRA gain/amplification. The second group of DMG exhibited a mesenchymal and pro-angiogenic phenotype. The first group had worse survival [38].

DMG mutations, clinical features, surgical treatments and survival analysis

Analysis of 43 cases of DMG and examination of clinical features, surgical treatment, molecular characteristics and survival was conducted. Limb weakness or numbness was the most frequently observed symptom. Partial resection and subtotal resection were performed in the majority of patients. Loss of expression of H3K27me3 and ATRX while p53 was overexpressed and demonstrated worse prognosis. Better preoperative Preoperative Karnofsky Performance Score and treatment with adjuvant radiotherapy showed better prognosis [39].

Response to chemotherapy/predict prognosis based on T2-FLAIR mismatch

T2-FLAIR mismatch in DMG could indicate better outcome of radiotherapy. 21 patients with DIPG were included in the study and T2-FLAIR mismatch was found in 5. All patients received radiotherapy. Response rate of radiotherapy in patients positive for T2-FLAIR mismatch was 100%, while it was 25.0% in patients negative for T2-FLAIR mismatch [40].

Discussion/conclusion

Unfortunately, despite decades of research, diffuse midline gliomas (DMGs) remain a devastating disease. Although no cure has been found, efforts to more clearly characterize DMG prognoses, as well as tailor therapeutic treatments, have been made. Understanding of DMG mutations have improved as attempts to understand the difference in prognosis with specific mutations has proven controversial. Furthermore, some clinical trials have found ways to prolong overall survival and improve the quality of life for patients afflicted with this disease.

As recent molecular studies have elucidated, there are various subgroups within DMG suggesting that patients may best be treated with an individualized approach. A variety of chemotherapeutic agents have been studied that inhibit signal transduction pathways within DMG tumors. ONC201, an inhibitor of the Akt/Erk pathway, is a promising agent that resulted in a median OS of 17 weeks regardless of the patient's p53 mutation status. Olaparib, a PARP inhibitor, did achieve complete remission, but the study referenced was a case study with a single patient and may not hold true if the sample size is expanded. Nimotuzumab, an inhibitor of the EGF receptor, provided a median OS of 9.4 months and was well tolerated by patients. Due to this property, Nimotuzumab may be given in combination with other therapeutics. Next, ribociclib, a cyclin D-CDK4/6 inhibitor, was associated with a mean OS of 16.1 months and is effective in RB+ tumors. Shifting focus to drug delivery techniques, CED has also been explored to deliver chemotherapeutic agents in a more targeted manner. When CED procedures were implemented, patients experienced a median OS of 17.5 months. Lastly, immunotherapy utilizing vaccines have also been explored as a treatment for DMG. Although this treatment method did not elicit an immune response in all participants, it was associated with a longer OS in patients who demonstrated a sufficient response. Although not discussed in this paper, scientists are actively exploring other immunotherapy options, such as Chimeric Antigen Receptor (CAR) T-cells [41].

While all treatment methods mentioned above prolonged overall survival, the studies are limited by small sample size. Unfortunately, this is an unavoidable complication due to the rare incidence of the disease.

More research is needed to discover other treatment methods for DMG. Based on the molecular findings of DMG, it is unlikely there will be a stand-alone cure for DMG, rather patients should be treated based on the molecular profiles of their specific diseases to offer the best chance of survival. The door remains open for future research in the treatment and management of DMG. The recent WHO classification has already helped yield new research and discovery with some promising new treatments starting to garner attention from the medical community and hope from patients.

Declarations

Authors' contributions: Michael Fiorino and Nathan Kostick contributed to the study conception and design. Literature search and data analysis were performed by Caroline Baughn, Alexander Bolufer, Takuma Iwai, and, Fariz Alkassis, All authors contributed in drafting and critically revision of the work. All authors read and approved the final manuscript.

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Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

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