Advances in Molecular Biological and Translational Studies in World Health Organization Grades 2 and 3 Meningiomas: A Literature Review

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Abstract

The treatment of World Health Organization (WHO) grades 2 and 3 meningiomas remains difficult and controversial. The pathogenesis of high-grade meningiomas was expected to be elucidated to improve treatment strategies. The molecular biology of meningiomas has been clarified in recent years. High-grade meningiomas have been linked to NF2 mutations and 22q deletion. CDKN2A/B homozygous deletion and TERT promoter mutations are independent prognostic factors for WHO grade 3 meningiomas. In addition to 22q loss, 1p, 14p, and 9q loss have been linked to high-grade meningiomas. Meningiomas enriched in copy number alterations may be biologically invasive. Furthermore, several new comprehensive classifications of meningiomas have been proposed based on these molecular biological features, including DNA methylation status. The new classifications may have implications for treatment strategies for refractory aggressive meningiomas because they provide a more accurate prognosis compared to the conventional WHO classification. Although several systemic therapies, including molecular targeted therapies, may be effective in treating refractory aggressive meningiomas, these drugs are being tested. Systemic drug therapy for meningioma is expected to be developed in the future. Thus, this review aims to discuss the distinct genomic alterations observed in WHO grade 2 and 3 meningiomas, as well as their diagnostic and therapeutic implications and systemic drug therapies for high-grade meningiomas.

Keywords: genomic alteration, copy number alteration, mRNA expression, DNA methylation, systemic medical therapy

Introduction

Meningiomas in adults are the most common primary intracranial tumors.11 Approximately 80%, 15%-20%, and 1%-3% of meningiomas are benign (World Health Organization [WHO] grade 1), atypical (WHO grade 2), and malignant (WHO grade 3), respectively.11 Recurrence occurs in 3%-20%, 30%-40%, and 50%-58% of grades 1, 2, and 3 meningiomas, respectively.1-11 High-grade meningiomas often become refractory to standard surgical and radiation therapy and are therefore difficult to manage. Chemotherapy and other systemic medical therapies are reserved as salvage therapy in these patients. These therapies, however, have had only limited success and have shown little clinical benefit.13,14 Thus, the molecular biological characteristics of these high-grade meningiomas should be clarified. Systemic medical therapies are also expected to be developed to combat them. The World Health Organization Classification of Tumors of the Central Nervous System, fifth edition, published in 2021, described these genetic characteristics.15 The WHO 2021 classification introduced significant changes that advance the role of molecular diagnostics of central nervous system tumors. TERT promoter (TERTp) mutation and homozygous CDKN2A/B deletion have been included as independent criteria for WHO grade 3 meningiomas15 (Table 1). Novel molecular classifications based on multimolecular omics analysis have been recently reported and appear to have clinical application.16,17
### Table 1 2021 WHO classification of meningiomas

| WHO grade | Subtype                          | Criteria                                                                                   |
|-----------|----------------------------------|-------------------------------------------------------------------------------------------|
| Grade 1   | Meningothelial                   |                                                                                           |
|           | Fibrous                          |                                                                                           |
|           | Transitional                     |                                                                                           |
|           | Psammomatous                     |                                                                                           |
|           | Angiomatous                      |                                                                                           |
|           | Microcystic                      |                                                                                           |
|           | Secretory                        |                                                                                           |
|           | Lymphoplasmacyte-rich            |                                                                                           |
|           | Metaplastic                      |                                                                                           |
| Grade 2   | Atypical                         | 4-19 mitotic figures in 10 consecutive HPF of each 0.16 mm² or Unequivocal brain invasion (not only perivascular spread or indentation of brain without pial breach) or Specific morphological subtype (chordoid or clear cell) or At least three of the following: 1. Increased cellularity 2. Small cells with high N:C ratio 3. Prominent nucleoli 4. Sheeting (uninterrupted pattern-less or sheet-like growth) 5. Foci of spontaneous (non-iatrogenic) necrosis |
|           | Chordoid                         |                                                                                           |
|           | Clear cell                       |                                                                                           |
| Grade 3   | Anaplastic                       | 20 or more mitotic figures in 10 consecutive HPF of each 0.16 mm² (at least 12.5/mm²) or Frank anaplasia (sarcoma-, carcinoma-, or melanoma-like appearance) or \( TERTp \) promoter mutation or Homozygous deletion of \( CDKN2A \) and/or \( CDKN2B \) |
|           | Rhabdoid                         |                                                                                           |
|           | Papillary                        |                                                                                           |

HPF: high power field.

This article aims to review the distinct genomic alterations observed in WHO grade 2 and 3 meningiomas and discuss their diagnostic and therapeutic implications, as well as systemic drug therapies for high-grade meningiomas.\(^{15,18,19}\)

### Genomic Alterations and mRNA Expressions (Table 2)

\( NF2 \) gene encodes the tumor suppressor protein merlin, a negative regulator of mTORC1.\(^{20,22}\) The rate of \( NF2 \) mutations in low-grade meningiomas is ~40%, whereas, the rate of \( NF2 \) mutations in high-grade meningiomas is significantly higher at 80%.\(^{20}\) The incidence of non-\( NF2 \) mutations is <5% in 20% of high-grade meningiomas without \( NF2 \) mutations, compared to 35% in grade 1 non-\( NF2 \) meningiomas. This significantly lower incidence suggests that high-grade meningiomas have a different genetic basis.\(^{23}\)

Homozygous deletion of the \( CDKN2A/B \) gene located at 9p21 has been frequently observed in anaplastic meningiomas.\(^{18,24-29}\) \( CDKN2A/B \) homozygous deletion was found in about 4.9% of meningiomas of all WHO grades and subtypes. Atypical meningiomas made up 27% of the cases with \( CDKN2A/B \) homozygous deletion, while anaplastic meningiomas made up 73%. In particular, \( CDKN2A/B \) homozygous deletion, in particular, was able to identify patients with poor prognosis among WHO grade 2 and 3 cases.\(^{20}\) Consequently, \( CDKN2A/B \) homozygous deletion has been added as an independent criterion for WHO grade 3 meningiomas in the 2021 WHO classification.\(^{15}\)

\( TERTp \) mutations occur at specific hotspots known as C228T and C250T in meningiomas.\(^{19,30,31}\) \( TERTp \) mutations occur in 4.7%, 7.9%, and 15.4% of WHO grades 1, 2, and 3 meningiomas, respectively.\(^{20}\) \( TERTp \) mutations are associ-
Table 2  Main genomic alterations in WHO grades 2 and 3 meningiomas

| Gene       | Locus    | Product                                      | Frequency | Histology                | Pathway                        |
|------------|----------|----------------------------------------------|-----------|--------------------------|--------------------------------|
| NF2         | 22q12.2  | Merlin                                       | 40%-80%   | Atypical, anaplastic      | PI3K/AKT/mTOR and hippo         |
| CDKN2A/2B   | 9p21.34  | p16(INK4A)/p15(INK4B)                         | <5%       | Atypical, anaplastic      | Cell cycle regulation           |
| TERTp       | 5p15.33  | TERT                                         | 5%-15%    | Atypical, anaplastic      | Telomerase activity             |
| BAP1        | 3p21.1   | Ubiquitin carboxy-terminal hydrolase 1       | <1%       | Rhabdoid                 | DNA repair                      |
| PBRM1       | 3p21.1   | Subunit of PBAF complex                      | 2.8%      | Papillary                | Chromatin remodeling            |
| DMD         | Xp21     | Dystrophin                                   | NA        | Atypical, anaplastic      | Cytoskeleton                    |
| SMARCB1     | 22p11.23 | Subunit of SWI/SNF complex                   | 5%        | Atypical, anaplastic      | Chromatin remodeling            |
| SMARCE1     | 17q21.2  | Subunit of SWI/SNF complex                   | 3%-4%     | Clear cell                | Chromatin remodeling            |
| SMARCA4     | 19p13.2  | Subunit of SWI/SNF complex                   | NA        | Atypical, anaplastic      | Chromatin remodeling            |
| ARID1A      | 1p36.11  | Subunit of SWI/SNF complex                   | 12% in grade 3 | Anaplastic | Chromatin remodeling |
| PIK3CA      | 3p26.32  | Catalytic subunit of kinase, PI3K             | 3%-7%     | Grades 1-3                | PI3K/AKT/mTOR                   |

ated with increased TERT expression and telomerase activity but not with telomere length. The recurrence rate in WHO grade 1 and 2 cases with TERTp mutation is higher than in WHO grade 3 cases without TERTp mutation. This suggests that TERTp mutation is a prognostic factor independent of WHO grade. Therefore, the presence of TERTp mutation has been added as an independent criterion for WHO grade 3 meningiomas in the WHO classification 2021. Furthermore, TERTp mutations are associated with tumor progression and poor outcome of de novo high-grade meningiomas after following adjuvant radiotherapy.

Somatic mutations in BAP1 have been identified in a rare subset of aggressive meningiomas with rhabdoid morphology. BAP1 codes a BRCA1-associated protein and is essential for DNA repair. Its inactivation is oncogenic. Cases with germline BAP1 mutations also exist in the subset of cases with somatic BAP1 mutations. This indicates that such meningiomas can occur as part of the BAP1 cancer predisposition syndrome. Furthermore, immunohistochemistry-based negative nuclear staining for BAP1 reveals the absence of BAP1 expression. Therefore, immunohistochemistry can help predict the prognosis of meningiomas with rhabdoid features.

Biallelic inactivation of PBRM1 in papillary meningiomas was recently reported. BAF180 protein, a subunit of the polybromo-associated BAF complex chromatin remodeling complex, is encoded by PBRM1. PBRM1 mutations, which is a tumor suppressor gene, have been found in clear cell renal cell carcinoma, papillary renal cell carcinoma, and bladder carcinoma. PBRM1 mutations significantly increase cell proliferation and migration. BAF180 protein is required for centromeric cohesion, and cells lacking PBRM1 have DNA damage and dynamic chromosome instability. PBRM1 mutations can overlap with BAP1 mutations, and their prognostic role in meningiomas remains unknown.

Mutations in the DMD gene, which codes for dystrophin, have also been linked to progressive/high-grade meningiomas. DMD inactivation was found in 32% of progressive meningiomas, either through genomic deletion or loss of protein expression. Furthermore, the presence of DMD inactivation in advanced or high-grade meningiomas reduces overall and progression-free survival. Importantly, somatic DMD mutations and TERTp mutations are mutually independent in predicting unfavorable outcomes.

Mutations in SWI/SNF chromatin remodeling complex members have been found in high-grade meningiomas. SMARCB1 is also found on 22q, and mutations in this gene may be found in cases with NF2 mutations. Other SWI/SNF complex members, e.g., SMARCE1, SMARCA4, and ARID1A, have also been shown to be mutated on multiple occasions. SWI/SNF gene mutations are more frequently detected in anaplastic (16%) meningiomas than in benign and atypical meningiomas (<5%). ARID1A mutations were found in 19.1%, 16.8%, and 15.8% of WHO grades 1, 2, and 3 meningiomas, respectively, and the presence of an ARID1A mutation was associated with a 7.4-fold mortality risk.

PIK3CA mutations are most commonly found in WHO grade 1 meningioma, which accounts for 4%-7% of all meningioma cases. The presence of PIK3CA mutations in high-grade meningiomas was first reported in 2006. PIK3CA mutations are found in 3.7% of anaplastic meningiomas and are relatively rare in high-grade meningiomas. Moreover, PIK3CA mutations are found in meningiomas without additional copy number alterations or somatic mutations. This suggests that PIK3CA may have played a role in the tumorigenesis of malignant meningioma.

Only 0.6% of meningiomas have mutations in mismatch repair genes (MMR), e.g., MSH2, MSH6, SETD2, and POLE, but interest exists in studying these mutations in aggressive meningiomas. Firstly, these mutations can be targets for immunotherapy because MMR mutations are often associated with neoantigens. Pembrolizumab, a PD-1 inhibitor, has been approved for solid tumors with MMR muta-
meningiomas after gross total resection. Secondly, MMR mutation frequency is rare in high-grade meningiomas despite genetic instability. Thus, other driver events may be involved in high-grade meningioma development.

NF2 mutations have been linked to chromatin remodeling genes like SUZ12, KDM5D, KDM6A, SETD6, KMT2C, KMT2D, or CREBBP as well as DNA damage response genes like ATM, ATR, or BAP1 in chordoid meningiomas. Importantly, these mutations are independent prognostic factors for chordoid meningioma’s aggressive course.

Although many factors have been identified through transcriptome analysis, the current study focused on the FOXM1 gene, which is of particular importance. FOXM1 was identified as a key transcription factor for tumor growth and a marker of poor clinical outcome. FOXM1 is a promitotic transcription factor necessary for cell proliferation during development. FOXM1 expression in meningioma has previously been reported to be high in invasive tumors. Furthermore, meningiomas with a poor prognosis had a high somatic mutation burden. The FOXM1-wnt signaling pathway was associated with a mitotic gene expression program, poor clinical outcome, and primary meningioma growth. To summarize, FOXM1 activity promotes meningioma proliferation and tumor growth by collaborating with the dysregulated FOXM1-wnt signaling pathway.

Unlike WHO grade 1 meningioma, the association between tumor location and genetic genomic alterations in high-grade meningiomas is not reported in detail. Thus, further studies are needed.

Copy Number Alterations

Genomic instability is linked to tumor aggressiveness, and karyotypic abnormalities are noted to gradually increase as meningiomas become more aggressive. The most noticeable difference between grades 2 and 3 meningiomas is an increase in copy number alterations (CNAs) when compared to grade 1 meningiomas. Loss of chromosomes 1p, 4p, 6q, 9q, 10, 14q, and 22q or gain of chromosomes 1q, 9q, 12q, 15q, 17q, 19, 20, and 5 have also been described. CNAs become more common as the WHO grade of meningioma rises. The number of CNAs is strongly associated with the risk of recurrence in atypical meningiomas after gross total resection. These results suggest that meningiomas with a high number of CNAs may have a biologically aggressive behavior.

Grades 2 and 3 meningiomas are strongly linked to deletion or loss of genetic locus on chromosome 22q that contains the NF2 gene. The rate of loss of heterozygosity for 22q increases with the grade, from 50% in WHO grade 1 meningioma to 75%-85% in WHO grade 3 meningioma. Other tumor suppressor genes found on chromosome 22q include SMARCB1, CHEK2, and CLH22. Loss of 22q loss results in a state of genetic instability that is prone to somatic mutations. This results in a genetically diverse and aggressive tumor phenotype.

After 22q loss, the second most common copy number in meningiomas is 1p loss which is associated with higher WHO grade. 1p loss is found in 40%-76% and 70%-100% of WHO grades 2 and 3 meningiomas, respectively, and is especially common in recurrent and high-grade tumors. Interestingly, 1p loss is an independent marker of meningioma recurrence and progression. However, 1p loss is observed at a significantly lower frequency in grade 3 chordoid meningiomas, a particularly aggressive subtype, compared to other high-grade subtypes. Recently, 1p36 loss was reported as the prognostic marker of regrowth after gamma knife surgery for WHO grade 1 meningiomas. However, genetic alterations associated with radiation therapy efficacy in high-grade meningiomas have not been identified.

The loss of chromosomes 14q, 9p, and 6q are major additional alterations found in high-grade meningiomas. 1q, 9p, and 14q loss is detected in 40%-57% and 55%-100% of WHO grades 2 and 3 meningiomas, respectively, especially in high-grade tumors. Loss of both 1p and 14q has been associated with early tumor recurrence and is a prognostic factor independent of WHO grade. 9p loss is a common finding in WHO grade 3 meningiomas. CDKN2A/B deletions on 9p are especially linked to tumor recurrence. As aforementioned, these genes have recently been studied as biomarkers of poor prognosis.

Other chromosome abnormalities have been reported, as summarized in Table 3.

Epigenetic Alteration

H3K27 me3 was referred to in the WHO 2021 classification. Lack of H3K27 me3 staining in meningioma cells has been linked to faster progression, establishing its role as an adjunct prognostic marker. This provides important prognostic information, particularly in WHO grade 2 or borderline cases between WHO grades 1 and 2. In another large cohort study including 1,268 cases, lack of H3K27 me3 staining was found in 4.7% of meningiomas and was noted to be more common in females, in convexity or falx. The WHO grading system also revealed a significant difference in trimethylation loss: 3.1%, 10.4%, and 17.7% in grades 1, 2, and 3, respectively. Anaplastic (16.7%) and chordoid (20.0%) meningioma had the highest rate of trimethylation loss, followed by atypical and chordoid meningiomas (9.9% and 14.3%). Furthermore, significantly more cases were noted with a MIB1 labeling index (LI) of ≥6.9% in 18.3% of cases where H3K27 me3 staining was missing. The combination of H3K27 me3 loss and MIB1 LI has been reported to be a poor prognostic marker for meningiomas. The importance of H3K27 me3 loss in IHC has been highlighted.
Global DNA Methylation Profiling

Meningiomas are classified into six groups, according to Sahm et al., based on global DNA methylation profiling using a genome-wide methylation array.\(^{27}\) Higher methylation levels have been linked to a higher risk of tumor aggressiveness and recurrence according to this classification.\(^{27}\) DNA methylation is a type of epigenetic change that has been linked to genomic instability by silencing genes involved in DNA repair and cell cycle regulation. This group reported that DNA methylation-based classification can be used to diagnose other types of tumors.\(^{80,81}\)
Integrative Molecular Classifications of Meningiomas (Tables 4 and 5)

Meningioma integrative molecular classifications have recently been proposed.\cite{1,2,3} A combined model score based on WHO grading, CNAs, and global DNA methylation classification has been developed\cite{4} (Table 4). Patients were classified as having low (0-2), intermediate (3-5), and high (>5) integrated risk in that model. Although both methylation classification and the classification by CNAs have been independently proven to be better predictors than WHO grade alone, this integrated score consistently outperforms each component.\cite{5} In another study, an integrated molecular analysis of CNAs, DNA somatic mutations, global DNA methylation status, and transcriptome revealed four consensus molecular groups\cite{6} (Table 5). These molecular groups outperformed traditional classification in predicting clinical outcomes. Furthermore, each group exhibited distinctive and prototypical biology (MG1, immunogenic; MG2, benign NF2 wild-type; MG3, hypermetabolic; and MG4 proliferative), making them potential therapeutic targets.\cite{7} MG1 group demonstrated large immune infiltration and was enriched by pathways involved in immune regulation and signaling. The MG2 subset’s transcriptome is enriched for vascular and angiogenic pathways. The pathways converging the metabolism of several macromolecules were specifically enriched in MG3 tumors. MG4 group was enriched in pathways involved in cell cycle regulation and several important and complementary transcription factor networks related to proliferation, e.g., MYC, CDKs, and kinesins.\cite{8} Meningioma classification based on molecular biological features is being proposed. These classifications, along with those for other gliomas, have the potential to change the way diagnostic meningioma samples are processed.

Systemic Medical Therapies (Table 6)

Molecular targeted therapies

Neurosurgeons face therapeutic challenges when dealing with aggressive high-grade meningiomas that do not respond to surgeries and radiation therapy. Advances in understanding intracellular signaling pathways and microenvironment in meningiomas have led to the promise of molecular targeted therapies for meningiomas.\cite{9} NF2 mutations and 22q loss are most frequently observed in recurrent high-grade meningiomas and are potential therapeutic targets. GSK2256098, a FAK inhibitor that is supposed to be active when Merlin expression is defective, is currently being studied in an umbrella clinical trial that is specifically targeting meningiomas with NF2 mutations.\cite{10} BAP1

| Components of classification | Score |
|-----------------------------|-------|
| WHO grading | |
| Grade 1 | 0 |
| Grade 2 | 1 |
| Grade 3 | 2 |
| DNA copy number alterations | |
| None present | 0 |
| 1-2 present | 2 |
| 3 present | 3 |
| Losses chromosome 1p, 6q, and 14q | |
| Benign | 0 |
| Intermediate | 2 |
| Malignant | 4 |

| Classifications | Total score |
|-----------------|-------------|
| Low risk | 0-2 |
| Intermediate risk | 3-5 |
| High risk | 6-10 |

| Outcome | |
|---------|----------------|
| Low > intermediate > high |

Table 5 Integrative molecular classification of meningiomas 2

| DNA somatic point mutations | DNA copy number alterations | Messenger RNA abundance (transcriptome) | Global DNA methylation status |
|-----------------------------|-----------------------------|----------------------------------------|-----------------------------|
| MG1 Immunogenic | **NF2 and SMARCB1** | 22q loss | Immunogenic | Differences in genome-wide DNA methylation patterns between groups |
| MG2 Benign NF2 wild-type | **AKT1, KLF4, SMO, POLR2A, and TRAF7** | 5, 12, and 20 gain | Vascular/angiogenesis |
| MG3 Hypermetabolic | **NF2, TERTp, and CREBBP** | 1p, 6, 14p, 18, and 22q loss | Hypermetabolic |
| MG4 Proliferative | **NF2, TERTp, CREBBP, and CHD2** | 1p, 6, 10, 14q, 18, 22q loss, and 1q gain | Proliferative |

| Outcome | |
|---------|----------------|
| MG1 > MG2 > MG3 > MG |

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| Classification                  | Drugs                  | Mechanism            | Phase | Case                                                                 | Result                          | Study                                      |
|--------------------------------|------------------------|----------------------|-------|----------------------------------------------------------------------|---------------------------------|--------------------------------------------|
| Molecular-targeted therapy     | GSK2256098             | FAK inhibitor        | Phase II | Recurrent or progressive cases with NF2 mutations                     | Improving PFS6 rate             | Brastianos et al. 2020 NCT02523014       |
| Tazemetostat                   | EZH2 inhibitor         |                      | Phase II | BAPI1 mutation (Rhabdoid)                                            | Ongoing                         | NCT02860286                               |
| Ribociclib                     | CDK4/6 inhibitor       |                      | Phase II | Grades 2 and 3 with CDKN2A/B deletion                                | Ongoing                         | NCT02933736 Tien et al. 2019             |
| Vistusertib (AZD2014)          | mTORC1/C2 inhibitor    |                      | Phase II | Recurrent grades 2 and 3 with NF2 mutation                           | Ongoing                         | NCT03071874                               |
| Vistusertib (AZD2014)          | mTORC1/C2 inhibitor    |                      | Phase II | Progressive cases with NF2 mutation                                  | Ongoing                         | NCT02831257                               |
| Everolimus + octreotide        | mTOR inhibitor +       |                      | Phase II | Refractory aggressive/progressive cases                               | Improving PFS6 rate             | Graillon et al. 2020 CEVOREM trial        |
| Everolimus + bevacizumab       | Anti-VEGF              |                      | Phase II | Recurrent/progressive cases                                           | Improving PFS6 rate             | Shih et al. 2016                           |
| Alpelisib + trametinib         | PI3K inhibitor +       |                      | Phase II | Progressive refractory cases with PIK3CA mutation                    | Ongoing                         | NCT03631953                               |
| Vismodegib                     | Hedgehog pathway      |                      | Phase II | Recurrent/progressive cases with SMO/PTCH1 mutation                  | Ongoing                         | NCT02523014 Alliance clinical trial       |
| Afuresertib                    | AKT1 inhibitor         |                      | Case report | Grade 1 with AKT1 mutation                                            | Potential                       | Weller et al. 2017                        |
| Bevacizumab                    | Anti-VEGF monoclonal antibody |              | Phase II | Grades 2 and 3                                                       | PFS6 rate of 43.8%              | Nayak et al. 2012                         |
| Bevacizumab                    | Anti-VEGF monoclonal antibody |              | Phase II | Grades 1-3                                                           | PFS6 rate of 77% in grade 2 46% in grade 3 | Grimm et al. 2015                        |
| Bevacizumab                    | Anti-VEGF monoclonal antibody | Case series       | Grades 2 and 3 previ- ous treated with RT | 78.9% of edema improvement | Furuse et al. 2016                        |
| Vatalanib (PTK787)             | VEGF and PDGF receptors inhibitor | Phase II | Recurrent or progres- sive cases                                    | Response rate of 0% PFS6 rate of 64.3% in grade 2 37.5% in grade 3 | Raizer et al. 2014                      |
| Sunitinib                      | Multitarget tyrosine kinase inhibitor | Phase II | Recurrent grades 2 and 3                                            | Response rate of 6% PFS6 rate of 42% | Kaley et al. 2015                        |
| Erlotinib or gefitinib         | EGF receptor inhibitor |                       | Phase II | Recurrent cases                                                       | No significant efficacy PFS6 rate of 29% in grades 2 and 3 | Norden et al. 2010                      |
| Imatinib                       | PDGF receptor inhibitor |                       | Phase II | Recurrent cases                                                       | No significant efficacy PFS6 rate of 0% in grades 2 and 3 | Wen et al. 2009                         |
| Cabozantinib                   | Multitarget tyrosine kinase inhibitor | Case report | Recurrent cases                                                       | Potential                       | Kotecha et al. 2021                      |
| Apatinib                       | VEGF receptor inhibitor |                       | Case series | Recurrent anaplastic case                                             | Potential                       | Wang et al. 2020                         |
| Classification | Drugs            | Mechanism    | Phase | Case                              | Result                        | Study                  |
|----------------|------------------|--------------|-------|-----------------------------------|-------------------------------|------------------------|
| SSTR2A agonist| Octreotide       | Somatostatin agonist | Phase II | Recurrent cases with overexpression of SR | Limited efficacy | Chamberlain et al. 2007 |
|                | Octreotide       | Somatostatin agonist | Phase II | Recurrent cases with overexpression of SR | No significant efficacy | Johnson et al. 2011   |
|                | Octreotide       | Somatostatin agonist | Phase II | Recurrent grade 2 or 3 with positive octreotide SPECT | Limited efficacy | Simo et al. 2014 |
|                | Pasireotide LAR  | Somatostatin agonist | Phase II | Recurrent cases with SR overexpression | Limited efficacy | Norden et al. 2015 |
| PRRT           | ^90Y-DOTATOC     |               | Phase II | SR-positive progressive cases     | PFS6 rate of 78.6% in grade 1 | Bartolomei et al. 2009 |
|                | ^90Y-DOTATOC     |               | Phase II | SR-positive or recurrent cases    | PFS6 rate of 100% in grade 1  | Geyster-Gillieron et al. 2015 |
|                | ^90Y-DOTATOC and |               | Phase II | SR-positive progressive WHO grade 1 | SD of 65.6%, PD of 34.4%       | Marineck et al. 2015   |
|                | Luathera (177Lu-DOTATATE) |             | Phase II | Progressive grades 1-3            | Ongoing                      | NCT03971461            |
|                | Luathera (177Lu-DOTATATE) |             | Phase II | Refractory grades 1-3            | Ongoing                      | NCT03936426            |
| Hydroxyurea    | Hydroxyurea      |               | Phase II | Recurrent grade 1 or 2            | No significant efficacy       | Loven et al. 2004      |
| Hydroxyurea    | Hydroxyurea      |               | Phase II | Recurrent grade 1                 | Limited efficacy              | Weston et al. 2006     |
| Immunotherapy  | Nivolumab/Ipilimumab | PD-1/CTLA4 blocking antibody | Phase II | Recurrent grades 2 or 3           | No significant efficacy PFS6 rate of 42.4% in grades 2 and 3 | Bi et al. 2021 NCT02648997 |
|                | Pembrolizomab    | PD-1 blocking antibody | Phase II | Refractory grades 2 or 3          | Ongoing                      | NCT03016091            |
|                | Pembrolizomab    | PD-1 blocking antibody | Phase II | Recurrent grades 2 or 3           | PFS6 rate of 48% in grades 2 and 3 Median PFS of 7.6 months | Brastianos et al. 2022 NCT03279692 |
|                | Nivolumab/Ipilimumab | PD-1/CTLA4 blocking antibody | Phase II | Recurrent grades 2 or 3           | Ongoing                      | NCT03604978            |
|                | Avelumab         | PD-L1         | Phase II | Recurrent, radiation refractory cases | Ongoing                      | NCT03267836            |
| Progesterone receptor antagonist | Mifepristone | Progesterone receptor antagonist | Phase III | Unresectable grades 1 or 2       | No significant efficacy | Ji et al. 2015 |
|                | Trabectedin      | Trabectedin   | Phase II | Recurrent grades 2 or 3           | No significant efficacy       | Preussuer et al. 2019 EORTC-1320-BTG |

PFS6 6 months progression-free survival, SSTR2A somatostatin receptor 2A, PRRT peptide receptor radionuclide therapy, SD stable disease, and PD progression disease.
mutations are potential targets for the BAP1 inhibitor, tazemetostat.\textsuperscript{37,86} Ribociclib, a CDK 4/6 inhibitor, has been tested in vitro and is currently being tested in recurrent WHO grades 2 and 3 meningiomas with CDKN2A/B homozygous deletion.\textsuperscript{38,85}

The PI3K/AKT/mTOR pathway has recently been shown to be overactivated in the majority of meningiomas with NF2 mutations.\textsuperscript{86,87} Merlin functions as a negative regulator of mTORC1, and its loss is important for NF2-dependent tumorigenesis.\textsuperscript{88,21} These results suggest that mTORC1 may be a promising therapeutic target. Vistusertib (AZD2014), a dual mTORC1-mTORC2 inhibitor, is currently in clinical trials.\textsuperscript{80}

The function of somatostatin receptor 2A (SSTR2A) in meningioma is unknown. However, they are present in almost all meningiomas and are strongly present in 70% of cases.\textsuperscript{91} SSTR2A activation by somatostatin agonist, octreotide, leads to inhibiting meningioma cell proliferation via PI3K/AKT/mTOR pathway inhibition.\textsuperscript{92} Somatostatin agonists were found to be ineffective in the majority of aggressive meningiomas in multiple clinical trials.\textsuperscript{89-91} The CEVOREM study, which combined an mTOR inhibitor, everolimus, and a somatostatin agonist, octreotide, for refractory and progressive meningiomas, revealed a radiographic response in four of 20 patients at 3 months and encouraged PFS at 6 and 12 months of 58.2% and 38%, respectively, with a median follow-up of 12.3 months.\textsuperscript{93} Therefore, additional studies are needed to assess the efficacy of everolimus and octreotide in a randomized trial. A phase II clinical trial with everolimus plus antivascular endothelial growth factor (VEGF) drug, bevacizumab, for the treatment of recurrent or progressive meningioma revealed that stable disease was achieved in 15 of 17 patients.\textsuperscript{94} Furthermore, one of the advantages of everolimus is that it is an oral medication. In vitro data on primary meningioma cell lines have demonstrated caspase-induced cell death mediated by the MEK inhibitor, trametinib. Therefore, alpelisib, a PI3K inhibitor, in combination with trametinib may be effective in meningioma treatment. This combination therapy is currently being studied.\textsuperscript{95}

In the case of AKT1 inhibitor, the AKT1 inhibitor afuresertib (AZD5363) is effective. Afuresertib was used to treat a WHO grade 1 meningioma with AKT1 mutation, which resulted in long-term treated disease control.\textsuperscript{96} According to this study, the AKT1 mutation could be a potential therapeutic target.

SMO mutations cause the sonic hedgehog signaling pathway to be overexpressed. SMO mutations are more common in the anterior skull base of meningiomas.\textsuperscript{97,98} A phase II clinical trial with vismodegib, which is an SMO receptor antagonist, is currently ongoing.

Anti-VEGF drugs remain the most commonly used drugs in aggressive meningiomas today. When compared to WHO grade 1 meningiomas, it is secreted twofold in atypical meningiomas and tenfold in anaplastic meningiomas.\textsuperscript{99-101} Bevacizumab was found to have the most significant tumor growth inhibition effect in recurrent WHO grades 2 and 3 meningiomas and anti-edematous activity in 2016.\textsuperscript{102} PFS6 rates in grades 2 and 3 meningiomas ranged from 43.8% to 77% in several prospective studies.\textsuperscript{93,103} Another study found that bevacizumab showed a significant reduction in volume and peritumoral edema in meningiomas that had been previously treated with radiation therapy. These findings suggest that bevacizumab has an important role in postradiation changes and radiation necrosis.\textsuperscript{104} Future studies should look for more predictors to further determine efficacy. Other anti-angiogenic agents, e.g., vatalanib, an inhibitor of VEGF and platelet-derived growth factor (PDGF) receptors, and sunitinib, a multitargeted tyrosine kinase inhibitor, have shown limited efficacy with response rates of 0% and 6%, respectively,\textsuperscript{105,106} In a phase II trial, erlotinib or gefitinib, an EGF receptor inhibitor and PDGF receptor inhibitor, were investigated. However, no statistically significant changes were noted in PFS or OS.\textsuperscript{104,105} Two new VEGF targeting drugs, cabozantinib and apatinib, have been reported to be active.\textsuperscript{106,107}

**SSTR2A-targeted drug**

Several clinical trials have found that low somatostatin agonists have low activity against aggressive meningiomas.\textsuperscript{89-91} In contrast, the use of somatostatin analog has been shown to slow tumor growth in WHO grade 1 skull base meningiomas.\textsuperscript{108,109} Peptide receptor radionuclide therapy (PRRT) for recurrent meningiomas was proposed based on high SSTR expression. This treatment is designed to specifically target the tumors that express and internalize SSTR2A. Several retrospective studies have been conducted using various agents, e.g., \textit{99m-Y-DOTATOC or 177Lu-DOTATATE, Lutathera.}\textsuperscript{110-116} These findings concluded that PRRT has a promising effect on WHO grades 1 and 2 meningiomas, but is less useful in aggressive WHO grades 2 and 3 meningiomas.\textsuperscript{103} A possible reason is that in aggressive WHO grades 2 and 3 meningiomas, SSTR2A expression is lower than in WHO grade 1 and meningiomas.\textsuperscript{114} Thus, PRRT could be less effective for this group. However, SSTR1 and SSTR5 expressions are higher than in WHO grades 1 and meningiomas.\textsuperscript{114} A broader affinity of substances used for PRRT has the potential to improve the efficacy.\textsuperscript{116} New drugs in the USA, Copper 64 labeled sartate and \textit{177Lu-DOTA-Tyr3-octreotate}, are being investigated.\textsuperscript{117}

**Hydroxyurea**

Hydroxyurea was the first drug proposed for the treatment of meningiomas;\textsuperscript{118-119} it is an oral inhibitor of ribonucleotide reductase. Several clinical trials have been conducted,\textsuperscript{120-122} wherein their findings suggest that hydroxyurea may have potential but uncertain activity in low-grade meningiomas, whereas no significant effect has been reported in WHO grades 2 and 3 meningiomas.
Immunotherapy

The immune system's role in the progression of meningioma has long been suspected. According to studies, the immune microenvironment may have an impact on high-grade meningioma. According to some studies, programmed death-ligand 1 (PD-L1) expression is increased in high-grade meningiomas. However, a phase II clinical trial of PD-1 blocking antibody, nivolumab, in recurrent high-grade meningiomas showed no improvement in PFS6. Most recently, another PD-1 blocking antibody, pembrolizumab, in recurrent high-grade meningiomas showed promising efficacy. Several studies are being done with anti-CTLA4, pembrolizumab, either alone or with the combination of radiation therapy and anti-PD1, PD-L1, or CTLA4 agents. Since meningiomas express different potential immunotherapy targets, e.g., PD-L2, CTLA-4, and B7-H3, it has been suggested that the combination of immunotherapy with radiotherapy or targeted therapy may improve the local immune response.

Progesterone receptor antagonist (mifepristone)

Progesterone receptor (PR) expression is found in 70% of meningiomas. PR is strongly expressed in low-grade meningiomas, while the PR expression is reduced in high-grade meningiomas. Although PR was expected to be a potential therapeutic target for growth inhibition, a randomized double-blind placebo-controlled phase III trial concluded that the PR antagonist, mifepristone, lacked efficacy.

Trabectedin

Trabectedin binds to the minor groove of the DNA double helix. It affects several transcription factors and DNA repair mechanisms and has immunomodulatory and antiangiogenic effects. It is currently approved for advanced soft tissue sarcoma and ovarian cancer. Trabectedin suppressed meningioma cells from WHO grades 2 and 3 meningiomas through multiple mechanisms, and a favorable response was observed in a patient with recurrent anaplastic meningioma treated with trabectedin. However, in the EORTC Brain Tumor Group's randomized phase II trial (EORTC-1320-BTG), trabectedin did not improve overall survival in recurrent WHO grades 2 and 3 meningiomas.

Conclusion

Meningiomas' molecular biological characteristics have been clarified. Furthermore, several new comprehensive classifications of meningiomas based on these molecular biological features have been proposed. These classifications are expected to provide a more accurate prognosis than the traditional WHO classification and to influence treatment strategies for refractory aggressive meningiomas. Future systemic drug therapy research, including molecular targeted therapies, is also expected to be developed.

Ethical Approval and Informed Consent

No informed consent was required in this study because no humans were directly involved.

Conflicts of Interest Disclosure

None

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