Latest classification of ependymoma in the molecular era and advances in its treatment: a review

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Running head

Classification and treatment of ependymoma

Abbreviation

WHO, World Health Organization; CNS, Central Nervous System; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; AYA, Adolescent and young adults; OS, Overall Survival; NEC, not elsewhere classified; NOS, not otherwise specified; GTR, gross total resection; CCG, Children's Cancer Group; CSI,

cerebrospinal irradiation; AIEOP, Associazione Italiana Ematologia Oncologia Pediatrica; HFRT, hyper-fractionated irradiation; VEC, Vincristine, Etoposide, and Cyclophosphamide; CR, complete response; PR, partial response; TMZ, temozolomide; SD, stable disease; PD, progressive disease; GMCI, gene-mediated cytotoxic immunotherapy; CAR-T, Chimeric antigen receptor T-cell

Abstract

Ependymoma is a rare central nervous system tumor occurring in all age groups and is one of the most common pediatric malignant brain tumors. Unlike other malignant brain tumors, ependymomas have few identified point mutations and genetic and epigenetic features. With advances in molecular understanding, the latest 2021 World Health Organization (WHO) classification of central nervous system tumors divided ependymomas into 10 diagnostic categories based on the histology, molecular information, and location; this accurately reflected the prognosis and biology of this tumor. Although maximal surgical resection followed by radiotherapy is considered the standard treatment method, and chemotherapy is considered ineffective, the validation of the role of these treatment modalities continues. Although the rarity and long-term clinical course of ependymoma make designing and conducting prospective clinical trials challenging, knowledge is steadily accumulating and progress is being made. Much of the clinical knowledge obtained from clinical trials to date was based on the previous histology-based WHO classifications, and the addition of new molecular information may lead to more complex treatment strategies. Therefore, this review presents the latest findings on the molecular classification of ependymomas and advances in its treatment.

Mini-abstract

This review summarizes the latest findings on the molecular classification of ependymomas and advances in its treatment.

Keywords

Ependymoma**,** Molecular Pathology, DNA Methylation, Multimodal Treatment

Introduction

Ependymoma is a neuroepithelial tumor that has a tendency to differentiate into ependymal cells that make up the ventricular walls and the central canal of the spinal cord. Although it has been reported that the radial glia produced during the embryonic period are the origin of the disease, yet the origin of ependymoma is not well understood(1). Ependymoma begins in the central nervous system (CNS), including the spinal cord. Ependymoma is a rare tumor that occurs in all age groups, accounting for 1.6% of all brain tumors and 5.4% of pediatric brain tumors, being one of the most frequent pediatric brain tumors (2). Ependymomas are a heterogeneous tumors; however, not all associated oncogenic drivers have been identified, and unlike other CNS tumors, pathogenic point mutations are rare, and fusion genes and copy number abnormalities play important roles in its tumorigenesis (3). Although the progression of ependymomas is not rapid, there are many cases of recurrence and dissemination after initial treatment. Surgery and radiotherapy have been the mainstay of treatment for chemo-resistant tumors; however, recent clinical trials have reassessed the role of chemotherapy. With the introduction of molecular classification, the classification of ependymomas has become more complicated according to the latest 2021 World Health Organization (WHO) classification of CNS tumors, which may make treatment strategies become more complicated in the future (4). This review aimed to present the latest molecular findings and therapeutic directions for intracranial ependymomas.

Classification

Ependymoma was once classified based only on histological findings; however, with a progressive understanding of the molecular landscape, molecular information

was incorporated into the diagnosis of ependymoma for the first time in the 2016 WHO classification of CNS tumors (5). However, because of the poor correlation between tumor grading and outcome remains a problem (6, 7) and it has been found that ependymomas can be classified into distinct subgroups through DNA methylation profiling (3, 8), the latest 2021 WHO classification of CNS tumor adopted a classification based on histological findings, genetic abnormalities, DNA methylation patterns, and anatomical sites (4). The 2021 WHO classification of CNS tumor eliminated “anaplastic ependymoma” and introduced several new entities. As with other CNS tumors, this classification was based on an integrated diagnosis that incorporated histological and molecular diagnoses. The WHO grades were assigned based on histological findings (grades 1–3). Unlike other CNS tumors, point mutations are rare in ependymomas and are only marginally found in a few subgroups. Instead, fusion genes that define specific entities and several patterns of copy number abnormalities are found. Another challenge is that an accurate classification requires advanced gene analysis technologies, including methylation analysis and the use of surrogate markers. The 2021 WHO classification of ependymomas is summarized in Table 1.

Supratentorial ependymoma, ZFTA-fusion positive

Supratentorial ependymoma, *ZFTA*-fusion positive is diagnosed when supratentorial tumors present with ependymoma-like morphological and immunohistochemical features and gene fusion involving *ZFTA* (*C11orf95*) occurs (4). This entity is including *RELA*-fusion positive ependymoma according to the 2016 WHO classification of CNS tumors. Its degree of histologic atypia varies, and it is assigned grade 2 or 3 depending on histological findings; however, most cases have

a grade 3 histology (9, 10). The *ZFTA* fusion gene is considered an oncogenic driver that induces the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway (11). Immunostaining for L1CAM, p65, and cycline D1, whose expression are induced downstream of the NF-KB pathway activated by *ZFTA*-fusion gene, are useful as surrogate markers. p65 is highly specific (93.8%) and L1CAM is highly sensitive (92.3%) (12). The *ZFTA* fusion gene is not a genetic abnormality specific to supratentorial ependymoma and although it is rare, it has been detected in the posterior fossa and spinal ependymoma (3, 13). *ZFTA* forms a fusion gene mainly with *RELA*. However, other fusions with *MAML2, MAML3, NCOA1*, and *NCOA2* have also been reported (14). Non-*RELA*-*ZFTA* fusion has worse progression-free survival (PFS) than *RELA*-*ZFTA* fusion (15). In all fusion patterns, the DNA-binding domain of *ZFTA* and the transcriptionally active domain of its partner must be conserved; experiments involving mice have shown that *GLI1*, which is commonly upregulated by any *ZFTA* fusion gene, is important for tumorigenesis (14). Supratentorial ependymoma, *ZFTA*-fusion positive accounts for approximately 70% of all supratentorial ependymomas occurring in all age groups, with the highest occurrence among the adolescent and young adults (AYA) generation (3). Although the prognosis of supratentorial ependymoma, *ZFTA*-fusion positive is considered poor (3), it is no longer necessarily a poor prognostic subgroup, as several retrospective analyses and a recent prospective clinical trial have shown that *ZFTA*-fusion gene does not affect prognosis (9, 16-19). *CDKN2A/B* homozygous deletion in 16% of supratentorial ependymomas, *ZFTA*-fusion positive have been reported to be independent poor prognostic factor (20).

Supratentorial ependymoma, YAP1-fusion positive

Supratentorial ependymoma, *YAP1*-fusion positive is diagnosed when

supratentorial tumors present with ependymoma-like morphological and immunohistochemical features and gene fusion involving *YAP1* occurs (4). It is a newly established entity, according to the 2021 WHO classification. It is characterized by a well-defined cystic lesion. It occurs primarily in infants and is extremely rare among adults, accounting for approximately 6–7.4% of all supratentorial ependymomas (3, 21, 22). Its degree of histologic atypia varies, and it is assigned grades 2 or 3 depending on histological findings. A fusion protein, mainly MAMLD1 fused with YAP1, a Hippo pathway regulator, functions as an oncogenic driver by recruiting TEADs and NF1s (23). Unlike the *ZFTA*-fusion positive supratentorial ependymomas, no coexisting genetic abnormalities other than the *YAP1*-fusion gene have been identified in supratentorial ependymomas, *YAP1*-fusion positive (3, 23, 24). Its prognosis is good, with a 5-year overall survival (OS) of 100% when gross total resection (GTR) was achieved (3, 17).

Supratentorial ependymoma

Supratentorial ependymoma is diagnosed when supratentorial tumors present with ependymoma-like morphological and immunohistochemical features and the detected genetic alteration is not a fusion gene involving either *ZFTA* (*C11orf95*) or *YAP1* for not elsewhere classified (NEC), or genetic analysis was unsuccessful or unfeasible for not otherwise specified (NOS) (4). A detailed study of ependymomas with non-*ZFTA*-fusion gene revealed various gene alterations other than *YAP1*-fusion, including *BCOR* tandem duplication, *EP300-BCORL1* fusion, and *FOXO1-STK24* fusion. Supratentorial ependymoma is a suspected entity in cases involving tumors that are not ependymoma but exhibit histological features similar to those of ependymoma (9, 16, 22).

Posterior fossa group A ependymoma (PFA-EPN)

PFA-EPN is diagnosed when posterior fossa tumors present with ependymoma-like morphological and immunohistochemical features and there is reduction in H3K27Me3 in tumor cell nuclei or DNA methylation profile aligned with PFA-EPN (4). Immunostaining for H3K27Me3 is considered a robust surrogate marker; however, its results should be interpreted with caution because varying degrees of staining can be observed (17, 25, 26). A cut-off value of 80% immunopositive cells has been suggested (26). PFA-EPN occurs predominantly in children (median age, 3 years), and accounts for almost all of the posterior fossa ependymomas cases in children aged < 4 years (3, 27, 28). It tends to include lateral extension of the posterior fossa and cerebellar invasion, making total surgical resection more difficult in most cases than in PFB-EPN (27). It has a poor prognosis, particularly in cases with 1q gain or 6q loss (independent poor prognostic factors), which occurs in 25% and 8.6% cases of PFA-EPN, respectively (3, 17-19). Furthermore, the prognosis of cases with 6q loss is reportedly poorer than that of cases with 1q gain. In some cases, 1q gain and 6q loss may coexist, leading to a particularly poor prognosis (29).

Posterior fossa group B ependymoma (PFB-EPN)

PFB-EPN is diagnosed when posterior fossa tumors present with ependymoma-like morphological and immunohistochemical features and DNA methylation profile aligns with PFB-EPN (4). PFB-EPN is characterized by H3K27Me3 retention, which is not a specific observation as it has been observed in sub-ependymomas. PFB-EPN occurs in all age groups; however, it is more common among the AYA generations and adults. Its degree of histologic atypia varies, and it is assigned grade 2 or 3 depending on histological findings; however, most cases present with grade 2 histology. Compared to other subgroups, it is characterized by a high degree of genomic instability, accompanied by many copy number aberrations and

indistinguishable oncogenic drivers (3, 30). It occurs mainly in the medial posterior fossa and can be completely removed in many cases with a good prognosis (30).

Posterior fossa ependymoma (PF-EPN)

PF-EPN is diagnosed when posterior fossa tumors present with ependymoma-like morphological and immunohistochemical features, morphological features of subependymoma are absent, and molecular group evaluation was indeterminate, generated no result, or was not feasible for NOS (4). PF-EPN, NEC is diagnosed when result of proper molecular analysis is not specific for a molecular group. Pratt et al. reported a case of posterior fossa ependymoma with *ACVR1* gene mutation and a DNA methylation pattern that did not belong to either PFA-EPN or PFB-EPN subgroups (31). In adult cases of histologically diagnosed PF-EPNs, those classified as subependymoma by DNA methylation analysis have been observed.

Spinal ependymoma (SP-EPN)

SP-EPN is diagnosed when spinal tumors present with ependymoma-like morphological and immunohistochemical features and the morphological features of myxopapillary ependymoma and subependymoma are absent (4). It accounts for 20.6% and 17 % of primary spinal tumors in children and adults, respectively (2). It occurs in 33–53% of patients with neurofibromatosis type 2, most often in the transition zone of the medullary cervical cord, shows an indolent growth pattern, and does not require surgery (32, 33). In experiments involving mice, increased proliferative capacity and decreased apoptosis of embryonal spinal cord neural progenitors were observed upon NF2 inactivation, suggesting that *NF2* is an important driver of SP-EPN (34). Loss of 22q containing *NF2*, was observed in approximately 90% of cases, perhaps reflecting the role of the inactivation of NF2 functions as an oncogenic driver (3). Its prognosis is good, particularly in cases

which GTR was achieved (35, 36).

SP-EPN, MYCN-amplified

SP-EPN, *MYCN*-amplified is diagnosed when spinal tumors present with ependymoma-like morphological features and *MYCN* amplification is observed (4). SP-EPN, *MYCN*-amplified, is very rare, with only 27 cases reported to date (37-39). It occurs in the cervical or thoracic spinal cord in young adults with a poor prognosis. Dissemination occurred in all the reported cases. The median PFS and OS were 17 months and 87 months, respectively (39). Although *MYCN* regulates the expression of genes involved in cellular growth, and its amplification accelerates tumor growth, the role of *MYCN* amplification in SP-EPN development is unknown. *MYCN* amplification is not specific to SP-EPN because it is present in pediatric-type glioblastomas, neuroblastoma, and medulloblastoma, non-WNT/non-SHH (Group 4) (40-43).

Myxopapillary ependymoma

Myxopapillary ependymoma is diagnosed when gliomas present with papillary structures and perivascular myxoid changes or at least focal myxoid microcysts, immunoreactivity for GFAP, and DNA methylation profile aligning with myxopapillary ependymoma is observed (4). Most cases occur in the conus medullaris and filum terminale; however, they can occur intracranially and in the spinal cord (44-47). Its prognosis is good with a 9-year OS rate exceeding 90% (48). However, approximately 20% of cases recur, and disseminated disease may occur (48). Various degrees of chromosome copy number loss have been reported, including a gain in chromosome 16 and loss of chromosome 10, and chromosome-wide and arm-wide copy number abnormalities are common. No structural abnormalities or driver mutations have been identified (3, 21).

Subependymoma

Subependymoma is diagnosed when circumscribed gliomas present with clustered tumor cell nuclei within expansive, focally, microcystic fibrillary matrix, there is lack of conspicuous nuclear atypia, absent or minimal mitotic activity, and DNA methylation profile aligning with subependymoma is observed (4). It is assigned grade 1 according to the WHO classification. Although it can occur at any CNS site, the fourth ventricle is the most common site, followed by the lateral ventricles. When it occurs in the spinal cord, it is most often in the cervicothoracic segment. Childhood occurrence is rare, with a peak onset at 40–84 years of age (49). Its prognosis is good with approximately 90% 9-year OS rate (49). Some cases histologically present as PF-EPN grade 2 but are molecularly classified as subependymoma by DNA methylation analysis. The prognosis of this molecularly defined posterior fossa subependymoma is reportedly not as good as that of histologically defined subependymoma (9, 21). Loss of chromosome 19 is commonly observed, especially in posterior fossa subependymomas, whereas partial loss of chromosome 6 may be observed in posterior fossa and spinal subependymomas. There are subsets that harbor germline or somatic lineage of *TRPS1* mutations (21, 50). The pathogenesis nor prognostic relevance of these molecular abnormalities are clear.

Current and advanced treatment of ependymoma

The basic treatment strategy for primary intracranial ependymomas is maximal surgical resection followed by postoperative radiation therapy. Several prospective clinical trials have been conducted on pediatric intracranial ependymomas and information on its treatment has been accumulated; however, prospective clinical trials for adult intracranial ependymomas are scarce owing to the small number of cases. Major prospective clinical trials on pediatric ependymoma are summarized in

Table 2.

Clinical trial on pediatric intracranial ependymoma

Prospective clinical trials conducted by the Children's Cancer Group (CCG) and the German Pediatric Society for Hematology and Oncology were initiated in the 1980s. The CCG921 trial included malignant brain tumors such as primitive neuroectodermal tumor, medulloblastoma, pineoblastoma, ependymoblastoma, anaplastic ependymoma, and central neuroblastoma, using cerebrospinal irradiation (CSI) and intensive chemotherapy as initial treatment approaches (51).The only prognostic factor detected was the extent of resection, suggesting that intensive chemotherapy and CSI were not effective for ependymomas. The German HIT trial on medulloblastomas and anaplastic ependymomas performed intensive chemotherapy before and after CSI (52). Based on the results of these two trials, the prospective clinical trials of the CCG and Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) initiated in the 1990s adopted stratification by resectability and administered chemotherapy before radiotherapy to patients with residual tumors. AIEOP attempted hyper-fractionated irradiation (HFRT) to increase dose locally; however, the 5 year-PFS and OS were 56% and 75%, respectively, and the effectiveness of HFRT could not be demonstrated (53). In both clinical trials, the effect of chemotherapy before radiotherapy on the prolongation of PFS and OS was unclear and the significance of chemotherapy could not be demonstrated (53, 54). In a single-center prospective study conducted at St. Jude Children's Research Hospital, the GTR rate improved to 81.7% by performing second-look surgery in patients with residual tumors after the initial surgery, without stratification, and without chemotherapy (55), resulting in an excellent 7-year PFS and OS rates of 69.1% and 81.0%, respectively. In the study, 43.1% of patients underwent two or

more surgeries. The result of the study was a turning point in the treatment of ependymoma, supporting the importance of increasing the rate of GTR, even with multiple surgeries, for residual tumors after initial surgery. Three prospective clinical trials initiated in the 2000s are presented. The AIEOP prospective clinical trial enrolled 160 pediatric patients with intracranial ependymomas stratified by the extent of resection and grade, patients with grade III intracranial ependymoma with GTR receiving maintenance chemotherapy after radiotherapy, and patients with grade II intracranial ependymoma with GTR receiving radiotherapy only (56). Patients with residual tumors after initial surgery were treated with chemotherapy before radiotherapy. After chemotherapy, they underwent second-look surgery if possible and were subsequently treated with radiotherapy, including boost irradiation. A high total resection rate of 69% was achieved during the first surgery, and 23 patients achieved GTR after additional surgery. The PFS for patients with residual tumors (58.1%) who received boost irradiation was not significantly different from that of those who do not receive boost irradiation; however, it was superior to that of previous reports that supported the efficacy of boost irradiation. The significance of maintenance chemotherapy in patients with grade III ependymoma with GTR was unclear. Although different from previous reports, the WHO grading system was found to be a prognostic factor in multivariate analysis. It is a reliable grading with central pathological review that can be impacted by sample size. ACNS 0121, reported in 2019 by the Children Oncology Group (COG), enrolled the largest number of cases to date (n = 356) (18). Stratification was performed based on the extent of resection, grade and location. Radiotherapy was omitted for supratentorial classic (grade II) ependymomas with GTR, and although the number of patients enrolled was small (n=11), good results were reported, with 5-year PFS and OS

rates of 62.7% and 100%, respectively. There were no significant differences in PFS and OS between patients aged < 3 and > 3 years, supporting immediate postoperative radiotherapy in patients aged > 1 and < 3 years. Patients with residual tumors were treated with chemotherapy and underwent a second-look surgery, if possible. Second-look surgery was performed in 39% of the patients with residual tumors, of which 56% underwent GTR. In this trial, molecular analysis was performed, and the *RELA*-fusion did not affect prognosis. A clinical trial by the International Society of Pediatric Oncology reported in 2022 (17) that stratification by the extent of resection was adopted, and patients with residual tumors were treated with Vincristine, Etoposide, and Cyclophosphamide (VEC) regimen and second-look surgery was performed if necessary. In 74 patients, a lower GTR rate and slightly inferior outcomes compared to those of previous clinical trials were observed. The VEC regimen administered before radiotherapy demonstrated high complete response (CR) (31%) and partial response (PR) (34.5%) rates. Molecular analysis was also performed, and although classification by DNA methylation profiling showed no significant difference in prognosis, DNA methylation analysis was not performed in all cases, and the small number of analyzed cases might have influenced the results.

The rarity of ependymomas makes it difficult to conduct randomized controlled trials with sufficient numbers of patients to detect significant differences, and a standard treatment has not yet been established. Based on the results of clinical trials to date, there seems to be a consensus that CSI is unnecessary, local irradiation is sufficient, the extent of resection is the most important factor affecting prognosis, and GTR rate before radiotherapy should be improved, even if second-look surgery is performed. The significance of chemotherapy is not clear; however,

there is support for its preoperative use to improve the extent of resection by second-look surgery. There is no consensus on the regimen that should be adopted; however, intensive regimens performed for medulloblastoma are unnecessary. VEC regimen has been employed in several clinical trials to date with reported good responses.

Surgery for ependymoma

Clinical trials have demonstrated that maximal surgical resection is the most prognostic factor for ependymoma (considered a “surgical disease”) treatment (17-19, 51-56). Even if GTR cannot be achieved during the initial operation, prognosis improves if GTR can be achieved in multiple subsequent surgeries. To increase the GTR raste in second-look surgery, postoperative chemotherapy, central reviews and recommendations are being attempted (17, 18, 54, 55, 57-59). The definition of the extent of resection differs from that used in clinical trials. Some reports considered residuals less than 5 mm, the largest dimension, to be NTR. The St. Jude trial distinguished between NTR and GTR, and reported a significant difference in their prognosis; however, ACNS0121 reported comparable outcomes for GTR and NTR (18, 55, 56). In addition, a 90% removal rate and a postoperative lesion size of <1.5 cm^2 are defined as cutoffs for residual disease, and a better prognosis than that of the residual group has been reported (53, 54). CCG9942 indicated that patients with 90–99% removal rate may benefit from postoperative chemotherapy (54). There is no doubt that GTR is the most important prognostic factor; however, comparable outcomes have been reported with NTR, and postoperative complications should be avoided by aiming for microscopic GTR.

Radiotherapy for ependymoma

The efficacy of radiotherapy has been validated in previous prospective and

retrospective studies (55, 60-62). Irradiation of the tumor bed with 54–59.4 Gy (1.8 Gy/Fr) has been advocated (63). Owing to the lack of efficacy of chemotherapy and limited localization of the irradiation field, 59.4 Gy (1.8 Gy/Fr) is used in patients aged >18 months and doses of 54 Gy (1.8 Gy/Fr) in patients aged 12–18 months (18, 19, 63). Younger children have a higher proportion of biologically poor prognoses for PFA-EPN; therefore, irradiation is considered necessary even in children aged < 3 years. In children, Merchant et al. reported a statistically significant correlation between the mean dose in the posterior fossa and a decline in cognitive function (IQ, calculation, writing and reading); however, the risk was small (64). Conklln et al. found a significant decrease in reading with conformal radiotherapy with stable intellectual functioning, and reported that supratentorial lesions and multiple surgeries were predictive factors for worse reading (65). Proton therapy has the advantage of reducing radiation exposure to the normal tissue surrounding the tumor, which may prevent posttreatment neurological damage. Shannon et al. reported results comparable to those of previous conformal radiotherapy, with little toxicity and no brain stem necrosis in their experience with proton therapy in 70 pediatric ependymomas (66).

Treatment for ependymoma in adult

Owing to the rarity of ependymomas in adult, no prospective studies have been conducted, and most treatment information is based on retrospective studies. Adult ependymomas differ from pediatric ependymomas because they include subependymomas. Ependymomas of the posterior fossa in adults are mainly PFB-EPN and subependymoma, composed of subgroups with a good biological prognosis, and require different treatment strategies than pediatric ependymomas. Current standard treatment for grade III ependymomas and grade II ependymomas

with residual tumors is maximal surgical resection followed by radiotherapy (63, 67). Mattellus et al. reported 152 cases of ependymoma in adult enrolled from multiple centers in France; 71.7% of the enrolled cases were grade II (60). Total resection was achieved in 58.6% of the cases, and no radiotherapy was administered to patients with low-grade histology and GTR. The 5-year PFS and OS rates were 63.5% and 84.8%, respectively, and multivariate analysis detected grade, the extent of resection, and the Karnofsky Performance Status as prognostic factors. Radiotherapy appears to be effective for grade II ependymomas with residual tumors and grade III ependymomas with GTR. Nuno et al. reported a large sample of 1318 adult intracranial ependymomas registered in the USA National Cancer Database (68). Of the cases, 80% were grade II. Both GTR and NTR were low accounting for 36.8%, with biopsy accounting for 44% of the total. In this study, 49.2% patients did not receive postoperative radiotherapy and there was no prognostic impact of radiotherapy regardless of the grade or extent of resection (HR = 0.81 95% CI: 0.56–1.19, p = 0.29). The posterior fossa ependymoma prognosis was better than that of supratentorial ependymoma (HR = 0.64 95% CI: 0.43–0.97, p = 0.04), suggesting that posterior fossa ependymoma in adult comprised PFB-EPN with a good prognosis. Although the extent of resection is undoubtedly important, the importance of second-look surgery is not emphasized as much as in pediatric ependymomas, because there are subgroups with a good prognosis in adult cases of ependymomas, and even if there is a residual tumor, the outcome is good with postoperative radiotherapy.

Treatment for Recurrent Intracranial ependymoma

A standard treatment for recurrent ependymomas is yet to be established. However, surgical resection and re-irradiation are validated options in cases where

GTR is achieved postoperatively, and has been reported to have improved prognosis (60, 66-72). Conventional fractionated, stereotactic, and proton irradiation has been reported to be effective (69-72). Adolph et al. reported that patients who underwent GTR after recurrence had a significantly better prognosis than those who did not (5-year OS, 48.7% vs. 5.3%) and that the benefit of re-irradiation was limited to those who did not undergo GTR (73).

Several prospective and retrospective clinical trials have tested the efficacy of chemotherapy for recurrent ependymomas. The efficacy of temozolomide (TMZ), widely used for the treatment of malignant gliomas and recurrent ependymomas, has been tested. Adolpf et al. examined the efficacy of TMZ, oral etoposide, and trofosfamide in 53 pediatric patients with recurrent intracranial ependymomas and found no benefit in most cases, although some responded to TMZ (73). Komori et al. used TMZ in two pediatric patients with recurrent anaplastic ependymoma with low MGMT expression and reported 7-month of CR and prolonged stable disease (SD) for 15 months (74). Ruda et al. treated 18 adult patients with recurrent ependymoma with TMZ, using the maintenance protocol performed for malignant glioma, with a good response rate of 61% including SD, and median PFS and OS of 9.69 and 30.55 months, respectively (75). Methylation of the MGMT promoter was observed in half of the patients, but there was no correlation with response. Gilbert conducted a phase 2 trial on dose-dense TMZ in combination with lapatinib for adult recurrent ependymoma, including SP-EPN (76). Fifty patients were enrolled, with two CR and six PR. The PFS rates at 6 and 12 months were 55% and 38%, respectively, indicating good antitumor activity. However, spinal ependymomas accounted for half of the enrolled cases, and grade 1 cases accounted for 18.2%. Based on the results of these studies, TMZ may have some effect on recurrent ependymomas in adults.

Robinson et al. conducted a phase 2 trial of a metronomic therapy consisting of celecoxib, thalidomide, fenofibrate, low-dose cyclophosphamide, and etoposide for the treatment of recurrent and advanced cancer in children. Clinical benefits, including PR and prolonged SD were observed in 97 patients that were treated, including 19 with ependymomas. (77)

The use of molecular-targeted drugs has been considered. Given the high expression of EGFR, HER2, and HER4 in pediatric ependymomas and their correlation with poor prognosis (78-80), Jakacki et al. conducted a randomized trial to test the efficacy of erlotinib, an EGFR tyrosine kinase inhibitor, versus oral etoposide and found no benefit with erlotinib, whereas oral etoposide was effective in some cases (81). DeWire et al. tested the efficacy of lapatinib, an EGFR and HER2 dual tyrosine kinase inhibitor, in combination with bevacizumab and did not observed any benefit. ACNS1021 tested the safety and efficacy of sunitinib, a multi-targeted receptor tyrosine kinase inhibitor, in recurrent pediatric ependymomas in a phase 2 clinical trial and found no efficacy (82). Cash et al. conducted a phase 1 study of prexasertib (LY2606368), a selective dual inhibitor of CHK1 and CHK2, in pediatric patients with relapsed/refractory solid tumors, including CNS tumors, including one case of ependymoma among 30 patients and could not observe any benefit (83). Bukowlnski conducted a phase 1 study of entinostat, a histone deacetylase inhibitor, in children and adolescent patients with relapsed/refractory solid tumors, including CNS tumors; two of 21 patients had ependymoma, one had SD, and the other had progressive disease (PD) (84). Qayed et al. conducted a phase 1 study of sirolimus, an mTOR inhibitor, in combination with metronomic therapy in pediatric patients with relapsed/refractory solid tumors, including CNS tumors, and confirmed the tolerability of sirolimus; however, approximately half of the patients had PD during treatment

(85). A phase 2 clinical trial of everolimus, an mTOR inhibitor, is currently ongoing (NCT02155920). Cole et al. conducted a phase 1 trial of adavosertib, a Wee1 inhibitor, in combination with irinotecan in pediatric patients with relapsed solid tumors (86). Four of 27 patients had ependymomas, and tolerability was confirmed in one ependymoma case with prolonged SD. In a pilot study, Sandberg et al. tested the efficacy and acceptability of 5-azacytidine, a DNA methylation inhibitor, by infusing it into the fourth ventricle or tumor resection cavity to treat recurrent posterior fossa ependymoma in children (87). All five patients treated with 5-azacytidine had PD; however, two had partial residual tumor shrinkage. Other Phase 1 clinical trials of 5-azacytidine are currently ongoing (NCT04958486 and NCT03572530).

The efficacy of immunotherapy was also investigated. Pasqualini et al. tested the efficacy of nivolumab, a PD-1 inhibitor, in combination with metronomic cyclophosphamide in pediatric patients with relapsed/refractory cancer, including one patient with ependymoma (88). There was an unconfirmed PR and prolonged SD; however, no overall efficacy was observed. Cacciotti et al. reported their institution's experience with immune checkpoint inhibitor in pediatric patients with relapsed/refractory CNS tumors (89). Ipilimumab, CTLK4 inhibitor, and nivolumab were administered in combination for recurrent anaplastic ependymoma, and SD was maintained for 18 months. A phase 1 trial of pembrolizumab, a PD-1 inhibitor, is currently ongoing and includes patients with recurrent ependymomas (NCT02359565). Khatua et al. conducted a phase 1 trial of intraventricular infusion of autologous natural killer cells in children with recurrent medulloblastoma and ependymoma; although tolerability was confirmed, most children had PD during treatment (90). Kieran et al. conducted a phase I trial of gene-mediated cytotoxic

immunotherapy (GMCI) with aglatimagene besadenovec (Adv-tk) in pediatric malignant glioma and recurrent ependymoma after surgery and radiotherapy, and confirmed its tolerability (91). One patient with recurrent ependymoma showed long-term PFS and OS; however, the efficacy of GMCI was uncertain because the ependymoma was supratentorial and had been totally resected before treatment. Chimeric antigen receptor T-cell (CAR-T) therapy has proven to be effective in hematological cancers and is a promising treatment option. Since ependymomas show tumor-specific expression of ephrin type-A receptor 2, HER2, and interleukin-13 receptor subunit alpha-2, CAR-T therapy targeting these proteins is currently being tested (NCT04661384 and NCT04903080). Although not a drug therapy, a phase 1/2 trial of Novo-TTF, which has been shown to be effective for glioblastoma, is ongoing (NCT03033992) and includes patients with recurrent ependymomas. Many clinical trials are in phase 1, and results from phase 2 and beyond are expected.

Conclusions

Molecular classification was introduced for ependymomas, making its classification more complex but accurately reflecting its prognosis and biology. However, poor prognostic molecular markers, exceptions, and the problems of the current molecular classification system have been identified and need to be reviewed. The latest classification requires advanced molecular analyses and more convenient surrogate markers may be required for widespread clinical use. Maximal surgical resection is crucial to achieve the best outcomes in the treatment of any of the ependymoma classified entities. Chemotherapy, once thought to be ineffective, is being given a new role; its effectiveness as a bridge to second-look surgery or as

maintenance treatment will become clear. Although the outcome of recurrent ependymomas remains unsatisfactory, new therapeutic approaches are emerging, and the efficacy of molecular-targeted drugs, immunotherapy, and alternating electric field therapy will hopefully be demonstrated in future clinical trials.

Conflict of Interest Statement

The authors declare no Conflict of Interest for this article.

Funding

This work received no specific grant from any funding agency.

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