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Review

New Treatment Paradigm for Patients with Anaplastic Oligodendroglial Tumors

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Abstract. *Oligodendrogliomas are uncommon tumors in neurooncology that represent about 5% of primary brain malignancies. Their high sensitivity to radiotherapy and chemotherapy was observed a long time ago. Nonetheless, the evidence-based proof of the significantly longer survival in patients with oligodendrogliomas treated with combined chemotherapy and radiotherapy in comparison to radiotherapy-alone did not exist. The long-term follow-up of two landmark phase III clinical trials: RTOG 9402 and EORTC 26951, recently demonstrated favorable effects of combined radiotherapy and chemotherapy (procarbazine, lomustine and vincristine) in patients with anaplastic oligodendrogliomas and anaplastic oligoastrocytomas carrying the chromosomal mutation of co-deletion of 1p/19q. There is also an increasing role of other molecular biomarkers, such as mutations in the metabolic enzyme isocitrate dehydrogenase 1/2, O6-methylguanine DNA methyltransferase gene promoter methylation, or glioma genome cytosine-phosphate-guanine islands methylator phenotype. The analysis of molecular genetics in oligodendrogliomas is now recommended as an important part of the management of these tumors and together with the novel chemotherapeutic regimens means a paradigm shift in current clinical practice in neurooncology.*

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Oligodendroglial tumors (oligodendrogliomas, oligoastrocytomas) represent approximately 5% of primary brain tumors. What sets them apart from other types of malignant gliomas is their more favorable response to radiotherapy and chemotherapy. According to the 2007 WHO classification of tumors of the central nervous system, they are characterized by a histopathological finding with an oligodendroglial component (1). However, the current WHO classification does not reflect on the molecular genetic characteristics of tumors. Research into molecular genetics of oligodendrogliomas offers new knowledge in the diagnosis and treatment of these tumors, and together with results from clinical studies, has an impact on management. The treatment paradigm of oligodendroglial tumors was recently changed, reflecting on the long-term results of two large independent phase III clinical trials, The Radiation Therapy Oncology Group (RTOG) 9402 and European Organisation for Research and Treatment of Cancer (EORTC) 26961. The analysis of molecular genetics in oligodendrogliomas is now well-established and recommended as an important part of treatment-decision algorithms in clinical practice. This review presents an overview of novel therapeutic approaches for patients with oligodendroglial tumors, primarily in regard to anaplastic oligodendrogliomas.

Diagnosis and Standard Treatment of Oligodendrogliomas

Oligodendroglial tumors can be differentiated by degree of malignancy into grade II and grade III oligodendrogliomas–anaplastic oligodendrogliomas (AO). Only about 30% of oligodendroglial tumors have anaplastic characteristics in the histopathological image: nuclear atypia, increased cellularity, increased proliferation activity and increased cell mitosis. Typical histopathological findings are round nuclei with a light or empty cytoplasm in the vicinity (perinuclear 'halo' effect) and the presence of microcalcification (1). AO

comprise about 0.5-1.2% of primary brain tumors (2, 3). The highest incidence of AO is between 45 and 50 years of age; grade II oligodendroglioma afflicts patients from seven to eight years younger. It is presumed that this difference corresponds to the progression from tumor grade II to grade III. The majority of oligodendrogliomas present with an epileptic seizure. The most frequent other symptoms affect the frontal and, in some cases, the temporal regions. Infiltrative growth and poorly defined perifocal edema later cause symptoms of intracranial hypertension.

The standard therapy of oligodendrogliomas includes neurosurgery and oncological treatment: radiotherapy and chemotherapy. Radiotherapy is administered to a total dose of 54 to 60 Gy. Chemotherapy is administered in a triple combination of procarbazine, lomustine and vincristine (PCV) or temozolomide (4, 5). The sensitivity to radiotherapy of oligodendrogliomas was discovered as early as the 1980s (6), and the positive effect of chemotherapy, PCV and temozolomide, was found later (7-9).

Neurosurgery is fundamental to remove the tumor and obtain neoplastic tissue in order to make a precise diagnosis. Total resection of the tumor is considered optimal. Sophisticated diagnostic preoperative and perioperative methods (magnetic resonance imaging - MRI, use of 5-aminolevulinic acid, MRI tractography, perioperative ultrasound and MRI, awake surgical method, hybrid positron emission tomography and computed tomography - PET/CT) and navigated microsurgical techniques are important parts of surgical treatment (4, 10, 11). A postoperative MRI (24 to 72 h after surgery) is required to confirm the extent of tumor resection, found to be an independent positive prognostic factor (12, 13). Targeted-biopsy of the tumor is reserved for cases where tumor resection is impossible (11, 14). It is important to note that total biological radicality of tumor resection is still unrealistic. Favorable prognostic factors include young age, good overall medical condition (Karnofsky score), extent of tumor resection and combined oncological treatment (15).

Molecular Genetics of Oligodendrogliomas

Characteristic of oligodendroglial tumors are frequent co-deletions of chromosome 1p and 19q. This genetic aberration was discovered in 1994 and became the first biomarker in neuro-oncology (16). 1p/19q co-deletion means the loss of genetic material from the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). The mechanism of 1p/19q co-deletion, the unbalanced translocation t(1;19)(q10;p10) and formation of derived chromosome 1p/19q, was identified later (17). It appears almost exclusively in oligodendroglial tumors. The frequency of 1p/19q co-deletion is estimated to be 80% to 90% for grade II oligodendrogliomas and 50% to 70% for AO (18, 19). Recently, the presence of mutations in two important tumor-suppressor genes, CIC (a homolog of the *Drosophila* gene *capicua*) located on 19q13.2, and far upstream element-binding protein (*FUBP1*) on the 1p chromosome, was discovered in the majority of oligodendrogliomas with 1p/19q co-deletion. The prevalence of *CIC* and *FUBP1* mutations among 1p/19q co-deleted oligodendroglial tumors are 50-70% and 15%, respectively. Mutations in these genes are probablyinvolved in the formation and progression of oligodendrogliomas. CIC protein binds to regulatory regions and blocks gene transcription. *CIC* is also negatively-regulated by the mitogen activated protein kinase (MAPK) signaling pathway. *FUBP1* mutations closely related to a myelocytomatosis viral oncogene homolog (MYC) activation. However, their true significance in neoplastic diseases remains to be verified (20, 21). Currently, 1p/19q co-deletion serves as an important diagnostic, prognostic and predictive biomarker in oligodendroglial tumors and is discussed later from the perspective of novel therapeutic approach to this disease.

Recurrent mutations of the enzymes isocitrate dehydrogenase 1 and 2 (*IDH1/2*) were first demonstrated in glioblastoma multiforme, even if the prevalence was relatively low (about 5%) (22). A high frequency of mutations in the *IDH1* and *IDH2* genes was found in low-grade glioma; in grade II and grade III oligodendrogliomas up to 69%-94% of patients (23, 24). Mutation of *IDH1/2* causes neomorphic enzyme activity with subsequent accumulation of the cancer-associated metabolite 2-hydroxyglutarate (2-HG) in the tumor tissue (25). Cells with mutations in *IDH1/2* and 2-HG accumulation undergo massive epigenetic changes (DNA and histone methylation, chromatin remodeling), which leads to an extensive impact on gene expression and likely supports the onset and progression of neoplastic disease (26, 27). The presence of the IDH1/2 mutations is a significant positive prognostic biomarker for patients with glioma (28-30). It has been found that all patients with a tumor positive for 1p/19q co-deletion also have a mutation in *IDH1* or *IDH2*. These patients have the best prognosis (31). On the other hand, there is a group of gliomas with *IDH1/2* mutations, but without the presence of 1p/19q co-deletion. Patients with these tumor types have a worse prognosis than tumors with co-deletion, but still a significantly better prognosis than gliomas without the *IDH1/2* mutations (32, 33).

The promoter methylation of the gene O^6-methylguanine DNA methyltransferase (*MGMT*) was discovered as a significant prognostic, as well as predictive, biomarker in patients with glioblastoma. Patients with a methylated *MGMT* promoter responded better to temozolomide and had significantly longer overall survival (OS) than patients with intact *MGMT* (34-36). This aberration was also found in 80% of AO and in 73% of anaplastic oligoastrocytomas (37, 38). In oligodendroglial tumors, *MGMT* promoter methylation

Table I. *Important molecular biomarkers and their relevance in glioma.*

Molecular biomarker	Assessment method	Biomarker Relevance		
		Diffuse glioma	Anaplastic glioma	Glioblastoma multiforme
1p/19q co-deletion	FISH, PCR	Positively prognostic	Positively prognostic for RT or CHT Predictive for PCV & RT	Very rare, unclear
IDH1/2 mutations	RT-PCR, IHC, sequencing	Positively prognostic	Positively prognostic	Positively prognostic, rare Distinguishing secondary GBM
MGMT promoter methylation	Methylation-specific PCR	Unclear	Positively prognostic	Predictive for temozolomide
G-CIMP	Methylation-specific PCR	Positively prognostic	Positively prognostic	Positively prognostic

IDH1/2: Isocitrate dehydrogenase 1 and 2; MGMT: O^6-methylguanine DNA methyltransferase; G-CIMP: hypermethylator phenotype of cytosine-phosphate-guanine islands in glioma genome; GBM: glioblastoma multiforme; RT: radiotherapy; CHT: chemotherapy; FISH: fluorescent *in situ* hybridization; RT-PCR: real-time polymerase chain reaction; IHC: immunohistochemistry.

serves mainly as a positive prognostic, not predictive, biomarker when the patient is treated with PCV, as was proven in the EORTC 26951 study and in current results of the NOA-4 trial (39, 40).

Another molecular genetics characteristic, as well as important prognostic biomarker for patients with glioma, is the hypermethylator phenotype of cytosine-phosphate-guanine islands (CpG) in the tumor genome (G-CIMP). Positivity for G-CIMP probably is not an entirely independent biomarker, as it is closely related to the presence of the *IDH1/2* mutations (27, 41). G-CIMP-positive grade II and III gliomas usually also have a methylated *MGMT* promoter. G-CIMP positivity is approximately two-times more frequent in oligodendrogliomas (93%) than astrocytomas (45%). G-CIMP is an important positive prognostic factor for all types of glioma, including oligodendroglioma (41). The important molecular biomarkers in glioma, together with their clinical relevance, are summarized in Table I.

The alteration of certain other known pro-oncogenes and tumor-suppressor genes in patients with AO was also identified, even if in rare cases. These alterations include mutations in phosphatidylinositiol 3-kinase (*PI3K*), amplification of epidermal growth factor receptor (*EGFR*) or loss of the phosphatase and tensin homolog (*PTEN*) tumor-suppressor and correlate with a worse prognosis of AO (42, 43).

Clinical Relevance of 1p/19q Co-Deletion in Oligodendroglioma

The 1p/19q co-deletion status can be used in clinical practice as an important diagnostic, prognostic, as well as predictive, biomarker in patients with oligodendroglial tumors. The presence of 1p/19q co-deletion supports the diagnosis of oligodendroglioma, especially in cases where the histological findings are atypical (44). However, the very presence of co-deletion is not sufficient to diagnose oligodendroglioma. As many as 20% of glioblastomas may have the oligodendroglial component, 5 to 25% of which have 1p/19q co-deletion (45). Some other tumor types may also mimic oligodendrogliomas: dysembryoplastic neuroepithelial tumors (DNET), neurocytomas, clear cell ependymomas and small cell anaplastic astrocytomas. As these tumors do not have 1p/19q co-deletion, this biomarker is a useful diagnostic aid (44).

The presence of 1p/19q co-deletion also has a role as an important and independent positive prognostic biomarker of the disease. Retrospective and prospective studies showed that when patients with 1p/19q co-deletion are given standard treatment, they have significantly better survival outcome than patients without 1p/19q co-deletion (5, 12, 13, 44, 46, 47). 1p/19q co-deletion also has substantial clinical significance as a strong predictive biomarker for patients with anaplastic oligodendroglial tumors. Its detection predicts longer survival with PCV and radiotherapy in comparison with radiotherapy alone (13, 47), as will be discussed in detail below.

Novel Treatment Paradigm for Anaplastic Oligodendroglioma

As early as 1998, it was found that patients with 1p/19q co-deletion are more sensitive to PCV (48). Nonetheless the evidence-based proof of the significantly longer survival in patients with oligodendrogliomas and 1p/19q co-deletion treated with combined chemotherapy and radiotherapy did not exist for a long time. The long-term follow-up of two important phase III randomized clinical trials with patients suffering from AO treated with PCV, namely RTOG 9402 and EORTC 26951, is bringing substantial results and leading to a paradigm shift of the disease treatment (12,13,46,47).

In the RTOG study 9402, conducted between 1994 and 2002, 291 patients with AO and anaplastic oligoastrocytomas were included and randomized into two treatment arms: PCV with follow-up radiotherapy, and radiotherapy-alone. In the EORTC, study 26951 conducted from 1996 until 2002, 368 patients with AO and anaplastic oligoastrocytomas were randomized into two arms: radiotherapy-alone and RT followed by PCV chemotherapy. The 1p/19q status was determined through fluorescent *in situ* hybridization (FISH) in both studies.

In RTOG 9402, 1p/19q co-deletion was found in 46% of the patients. Over the course of the study, 80% of the patients randomized for radiotherapy subsequently received PCV therapy due to the progression of the disease. After a minimum three-year follow-up in 2006, the median progression-free survival (PFS) was different for the PCV-plus-radiotherapy arm and the radiotherapy-only arm (2.6 and 1.7 years, $p=0.004$), but the medial OS was similar in both study arms (4.9 and 4.7 years, $p=0.26$). The OS in patients with 1p/19q co-deletion was longer than in patients without co-deletion (>7 and 2.8 years, $p<0.001$), but the OS in both treatment arms was not significantly different based on the presence of 1p/19q co-deletion (12). As a result, the positive predictive significance of 1p/19q co-deletion in relation to PCV-plus-radiotherapy was not proven. The absence of a positive effect of combined therapy on the OS and the occurrence of serious adverse effects of PCV in more than 65% of the patients led to skepticism in regard to PCV.

The EORTC 26951 study gave similar results after an average five-year follow-up in 2006. 1p/19q co-deletion was found in 21% of patients. The patients in the arm that received PCV and radiotherapy benefited more than those receiving radiotherapy-alone in PFS (median of 23 and 13.2 months), but the median OS was similar (40.3 and 30.6 months, $p=0.23$) (13). Patients with 1p/19q co-deletion had longer OS than patients without co-deletion, irrespective of the therapy arm. The results of both studies were considered rather negative in 2006. They did not prove the significance of 1p/19q co-deletion as a predictive biomarker in relation to chemotherapy, but rather showed the significance of 1p/19q co-deletion as a prognostic biomarker.

However, both studies produced decisive results in 2013 following long-term patient monitoring and proved the positive effect of combined oncological treatment (PCV plus radiotherapy) for AO tumors. In the RTOG 9402 study, the median OS in patients without 1p/19q co-deletion remained similar to the results in 2006 in both groups receiving PCV-plus-radiotherapy and radiotherapy-alone (2.6 and 2.7 years). On the other hand in patients with 1p/19q co-deletion, the OS was significantly longer in the PCV-plus-radiotherapy arm than in the radiotherapy-alone arm (14.7 *vs*. 7,3 years respectively, $p=0.03$). The results were similar in the EORTC 26951 trial. After more than 10 years' follow-up, the OS in patients without 1p/19q co-deletion was similar in the group receiving PCV-plus-radiotherapy and radiotherapy alone (25 and 21 months, $p=0.19$). However, the median OS was not reached for patients with co-deletion in the PCV plus radiotherapy arm, whereas it was just 9.3 years in patients primarily receiving only radiotherapy.

The positive effect of combined oncological treatment (PCV plus radiotherapy) in patients with 1p/19q co-deletion was present in both clinical studies, irrespective of which type of therapy was started first. The positive effect on OS was also confirmed in patients who, due to the occurrence of adverse effects to therapy, received lower doses of PCV than planned (in RTOG 9402 only 42% of patients tolerated all four intended PCV cycles; in EORTC 26951 only 30% of patients completed all four planned cycles. Both studies proved that neither radiotherapy nor chemotherapy alone is sufficient in AO treatment. These results led to an important paradigm shift in the treatment algorithm of patients with AO tumors.

However, the positive effect of treatment is negatively impacted by the adverse effects. Late radiotherapy toxicity (post-radiation necrosis, dementia) is known, occurring in as many as 10% of patients, even in cases of focused therapy (6, 49). The toxic effects of PCV are even more frequent (50). It is necessary to carefully monitor patients and detect the toxic effects of the treatment early.

Another important question is the administration of combined oncological treatment in patients with AO who do not have 1p/19q co-deletion. The results of the RTOG 9402 and EORTC 26951 studies show this treatment has a positive effect on PFS even among patients without 1p/19q co-deletion. There are probably other molecular factors that have a positive impact on patients prognosis in relation to the combined therapy (33). To answer this important clinically relevant question, the CATNON study (NCT00626990) is currently randomizing patients with AO without 1p/19q co-deletion. The study is investigating the efficacy of another chemotherapeutic agent, temozolomide, during or after radiotherapy compared to radiotherapy alone.

Temozolomide is an effective alkylating cytostatic agent more frequently used for AO than PCV. It has the advantage of oral administration *versus* the intravenous administration of PCV, has fewer adverse events and less frequent termination of treatment due to toxicity (18, 35, 51, 52). The Food and Drug Administration approved temozolomide for the treatment of AO in 1999. The negative results of RTOG 9402 and EORTC 26951 trials in 2006 contributed to its frequent use for AO. For example, in one survey among physicians, temozolomide represents up to 87% of chemotherapy used for AO (4, 53, 54). Positive results of temozolomide therapy for AO comparable to PCV have been described (55). However the study was very small and included only 20 patients. In contrast, a large retrospective analysis assessing the efficacy of PCV-plus-radiotherapy and temozolomide-plus-radiotherapy for the treatment of AO in

1,013 patients reported a median OS of 7.6 years for the PCV regimen compared to only 3.3 years for that with temozolomide (38). For second-line AO treatment in cases of relapse following the failure of PCV, temozolomide was also tested and produced promising results (56).

The German NOA-4 study randomized 318 patients with AO, anaplastic oligoastrocytoma, as well as anaplastic astrocytoma, for radiotherapy, PCV or temozolomide therapy. In cases of toxicity or progression, patients undergoing radiotherapy were randomized into PCV or temozolomide arms and *vice versa*. After the first analysis, there was no significant difference among the individual study arms in PFS or OS. However, in all arms, patients with 1p/19q co-deletion had a better prognosis and reduced relative risk of treatment failure, disease progression or death by about 50%. On the other hand, the follow-up of the study is still too short (maximum 54 months) and features frequent cross-over to other treatment arms (33). To evaluate the effect of temozolomide on oligodendroglioma with 1p/19q co-deletion, the CODEL study (NCT00887146) was planned with three parallel arms: radiotherapy plus temozolomide, radiotherapy alone, and temozolomide alone. Based on the results of RTOG 9402 and EORTC 26951 trials, the radiotherapy monotherapy arm was abolished and it is uncertain whether the study will be reopened. It is expected that the radiotherapy monotherapy arm will be replaced with the PCV plus radiotherapy (4).

Based on the results of these discussed clinical trials, it is currently recommended the 1p/19q status in all patients AO be determined as routine clinical practice as a part of the standard decision-making algorithm in the treatment planning (57). The PCV chemotherapeutic regimen in combination with radiotherapy should now be implemented for all patients with AO with 1p/19q co-deletion. These recommendations mean important changes in novel treatment strategies for patients with AO and anaplastic oligoastrocytoma.

Conclusion

Oligodendrogliomas are among the most explored tumors of the nervous system. Despite the considerable malignant potential of these tumors, a significant number has been shown to respond well to treatment. The positive effect of combined early radiotherapy and PCV chemotherapy for AO and mixed forms, anaplastic oligoastrocytomas with 1p/19q co-deletion, has recently been clearly demonstrated. An equally significant or more positive effect of frequently used temozolomide has not yet been proven. The presence of 1p/19q co-deletion in oligodendroglial tumors is important for diagnosis, and prognosis, as well as prediction of therapy outcome. *IDH1/2* mutations, *MGMT* gene promoter methylation and the hypermethylator status of G-CIMP also have positive prognostic significance. The secondary product of oligodendroglioma research is demonstration of the significance of monitoring patients over the long-term in well-designed clinical trials, in which preliminary results may be inconclusive and only the final results are decisive with regard to evidence-based medicine. The use of PCV-plus-radiotherapy regimen means a novel treatment paradigm for all patients with AO with 1p/19q co-deletion at the moment.

Conflicts of Interests

The Authors declare that they have no conflicts of interests regarding the publication of this article.

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