Grade II and III Oligodendroglioma and Astrocytoma

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KEYWORDS

• Astrocytoma • Oligodendroglioma • Anaplastic • *IDH* • 1p/19q codeletion • PCV • Temozolomide • Bevacizumab

KEY POINTS

- The World Health Organization classification of glioma is now based on molecular criteria, in particular, based on the presence or absence of *IDH* mutations and 1p/19q codeletion. *IDH*-mutated gliomas have a more favorable outcome, especially if combined with 1p/19q codeletion.
- If an extensive resection is safely possible, early surgery should be considered in patients presenting with seizures only and a nonenhancing lesion on MRI presumed to represent a low-grade glioma.
- Delayed effects of radiotherapy on cognition warrant postponing adjuvant radiotherapy if safely possible.
- Adjuvant chemotherapy given immediately after radiotherapy improves survival in grade II and III glioma.
- Upfront treatment with chemotherapy alone as opposed to radiotherapy followed by adjuvant chemotherapy may jeopardize survival.

INTRODUCTION

With its emphasis on molecular tumor characteristics, the 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System has radically changed the diagnostics of diffuse glioma.[1] Traditionally, diffuse grade II and III gliomas were separated into 2 basic morphologic subtypes: oligodendroglioma and astrocytoma, with a third "mixed" category of oligoastrocytoma for those cases in which histologic examination showed elements of both. Today, to make the diagnosis

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of an (anaplastic) oligodendroglioma, the presence of both codeletion of chromosome arms 1p and19q and mutation (mt) of the isocitrate dehydrogenase gene (*IDH1* or *IDH2*) is required; for (anaplastic) astrocytoma, both an *IDHmt* and an *IDH* wild-type (wt) exist. This revised classification of diffuse gliomas is far more robust and much more informative prognostically than the classic histopathological approach. Clinicians must now incorporate these revisions into their everyday diagnostics and treatment of diffuse glioma.[2]

CLINICAL PRESENTATION

Each year, 4500 to 5000 patients in the United States are diagnosed with a grade II (low-grade) or III (anaplastic) astrocytoma or oligodendroglioma.[3] Low-grade glioma (LGG) usually presents in patients between 25 and 45 years of age; patients with anaplastic tumors tend to be somewhat older (30–50 years). Occasionally, *IDHmt* astrocytomas are diagnosed in older children and adolescents (even those younger than 15), whereas some 1/19q codeleted *IDHmt* oligodendrogliomas are first diagnosed in patients older than 60 to 65 years. In general, the chance of diagnosing an *IDH* mutation in grade II and III glioma decreases in patients who are older than 50 to 55 years. The clinical presentation of brain tumors is nonspecific and depends on tumor localization and rate of growth. Most low-grade and anaplastic tumors first present with seizures; focal deficits are less common at the time of first diagnosis. Typically, LGGs are slow-growing lesions with an annual growth rate of 4 to 6 mm if left untreated.[4] Clinical prognostic factors include age of the patient, size of the tumor, frontal location, and performance status of the patient; favorable factors are in general associated with the presence of *IDH* mutations.[5,6]

MOLECULAR BACKGROUND

In 2008, genetic analysis of a series of glioblastomas discovered mutations in the gene encoding for *IDH1* and *IDH2*, which were subsequently shown to be present in 70% to 80% of grade II and III glioma.[7] Tumors with *IDH* mutations are associated with an increased survival compared with histologically similar tumors without *IDH* mutations.[7–9] *IDH* mutations represent early mutations and may very well represent the driving mutation in *IDHmt* glioma. The mutations in the *IDH1* and *IDH2* genes are somatic, missense, heterozygous, and involve either codon 132 (*IDH1*) or codon 172 (*IDH2*). *IDH* mutations induce an altered substrate affinity of the *IDH* enzyme resulting in increased levels of 2-hydroxyglutarate and lower levels of α-ketoglutarate and nicotinamide adenine dinucleotide phosphate (NADPH).[10] This can induce the development of a global methylation of CpG islands, which often includes the *MGMT* promoter region.[10,11] This may at least partially explain the sensitivity to chemotherapy of *IDHmt* tumors. Another plausible explanation is that resistance mechanisms to alkylating chemotherapy are dependent on the level of α-ketoglutarate.[12] Similarly, the lower levels of NADPH production by *IDHmt* cells have been correlated to increased sensitivity to radiotherapy.[13] There is preliminary evidence that *IDHmt* induces a defective homologous recombination and in vitro studies suggest this may render them sensitive to poly ADP ribose polymerase (PARP) inhibitors.[14,15] Previously, genetic analysis demonstrated that combined loss of 1p/19q is a typical molecular feature for (anaplastic) oligodendroglioma and is associated with increased responsiveness to procarbazine, CCNU (lomustine), vincristine (PCV) chemotherapy and temozolomide chemotherapy.[16–18] This 1p/19q codeletion is an early event that remains present at the time of tumor progression. More recent studies indicate that 1p/19q codeletion develops in tumors in which an *IDH* mutation has already occurred.[19]