

Current Treatment of Oligodendrogliomas

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That a neurological review is dedicated specifically to the oligodendroglioma is testimony to a decade of progress. The unique molecular features and chemosensitivity of the oligodendroglioma were not appreciated 10 years ago; yet today, these features merit such interest to clinicians and pathologists alike that the oligodendroglioma is separated from other types of primary brain tumors in both the laboratory and in practice.

DIAGNOSIS OF OLIGODENDROGLIOMA

The diagnosis of oligodendroglioma currently rests on standard light microscopic assessment of hematoxylin-eosin-stained slides. Oligodendroglioma cells bear some resemblance to oligodendrocytes, suggesting that oligodendrogliomas arise from a cell committed to oligodendrocytic differentiation. Nonetheless, there are as yet no immunohistochemical markers to diagnose oligodendroglial neoplasms, and attempts to use various markers of oligodendrocytic differentiation have not proved reliable in tumor sections. Consequently, the pathologist renders a diagnosis of oligodendroglioma based on the subjective light microscopic impression of a moderately cellular tumor with regular, rounded nuclei, sometimes with perinuclear halos ("fried-egg appearance") and sometimes with branching vasculature and calcifications.

The diagnosis is further complicated by the fact that many oligodendrogliomas contain an astrocytic component, which may be substantial at times; such mixed tumors are termed *oligoastrocytomas*. Oligoastrocytomas are not "collision" tumors but rather are clonal neoplasms with the his-

tologically disparate oligodendroglial and astrocytic components sharing the same genetic alterations. In practice, the distinction of oligodendroglioma from oligoastrocytoma is probably not as important as the distinction between these 2 oligodendroglial lesions and pure astrocytoma, since many oligoastrocytomas, grade for grade, behave clinically and respond to both radiotherapy and chemotherapy in a fashion very similar to pure oligodendrogliomas.¹ Furthermore, high-grade oligodendrogliomas with perinecrotic pseudopalisading should not be equated with typical glioblastomas; these necrotic oligodendrogliomas may also be chemosensitive.² These diagnostic difficulties underscore the need to improve the nosological criteria for oligodendroglial neoplasms; molecular analyses may resolve some of the uncertainties, since pure and mixed oligodendrogliomas have characteristic patterns of chromosomal loss. For instance, combined chromosome 1p and 19q loss is frequently associated with oligodendroglial tumors and may therefore constitute important adjuncts for diagnosis of these lesions.³

OLIGODENDROGLIOMAS ARE ONE OF THE MORE CHEMOSENSITIVE HUMAN SOLID CANCERS

Ten years after Cairncross and Macdonald⁴ first reported remarkable examples of tumor shrinkage after chemotherapy in patients with recurrent anaplastic oligodendroglioma, it is clear that oligodendrogliomas are among the most chemosensitive of

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all human solid malignancies. While procarbazine, lomustine (CCNU), and vincristine sulfate, a chemotherapy regimen designated PCV, are most often used in practice, oligodendrogliomas have been shown to be sensitive to a variety of cytotoxic drugs including melphalan, thiotepa, temozolamide, paclitaxel (Taxol), and platinum-based regimens.^{1,5,6} Response, defined by at least a 50% reduction in area of enhancing tumor, is seen in about 75% of patients treated with PCV chemotherapy for recurrent anaplastic oligodendroglioma; many of these responses are complete. Responses also have been shown in patients treated upfront with PCV chemotherapy before radiotherapy, patients with both pure and mixed oligodendroglial tumors, and patients with low-grade oligodendroglioma.^{1,7}

The basis of this unique chemosensitivity is unclear; presumably, neoplastic cells in the oligodendroglial lineage are inherently susceptible to the alkylating effects of cytotoxic chemotherapy. Low levels of the DNA repair protein O6-methylguanine-DNA methyltransferase have been found in oligodendroglial cells lines, and Silber et al⁸ recently observed significantly lower O6-methylguanine-DNA methyltransferase activity in human oligodendrogliomas and mixed glioma samples than in astroglial tumors. Glioma O6-methylguanine-DNA methyltransferase levels are also inversely correlated with age, which perhaps explains, at least in part, the well-known survival advantage associated with young age (<45 years) in patients with malignant glioma. Another intriguing hypothesis asserts that, in addition to these mechanisms, a p53-mediated programmed cell death pathway may be activated in oligodendrogliomas after exposure to cytotoxic chemotherapy.⁹ This mechanism may be similar to observations made in testicular neoplasms; oligodendrogliomas rarely harbor p53 gene mutations and frequently display apoptotic tumor cells, yet, like testicular cancers, are known to accumulate wild-type p53 protein. Other authors have suggested that these events may "prime" the cancer cell to undergo programmed cell death after exposure to chemotherapy.¹⁰ Explanations for the chemosensitive nature of oligodendrogliomas await the cloning and characterization of the responsible genes.

GENETIC PREDICTORS OF TREATMENT RESPONSE AND SURVIVAL

Cairncross et al³ recently studied 39 patients with anaplastic or aggressive oligodendrogliomas treated with alkylating chemotherapy, usually the PCV regimen, who had known response and survival outcomes. A variety of clinical prognostic factors, genetic alterations, and immunohistochemical findings were examined in relation to these outcomes. Chromosome 1p loss, found in 70% of cases, correlated strikingly with radiological responses to chemotherapy; in fact, 100% of tumors with 1p loss were chemosensitive. Chromosome 19q loss alone was not associated with response, but the combination of 1p and 19q loss was tightly associated and predictive of longer recurrence-free survival. Patients without 1p loss were unlikely to harbor chemosensitive tumors and had a 17-fold increase in relative risk of death. Other analyses from this study also suggested that deletion of CDKN2A (p16 pro-

tein) and the presence of a ring-enhancing tumor conferred significantly worse prognosis.

These observations demonstrated for the first time that specific molecular genetic changes may be used as markers of chemosensitivity in malignant gliomas. Also, these molecular features provided important survival information above and beyond traditional prognostic factors such as age and performance status. A patient whose anaplastic oligodendroglioma has both 1p and 19q loss would be predicted to show a radiographic response to PCV chemotherapy and have a 5-year survival rate of 95%. A patient with a histologically identical tumor, but with CDKN2A deletion, would be less likely to respond to chemotherapy and have an expected survival of 2 years. Lastly, a patient with a ring-enhancing anaplastic oligodendroglioma will probably not respond to chemotherapy and have a median survival of less than 1 year despite surgery and radiotherapy.

TREATMENT OF LOW-GRADE OLIGODENDROGLIOMAS

Oligodendrogliomas are classified as low grade if they lack or have few histological features suggestive of anaplasia: namely, high cellularity, nuclear pleomorphism, mitotic figures, endothelial proliferation, and necrosis. The appropriate management of low-grade oligodendrogliomas requires individualized consideration, because these tumors can be indolently progressive and manifest only as a partial seizure disorder that may often be present for a decade or more; yet, they can also be clinically aggressive and cause a symptomatic, progressively enlarging contrast-enhancing brain mass. Timing and intensity of postoperative therapy is controversial, and it is unclear if patients are best treated at the time of surgical diagnosis or whether radiotherapy or chemotherapy is best reserved for the time of clinical or radiographic tumor progression. At present, nonrandomized retrospective studies support maximal feasible surgical resection and external-beam radiotherapy when significant residual disease is identified on postoperative imaging or when aggressive clinical or pathological features are identified.¹ Undoubtedly, radiotherapy is an effective treatment to stabilize progressing tumor and to control symptoms such as seizures; however, toxic effects appearing years after cerebral irradiation are a major concern in these patients because of relatively long survival rates (ie, 80% at 5 years and 30%-50% at 10 years). It is unclear whether the tumor-controlling benefits of radiation therapy outweigh its risks in patients with low-grade tumors, although it must be stated that radiotherapy is probably becoming safer as delivery systems and targeting methods improve.

There is now a growing body of evidence to support the notion that low-grade oligodendrogliomas, pure or mixed, are chemosensitive. Paleologos et al¹¹ found partial responses in 3 patients and stable responses in 2 patients (out of a total of 5) with low-grade oligodendroglioma treated with PCV chemotherapy, and Mason et al⁷ confirmed these results in another study. From these studies and additional anecdotal observations, there is little doubt that low-grade oligodendrogliomas are sen-

sitive to chemotherapy; however, the kinetics of radiographic response may be different from what is seen in more aggressive or anaplastic tumors. For example, we and others have noted that nonenhancing low-grade oligodendrogliomas typically respond gradually and only partially when treated with PCV chemotherapy, and sometimes only radiographic disease stabilization is achieved.⁹ These observations have generated interest in the use of lower-dose but longer duration PCV chemotherapy for these tumors, and clinical trials to evaluate so-called mini-dose PCV chemotherapy are underway.

TREATMENT OF ANAPLASTIC OLIGODENDROGLIOMAS

Most patients with anaplastic oligodendrogliomas will respond to PCV chemotherapy; however, as with their less aggressive counterparts, the best timing of such therapy is unclear. Genetic prediction of chemosensitivity using molecular genetic analysis will likely enter into future treatment decisions. For example, a patient with a newly diagnosed anaplastic oligodendroglioma harboring a chromosome 1p deletion is so likely to be chemosensitive and have prolonged survival that the best therapy may consist of early postoperative chemotherapy using PCV together with radiotherapy or using PCV alone until there is evidence of tumor progression.³ On the other hand, a similar patient with unfavorable genetic features might be best treated with current standard care, namely postoperative external beam radiotherapy and novel therapy at the time of tumor recurrence. These dilemmas may be answered in part by the ongoing randomized intergroup study of neo-adjuvant PCV chemotherapy vs radiotherapy for patients with newly diagnosed anaplastic oligodendroglioma.

In the past decade, we have witnessed the emergence of the oligodendroglioma as a diamond in the rough; while treatment advances in glioma therapy have been modest at best, the unique molecular nature and chemosensitivity of oligodendrogliomas set them apart from other types of glial neoplasms. We know now that oligodendrogliomas, pure and mixed, low grade and ag-

gressive, are chemosensitive and that chromosome 1p loss is an important marker of this phenomenon. As the optimal timing and intensity of PCV chemotherapy is clarified for patients with oligodendrogliomas, especially those with 1p losses, other novel treatment approaches will undoubtedly be tested. While other types of gliomas may or may not be chemosensitive, lessons are yet to be learned from oligodendrogliomas; we strongly support the separation of oligodendrogliomas from other gliomas in the laboratory and in clinical trials.¹²

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