Recent developments in the molecular characterization and treatment of oligodendroglial tumors

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Although many patients with oligodendrogliomas (ODs) and oligoastrocytomas (OAs) benefit from a combination of surgery and adjuvant radiotherapy, most patients eventually experience recurrence of their disease. Recent evidence has shown that ODs are more chemosensitive than other gliomas, including astrocytomas or glioblastoma multiforme. These initial findings have prompted further study of chemotherapy in treating ODs and mixed OAs. Advances in molecular genetic analysis have led to improvements in predicting response to chemotherapy and prognosis for ODs, OAs, and astrocytomas. Pure ODs are more chemosensitive than mixed ODs. This difference is related to different proportions of 1p/19q loss of heterozygosity in these neoplasms. Therefore, genetic analysis is likely to be key in determining appropriate treatment. The most common first-line chemotherapy for patients with OD is a procarbazine, lomustine, and vincristine (PCV) combination regimen. However, this regimen is associated with cumulative myelosuppression, nausea,

vomiting, and weight loss. Therefore, other chemotherapy agents and regimens have been investigated. Perhaps the most promising is temozolomide, a novel alkylating agent that freely crosses the blood-brain barrier. Temozolomide is approved in the United States for the treatment of recurrent anaplastic astrocytomas and in Europe for any recurrent high-grade gliomas. Initial reports suggest that temozolomide is effective in treating ODs as first- and second-line chemotherapy. Unlike the PCV regimen, temozolomide is not associated with cumulative myelosuppression and is usually well tolerated. Further studies are needed to confirm the efficacy and safety profile of temozolomide and to determine the optimal dose and schedule for treating ODs. *Neuro-Oncology* 5, 128–138, 2003 (Posted to *Neuro-Oncology* [serial online], Doc. 02-028, February 18, 2003. URL <http://neuro-oncology.mc.duke.edu>)

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²Abbreviations used are as follows: AA, anaplastic astrocytoma; AOA, anaplastic oligoastrocytoma; AOD, anaplastic oligodendroglioma; CBTRUS, Central Brain Tumor Registry of the United States; EGFR, epidermal growth factor receptor; EORTC, European Organization for Research and Treatment of Cancer; GBM, glioblastoma multiforme; GFAP, glial fibrillary acidic protein; MTIC, 5-(3-N-methyltriazen-1-yl)-imidazole-4-carboxamide; OA, oligoastrocytoma; OD, oligodendroglioma; PCV, procarbazine, lomustine, and vincristine; PCV-I, intensified procarbazine, lomustine, and vincristine; PR, partial response; RT, radiotherapy; SD, stable disease.

Primary brain tumors compose approximately 1% of new cancer cases in the United States, with an estimated 17,200 new cases in 2001 (Greenlee et al., 2001). Given the U.S. mortality rate of 4.1 per 100,000 persons, it is estimated that brain tumors accounted for approximately 13,100 deaths in 2001 (Greenlee et al., 2001; Ries et al., 2001). In adults, the most common brain tumors are anaplastic astrocytoma (AA)³ and glioblastoma multiforme (GBM) (Burger et al., 1985; Kleihues et al., 1993). Of all the brain tumors reported to the Central Brain Tumor Registry of the United States (CBTRUS) between 1992 and 1997, 3.5% were oligodendrogliomas (ODs) (CBTRUS, 2001). This is in agreement with initial estimates that suggested that approximately 4% of primary brain tumors were ODs (Mork et al., 1985). However, recent changes in histologic cri-

teria (distinguishing ODs and oligoastrocytomas [OAs] from diffuse and pilocytic astrocytomas) have increased this estimate to 25% (Coons et al., 1997).

In general, malignant gliomas are resistant to chemotherapy. However, reports in the late 1980s suggested that ODs are more chemosensitive than astrocytomas or GBMs (Cairncross and Macdonald, 1988; Cairncross and Macdonald, 1991). Additional studies have confirmed these initial findings, with reports showing that roughly 60% to 70% of ODs are sensitive to a combination regimen of procarbazine, lomustine, and vincristine (PCV) (Allison et al., 1997; Cairncross et al., 1994; Kyritsis et al., 1993; van den Bent et al., 1998). However, the PCV regimen is associated with cumulative myelosuppression, nausea, vomiting, and weight loss. In addition, all patients who respond to PCV ultimately experience relapse. Recently, other chemotherapy agents, including carboplatin, cisplatin, etoposide, paclitaxel, and temozolomide, have been investigated as second-line chemotherapy for the treatment of OD. Temozolomide is a new oral alkylating agent that has been approved in the United States for the treatment of refractory AA and in Europe for recurrent AA and GBM. This novel agent with non-cumulative and manageable myelosuppression has also shown promise in the treatment of OD.

Herein we review the importance of distinguishing ODs from astrocytomas and mixed astrocytic tumors. In addition, we discuss the effectiveness of first- and second-line chemotherapy in the treatment of OD, with a focus on temozolomide.

Clinical Features of Oligodendrogliomas

Several genetic markers (i.e., specific chromosomal abnormalities) have recently been identified that are characteristic of ODs; however, histologic markers that can definitively distinguish ODs from astrocytomas or mixed OAs remain elusive. Histologic criteria for distinguishing ODs from astrocytomas remain subjective, with significant interobserver variability (Coons et al., 1997; Mork et al., 1985; Smith et al., 1999). Nevertheless, advances in genetic analysis have improved the identification of and distinction between these gliomas. The following is a discussion of the known clinical, histologic, and genetic characteristics of low-grade OD, anaplastic oligodendroglioma (AOD), and anaplastic oligoastrocytoma (AOA).

Low-grade Oligodendrogliomas

Low-grade (WHO grade II) ODs typically emerge in patients <40 years of age. These tumors are slow growing and are typically located supratentorially and in the frontal lobe. On MRI, low-grade ODs show increased signal intensity on T2-weighted images without enhancement. On CT, these tumors appear as low-density masses with no enhancement and may exhibit calcification. The presence of calcification is suggestive of but not specific for OD. Before the widespread use of MRI, approximately 70% of patients presented with either generalized or focal seizures of long-standing duration with an antecedent history of 7 to 8 years (Celli et al., 1994; Olson

et al., 2000). The remainder of patients presented with signs of increased intracranial pressure, focal deficits, or changes in mental state. The prognosis for those patients with increased intracranial pressure or focal deficit is similar to the prognosis for patients with AA (Celli et al., 1994; Daumas-Duport et al., 1997a).

Histologically, low-grade ODs are characterized by uniformly round to oval cells with round nuclei and bland chromatin. The cell density is usually low to moderate. The morphology of these cells is often referred to as the "fried egg appearance" because of a perinuclear halo. A delicate network of branching blood vessels (chicken-wire pattern) is also indicative of low-grade OD. In addition, these tumors often demonstrate perineuronal satellitosis and microcalcifications (Bauman and Cairncross, 2001; Reifenberger et al., 2000). Oligodendrogliomas rarely exhibit the sparse glial fibrillary acidic protein (GFAP) staining that is usually due to the presence of reactive astrocytes. However, ODs occasionally express GFAP; therefore, GFAP staining alone is not a reliable assay to rule out OD. Coons et al. (1997) suggested that the classic histologic features described above are not sufficient for the differential diagnosis of OD, and therefore OD may often be misdiagnosed as AA or GBM. These authors suggested that when histologic features are used to diagnose OD, special emphasis should be given to identifying other signs, such as microgemistocytes, gliofibrillary oligodendrocytes, and protoplasmic astrocytes, which may suggest that the tumor is of oligodendroglial origin.

Advances in genetic analysis have provided an opportunity to improve the differential diagnosis of OD. The most frequently reported chromosomal lesions in OD are allelic loss of the 1p and 19q loci (Kraus et al., 1995; Reifenberger et al., 1994), as shown in Table 1. The incidence of either 1p or 19q chromosomal deletions in OD is reported to be approximately 75% (Cairncross et al., 1998; Smith et al., 1999), and the combined loss of 1p and 19q has been reported to occur in 60% to 70% of all ODs (van den Bent, 2000). In contrast, this combination of chromosomal lesions is present in <11% of tumors thought to be of astrocytic origin because of their microscopic appearance (Maintz et al., 1997; Smith et al., 1999, 2000). Bigner et al. (1999) reported that the loss of heterozygosity for 1p and 19q was seen in 17 of 23 (74%) well-differentiated ODs, whereas only 3 of 8 (38%) OAs exhibited loss of heterozygosity for 1p and 19q. Moreover, these chromosomal abnormalities have prognostic significance: ODs with combined 1p and 19q deletions are more likely to respond to chemotherapy (Cairncross et al., 1998; van den Bent, 2003b), and the presence of 1p deletions is associated with longer progression-free survival after radiotherapy (RT) or chemotherapy compared with the survival associated with other chromosomal abnormalities, including *TP53* mutations observed in many tumors of astrocytic origin (Bauman et al., 2000). Studies that have combined morphology and genetic analysis suggest that oligodendroglial tumors with a classical histologic appearance (perinuclear halo, chicken-wire vascular pattern) are associated with the loss of 1p/19q, whereas in tumors with an atypical appearance, other chromosomal abnormalities are found

Table 1. Common molecular genetic abnormalities, tumor grade, and estimated 5-year survival rate in glioma subtypes

Glioma subtype	Genetic abnormalities ^a	WHO tumor grade	5-year survival rate, % ^b
Oligodendroglioma	Chromosome 1p loss Chromosome 19q loss	II	62
Anaplastic oligodendroglioma	Chromosome 1p loss and/or chromosome 19q loss plus: Chromosome 9p loss <i>CDKN2A</i> mutations Chromosome 10 loss Chromosome 7 amplification	III	38
Oligoastrocytoma	<i>TP53</i> /chromosome 17p loss	II and III	56
Astrocytoma	<i>TP53</i> mutation/chromosome 17p loss Chromosome 22q loss	II	45
Anaplastic astrocytoma	<i>TP53</i> mutation/chromosome 17p loss or chromosome 22q loss plus: <i>CDKN2A</i> and <i>CDKN2B</i> deletion/chromosome 9p loss Chromosome 19q loss Chromosome 11p loss	III	28
Glioblastoma multiforme	<i>PTEN</i> mutation/chromosome 10q loss EGFR amplification and rearrangement	IV	3

Abbreviation: EGFR, epidermal growth factor receptor.

^aLouis and Cavenee, 2001.^bCBTRUS, 2001.

(e.g., *TP53* mutations) (Sasaki et al., 2002; Watanabe et al., 2002; van den Bent et al., 2003b). In a series of low-grade tumors, the genotype predicted response to chemotherapy better than the presence or absence of classical histologic OD features (Sasaki et al., 2002). However, there is evidence that the reverse can also be true; some atypical ODs have 1p/19q loss of heterozygosity, and some typical OD tumors do not show these lesions (Sasaki et al., 2002). Nevertheless, a loosening of the histologic criteria for an OD diagnosis, as proposed by some, will likely result in a heterogeneous tumor population in terms of genetic analysis (Coons et al., 1997). The anatomic location of ODs also seems to correlate with the genotype. Oligodendrogliomas with 1p/19q loss of heterozygosity tend to occur in the frontal, parietal, and occipital lobes, and have a tendency for widespread growth across the midline (Zlatescu et al., 2001). They also tend to present with seizures (in contrast to focal deficits) and with a low-grade tumor (van den Bent et al., 2003b).

Patients with low-grade OD (WHO grades I and II) have a median survival of 10 to 17 years (Leighton et al., 1997; Olson et al., 2000; Shaw et al., 1992) and a 5-year survival rate of approximately 75%. In addition, patients with low-grade OD or OA experience longer overall survival compared with patients with low-grade astrocytoma (13 vs. 7.5 years, $P = 0.003$) (Leighton et al., 1997). Despite this favorable clinical prognosis, virtually all low-grade ODs will eventually recur, usually after malignant transformation to AOD (WHO grade III).

Anaplastic Oligodendrogliomas

De novo AODs typically occur in patients >40 years of age (Daumas-Duport et al., 1997a). These tumors are clinically aggressive and usually present following a short duration of acute symptoms including focal neurologic

deficits or symptoms of mass effect (Daumas-Duport et al., 1997b; Dehghani et al., 1998). Anaplastic oligodendrogliomas are characterized by high cellularity, high mitotic activity, microvascular proliferation, nuclear abnormalities, and necrosis (WHO grade III) (Bauman and Cairncross, 2001; Reifenberger et al., 2000). On MRI or CT, these tumors are characterized by enhancement, which is thought to be the macroscopic equivalent of microvascular proliferation (Bauman and Cairncross, 2001). A number of histologic features, including cell density (Mork et al., 1985), the number of mitoses (Burger et al., 1987), the presence of endothelial hyperplasia (Daumas-Duport et al., 1997b), necrosis (Burger et al., 1987; Gannett et al., 1994; Mork et al., 1985), and the presence of pleomorphism (Smith et al., 1999), have all been identified as important prognostic factors for AOD. Several studies showed endothelial hyperplasia to be the strongest and most independent variable in prognosis compared with the other histologic characteristics (Daumas-Duport et al., 1997a; Giannini et al., 2001).

Genetic analysis has shown that in addition to the allelic loss of 1p and 19q, AODs often exhibit additional chromosomal deletions (Table 1). Loss of heterozygosity for 9p and/or deletion of the *CDKN2A* gene occurs in 33% to 42% of AODs, and deletions on chromosome 10 occur in 19% to 25% of cases (Bigner et al., 1999; Reifenberger et al., 1994). Despite a clear oligodendroglial morphology, some AOD tumors display a combination of chromosome 7 amplification and chromosome 10 deletions, which is more characteristic of an astrocytic lineage (Bigner et al., 1999; Jeuken et al., 1999). Amplification of the epidermal growth factor receptor (EGFR) has also recently been described in 20% to 25% of AODs (Chinot et al., 2001a; Hoang-Xuan et al., 2001). Both the loss of 10q and the amplification of EGFR are inversely related to 1p/19q loss, and both are associated with poor chemosensitivity and short survival (Chinot et al., 2001a;

Hoang-Xuan et al., 2001; Sasaki et al., 2001). Studies investigating *PTEN* mutations have provided conflicting results. Sasaki et al. (2001) reported 7 *PTEN* mutations in 72 cases, with a combined loss of 10q in 6 of these tumors. In contrast, Jeuken et al. (2000) and Hoang-Xuan et al. (2001) reported no *PTEN* mutations in oligodendroglial tumors. The mutually exclusive occurrence of 1p/19q loss and *TP53* mutations, EGFR amplification, 10q loss, or *PTEN* mutations suggests that these tumors are in fact derived from different precursor cells. This hypothesis is supported by the marked differences in the response to treatment and the prognosis for these genetically diverse tumors.

It has been suggested that the single most important prognostic factor affecting progression-free and overall survival in patients with OD is the pathologic tumor grade (Allam et al., 2000; Shaw et al., 1992). Patients with AOD have a substantially worse prognosis than do patients with low-grade OD, with reported median survivals of 4 to 5 years and a 5-year survival rate of only approximately 40% (Shaw et al., 1992, 1997). However, AOD is associated with a better prognosis than other anaplastic gliomas; patients with AA survive for 2 to 3 years, and patients with GBM survive for <2 years (Louis and Cavenee, 2001). Winger et al. (1989) reported that in 285 patients with supratentorial anaplastic gliomas, patients with AOD had the longest median survival time (5.3 years), compared with patients with GBM, AA, and AOA.

Oligoastrocytomas

The existence of the OA subtype is a matter of controversy. Mixed tumors have morphologic characteristics of both astrocytic tumors and pure ODs. These tumors are generally associated with tumoral oligodendroglial foci and gemistocytic astrocytic components mixed within the same region of the tumor. However, unlike pure ODs, OAs typically have areas that are GFAP positive (Reifenberger et al., 2000). This staining pattern may be due to the astrocytic component of the tumor but may also be due to reactive astrocytes. Some centers consider a tumor to be an OA if $\geq 10\%$ of the cells are astrocytic in origin (Krouwer et al., 1997). In contrast, the European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group have defined OA as an astrocytic tumor that contains $\geq 25\%$ oligodendroglial elements (van den Bent, 2000). However, these are arbitrary definitions that may have no biologic or clinical relevance. Attempts to establish clear-cut definitions are confounded by the fact that the percentage of astrocytic and oligodendroglial elements is subject to significant interobserver variation (Krouwer et al., 1997). Therefore, there is considerable disagreement with regard to the diagnosis of an OA based on the percentage of either astrocytic or oligodendrocytic components (Bigner et al., 1999; Krouwer et al., 1997).

Clinically, there does appear to be a distinction between OA and pure astrocytoma. The prognosis for patients with OA is better than the prognosis for patients with astrocytoma (Donahue et al., 1997; Krouwer et al.,

1997; Leighton et al., 1997; Shaw et al., 1994). In contrast, patients with OA have a worse prognosis than patients with OD. Patients with OA have 5- and 10-year survival rates of 63% and 33%, respectively, whereas patients with so-called pure OD have 5- and 10-year survival rates of 75% and 46%, respectively, although this difference is moderate and not constant (Shaw et al., 1992). Nevertheless, the explanation for these differences may lie in the molecular heterogeneity of mixed tumors.

Maintz et al. (1997) have recently provided genetic evidence that OAs are not mixed tumors at all, but rather tumors of either oligodendroglial or astrocytic origin. In this study, OAs fell into 2 categories: those that had 1p and 19q deletions, typical of ODs, and those that had *TP53* mutations, typical of astrocytomas (Table 1). Bigner et al. (1999) reported that among 55 OD, AOD, and AOA tumors, 14 had 17p loss of heterozygosity and/or *TP53* mutations, and the majority of these 14 tumors had significant astrocytic histologic elements. Only 1 of the 14 tumors with 17p loss of heterozygosity and/or *TP53* mutations also had 1p and 19q loss of heterozygosity. These data further support the idea that OAs are of either oligodendroglial or astrocytic lineage.

Clinical observations appear to correlate with the genetic profile of these tumors. Patients with OD and 1p/19q deletions have higher survival rates, which can probably be attributed to the sensitivity of these tumors to treatment, particularly chemotherapy, and the less aggressive clinical behavior of these tumors. Similarly, the lower survival rates in patients with OA can partially be explained by the presence of more unfavorable prognostic factors in tumors without 1p/19q lesions. Similar observations have been made in patients with AOD. Among 50 patients diagnosed with AOD, 23 patients who had 1p/19q deletions had a higher response rate (100%) to chemotherapy and a longer median survival (123 months) than 8 patients with *TP53* mutations (33% response rate; 71-month median survival) (Ino et al., 2001).

New developments may provide more specific molecular markers for tumors of true oligodendroglial lineage. There is accumulating evidence that suggests that oligodendroglial tumors arise from O2-A oligodendroglial progenitor cells. Both the O2-A progenitor cell and oligodendroglial tumors coexpress NG2 chondroitin proteoglycan and platelet-derived growth factor receptor- α . The combined expression of these 2 proteins is not observed in normal brain tissue or GBM (Shoshan et al., 1999). The recently discovered OLIG1/2 basic helix-loop-helix transcription factors are the earliest known markers of oligodendrocyte precursor cells. These transcription factors are also expressed in ODs but not in astrocytic tumors (Lu et al., 2001; Marie et al., 2001). These and other as yet unidentified markers may eventually be used to determine treatment options and predict prognosis.

In summary, histologic characterization appears insufficient to clearly distinguish glioma subtypes. Recent advances in molecular genetics have improved the differential diagnosis of these tumors. These advances have initiated discussions on reevaluating the current subtype classification of gliomas based on histology and the cel-

lular origin of the major component of the tumor in favor of a system based on genetic markers (Bigner et al., 1999; Ino et al., 2001). This reevaluation has led to an increasing proportion of gliomas being identified as oligodendroglial tumors. With further advances in genetic analysis, the OA tumor subtype may disappear and be replaced with a diagnosis of either OD or astrocytoma. Further, molecular genetic characterization of glioma subtypes may provide better guidance in selecting the appropriate treatment option for these patients. Eventually, genetic analysis may result in individualized rational treatments that are tailored to tumors with specific genetic abnormalities.

Treatment of Oligodendrogliomas

Surgery

Surgical resection is the primary treatment modality for patients with operable tumors and provides tissue for the classification, grading, and genetic analysis of the tumor. In addition, debulking surgery can relieve neurologic deficits and symptoms due to mass effect and can improve seizure control. In low-grade glioma, one uncontrolled study demonstrated that complete resection is associated with long disease-free intervals (Berger et al., 1994). In another study, OD patients who underwent subtotal resection had improved survival, although many of these patients were young and had low-grade tumors (Celli et al., 1994; Schiffer et al., 1997; Shaw et al., 1994). In contrast, other studies have shown that gross total resection in patients with OD provided no survival benefit (Daumas-Duport et al., 1997b; Kros et al., 1994). Nonetheless, given the potential clinical benefits associated with surgical resection, the tumor should be resected as extensively as is safely possible whenever warranted.

Radiotherapy

Surgical resection followed by adjuvant RT is currently the standard of care for patients with high-grade gliomas. Randomized trials comparing adjuvant RT and best standard of care after surgery have confirmed that adjuvant RT provides significant yet modest improvements in survival among these patients (Walker et al., 1978, 1980). However, the value of RT in patients with low-grade OD or OA has not been studied in controlled, randomized trials and remains controversial. Some retrospective studies have supported postoperative RT in patients with OD (Gannett et al., 1994; Wallner et al., 1988). Some studies suggest that RT provides a survival benefit in patients with OD, mainly in the subgroup of patients with neurologic deficit or for whom surgery was limited to biopsy or partial surgery (Celli et al., 1994; Shaw et al., 1992), whereas other studies have reported no benefit of postoperative RT in the treatment of OD (Bullard et al., 1987; Nijjar et al., 1993; Reedy et al., 1983). Until controlled, randomized studies are conducted, a prudent approach for treating patients with low-grade OD who can undergo complete resection may be to observe the patient

and withhold RT until progression. An important rationale for the deferral of RT is provided by compelling data demonstrating pronounced cognitive deficits in patients with low-grade gliomas who have undergone early RT (Surma-aho et al., 2001; Taphoorn et al., 1994). In contrast, patients with large, unresectable, or incompletely resected tumors; focal deficits; anaplastic tumors; or enhancing lesions should be treated without delay (Macdonald, 1994). Radiotherapy is the standard treatment approach, although first-line chemotherapy is also an option. Further, advances in the genetic characterization of ODs may also facilitate the decision-making process for the timing of RT.

Chemotherapy in Low-grade Oligodendrogliomas

Data on the use of chemotherapy in the treatment of low-grade OD and OA are limited, and the role of chemotherapy in this patient population remains unclear. Although chemotherapy is generally proposed for symptomatic aggressive tumors (i.e., with focal deficits) that behave like anaplastic tumors, there are mixed reports on the efficacy of chemotherapy in low-grade OD. Further, because of the nonenhancing characteristic of low-grade tumors, it is difficult to assess response. More studies in OD patients with nonenhancing indolent tumors, symptoms limited to seizures, and a more favorable prognosis are needed. Nevertheless, several small studies have investigated the PCV regimen for the treatment of patients with low-grade OD. Paleologos et al. (1994) reported that 3 of 5 (60%) patients with nonenhancing grade I/II OD responded to PCV. These patients had not received prior RT and were not receiving steroids. Mason et al. (1996) reported that all 9 patients with low-grade OD treated with PCV improved by clinical or MRI criteria, and no patients experienced deterioration while receiving therapy. Soffietti et al. (1999) investigated the use of PCV in a group of chemotherapy-naïve patients with low-grade, nonenhancing OD or OA. Of 13 newly diagnosed patients, 3 (23%) achieved a partial response (PR) and 10 (77%) achieved stable disease (SD). In this same study, 2 of 7 (29%) patients with recurrent low-grade OD achieved a PR and 5 (71%) achieved SD. Recently, van den Bent et al. (2002a) reported that of 12 patients treated with the standard PCV regimen, 9 showed either clinical or radiological improvement. Therefore, in patients with low-grade OD, the PCV regimen appears to be effective. However, larger, prospective studies and standardization of efficacy end points are required to fully evaluate the effectiveness of the PCV regimen in this patient population.

Chemotherapy in Anaplastic Oligodendrogliomas and Oligoastrocytomas

The first demonstration that AODs are sensitive to chemotherapy was reported by Cairncross and Macdonald (1988). The PCV regimen was shown to be effective in AOD, which prompted further studies. The PCV regimen is the most common chemotherapy used to treat AOD and AOA, and has been investigated as both first- and second-line chemotherapy (first and second recur-

rence after surgery and RT). Other agents, including carboplatin, paclitaxel, CPT-11, and temozolomide, have also been investigated as second-line chemotherapy.

First-line chemotherapy with PCV. Several single-institution studies have demonstrated high response rates with PCV at first recurrence. Cairncross and Macdonald (1991) reported that all 7 patients with AOD who were treated with PCV responded to treatment, with median response duration of 14 months (Table 2). Their subsequent phase 2, multicenter trial of intensified PCV (PCV-I) in first-relapsed patients with AOD demonstrated a 75% response rate among eligible patients (tumors with >90% oligodendroglial origin), a median time to progression of ≥ 16 months for the entire group and ≥ 25 months for complete responders (Table 2) (Cairncross et al., 1994). However, hematologic toxicity was substantial, and dose reductions and delays due to toxicity were frequent. Five patients had serious or unexpected adverse reactions possibly related to PCV-I. Grade 3/4 neutropenia and thrombocytopenia were observed in 40% and 15% of cycles, respectively. Vincristine-associated side effects were common (70% of patients experiencing distal numbness or paresthesia). Although the PCV-I regimen was very active in this patient population, it proved to be a debilitating regimen.

Van den Bent et al. (1998) reported a 63% overall response rate among 43 AOD and 9 AOA previously irradiated patients in first relapse with tumors exhibiting $\geq 25\%$ of oligodendroglial elements (Table 2). The median survival time for these patients was 20 months, and the median duration of response was 25 months and 12 months for complete and partial responders, respectively. In this study, 31% of patients experienced grade 3/4 hematologic toxicities: 25% and 13% of patients experienced grade 3/4 neutropenia and thrombocytopenia, respectively, and 6% of patients experienced grade 3 anemia. Similarly, Streffer et al. (2000) reported an overall response rate of 55% with a median progression-free survival of ≥ 18 months in a mixed patient population that included first-relapse (after irradiation) patients with AOA, AOD, and some low-grade OD and OA (Table 2). All of these studies suggest a role for PCV in treating AOD and AOA. However, the cumulative hematologic toxicity and gastrointestinal side effects associated with PCV often limit the duration of its administration.

Second-line chemotherapy. Although the majority of patients respond to first-line PCV, most patients with AOD experience a relapse within 2 years. The possibilities for repeated use of PCV are limited because of cumulative myelosuppression and acquired tumor resistance (Paleologos et al., 1999; Shaw et al., 1992, 1994; Soffietti et al., 1998). Peterson et al. (1996) reported an overall response of only 19% when chemotherapy was administered after previous neoadjuvant (i.e., prior to RT), first- or second-line PCV therapy. Of the 6 patients who received PCV as neoadjuvant therapy, 33% achieved an overall response to second-line chemotherapy. Of the 6 patients who received second-line PCV therapy after non-nitrosourea-based primary therapy, 5 patients (83%) achieved an overall response. Therefore, not unexpectedly, second-line PCV

chemotherapy was more effective in patients who had not received a nitrosourea-based first-line chemotherapy regimen or PCV as neoadjuvant therapy.

Only a few agents, including paclitaxel, CPT-11, carboplatin, etoposide plus cisplatin, and temozolomide, have been investigated for second-line chemotherapy in patients with AOD, and response rates are generally low (Table 3). Of 20 patients previously treated with surgery, RT, and PCV, 3 (15%) obtained a PR and 7 (35%) achieved SD when treated with paclitaxel (Chamberlain and Kormanik, 1997). Median duration of response and SD in these patients was 9 months (range, 4 to 10 months). All patients had progressive disease at 12 months. Toxicity was primarily hematologic; 10% of patients had grade 3 anemia, and 30% and 15% of patients experienced grade 3/4 thrombocytopenia and neutropenia, respectively. Similarly, 2 of 15 (13%) treated patients responded to CPT-11, and 33% of these patients remained free from disease progression at 6 months (Chamberlain, 2001). However, treatment with CPT-11 and paclitaxel is complicated by increased drug metabolism due to the induction of cytochrome P450 by many antiepileptic drugs. Likewise, 3 of 23 patients (13%) treated with second-line carboplatin achieved a response, and only 1 of these responding patients was free of disease progression at 12 months (Nobile et al., 2001). In addition, 4 of 10 patients treated with cisplatin and etoposide as second-line chemotherapy after first-line PCV experienced an overall response; however, none of the responding patients was progression-free at 12 months (Peterson et al., 1996).

Second-line PCV therapy is effective when administered after non-nitrosourea-based first-line therapy; however, most patients are treated with first-line PCV. Further, most second-line therapies following first-line PCV have only moderate response rates and low proportions of patients remaining free from progression at 6 and 12 months. Clearly, there is a need for improved second-line therapies for this patient population.

Clinical Trials with Temozolomide

Temozolomide, first synthesized by Stevens et al. (1987), is a novel member of the imidazotetrazine family of chemotherapy agents. Like all alkylating agents, this family of compounds has broad antitumor activity. Temozolomide is rapidly and completely absorbed after oral administration, crosses the blood-brain barrier, and achieves effective concentrations in the central nervous system (Marzolini et al., 1998; Stupp et al., 2001). Temozolomide is absorbed as an inactive prodrug. However, on exposure to physiologic pH, temozolomide is spontaneously hydrolyzed to form MTIC (5-[3-N-methyltriazene-1-yl]-imidazole-4-carboxamide), the active form of the drug. The cytotoxicity of MTIC is thought to be due primarily to methylation of the O⁶ and N⁷ positions of guanine bases in double-stranded DNA.

The ability of temozolomide to cross the blood-brain barrier suggested that it might be effective in treating gliomas. Indeed, temozolomide has been shown to be effective in treating patients with newly diagnosed or

Table 2. PCV regimen in first-line chemotherapy administered at recurrence after radiotherapy in patients with AOD and AOA

Study	No. of Patients (histology)	n (%)			
		CR	PR	OR	SD
Cairncross and Macdonald, 1991	7 (AOD)	2 (29)	5 (71)	7 (100)	0
Cairncross et al., 1994	24 (AOD)	9 (38)	9 (38)	18 (75)	4 (17)
van den Bent et al., 1998	52 (43 AOD, 9 AOA)	9 (17)	24 (46)	33 (63)	10 (19)
Streffer et al., 2000	11 (low-grade OD, low-grade OA, AOD or AOA)	1 (9)	5 (45)	6 (55)	5 (45)

Abbreviations: PCV, procarbazine, lomustine, and vincristine; AOD, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma; CR, complete response; PR, partial response; OR, overall response; SD, stable disease; OD, oligodendroglioma; OA, oligoastrocytoma.

Table 3. Second-line chemotherapy administered at recurrence after first-line PCV in patients with AOD and AOA

Study	Agent	No. of Patients	OR, n (%)	SD, n (%)	MTP, months	6-month PFS (%)	12-month PFS (%)
Chamberlain and Kormanik, 1997	Paclitaxel	20	3 (15)	7 (35)	4	35	0
Chamberlain, 2001	CPT-11	15	2 (13)	5 (33)	—	33	—
Nobile et al., 2001	Carboplatin	23	3 (13)	10 (43)	3	35	4
Peterson et al., 1996	Etoposide plus cisplatin	10	4 (40)	1 (10)	—	20	0

Abbreviations: PCV, procarbazine, lomustine, and vincristine; AOD, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma; OR, overall response; SD, stable disease; MTP, median time to progression; PFS, progression-free survival.

Table 4. Second-line temozolomide administered at recurrence after first-line PCV in patients with AOD and AOA

Study	No. of Patients	Response to PCV (%)	OR, n (%)	SD, n (%)	Median PFS, months	6-month PFS (%)	12-month PFS (%)
Chinot et al., 2001b	48	83	21 (44)	19 (40)	6.7	50	25
van den Bent et al., 2001	27	38	7 (26)	8 (30)	4	44	27
van den Bent et al., 2003a	28	50	7 (23)	9 (30)	3.7	29	11
Costanza et al., 2001	34	50	9 (26)	15 (44)	6	48	30

Abbreviations: PCV, procarbazine, lomustine, and vincristine; AOD, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma; OR, overall response; SD, stable disease; PFS, progression-free survival.

recurrent relapsed GBM and AA (Bower et al., 1997; Brada et al., 2001; Brandes et al., 2001; Friedman et al., 1998; Newlands et al., 1996; O'Reilly et al., 1993; Yung et al., 1999, 2000). In a phase 2 trial, Brada et al. (2001) reported a 6-month progression-free survival rate of 18% and a median progression-free survival and median overall survival of 2.1 and 5.4 months, respectively, in GBM patients who received temozolomide at first relapse. In patients with AA or AOA, Yung et al. (1999) reported a 6-month progression-free survival rate of 46% and a median progression-free survival and median overall survival of 5.4 and 13.6 months, respectively. Temozolomide is currently approved in the United States for the treatment of adult patients with AA refractory to nitrosoureas and procarbazine-containing regimens and in Europe for the treatment of all recurrent high-grade gliomas.

The pivotal trial of temozolomide in 162 patients with recurrent AA included 14 patients with AOA (Yung et al., 1999). Patients in this trial had received prior RT, and 97 patients received adjuvant chemotherapy and were treated with temozolomide at first relapse. Of the 14 patients with AOA, 43% obtained an objective response

to temozolomide treatment with 2 (14%) complete responses, 4 (29%) PR, and 1 (7%) SD. Progression-free survival and median overall survival were 5.8 months and 14.8 months, respectively, and the 6-month survival rate for these patients was 79%. Temozolomide treatment was well tolerated; grade 3/4 thrombocytopenia was experienced by only 6% of patients, and grade 3/4 neutropenia and leukopenia each occurred in only 2% of patients. Hematologic toxicity was not cumulative.

The activity of temozolomide as second-line chemotherapy after first-line PCV chemotherapy and previous RT in the treatment of AOA and AOD has been more rigorously studied by Chinot et al. (2001b). They reported an overall response of 44% in 48 patients with AOD or AOA at second relapse (Table 4). Not unexpectedly, AOD patients had a higher (49%) response rate compared with AOA patients (22%). In addition, AOD patients tended to have longer progression-free survival (7.3 vs. 5.6 months) and longer median overall survival (9.9 vs. 8.7 months) compared with AOA patients. The 6-month and 1-year survival rates for all 48 patients were 77% and 46%, respectively. For patients with an

objective response, the median progression-free survival was 13.1 months, and the median overall survival was 16 months. Only 6% of patients experienced grade 3/4 thrombocytopenia, and no patients experienced grade 3/4 neutropenia. Dose reductions were required in only 1% of patients, and there were no discontinuations due to treatment-related toxicity.

These encouraging results have recently been confirmed in 2 studies. In a report by van den Bent et al. (2001) on AOD and AOA patients treated with temozolomide, 27 of 30 patients were previously treated with RT and a first-line PCV chemotherapy regimen (Table 4). Of the patients previously treated with PCV, 26% responded to temozolomide treatment. Further, 2 of 3 chemotherapy-naïve patients achieved a complete response. The median time to progression in responding patients was 13 months. Temozolomide was well tolerated in these patients, with grade 3/4 nausea and vomiting and grade 3/4 thrombocytopenia occurring in only 6% and 2% of cycles, respectively.

Recently, van den Bent et al. (2003a) reported the results of an EORTC phase 2 study demonstrating a 23% objective response rate in 30 evaluable AOD or AOA patients treated with temozolomide at recurrence after first-line PCV treatment (Table 4). The median duration of response for these patients was 6.2 months (range, 3 to 15 months). In general, treatment was well tolerated. Four patients developed grade 3/4 nausea and vomiting that was managed with prophylactic antiemetics. Three patients developed grade 3/4 thrombocytopenia, and 1 patient experienced grade 3 leukopenia. Grade 3 dysphagia or stomatitis was observed in 2 patients, and only 1 patient discontinued treatment because of thrombocytopenia. Costanza et al. (2001) reported a response rate of 22% in a similar patient population (Table 4), with 50% of patients free from disease progression at 6 months.

The lower response rates reported in these studies compared with those reported by Chinot et al. (2001b) might be explained in part by the fact that only 38% to 50% of patients enrolled in these trials responded to first-line PCV therapy, whereas 83% of patients enrolled in the study reported by Chinot et al. responded to first-line PCV treatment. Presumably, differences in response may be explained by different proportions of patients with 1p/19q loss of heterozygosity status. The correlation between 1p loss of heterozygosity and sensitivity to PCV suggests that similar studies should be performed to determine if this correlation also occurs in temozolomide-treated patients. Interestingly, these 4 studies investigating the use of second-line temozolomide therapy after prior PCV show 11% to 46% of patients free from disease progression at 12 months. These results are superior to those reported with other agents used in second-line therapy in the treatment of AOD or AOA.

Future Role of Temozolomide in the Treatment of Oligodendrogliomas

Recent studies have shown that treatment with PCV is effective in patients with OD; however, cumulative hema-

tologic toxicity remains an issue and limits subsequent treatment options. Further, the use of chemotherapy agents with a poor toxicity profile is not optimal for a relatively indolent disease. Thus, the use of an oral agent such as temozolomide, which is associated with a low incidence of noncumulative hematologic toxicity, may provide added survival benefit without significantly affecting the patient's quality of life.

Several studies have demonstrated the activity of temozolomide in patients with AOD and AOA in both first- and second-line settings. Early results suggest that the efficacy of temozolomide as second-line chemotherapy may be comparable to that of PCV, and that temozolomide is effective as salvage therapy after patients fail first-line PCV. Importantly, although PCV is associated with cumulative myelosuppression, treatment with temozolomide is well tolerated and results in few treatment delays or discontinuations due to myelosuppression. The activity of temozolomide and the proportion of patients remaining free from disease progression at 12 months also compare favorably to results with other single-agent or combination regimens as second-line chemotherapy. Further, the fact that temozolomide is an oral agent with an excellent toxicity profile may increase patient compliance compared with that associated with other agents currently being investigated as second-line therapy (e.g., etoposide/cisplatin, paclitaxel, and carboplatin) that require intravenous administration. As most glioma patients use antiepileptic drugs, the absence of drug interactions between temozolomide and cytochrome P450-inducing agents is another important advantage of temozolomide in this patient population.

At present, there are limited data on the use of temozolomide as first-line chemotherapy in patients with AOD and AOA. However, preliminary results from an EORTC phase 2 study suggest that temozolomide may be as active as PCV in treating patients with oligodendroglial tumors after first relapse (van den Bent et al., 2002b). Chemotherapy-naïve patients with recurrent OD after RT were treated with 200 mg/m² of temozolomide on days 1 through 5 of a 28-day cycle. Of 35 evaluable patients, 19 (54%) achieved an objective response, including 9 complete responses and 10 PRs. An additional 10 patients (29%) experienced SD. At 12 months, 40% of patients were free of disease progression. Further studies, including a phase 3 trial comparing temozolomide with PCV, are required to fully elucidate the role of temozolomide in the first-line setting. In addition, temozolomide should be investigated in the adjuvant setting.

The different mechanism of action and improved safety profile of temozolomide in comparison with other agents, including PCV and cisplatin, make it an attractive agent for combination therapy. Other studies are needed to investigate alternative schedules or the combination of other drugs (e.g., paclitaxel or the PCV regimen) with temozolomide. These additional studies may provide evidence of synergistic or additive activity against primary and recurrent OD and OA.

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