

Phase II Trial of Procarbazine, Lomustine, and Vincristine as Initial Therapy for Patients With Low-Grade Oligodendroglioma or Oligoastrocytoma: Efficacy and Associations With Chromosomal Abnormalities

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Purpose: The purpose of this article is to determine the response rate and toxicity of PCV administered before radiation therapy in patients with newly diagnosed LGO/LGOA and to explore correlations between response with 1p/19q deletions and aberrant p53 expression.

Background: Despite prolonged survival of patients with low-grade oligodendroglioma (LGO) and oligoastrocytoma (LGOA), the majority will succumb to progressive disease. Because procarbazine, lomustine (CCNU), and vincristine (PCV) is active in patients with recurrent LGO/LGOA, we hypothesized that it would be beneficial as primary therapy.

Methods: Adult patients with residual tumor on magnetic resonance imaging scan following biopsy or subtotal resection of LGO/LGOA received up to six cycles of PCV. Radiation therapy (59.4 or 54.0 Gy) began within 10 weeks of completing chemotherapy or immediately if there was evidence of tumor progression on PCV. Tumor tissue was

analyzed by fluorescent in situ hybridization for 1p and 19q deletion and by immunohistochemistry for p53 expression.

Results: Eight of 28 (29%) and 13 of 25 (52%) eligible patients demonstrated tumor regression as assessed by the treating physician and a blinded central neuroradiology reviewer, respectively. Myelosuppression was the predominant toxicity. Loss of 1p and 19q were associated with LGO but not LGOA ($P = .009$), were inversely associated with p53 detection, and were not associated with response to PCV (possibly because of the small sample size).

Conclusion: PCV produces tumor regressions in a meaningful proportion of patients with LGO/LGOA. Toxicity, especially myelosuppression, is significant. Loss of 1p and 19q seems limited to patients with pure LGO and is inversely related to p53 alterations.

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OLIGODENDROGLIOMAS ARE uncommon neoplasms, accounting for approximately 10% to 17% of all intracranial gliomas.¹ In patients with low-grade gliomas, the majority will have oligodendroglioma or mixed oligoastrocytoma with oligodendroglioma predominance.² Although more than two-thirds of patients remain alive at 5 years, most of them are young and eventually succumb to this disease.²

Appropriate management of patients with this disease remains controversial. Some clinicians advocate careful observation with symptom management until there is evidence of progressively worse symptoms or neuroimaging evidence of tumor growth. Others recommend radiation therapy as initial treatment. Three randomized trials have recently evaluated the role of radiation. Two of the studies failed to identify a relationship between the dose of radiation and survival.^{2,3} A third study failed to identify a survival advantage for early compared with delayed radiation.⁴

Although chemotherapy has been found to be effective for anaplastic oligodendroglioma,⁵ its role in treatment of patients with low-grade gliomas has not been defined previously. Cairncross et al⁵ noted responses in nine of 10 patients with recurrent anaplastic oligodendroglioma who had presented initially with low-grade pure oligodendroglioma. In the North Central Cancer Treatment Group experience with nitrosourea-based chemotherapy, seven of 20 (35%) patients with low-grade glioma recurrent after radiotherapy treated with BCNU and interferon alfa responded to treatment.⁶ In a small case series, Mason et al,⁷ reported that patients with previously untreated low-grade oligodendroglioma are responsive to chemotherapy. However, there has not been a previous prospective trial that assesses

chemotherapy responsiveness in low-grade oligodendroglioma patients. Therefore, we initiated this study.

METHODS

Eligibility Criteria

All patients had histologic confirmation of low-grade oligodendroglioma or mixed oligoastrocytoma by World Health Organization criteria by central review before patient registration. All patients had tumor in supratentorial

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Additional participating institutions include Iowa Oncology Research Association CCOP, Des Moines, IA (Roscoe F. Morton, MD); Geisinger Clinic and Medical Center CCOP, Danville, PA (Suresh Nair, MD); Altru Health Systems, Grand Forks, ND (Daniel J. Walsh, MD); Ann Arbor Regional CCOP, Ann Arbor, MI (Philip J. Stella, MD).

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sites, excluding those arising in the pons, medulla, or optic chiasm. All patients were 18 years of age or older, with acceptable bone marrow (hemoglobin > 9.0 g/dL, leukocytes > 3,500/ μ L, platelets > 130,000/ μ L), renal (creatinine < 1.5 \times upper limit of institutional normal), and hepatic (aspartate aminotransferase, total bilirubin, and alkaline phosphatase < 2.0 \times upper limit of normal) function. All patients had either biopsy or subtotal resection of tumor with measurable or evaluable disease remaining on a T2-weighted magnetic resonance imaging (MRI) scan following surgery. In patients with contrast-enhancing tumor, accepted practice was to biopsy the enhancing portion; however, stereotactic technique was not mandatory. For those tumors with some contrast enhancement, the boost volume included any enhancing tumor on the T1 contrast-enhanced images with a 1-cm margin. If the tumor had no contrast enhancement, then the boost volume was the initial volume with a 1-cm margin. Patients with gross total resection of tumor were ineligible. Patients unable to have an MRI scan were also ineligible. Treatment began \geq 3 weeks but \leq 12 weeks following histologic confirmation of disease unless the patient had a stereotactic biopsy, in which case the patient could begin treatment within 1 week after the biopsy. All patients were on a stable dose of corticosteroids for at least 1 week before the baseline scan.

Patients with pilocytic astrocytoma, tumors with grade 3 or 4 elements, or mixed tumor with ependymoma elements were ineligible. Patients could not have active or uncontrolled infection, prior malignancy, prior radiation to the cranium or head and neck, prior chemotherapy, or Eastern Cooperative Oncology Group performance score of 3 or 4. Pregnant or lactating women were not eligible for participation. All patients signed a written informed consent, and this study had institutional review board approval throughout its course.

Protocol Therapy

Patients received CCNU (lomustine) 130 mg/m² orally on day 1, procarbazine 75 mg/m² orally days 8 to 21, and vincristine 1.4 mg/m² intravenously on days 8 and 29. There was not a dosage cap for vincristine. Cycles were repeated every 8 weeks for a total of six cycles, assuming acceptable toxicity and absence of tumor growth. Radiation began within 10 weeks of completion of the last cycle of chemotherapy or immediately if there was evidence of tumor progression. Specifications for radiation therapy delivery included an energy \geq 6 megavolts, distance from skin to axis \geq 100 cm, multiple (\geq 2) treatment fields, and two-dimensional or three-dimensional treatment planning. Port films of each field were taken weekly except for opposed fields with identical blocking, for which films could be taken every other week. The initial target tumor volume was the postchemotherapy tumor volume as seen on the T2-weighted MRI scan plus a 2-cm margin. For those tumors with some contrast enhancement, the boost volume included any enhancing tumor on the T1 contrast-enhanced images with a 1-cm margin. If the tumor had no contrast enhancement, then the boost volume was the initial volume with a 1-cm margin. If the boost volume included critical structures such as the brainstem or optic chiasm, the margin could be less than 1 cm adjacent to these structures. At the beginning of the trial, patients received 50.4 Gy in 1.8-Gy fractions (one fraction per day and five fractions per week), then 9.0 Gy in five fractions (one fraction per day and five fractions per week) to the boost volume as specified above. As information became available demonstrating that higher-dose radiation was not superior to lower-dose radiation,² the treatment plan was modified. Specifically, the boost dose was reduced from 9.0 Gy in five fractions to 3.6 Gy in two fractions, reducing the total dose from 59.4 to 54.0 Gy.

Isodose plots were required for a central axis, midway between the central axis in the superior field edge, and midway between the central axis in the inferior field edge. Other levels could be added as needed to ensure dose homogeneity. Quality control guidelines stated that there was no deviation if the initial and boost volumes received \pm 5% of the prescribed doses. A minor deviation was assigned if the volumes received 6% to 10% of the prescribed dose. If the volumes received more or less than 10% of the prescribed dose, a major deviation was assessed.

On Study Examinations

Within 2 weeks before registration, patients had a complete blood count, serum chemistries including creatinine, AST, total bilirubin, alkaline phospho-

phatase, glucose, and total thyroxine. Women with child-bearing potential had a serum pregnancy test within 7 days before study registration. Imaging studies included chest x-ray and MRI with contrast. Carbon monoxide diffusing capacity was obtained if patients had a history of chronic obstructive pulmonary disease or if there was evidence of pulmonary disease on chest x-ray. Each patient had Folstein and Folstein Mini-Mental Status Examination (MMSE) before study registration.

During chemotherapy and radiation, patients had a complete blood count weekly. Chemistries were monitored before each cycle of chemotherapy. MRI was obtained before each cycle of chemotherapy. Following completion of treatment, patients were to return every 4 months for 1 year, then every 6 months for 2 years, and annually for 7 years. With each evaluation, patients underwent a history and physical examination, including neurologic examination, tumor measurement, height, weight, performance score, Folstein and Folstein MMSE, complete blood count, total thyroxine, and MRI with contrast.

Neuroradiology Review

Following completion of the trial, all available baseline and preradiation MRI scans were reviewed by a single neuroradiologist (B.J.E.), who was blinded to the assessment provided by the clinicians. Scans were scored on a scale of -3 to +3 with -3 indicating marked progression, 0 stable, and +3 marked improvement.

Laboratory Methods

The fluorescence in situ hybridization methods for detection of 1p and 19q deletion have been previously described in detail.⁸ Both 1p and 19q fluorescent in situ hybridization probes are located within the minimally deleted 1p and 19q regions in gliomas.⁹ Immunohistochemical analysis of *p53* overexpression (using the D0-7 antibody) was performed as previously described.¹⁰

Statistical Design

A two-stage Fleming design was used to test the null hypothesis that the true response probability to chemotherapy is \leq 15%, versus the alternate hypothesis that the true response probability is \geq 35%. The procedure has an overall significance level of 0.0461 and power of 0.8027 for detecting a true response probability of 35%. According to design, 15 patients were entered into the study. If zero to two confirmed responses were observed, then the regimen would not be considered worth pursuing and accrual would be stopped. If eight or more responses were documented, the regimen would be considered active and accrual could be stopped. If three to seven responses were observed, an additional 13 patients would be entered on study. If fewer than eight confirmed responses were observed in all 28 patients, we would conclude that the treatment was not active in this population. If eight or more confirmed responses were observed, then the treatment would be considered promising, and further testing and subsequent studies would be recommended.

RESULTS

Thirty-one patients were registered to the study between April 1994 and March 1998 (before the initiation of Radiation Therapy Oncology Group trial R9802: Phase II study of observation in favorable low-grade glioma and a phase III study of radiation with or without procarbazine, CCNU, and vincristine (PCV) chemotherapy in unfavorable low-grade glioma). One patient changed his mind and did not begin protocol therapy, and two were declared ineligible, one because of World Health Organization grade 3 tumor classification on pathology review, and one because of discovery of gliomatosis cerebri on review of the pretreatment MRI. Thus, 28 patients were evaluable for toxicity and response to chemotherapy. On-study characteristics of the patients are given in Table 1. The patients ranged in age from 23 to 62 years, with median age of 36 years. Almost all had a good performance score. Contrast enhancement was present in 13

Table 1. Patient Characteristics at Study Entry

Characteristic	n = 28	%
Median age (years)	36	
Range (years)	23-62	
Gender		
Male	15	54
Female	13	46
Performance score		
0	18	64
1	8	29
2	2	7
Histology		
Oligodendroglioma	17	61
Oligoastrocytoma	11	39
Contrast enhancement on preoperative MRI		
Yes	13	46
No	14	50
Missing	1	4
Family history of brain tumor	1	4

(46%) of the preoperative MRI scans. The enhancement was usually scant and diffuse, though occasionally it was focal and intense. Sixty-one percent of patients had pure oligodendroglioma. Of the 11 patients with oligoastrocytoma, 10 were oligodendroglioma predominant and one was astrocytoma predominant.

Nineteen (68%) of the 28 patients received all six cycles of chemotherapy, although nine of these patients did not get all three agents in some of the later cycles. Procarbazine was the agent most often omitted. Three patients received four cycles, two received three, two received two, and two received only one cycle. Only one patient stopped chemotherapy early (after four cycles) because of progressive tumor. One patient developed pulmonary histiocytosis, and protocol therapy was discontinued after three cycles. All remaining patients who failed to complete six cycles of study therapy had evidence of toxicity that precluded completion of chemotherapy, including cumulative and delayed myelosuppression in six, jaundice in one, and pulmonary toxicity in one.

Eighteen (64%) patients received 59.0 Gy, five (18%) received 54.0 Gy, two (8%) received 50.4 Gy, and one (4%) received 50.7 Gy. Two patients (7%) refused radiation therapy. In the 25 eligible patients who received radiation, there were six minor and four major deviations from prescribed irradiation.

Before irradiation, eight of the 28 patients (29%; 95% confidence interval [CI], 13% to 49%) had tumor regression as assessed by the primary physician. Tumor regression was observed in five of 13 (38%) patients whose tumors did and three of 15 (20%) patients whose tumors did not demonstrate variable degrees of contrast enhancement. Only two of 25 patients (8%) were receiving corticosteroids at the time radiation therapy was initiated.

Objective status at the time of crossover to radiation was classified as regression for eight patients (29%), stable for 17 (61%), and progression for three (11%). Two patients (one regression, one stable) chose to defer radiation, and radiation data are missing for one classified as progression. Following radiation of the remaining 25 patients, the best postirradiation response achieved was one complete response (4%) in a pre-

radiation regression, 11 regressions (44%; six in patients with preradiation regressions; five in preradiation stables), 11 stable (44%), and two immediate progressions (8%).

Twenty-five of the 28 (89%) eligible patients had both baseline and preirradiation MRI scans available for central neuroradiology review; of these, mild, moderate, or marked improvement was noted in five, five, and three patients, respectively. Thus, 13 of 25 patients (52%; 95% CI, 31% to 72%) were deemed to have scan improvement by neuroradiology review. The best responses for these 25 patients according to their treating physicians were regression for six (24%), stable for 16 (64%), and immediate progression for three (12%). All six patients classified as regression by the treating physician were confirmed to have mild (n = 1), moderate (n = 2), or marked (n = 3) improvement in scan appearance by the neuroradiologist. For the 16 patients called stable by clinicians' assessments, seven had scans that were classified by the neuroradiologist as mildly (n = 4) or moderately (n = 3) improved, eight had stable imaging, and one was called moderately worse. In three patients, both clinician and radiologist interpreted the scan as worse before radiation therapy (one after cycle 4, two after cycle 6). By neuroradiology review, five of nine (56%) available scans with contrast-enhancing tumor and eight of 16 (50%) without were improved before radiation therapy.

At the time of this analysis, three of the 28 patients (11%) had died, and follow-up in the remaining 25 living patients ranged from 3.24 to 7.38 years, with a median of 4.83 years. Progressions had been recorded for seven (25%) of the participants. Kaplan-Meier estimates of the percentage alive at 1, 2, and 5 years were 100%, 96%, and 89%, respectively. Kaplan-Meier estimates of the percentage recurrence free at 1, 2, and 5 years were 91%, 62%, and undefined, respectively.

Toxicity

The primary toxicity experienced by patients during PCV therapy was myelosuppression. Grade 3 or 4 leukopenia occurred in 39% of patients following the first cycle of therapy. In total, 75% of patients developed grade 3 or 4 leukopenia, demonstrating cumulative myelosuppression associated with CCNU. Similarly, while no grade 4 thrombocytopenia was seen in these patients, grade 3 thrombocytopenia was recorded for 18% of patients with their first cycle of treatment and 64% in total. Anorexia, nausea, vomiting, and diarrhea occurred in a substantial proportion of patients but was generally mild to moderate (Table 2). Neurologic toxicity consisted of lethargy, sensory changes related to peripheral neuropathy, and abdominal pain. These toxicities were also predominantly mild to moderate but were occasionally severe (Table 2).

Baseline Folstein and Folstein MMSE score was normal (27–30) in 23 patients, abnormal (< 27) in four patients, and not available in one patient. Mean number of exams was 7.96 (median, 8; range, 1 to 15) with follow-up ranging from 18.8 to 88.5 months (mean, 56.4; median, 55.0). In 23 patients with normal score at baseline, 21 remained normal at the time of the last MMSE given, and two had no MMSE given beyond baseline. Of four with abnormal scores at baseline, two remained stable (\pm 3 points) and two improved. In total, 23 patients had stable, and two patients had improved MMSE scores at last follow-up.

Table 2. Major Toxicities Observed During Pre-RT Chemotherapy

Toxicity Type	Grade in %			Total
	1-2	3	4	
Hematologic				
Leukopenia	25	64	11	100
Thrombocytopenia	36	64	—	100
GI				
Anorexia	46	7	—	54
Nausea	61	21	—	82
Vomiting	57	7	4	68
Diarrhea	29	4	—	32
Neurologic				
Lethargy	36	4	—	39
Sensory	57	4	—	61
Abdominal Pain	14	11	4	29
Others				
Allergy	25	7	—	32
Alopecia	39	—	—	39

Chromosomal Abnormalities

Tumor blocks were submitted in 25 of 28 patients (89%), and 19 (68%) were sufficient to assess chromosomal loss. Nine of 12 oligodendroglioma and none of seven oligoastrocytoma patients demonstrated loss of 19q, either alone or in association with 1p loss. No patient had 1p loss without 19q loss as well. Despite the small sample size, the differences were statistically significant ($P = .009$; Table 3). In those patients with loss of 1p, the percentage of cells staining positively for *p53* was negligible compared with those without loss of 1p (rank sum $P = .045$). Similarly, in patients with 19q loss, the percentage of cells staining positively for *p53* was also low compared with those with no loss of 19q (rank sum $P = .09$). This trend did not reach

Table 3. 1p Loss/19q Loss by Histology, Clinical Response, and Imaging Response

	Number of Tissues Analyzed	1p Loss and 19q Loss	19q Loss	No Loss	Tissues Not Analyzed
Histology*					
Oligo	12	5	4	3	6
Oligoastro	7	0	0	7	3
Response by clinician†					
Regression	4	0	1	3	4
Stable	13	5	3	5	4
Progression	2	0	0	2	1
Response by neuroradiologist‡					
3	2	0	0	2	1
2	4	1	1	2	1
1	3	1	1	1	2
0	6	2	1	3	2
-1	1	0	0	1	0
-2	2	1	0	1	1
Not done	1	0	1	0	2
Regression	9	2	2	5	4
Stable	6	2	1	3	2
Progression	3	1	0	2	3
(Not done)			(1)		

*Exact χ^2 -squared $P = 0.0091$.

†Exact Kruskal-Wallis $P = 0.81$.

‡Exact Kruskal-Wallis $P = 0.75$.

statistical significance, possibly because of the small sample size. We did not find any evidence of association between loss of 1p or 19q and response to chemotherapy. Loss of 19q with or without loss of 1p was seen in eight of 13 patients with stable disease and one of four patients with tumor regression, as assessed by their clinicians. Similarly, 19q loss with or without 1p loss occurred in three of six patients with stable disease and four of nine with tumor regression, as assessed by the neuroradiologist.

DISCUSSION

This study demonstrates for the first time that chemotherapy, specifically PCV, at diagnosis can induce tumor regression in patients harboring low-grade oligodendroglioma or oligoastrocytoma. The regressions occurred in both histologic types with or without loss of chromosomes 1p or 19q. The response rate observed by clinicians was 29% (95% CI, 13% to 49%). Regression was verified by visual inspection by a single neuroradiologist (B.J.E.) who did not know the clinicians' assessments. By this review, 13 of 25 (52%; 95% CI, 31% to 72%) patients were considered to have scan improvement. How can we explain these discrepant observations? First, the neuroradiologist reviewed all films from initiation through completion of chemotherapy for review at a single setting. It is plausible that changes that appeared slowly over time were apparent only on complete review of all available scans simultaneously. Second, the neuroradiologist's expertise may be superior in detecting smaller changes compared with that of the clinician. Of note, there was complete agreement between clinician and radiologist in patients of marked improvement (three of three), agreement in two of five patients with moderate improvement, and agreement in one of five patients with mild improvement. These data suggest a more conservative assessment of improvement from the clinician's perspective. Because a minority of scans demonstrated contrast enhancement (13 of 28), and because the enhancement was often faint and diffuse, the standard MacDonald criteria¹¹ could not be applied. Moreover, the largest discrepancy between clinicians and neuroradiologist was assessment of changes in the 15 nonenhancing scans; improvements were identified in three patients (20%) by the clinicians and seven patients (47%) by the neuroradiologist. In these patients, familiarity with MRI interpretation by the neuroradiologist may well account for differences in reporting benefits of chemotherapy. From these discrepancies, it is apparent that we need more objective standards of assessing tumor response in the nonenhancing or minimally enhancing brain tumors and that response rates in this disease must be interpreted with caution.

Despite the subjectivity of scan interpretation, there is still significant evidence that PCV produces tumor regression in low-grade oligodendroglioma patients. These observations may be somewhat counterintuitive. Typically, we expect chemotherapy to be most effective in tumors with higher proliferative rates. Patients with anaplastic astrocytoma respond to treatment in 22% to 39% of patients, whereas those with the most rapidly proliferating gliomas, that is, glioblastoma multiforme, rarely experience tumor regression.¹² These data indicate that chemoresponsiveness in glioma patients is not directly associated with proliferative rate. Furthermore, regressions occurred whether the

blood–tumor barrier was largely intact (nonenhancing) or disrupted (enhancing). Because both CCNU and procarbazine are known to cross the normal blood–brain barrier, this observation is not necessarily surprising.

Although tumor regression demonstrates biologic activity, the actual extent of clinical benefit is uncertain at this time. Patients received radiation therapy on completion of chemotherapy ($n = 19$), for tumor progression before completion of planned chemotherapy ($n = 1$), or if toxicity precluded completion of chemotherapy ($n = 8$). Because 89% of patients remain alive, it is not possible to report any putative effect on patient survival. To date, quality of life has been excellent, as assessed by performance score and serial Folstein MMSE scores. However, most patients with low-grade oligodendroglioma have good performance score in the absence of chemotherapy. Therefore, we would not extrapolate the data to suggest that PCV chemotherapy improves either duration or quality of life in these patients. The ongoing Intergroup phase III trial (R9802) comparing radiation alone with radiation plus PCV will eventually address these most important questions.

Toxicity of the regimen was significant. Eight of 28 patients were unable to complete protocol therapy owing to toxicity, primarily because of persistent leukopenia or thrombocytopenia 12 weeks from day 1 treatment. One patient developed jaundice from PCV. The risk of secondary leukemia remains a concern as well. Of note, patients in this trial received “intensive” PCV as used by Cairncross et al⁵ in patients with anaplastic oligodendroglioma. Standard doses of PCV likely would have produced less myelosuppression and was the regimen chosen for R9802 cited above. These limitations indicate that use of adjuvant PCV should be limited to the context of a clinical trial until there is further evidence of true clinical benefit.

The large majority of patients had normal MMSE scores at baseline and maintained normal scores throughout follow-up. This observation indicates that treatment did not cause major

cognitive decline and is consistent with our previous observations in patients treated with radiation therapy alone.¹³ Two patients actually improved with time, indicating that tumor control can improve cognitive function. To date, significant cognitive decline has been observed very infrequently. Admittedly, the Folstein MMSE is not sensitive to lesser changes in executive function. Therefore, these patients may have developed some degree of cognitive impairment that was not detected by the MMSE.

In contrast to reports in anaplastic oligoastrocytoma that 1p and 19q loss are associated with chemoresponsiveness, we were unable to demonstrate the same association in this study. Of note, Cairncross et al¹⁴ observed responses in 25% of patients whose tumors retained 1p and 19q. Subsequently, Ino et al¹⁵ reported that patients with tumors lacking 1p loss but containing *p53* mutations were more responsive to chemotherapy than those without either 1p loss or *p53* mutations. In this trial, we cannot rule out such associations, given the small number of patients with both tissue specimens and response to PCV. Furthermore, loss of 1p and 19q occurred exclusively in patients with oligodendroglioma rather than oligoastrocytoma, further reducing the chances of observing an association if there is one.

However, there does seem to be an association between 1p and 19q loss and the diagnosis of oligodendroglioma versus oligoastrocytoma ($P = .009$).

The inverse relationship between 1p/19q loss and *p53* abnormalities ($P < .09$) indicates that different pathogenetic mechanisms may produce similar morphologic patterns. Currently, we are assessing both 1p/19q loss and *p53* abnormalities in LGO and LGOA to confirm this preliminary observation.

In summary, PCV produces tumor regressions in a meaningful proportion of patients with low-grade oligodendroglioma or oligoastrocytoma. Toxicity, especially myelosuppression, is significant. Loss of 1p and 19q seems limited to patients with pure oligodendroglioma and is inversely related to *p53* alterations.

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