VOLUME 24 · NUMBER 18 · JUNE 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Trial of Chemotherapy Plus Radiotherapy Compared With Radiotherapy Alone for Pure and Mixed Anaplastic Oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402

Gregory Cairncross, Brian Berkey, Edward Shaw, Robert Jenkins, Bernd Scheithauer, David Brachman, Jan Buckner, Karen Fink, Luis Souhami, Normand Laperierre, Minesh Mehta, and Walter Curran

From the University of Calgary, Calgary, Alberta; McGill University, Montreal, Quebec; University of Toronto, Toronto, Ontario, Canada; American College of Radiology; Thomas Jefferson University Medical Center, Philadelphia, PA; Wake Forest University Medical Center, Winston-Salem, NC; Mayo Clinic, Rochester, MN; Foundation for Cancer Research, Phoenix, AZ; University of Texas Southwestern Medical Center, Dallas, TX; and the University of Wisconsin, Madison, WI.

Submitted September 28, 2005; accepted January 19, 2006.

Supported by National Cancer Institute Grants No. U10 CA21661 and U10 CA32115 to the Radiation Therapy Oncology Group; U10 CA25224 to the North Central Cancer Treatment Group; CA23318, CA66636, and CA2115 to the Eastern Cooperative Oncology Group; and U10 CA37422 to Community Clinical Oncology Programs.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to Gregory Cairncross, MD, Foothills Medical Centre, Department of Clinical Neurosciences, 1403 29th St NW, Calgary, Alberta, T2N 2T9, Canada; e-mail: jgcairnx@ucalgary.ca.

© 2006 by American Society of Clinical Oncology

0732-183X/06/2418-2707/$20.00

DOI: 10.1200/JCO.2005.04.3414

ABSTRACT

Purpose
Anaplastic oligodendroglioma (AO) and anaplastic oligoastrocytoma (AOA) are treated with surgery and radiotherapy (RT) at diagnosis, but they also respond to procarbazine, lomustine, and vincristine (PCV), raising the possibility that early chemotherapy will improve survival. Furthermore, better outcomes in AO have been associated with 1p and 19q allelic loss.

Patients and Methods
Patients with AO and AOA were randomly assigned to PCV chemotherapy followed by RT versus postoperative RT alone. The primary end point was overall survival. The status of 1p and 19q alleles was assessed by fluorescence in situ hybridization.

Results
Two hundred eighty-nine eligible patients were randomly assigned to either PCV plus RT (n = 147) or RT alone (n = 142). At progression, 80% of patients randomly assigned to RT had chemotherapy. With 3-year follow-up on most patients, the median survival times were similar (4.9 years after PCV plus RT *v* 4.7 years after RT alone; hazard ratio [HR] = 0.90; 95% CI, 0.66 to 1.24; $P = .26$). Progression-free survival time favored PCV plus RT (2.6 years *v* 1.7 years for RT alone; HR = 0.69; 95% CI, 0.52 to 0.91; $P = .004$), but 65% of patients experienced grade 3 or 4 toxicity, and one patient died. Patients with tumors lacking 1p and 19q (46%) compared with tumors not lacking 1p and 19q had longer median survival times (> 7 *v* 2.8 years, respectively; $P \leq .001$); longer progression-free survival was most apparent in this subset.

Conclusion
For patients with AO and AOA, PCV plus RT does not prolong survival. Longer progression-free survival after PCV plus RT is associated with significant toxicity. Tumors lacking 1p and 19q alleles are less aggressive or more responsive or both.

J Clin Oncol 24:2707-2714. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Anaplastic oligodendroglioma (AO) is a histologically distinct high-grade glioma that, when copopulated by neoplastic astrocytes, evokes a diagnosis of anaplastic oligoastrocytoma (AOA).[1] In recent years, the histologic criteria for the diagnosis of AO and AOA have liberalized, and as a result, the rate of diagnosis of both has increased. Today, up to 25% of newly diagnosed malignant gliomas are designated AO or AOA.[1]

Standard treatment for AO and AOA consists of maximum surgical resection and radiotherapy (RT).[2] Although seldom curative, long survival is relatively common after such treatment. Median survival time is also relatively long, ranging from 3 to 5 years.[3] In North America, initial treatment for AO and AOA has often included chemotherapy with carmustine or procarbazine, lomustine, and vincristine (PCV). Chemotherapy at diagnosis has been justified on the basis of weak evidence of a survival benefit in studies of adjuvant carmustine for malignant glioma (trials populated largely by patients with glioblastoma).[4] Early chemotherapy for oligodendroglioma was reinforced by the discovery that AO and AOA are often chemotherapy sensitive, responding dramatically on computed tomography (CT) or magnetic resonance imaging (MRI) after exposure to PCV.[5,6]

Downloaded from www.jco.org on June 17, 2006 . For personal use only. No other uses without permission.
Copyright © 2006 by the American Society of Clinical Oncology. All rights reserved.

To test the hypothesis that PCV plus RT is a better initial treatment than RT alone for AO and AOA, the Radiation Therapy Oncology Group (RTOG) and four other oncology cooperatives undertook a randomized trial, which opened in 1994. Anticipating that chromosomal analysis might identify clinically important subsets of patients,[7] paraffin sections and blood were requested from all participants, and during the trial, the potential prognostic and predictive value of 1p and 19q allelic loss in AO was reported.[8,9]

PATIENTS AND METHODS

Patients age ≥ 18 years with a newly diagnosed, supratentorial AO or AOA were eligible. Anaplasia was based on an evaluation of the following five microscopic features: tumor cellularity, nuclear pleomorphism, mitotic activity, vascular proliferation, and necrosis. To be high grade, the tumor had to contain two anaplastic features, one of which was frequent mitoses or endothelial proliferation. To be an oligoastrocytoma, a 25% or greater oligodendroglioma component was required. The diagnosis was confirmed by central pathology review on all patients before random assignment. Eligible patients also had a Karnofsky performance score (KPS) of ≥ 60 and adequate hematologic, pulmonary, renal, and hepatic function (absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelets $\geq 150 \times 10^9$/L, oxygen diffusing capacity ≥ 60%, serum creatinine ≤ 1.5× the upper limit of normal [ULN], total bilirubin ≤ 1.5× ULN, and liver function tests < 2× ULN). Patients with other serious illnesses or pregnancy were ineligible. All study centers had institutional review board approval, and all patients consented in writing.

Study Design and Treatment

Patients were randomly assigned at RTOG headquarters within 8 weeks of surgical diagnosis to either PCV followed by focal RT (the experimental arm) or to RT alone (the control arm). Patients were stratified by age younger than 50 years versus 50 years or older, KPS of 60 to 70 versus ≥ 80, and tumor grade of moderately anaplastic (two to three anaplastic features) versus highly anaplastic (four to five anaplastic features). Patients were required to begin the assigned treatment within 1 week of random assignment. Random assignment was performed by randomized permuted block within each stratification cell. In the experimental arm, up to four cycles of PCV were to be administered every 6 weeks before RT as follows: lomustine 130 mg/m^2 orally on day 1; procarbazine 75 mg/m^2 orally daily on days 8 to 21; and vincristine 1.4 mg/m^2 intravenously on days 8 and 29. Doses were calculated using actual body weight, reduced for toxicity, and not escalated. There was no upper limit on the dose of vincristine. Compliance was assessed by case reviews.

Except for timing, RT was prescribed identically in the experimental and control arms. Patients randomly assigned to PCV plus RT were required to begin RT within 6 weeks of the final dose of chemotherapy. The total RT dose was 59.4 Gy in 33 fractions (1.8 Gy each), administered 5 days a week (Monday through Friday). Megavoltage irradiation (≥ 4 MV) was required. RT was planned using a gadolinium-enhanced MRI obtained within 2 weeks of random assignment and administered in two phases. The initial treatment field included the T2-weighted abnormality (ie, tumor plus edema) plus a 2-cm margin (50.4 Gy in 28 fractions). The boost field included the gadolinium-enhanced T1-weighted abnormality (ie, tumor) plus a 1-cm margin (9 Gy in five fractions). After a complete resection, the surgical cavity and edema with a 2-cm margin received the initial 50.4 Gy, and the cavity with a 1-cm margin received the final 9-Gy boost. Quality assurance was determined by case reviews.

Corticosteroid medications were permitted for cerebral edema, antiemetics were permitted for nausea or vomiting, and anticonvulsants were permitted for seizures. Deletions of chromosomes 1p and 19q were evaluated by fluorescence in situ hybridization analysis on tumor tissue sections as described elsewhere.[10] The primary end point was overall survival. Secondary end points were progression-free survival, frequency of severe (≥ grade 3) treatment toxicities, and quality of life. Survival measurements were made from the date of random assignment.

Surveillance and Follow-Up

Baseline examination included a CBC, pulmonary and biochemistry screening, either MRI or CT scan, and a complete physical and neurologic examination, including a Folstein Mini-Mental Status Examination. Quality of life was assessed as described by Mackworth et al.[10] During PCV, blood counts were checked weekly, and serum chemistries were checked before each cycle. During RT, patients were assessed weekly. Follow-up MRI or CT scans were performed before each cycle of PCV and 4 to 6 weeks after RT. Thereafter, scans were performed every 3 months during post-treatment year 1, every 4 months during year 2, every 6 months during years 3 to 5, and then annually. Follow-up laboratory evaluations, general and neurologic examinations, recording of corticosteroid requirements, and Mini-Mental Status Examination and quality-of-life assessments were scheduled similarly. Tumor progression was defined following Macdonald et al[11] (25% increase in tumor size by contrast-enhanced imaging, new lesions, or increasing corticosteroids). At progression, PCV was recommended for patients randomly assigned to RT, but otherwise, treatment at recurrence was discretionary. Second-line therapy was recorded. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria (version 1). For RT toxicities, the RTOG acute morbidity criteria and the RTOG/European Organisation for Research and Treatment of Cancer late morbidity criteria were used.

Statistical Analysis

Overall and progression-free survival were analyzed by the Kaplan-Meier method with one-sided log-rank statistics. The study was designed to enroll 146 patients per arm, giving 80% power to detect a 50% increase in median survival time from 3.8 years in the control group to 5.7 years in the experimental group (hazard ratio [HR] for death = 0.67), with a type I error rate of 0.05. Analyses were performed on a patient-eligible basis. The Cox proportional hazards model was fitted to adjust for stratification factors and other confounding clinical and genetic variables. Quality of life and neurologic function will be analyzed and reported separately.

RESULTS

Patients

From July 1994 to March 2002, 289 eligible patients from 76 institutions were randomly assigned to PCV plus RT (n = 147) or RT alone (n = 142); 50% were enrolled at 12 centers. Ten randomly assigned patients (five in each arm) were declared ineligible. In the experimental arm, the reasons for ineligibility were varied and included the following: pregnancy (n = 1), missing baseline KPS (n = 1), failure to obtain a planning MRI (n = 1), incorrect diagnosis (n = 1), and missing documentation of central pathology review (n = 1). In the control arm, the reasons for ineligibility pertained to the diagnosis (n = 2) or central review process. Sixty-nine percent of participants were under age 50 years, 60% were male, 88% had debulking surgery, 90% had a KPS ≥ 80, and 74% had an AO or oligodendroglioma-dominant AOA. Moreover, the treatment groups were well balanced with respect to age, sex, KPS, imaging features, extent of resection, pure versus mixed histology, degree of anaplasia (moderate *v* high), and corticosteroid requirements at baseline (Table 1). Unstained sections were available for fluorescence in situ hybridization analysis on 206 (71%) of 289 eligible patients; 1p and 19q deletion status was successfully ascertained in 201 patients (70%). The median duration of follow-up was 5.1 years (range, 3 to 93 months).

Patient Disposition and Treatment Delivery

The median time from diagnosis to the start of treatment was 5 weeks (range, 1 to 14 weeks) in the experimental arm and 6 weeks (range, 1 to 12 weeks) in the control arm (Table 2). Chemotherapy was delivered per protocol in 72% of patients; minor or acceptable

Downloaded from www.jco.org on June 17, 2006 . For personal use only. No other uses without permission.
Copyright © 2006 by the American Society of Clinical Oncology. All rights reserved.

Table 1. Clinical and Molecular Characteristics

Characteristic	PCV/RT (n = 147) No. of Patients	PCV/RT (n = 147) %	RT (n = 142) No. of Patients	RT (n = 142) %
Age, years				
Median	43		43.5	
Range	18-75		19-76	
Age,*				
< 50 years	101	69	98	69
≥ 50 years	46	31	44	31
Sex				
Male	90	61	84	59
Female	57	39	58	41
Neurologic function				
No symptoms	47	32	46	32
Minor symptoms	72	49	69	49
Moderate, active	17	12	12	8
Moderate, inactive	11	7	14	10
Unknown	—	—	1	1
KPS*				
60-70	15	10	15	11
80-100	132	90	127	89
Contrast-enhancing tumor				
Yes	88	60	89	63
No	59	40	53	37
Surgery				
Debulking procedure	126	86	128	90
Biopsy only	21	14	14	10
Histologic type				
AO	76	52	72	51
AOA, oligodendroglioma dominant	28	19	37	26
AOA, no dominance	24	16	15	11
AOA, astrocytoma dominant	19	13	18	13
Tumor grade*				
Moderately anaplastic	80	54	80	56
Highly anaplastic	67	46	62	44
Multifocal tumor				
Yes	15	10	10	7
No	131	89	130	92
Unknown	1	1	2	1
Tumor size,† median area				
Nonenhancing, No.	96		95	
Preoperative, mm^2	36.1		34.0	
Postoperative, mm^2	22.4		24.1	
Enhancing, No.	71		78	
Preoperative, mm^2	13.6		16.9	
Postoperative, mm^2	7.4		9.5	
Corticosteroids at baseline				
Yes	91	62	79	56
No	56	38	63	44
Chromosome 1p				
Known	101		101	
1p deleted	50	50	59	58
1p intact	51	50	42	42
Unknown	46		41	
Chromosome 19q				
Known	102		103	
19q deleted	62	61	64	62
19q intact	40	39	39	38
Unknown	45		39	
Chromosomes 1p and 19q				
Known	100		101	
Both deleted	43	43	50	50
One or neither deleted	57	57	51	50
Unknown	47		41	

Abbreviations: PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy; KPS, Karnofsky performance score; AO, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma.
* Stratification factor at random assignment.
† Tumor size = estimated maximum cross-sectional area (largest diameter × largest perpendicular diameter).

Table 2. Patient Disposition and Treatment Intensity

Treatment	PCV/RT (n = 147) No. of Patients	PCV/RT (n = 147) %	RT (n = 142) No. of Patients	RT (n = 142) %
Chemotherapy				
Never started PCV	1	1	—	—
Median No. of cycles				
Median	4	—		
Range	1-4	—		
Patients starting fourth cycle	79	54	—	—
Patients completing fourth full dose cycle	70	48	—	—
Reason for < four cycles				
Tumor progression	20	14	—	—
Toxicity from chemotherapy	25	20	—	—
Patient preference	11	7	—	—
Other*/unknown	11	7	—	—
RT				
Never started RT	16	11	1	1
Dose, Gy				
Median	59.4		59.4	
Range	9-60.4		18-65.4	
No. of fractions				
Median	33		33	
Range	5-34		10-36	
Duration, weeks				
Median	6.5		6.6	
Range	0.6-10.3		2.4-9.3	
RT interruption/delay	39	30	50	36
Delay as a result of toxicity	0		1	
Received ≤ 90% planned RT dose	4	3	6	4
Early stoppage of RT	7	5	7	5
Reason for early stoppage				
Tumor progression	3	2	2	1
Other*/unknown	4	3	5	4

Abbreviations: PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy.
*Any missed dose or patient or prescription error.

variations occurred in 17% and 6% of patients, respectively. In 4% of patients, PCV was either administered incorrectly or could not be verified. Fifty-four percent of patients received four cycles of PCV (wholly or partly), 22% received three, 10% received two, 12% received one, and 1% did not receive PCV despite being randomly assigned to PCV plus RT. Forty-eight percent of patients completed all four cycles of the dose-intensive PCV formulation used in the study. The reasons for stopping PCV were progression or death, toxicity, patient refusal, and physician preference. RT was administered per protocol or acceptably in 76% of PCV patients and in 82% of controls; unacceptable variations occurred in 6% and 8% of patients, respectively. Because of progression, death, or patient preference, RT was stopped in 10% of patients in the experimental arm and 5% of patients in the control arm. RT delivery could not be confirmed in 7% of patients in the experimental arm and 5% of patients in the control arm.

Survival

Thirty-eight months after the last patient was enrolled, 158 (55%) of 289 patients had died (75 of 147 patients in the experimental arm and 83 of 142 patients in the control arm). The unadjusted HR for death after PCV plus RT versus RT alone was 0.90 (95% CI, 0.66 to

Downloaded from www.jco.org on June 17, 2006 . For personal use only. No other uses without permission.
Copyright © 2006 by the American Society of Clinical Oncology. All rights reserved.

Table 3. Overall and Progression-Free Survival by Treatment Group

Survival	PCV/RT (n = 147)		RT (n = 142)	
	Median	95% CI	Median	95% CI
Overall survival time, years	4.9	3.3 to 7.2	4.7	3.4 to 5.7
Overall survival rate, %				
1 year	85	78 to 90	91	85 to 95
2 years	70	62 to 77	74	66 to 81
5 years	49	40 to 57	46	37 to 54
Progression-free survival, years	2.6	1.9 to 4.1	1.7	1.3 to 2.4
Progression-free survival rate, %				
1 year	69	60 to 75	66	57 to 73
2 years	57	48 to 64	46	37 to 54
5 years	39	31 to 47	21	14 to 28

NOTE. Eighty-one patients in the RT arm had PCV ortemozolomide salvage therapy.
Abbreviations: PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy.

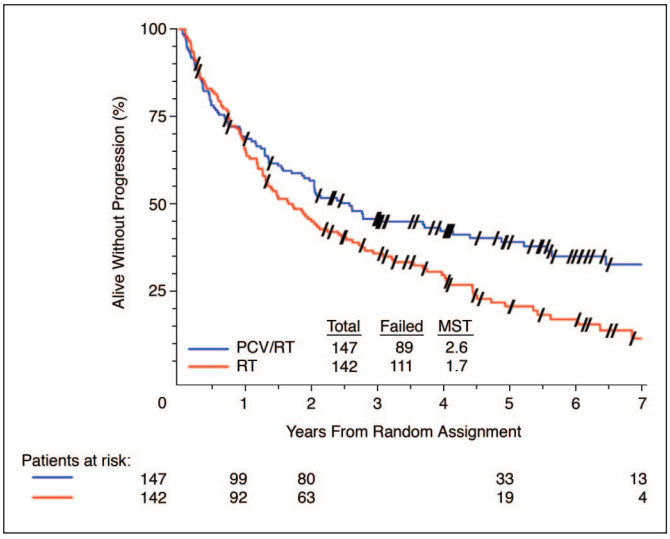

Fig 2. Kaplan-Meier estimates of progression-free survival by treatment group. The hazard ratio for survival of patients treated with procarbazine, lomustine, and vincristine (PCV) plus radiotherapy (RT) compared with RT alone was 0.69 (95% CI, 0.52 to 0.91; P = .004). MST, median survival time.

1.24; log-rank P = .26), indicating that survival was not prolonged by PCV plus RT at diagnosis. The median survival time was 4.9 years in the PCV plus RT group and 4.7 years in the RT group (Table 3 and Fig 1). Progression-free survival time was prolonged by PCV plus RT (HR = 0.69; 95% CI, 0.52 to 0.91; log-rank P = .004). Median progression-free survival time was 2.6 years with PCV plus RT compared with 1.7 years with RT alone (Fig 2).

Safety

Patients randomly assigned to the experimental arm experienced significant toxicity. Sixty-five percent of patients (94 of 144 patients) had a grade 3 (48 of 144 patients, 33%) or 4 (46 of 144 patients, 32%) toxic reaction on PCV. The most frequent severe toxicities were hematologic (n = 80), neurologic (cognitive or mood change and peripheral or autonomic neuropathy, n = 19), GI (nausea and vomiting, n = 13), hepatic (n = 6), and dermatologic (n = 6). One corticosteroid-dependent patient developed a severe pulmonary infection while neutropenic and died. Serious toxicities were uncommon during RT. Twelve patients (8%) in the PCV plus RT arm and seven patients (5%) in the RT arm had grade 3 or 4 toxicity (Table 4). Late toxicities were uncommon, occurring in 4% and 5% of patients in the experimental and control groups, respectively. No instances of dementia or radionecrosis have been reported in either group.

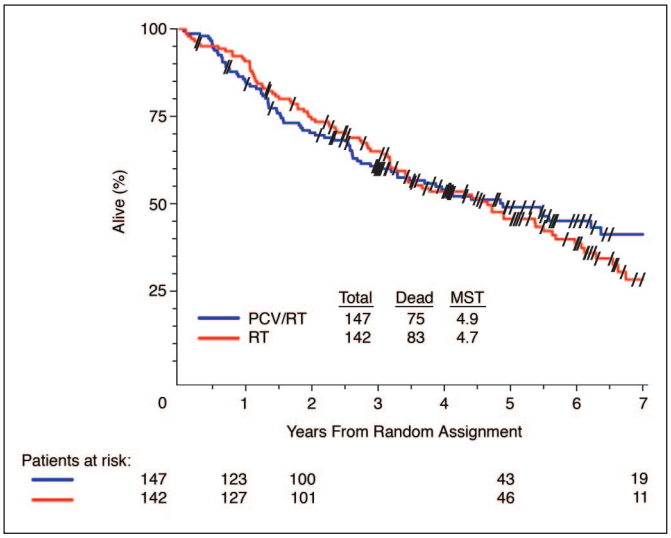

Fig 1. Kaplan-Meier estimates of overall survival by treatment group. The hazard ratio for survival of patients treated with procarbazine, lomustine, and vincristine (PCV) plus radiotherapy (RT) compared with RT alone was 0.90 (95% CI, 0.66 to 1.24; P = .26). MST, median survival time.

Table 4. Grade 3 or 4 Toxicities During Treatment

Toxicity	During PCV (n = 146)		RT* After PCV (n = 131)		RT* Only (n = 141)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Hematologic, any	80	56	6	4	0	0
Neutropenia	62	42	4	3	0	0
Thrombocytopenia	54	37	3	2	0	0
Anemia	7	5	0	0	0	0
Neurologic, any	19	13	3	2	2	1
Cognitive change	1	1	1	1	0	0
Affective disturbance	1	1	0	0	2	1
Peripheral neuropathy	12	8	0	0	0	0
Autonomic neuropathy	3	2	0	0	0	0
Other neurologic	7	5	2	1	1	1
GI, any	13	9	0	0	0	0
Nausea or vomiting	12	8	0	0	0	0
Other GI	3	2	0	0	0	0
Hepatic	6	4	0	0	0	0
Dermatologic	6	4	0	0	3	2
Pulmonary	6	4	2	1	0	0
Ototoxicity	1	1	1	1	2	1
Fever	2†	1	0	0	0	0

Abbreviations: PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy.
*Within 90 days of starting RT.
†Fatal in one patient.

Downloaded from www.jco.org on June 17, 2006 . For personal use only. No other uses without permission.
Copyright © 2006 by the American Society of Clinical Oncology. All rights reserved.

Treatment at Progression

For patients randomly assigned to RT, PCV at recurrence was recommended. In May 2005, 177 (61%) of 289 patients had experienced progression, including 76 (52%) of 147 patients in the experimental arm and 101 (71%) of 142 controls. Rates of salvage chemotherapy differed significantly between the groups. At progression, 81 (80%) of 101 patients assigned to RT received salvage chemotherapy compared with 29 (37%) of 76 patients assigned to PCV plus RT. In the control arm, the cytotoxics used at progression were PCV (n = 21), temozolomide (n = 10), both PCV and temozolomide (n = 11), or neither PCV nor temozolomide (n = 12) or were unspecified (n = 27). In the experimental arm, a variety of cytotoxics was used, often temozolomide (n = 14). Response to salvage chemotherapy was not recorded. Other therapies at progression included second surgery, focused reirradiation, and investigational maneuvers. Rates of second surgery also differed significantly between the groups. Sixty-one (60%) of 101 patients in the control group had second surgery compared with 30 (39%) of 76 patients assigned to PCV plus RT. Whether differences in the intensity or effectiveness of treatment at recurrence had a disproportionately favorable influence on the overall survival of patients in the control group is open to speculation.

Chromosomal Analysis

Loss of 1p was detected in 109 (54%) of 202 informative patients, including 50 (50%) of 101 patients in the PCV plus RT group and 59 (58%) of 101 patients in the RT group (Table 5). Loss of 19q was found in 126 (61%) of 205 informative patients, including 62 (61%) of 102 patients in the PCV plus RT group and 64 (62%) of 103 patients in the RT group. Combined loss of 1p and 19q was detected in 93 (46%) of 201 patients, including 43 (43%) of 100 patients in the PCV plus RT group and 50 (50%) of 101 patients in the RT group. Combined loss was more frequent in pure tumors (57% for AO *v* 14% for AOA, $P < .001$). Patients whose tumors had combined 1p and 19q loss also had longer survival time. The HR for death for 1p- and 19q-deleted patients was significantly reduced compared with all other patients (HR = 0.31; 95% CI, 0.20 to 0.47; log-rank $P < .001$; median overall survival time, not reached *v* 2.8 years, respectively; Fig 3). Similarly, combined loss of 1p and 19q was associated with a significantly lower risk of tumor progression compared with no loss (HR = 0.44; 95% CI, 0.32 to 0.62; log-rank $P < .001$; median progression-free survival time, 4.0 *v* 1.3 years, respectively).

There was no effect of treatment on survival analyzed by genotype (Fig 4). For 1p- and 19q-deleted patients, the HR for death after PCV plus RT versus RT alone was 0.81 (95% CI, 0.40 to 1.65; log-rank $P = .28$; median survival time, not reached *v* 6.6 years, respectively). Similarly, for patients with tumors with other genotypes, treatment had no effect on survival (HR = 0.91; 95% CI, 0.58 to 1.42; log-rank $P = .33$; median survival time, 2.7 years for PCV plus RT *v* 2.8 years for RT only). The lower risk of progression after PCV plus RT compared with RT only was statistically significant only for the patients with both 1p and 19q deletions (HR = 0.42; 95% CI, 0.24 to 0.75; log-rank $P = .001$; median progression-free survival time, not reached *v* 2.6 years, respectively; Fig 5). For the other patients, initial treatment had

Table 5. Overall and Progression-Free Survival by Genotype and Treatment

	PCV/RT (n = 147)		RT (n = 142)	
Genotype	Median	95% CI	Median	95% CI
Tumors with 1p and 19q deleted				
No.	43		50	
%	29		35	
Overall survival time, years	Not reached	—	6.6	5.4 to NA
Overall survival rates, %				
1 year	95	83 to 99	96	85 to 99
2 years	88	74 to 95	88	75 to 94
5 years	72	54 to 83	66	50 to 78
Progression-free survival time, years	Not reached	—	2.6	1.5 to 4.1
Progression-free survival rates, %				
1 year	86	72 to 93	84	70 to 92
2 years	77	61 to 87	55	40 to 68
5 years	57	40 to 71	27	15 to 41
Tumors with one or neither allele lost				
No.	57		51	
%	39		36	
Overall survival time, years	2.7	2.0 to 5.5	2.8	1.9 to 4.4
Overall survival rates, %				
1 year	77	64 to 86	84	71 to 92
2 years	61	47 to 72	62	47 to 74
5 years	37	24 to 50	31	19 to 45
Progression-free survival time, years	1.4	0.9 to 2.6	1.0	0.6 to 1.9
Progression-free survival rates, %				
1 year	61	48 to 73	46	32 to 59
2 years	47	34 to 59	34	21 to 47
5 years	20	11 to 33	8	2 to 18

NOTE. Eighty-one patients in the RT arm had PCV ortemozolomide salvage therapy.
Abbreviations: PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy; NA, not available.

Downloaded from www.jco.org on June 17, 2006 . For personal use only. No other uses without permission.
Copyright © 2006 by the American Society of Clinical Oncology. All rights reserved.

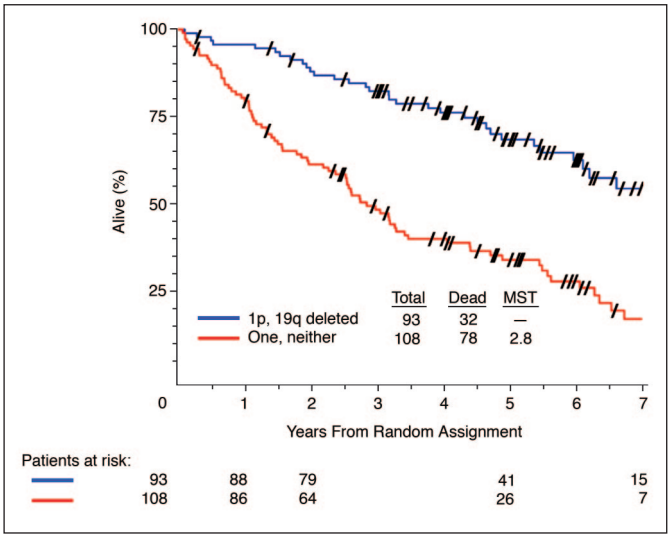

Fig 3. Kaplan-Meier estimates of overall survival by 1p and 19q deletion. The hazard ratio for survival of patients with 1p and 19q allelic loss compared with patients with one of neither allele lost was 0.31 (95% CI, 0.20 to 0.47; $P < .001$). MST, median survival time.

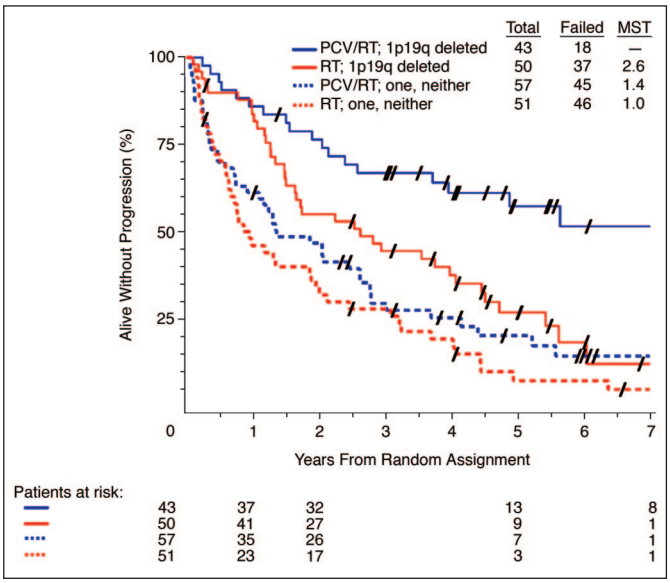

Fig 5. Kaplan-Meier estimates of progression-free survival by treatment and genotype. PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy; MST, median survival time.

no significant effect on the risk of progression (HR = 0.78; 95% CI, 0.51 to 1.18; log-rank $P = .12$; median progression-free survival time, 1.4 years for PCV plus RT *v* 1.0 years for RT only).

Cox Multivariate Regression Analysis

The influence of genetic and clinical variables on survival was analyzed in the Cox proportional hazards models with assigned treatment, age, KPS, and number of anaplastic features as fixed covariates. Loss of 1p, loss of 19q, younger age, normal neurologic function, moderate anaplasia, debulking surgery, and unifocality on baseline imaging were independently associated with longer overall survival time, whereas sex, race, tumor histology, and corticosteroid use were not. Loss of 1p, PCV therapy, younger age, moderate anaplasia, and unifocality predicted longer progression-free survival time. Loss of 19q was not associated with progression-free survival in the final Cox model.

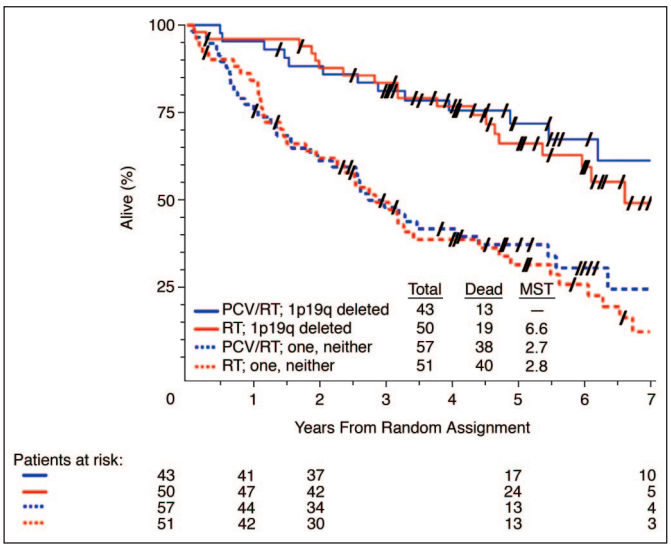

Fig 4. Kaplan-Meier estimates of overall survival by treatment and genotype. PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy; MST, median survival time.

DISCUSSION

This study, conceived in the early 1990s, tested the hypothesis that a dose-intensive PCV formulation administered immediately before RT would prolong the survival of patients with newly diagnosed AO and AOA compared with RT alone, which was then the standard of care for all types of anaplastic glioma. The idea that a recognizable subtype of malignant glioma might be cured by intensive initial therapy was an exciting prospect in 1994.[12,13] Instead, this study and a similar trial in Europe[14] demonstrate that PCV plus RT at diagnosis is not a better initial management strategy for AO and AOA compared with RT alone. Because most patients in the control group received PCV or similar chemotherapy at progression, one could argue that this study actually tested the hypothesis that intense initial therapy with PCV and RT is superior to sequential treatment for AO and AOA; it is not.

This result stands in sharp contrast to the findings in the study by Stupp et al,[15] in which the survival of patients with glioblastoma was prolonged by temozolomide plus RT at diagnosis. Why might early chemotherapy be effective for glioblastoma, a chemotherapy-resistant cancer, but not oligodendroglioma, a chemotherapy-sensitive cancer? Two possibilities come to mind. First, compared with glioblastoma, AO and AOA have favorable natural histories, which is a characteristic that may be a more important determinant of survival than any combination or sequence of noncurative therapies, like PCV and RT. Second, temozolomide, which also alkylates DNA, is well tolerated compared with PCV. Temozolomide can be administered daily during RT without significant myelosuppression,[15] whereas toxicity precludes chemoradiotherapy with PCV. The fact that progression-free

Downloaded from www.jco.org on June 17, 2006 . For personal use only. No other uses without permission.
Copyright © 2006 by the American Society of Clinical Oncology. All rights reserved.

survival was prolonged by adding PCV to RT at diagnosis suggests that early chemotherapy may have the potential to improve overall survival as well. Such potential might be realized by a drug like temozolomide, which is less toxic and can be administered daily with RT. Indeed, temozolomide has significant antioligodendroglioma activity.[16,17]

During the trial, retrospective studies drew attention to a possible association between 1p and 19q allelic loss and radiographic response to PCV, durable response to PCV, long progression-free survival after RT, and long overall survival in patients with AO.[8,9,18-23] In this study, tumor tissue was available for analysis in 71% of patients. Codeletion of 1p and 19q was detected in 46% of assessable patients. Patients whose tumors harbored a codeletion of 1p and 19q lived far longer than all other patients. In the Cox multivariate regression analysis, 1p loss and 19q loss were independent predictors of overall survival, suggesting that tumors with 1p or 19q loss, but especially a codeletion, have a more favorable natural history, response to treatment, or both. Indeed, tumors with 1p and 19q codeletion are a clinically and biologically distinct subgroup of oligodendrogliomas.

A post hoc analysis of the interaction of treatment and genotype showed that treatment assignment had no effect on survival. For both the 1p and 19q codeleted patients and the other patients, adding PCV to RT at diagnosis did not prolong life. Of note, the progression-free survival benefit observed in patients randomly assigned to PCV plus RT was only statistically significant in the 1p and 19q subset. This finding provides further evidence that loss of 1p and 19q is both a predictive and prognostic marker in AO and AOA, supporting earlier results linking this codeletion with radiographic response to PCV.[8] Whether 1p and 19q loss is a relative or absolute marker of chemotherapy sensitivity is unresolved by these data.

This study successfully examined the treatment of an uncommon brain tumor, demonstrating that multimodality treatment at diagnosis is no more effective in prolonging survival than a measured approach to initial treatment, using RT and chemotherapy sequentially, as needed. Although progression-free survival was prolonged by early intensive treatment, PCV plus RT at diagnosis was accompanied by substantial chemotherapy-related toxicity. Finally, this study confirmed the biologic and clinical importance of allelic loss of chromosomes 1p and 19q in AOs and AOAs, setting the stage for future trials designed specifically for patients with 1p and 19q codeletion.

REFERENCES

1. Reifenberger G, Louis DN: Oligodendroglioma: Toward molecular definitions in diagnostic neuro-oncology. J Neuropathol Exp Neurol 62:111-126, 2003

2. DeAngelis LM: Brain tumors. N Engl J Med 344:114-123, 2001

3. Puduvalli VK, Hashmi M, McAllister LD, et al: Anaplastic oligodendrogliomas: Prognostic factors for tumor recurrence and survival. Oncology 65:259-266, 2003

4. Walker MD, Green SB, Byar DP, et al: Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. N Engl J Med 303:1323-1329, 1980

5. Cairncross JG, Macdonald DR: Successful chemotherapy for recurrent malignant oligodendroglioma. Ann Neurol 23:360-364, 1988

6. Kim L, Hochberg FH, Thornton AF, et al: Procarbazine, lomustine, and vincristine (PCV) chemotherapy for grade III and grade IV oligoastrocytomas. J Neurosurg 85:602-607, 1996

7. Reifenberger J, Reifenberger G, Liu L, et al: Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p. Am J Pathol 145:1175-1190, 1994

8. Cairncross JG, Ueki K, Zlatescu MC, et al: Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst 90:1473-1479, 1998

9. Smith JS, Perry A, Borell TJ, et al: Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas. J Clin Oncol 18:636-645, 2000

10. Mackworth N, Fobair P, Prados MD: Quality of life self-reports from 200 brain tumor patients: Comparisons with Karnofsky performance scores. J Neurooncol 14:243-253, 1992

11. Macdonald DR, Cascino TL, Schold SC, et al: Response criteria for phase II studies of malignant glioma. J Clin Oncol 8:1277-1280, 1990

12. Macdonald DR, Gaspar LE, Cairncross JG: Successful chemotherapy for newly diagnosed aggressive oligodendroglioma. Ann Neurol 27:573-574, 1990

13. Cairncross G, Macdonald D, Ludwin S, et al: Chemotherapy for anaplastic oligodendroglioma. J Clin Oncol 12:2013-2021, 1994

14. van den Bent MJ, Delattre J-Y, Taphoorn MJB, et al: First analysis of EORTC trial 26951, a randomized phase III study of adjuvant PCV chemotherapy in patients with highly anaplastic oligodendroglioma. J Clin Oncol 23:114, 2005 (suppl, abstr 1503)

15. Stupp R, Mason WP, van den Bent MJ, et al: Radiotherapy plus concomitant and adjuvant temozolomide for patients with newly diagnosed glioblastoma. N Engl J Med 352:987-996, 2005

16. Chinot OL, Honore S, Dufour H, et al: Safety and efficacy of temozolomide in patients with recurrent anaplastic oligodendrogliomas after standard radiotherapy and chemotherapy. J Clin Oncol 19:2449-2455, 2001

17. van den Bent MJ, Taphoorn MJB, Brandes AA, et al: Phase II study of first line chemotherapy with temozolomide in recurrent oligodendroglial tumors: The European Organization for the Research and Treatment of Cancer Brain Tumor Group Study 26971. J Clin Oncol 21:2525-2528, 2003

18. Betensky RA, Zlatescu MC, Sasaki H, et al: Molecular subtypes of anaplastic oligodendroglioma: Implications for patient management at diagnosis. Clin Cancer Res 7:839-845, 2001

19. Thiessen B, Maguire JA, McNeil K, et al: Loss of heterozygosity for loci on chromosome arms 1p and 10q in oligodendroglial tumors: Relationship to outcome and chemosensitivity. J Neurooncol 64:271-278, 2003

20. Chahlavi A, Kanner A, Peereboom D, et al: Impact of chromosome 1p status in response of oligodendroglioma to temozolomide: Preliminary results. J Neurooncol 61:267-273, 2003

21. Bauman GS, Ino Y, Ueki K, et al: Allelic loss of chromosome 1p and radiotherapy plus chemotherapy in patients with oligodendrogliomas. Int J Radiat Oncol Biol Phys 48:825-830, 2000

22. van den Bent MJ, Looijenga LHJ, Langenberg K, et al: Chromosomal anomalies in oligodendroglial tumors are correlated to clinical features. Cancer 97:1276-1284, 2003

23. Hoang-Xuan K, Capelle L, Kujas M, et al: Temozolomide as initial treatment for adults with low-grade oligodendrogliomas and oligoastrocytomas and correlation with chromosome 1p deletions. J Clin Oncol 22:3133-3138, 2004

Acknowledgment

We are indebted to the patients who agreed to participate in this study and also to the nurses and managers at participating institutions, office staff of the participating groups, and staff in the pathology and molecular genetics laboratories of the Mayo Clinic whose support was critical to the success of this large trial.

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Downloaded from www.jco.org on June 17, 2006 . For personal use only. No other uses without permission.
Copyright © 2006 by the American Society of Clinical Oncology. All rights reserved.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Author Contributions

Conception and design: Gregory Cairncross, Edward Shaw, Robert Jenkins, Bernd Scheithauer, Jan Buckner, Minesh Mehta, Walter Curran
Financial support: Walter Curran
Administrative support: Gregory Cairncross, Edward Shaw, Robert Jenkins, Bernd Scheithauer, Minesh Mehta, Walter Curran
Provision of study materials or patients: Gregory Cairncross, Edward Shaw, Robert Jenkins, Bernd Scheithauer, David Brachman, Jan Buckner, Karen Fink, Luis Souhami, Normand Laperierre, Minesh Mehta, Walter Curran
Collection and assembly of data: Brian Berkey, Robert Jenkins, Bernd Scheithauer, Minesh Mehta, Walter Curran
Data analysis and interpretation: Gregory Cairncross, Brian Berkey, Edward Shaw, Robert Jenkins, David Brachman, Jan Buckner, Karen Fink, Luis Souhami, Normand Laperierre, Minesh Mehta, Walter Curran
Manuscript writing: Gregory Cairncross, Brian Berkey, Edward Shaw, Robert Jenkins, Bernd Scheithauer, David Brachman, Jan Buckner, Karen Fink, Luis Souhami, Normand Laperierre, Minesh Mehta, Walter Curran
Final approval of manuscript: Gregory Cairncross, Brian Berkey, Edward Shaw, Robert Jenkins, Bernd Scheithauer, David Brachman, Jan Buckner, Karen Fink, Luis Souhami, Normand Laperierre, Minesh Mehta, Walter Curran

Downloaded from www.jco.org on June 17, 2006 . For personal use only. No other uses without permission.
Copyright © 2006 by the American Society of Clinical Oncology. All rights reserved.