Randomized Phase III Trial in Childhood High-Grade Astrocytoma Comparing Vincristine, Lomustine, and Prednisone With the Eight-Drugs-in-1-Day Regimen

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Purpose: **In a previous randomized trial, the addition of adjuvant chemotherapy to postoperative radiotherapy proved beneficial in the treatment of childhood high-grade astrocytomas. The present study tests the hypothesis that an eight-drug adjuvant chemotherapy regimen would improve survival in such children compared with the three-drug regimen of the prior study.**

Patients and Methods: **Between April 1985 and May 1990, patients between the ages of 18 months and 21 years with newly diagnosed high-grade astrocytomas were eligible for this study, as determined by the treating institution's histopathologic diagnosis. Treatment consisted of postoperative local-field radiotherapy and adjuvant chemotherapy, either lomustine (CCNU), vincristine, and prednisone (control regimen) or eight-drugs-in-1-day chemotherapy (experimental regimen). Two cycles of postoperative preirradiation chemotherapy were administered in the experimental regimen. Patients were evaluated radiographically every 3 months after irradiation.**

Results: **Eighty-five eligible patients were randomized to the control regimen and 87 to the experimental regimen. The progression-free survival (PFS) and overall survival (OS) at 5 years were 33% (SE = 5%) and 36% (SE = 6%), respectively. There was no statistical difference in outcome between the two chemotherapy regimens. In patients with confirmed diagnoses of anaplastic astrocytoma (AA) or glioblastoma multiforme (GBM), anaplastic astrocytoma, greater than 90% resection, and nonmidline tumor location were characteristics predictive of an improved PFS. There was a difference in toxicity between the two chemotherapeutic regimens, with greater myelosuppression and hearing loss in the experimental regimen. Tumor recurrence occurred primarily within the primary tumor site.**

Conclusions: **There is no benefit to the treatment of high-grade astrocytomas in children with eight-drugs-in-1-day chemotherapy compared with CCNU, vincristine, and prednisone. Extent of tumor resection and histopathologic diagnosis are significant prognostic variables. The overall outcome for children with high-grade astrocytomas remains poor.**

J Clin Oncol 13:112-123. © 1995 by American Society of Clinical Oncology.

THE OUTCOME for both children and adults with high-grade astrocytomas (anaplastic astrocytoma [AA] and glioblastoma multiforme [GBM]) continues to be bleak. Historically, with surgery and irradiation, only rare patients with GBM survived beyond 2 years after diagnosis,[1] whereas approximately 20% of patients with AA survived 2 to 3 years after diagnosis.[1-5] Although several studies in adults have demonstrated modest benefit from the addition of nitrosourea-based chemotherapy, with some improvement in progression-free survival (PFS) after diagnosis, an impact on overall survival has not been convincingly demonstrated.[6-8]

The first randomized phase III trial for children with high-grade astrocytoma (Childrens Cancer Group [CCG]-943), conducted between 1976 and 1981, demonstrated benefit from adjuvant chemotherapy (lomustine [CCNU], vincristine, and prednisone) when added to irradiation; compared with irradiation alone, this benefit was noted both for PFS and overall survival (OS).[1] Accordingly, the present phase III trial (CCG-945) sought to compare the chemotherapy-containing regimen of the earlier CCG study with a more intensive regimen of eight drugs packaged together over an 18-hour period, known as the eight-drugs-in-1-day (8-in-1) regimen, which had generated promising preliminary data in pediatric patients with high-grade astrocytomas.[9] Here we report the outcome of that study.

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Submitted April 6, 1994; accepted September 12, 1994.

Supported by the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD. J.M.B. is supported by grant no. CA-21765 and by the American Syrian Associated Charities, Memphis, TN.

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0732-183X/95/1301-0017$3.00/0

PATIENTS AND METHODS

The CCG-945 study was opened to participating institutions of the CCG on April 1, 1985. All patients between 18 months and 21 years of age at diagnosis were to be randomized between two chemotherapy regimens using the same radiation therapy guidelines for each. Children less than 18 months of age, as well as children with primary spinal cord tumors, were eligible for the study, but were entered and nonrandomly assigned to the more intensive 8-in-1 regimen. These nonrandomly assigned patients will be the subject of separate publications. The randomized component of the study remained open to patient accrual for a period of 62 months and closed on May 31, 1990.

Eligibility

Eligibility for the study mandated histopathologic confirmation of an intracranial high-grade astrocytoma arising primarily outside of the brain stem or the spinal cord. Patients with brain stem involvement were considered eligible if the predominant location of the tumor lay beyond this site. Thus, cerebellar hemispheric tumors were eligible for this study. Patients were required to be entered onto the study within 28 days of definitive surgical resection and diagnosis; patients were permitted to be entered onto the study beyond 28 days if delays occurred as a result of difficulties in establishing the pathologic diagnosis of high-grade astrocytoma. Patients could not have received either irradiation or chemotherapy before study entry. Decisions concerning extent of resection were left to the discretion of the treating neurosurgeons; however, the protocol recommended attempting to remove as much tumor as feasible without jeopardizing the patient.

Extent of disease evaluation was required, but was not a determinant of eligibility; this was to include both a preoperative and postoperative contrast-enhanced computerized axial tomographic (CAT) scan. During the course of the study, magnetic resonance imaging (MRI) with gadolinium contrast was permitted in lieu of CAT scans and was performed in 66% of cases at diagnosis. Evaluation of CSF cytology was strongly recommended from either lumbar or ventricular routes, as dictated by safety. Myelography was also strongly encouraged, although not mandated. The neurosurgeon's report of extent of tumor resection was documented and evaluated in conjunction with the postoperative CT or MRI scans.

Central pathologic review by a single study neuropathologist (A.Y.) was performed on all patients entered onto the study; however, study eligibility was determined by the treating institution pathologist's interpretation of high-grade astrocytoma. In cases of discordance between the study neuropathologist and the institutional pathologist, additional blocks and/or slides were requested for further evaluation. Tumors were diagnosed and graded by the study neuropathologist using the criteria and classification scheme of the World Health Organization.[10] In this classification, GBM is grade IV, AA is grade III, low-grade fibrillary astrocytoma is grade II, juvenile pilocytic astrocytoma is grade I, and both anaplastic gangliogliomas and anaplastic oligodendrogliomas are grade III. Diagnoses were categorized into four groups by the study neuropathologist: GBM, AA, other eligible (mixed malignant gliomas, anaplastic gangliogliomas, anaplastic oligodendrogliomas, unclassified malignant glial neoplasms), and discordant (eg, low-grade astrocytomas, ependymomas, primitive neuroectodermal tumors [PNET]).

Standardized data capture forms collected information on neurosurgical practice and techniques, as well as tumor location, tumor size, extent of resection, extent of disease evaluations, neurologic examination, and other demographic features.

Treatment Protocol

The control regimen A consisted of the "standard" chemotherapy-containing regimen and is detailed in Fig 1. In brief, a 10-week induction period incorporated involved-field irradiation with eight weekly injections of vincristine. Thereafter, a maintenance period lasting a projected 48 weeks used eight cycles of vincristine, CCNU, and prednisone chemotherapy repeated at 6-week intervals. The experimental regimen consisted of the 8-in-1 chemotherapy, and is also detailed in Fig 1. A 10-week induction period consisted of two cycles of 8-in-1 chemotherapy, 14 days apart, followed by radiographic evaluation of response 2 weeks later, immediately before beginning involved-field irradiation. Thereafter, a maintenance period lasting a projected 48 weeks used eight cycles of the 8-in-1 regimen repeated at 6-week intervals.

The planned radiation dose was 54 Gy delivered in 30 fractions of 1.8 Gy each over 6 weeks. Allowable energies ranged from Co^{60} to 10 mV. Treatments were given with parallel opposed fields, and the dose was calculated at the midplane of the central axis. The prescribed treatment volume was the tumor volume, including edema, as observed on the preoperative imaging study plus a 2-cm margin of apparently normal brain parenchyma. Radiation treatment records as well as portal and simulation films were reviewed in conjunction with preoperative images by study radiation oncologists to determine compliance with protocol requirements for dose and volume.

Evaluation of Response

Patients were to be examined weekly during irradiation and at least every 6 weeks during maintenance chemotherapy. A head CAT scan, with and without contrast enhancement, was required after preirradiation chemotherapy on the experimental regimen and at the conclusion of the induction phase on both regimens. Thereafter, patients were to be evaluated radiographically every 3 months. During the conduct of the study, the MRI scan increasingly was used in place of CAT scans. Routine follow-up evaluations of the CSF and spine were not required unless clinically indicated.

Centralized review of the response to the two preirradiation cycles of 8-in-1 chemotherapy was required. The results of this comprehensive analysis of response to preirradiation chemotherapy are the subject of a separate publication and will not be discussed further.[11]

Patients were considered to have progressive disease if there was emergence of any new lesions or if enlargement of greater than 25% of tumor volume was observed in existing lesions. Neuroradiographic studies at the time of progression were not centrally reviewed; appropriate data capture forms indicating sites of recurrence were submitted on all patients who relapsed.

Evaluation of Toxicity

Patients who were randomized on the experimental regimen were required to undergo evaluations of renal function by creatinine clearance estimations before each cycle of 8-in-1 chemotherapy. Additionally, audiograms were mandated before each cycle of 8-in-1 chemotherapy to monitor hearing loss. Study guidelines dictated dose modifications of CCNU and cisplatin for renal dysfunction and dose modifications of cisplatin for hearing loss. A detailed analysis of ototoxicity on this study, and its relationship to the field of irradia-

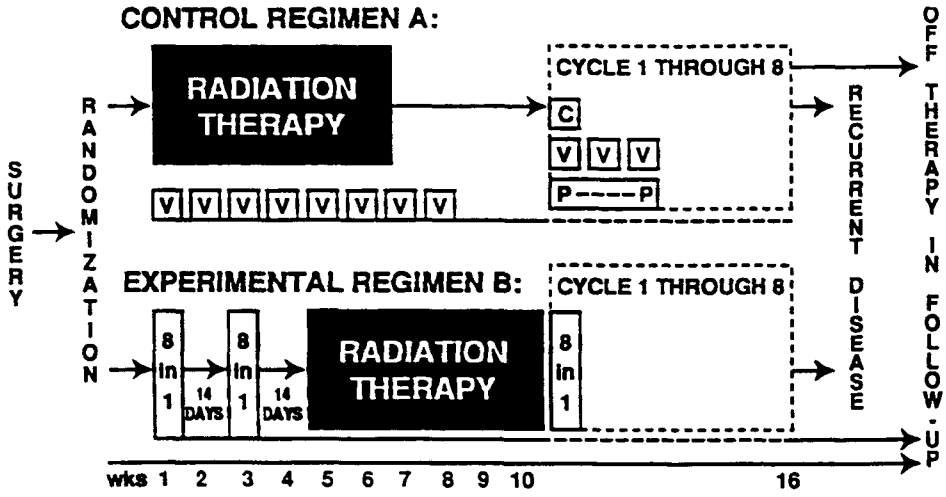

Fig 1. Schema for CCG-945. Control regimen A: V, vincristine (1.5 mg/m^2); C, CCNU (100 mg/m^2); P, prednisone (40 mg/m^2 per day for 14 days). Experimental regimen B: vincristine (1.5 mg/m^2), CCNU (100 mg/m^2), procarbazine (75 mg/m^2), hydroxyurea (3,000 mg/m^2), cisplatin (90 mg/m^2), mannitol (12 gm/m^2), cytarabine (300 mg/m^2), dacarbazine (150 mg/m^2), and methylprednisolone (300 mg/m^2 for 3 doses).

tion and the cumulative dosage as well as dose-intensity of cisplatin, will be the subject of a separate publication. Dose modifications were not permitted for nadir blood counts, only for inadequate neutrophil (< 1,000/μL) or platelet (< 100,000/μL) recovery by the time subsequent chemotherapy cycles were due. Dose modifications for vincristine were required in the face of neuropathy or hyperbilirubinemia.

Data were also collected on the development of hypomagnesemia and the use of magnesium supplementation on the experimental regimen. Hepatic function was to be monitored on both regimens, and dosage reductions of CCNU were to be undertaken in the face of hepatic dysfunction.

Statistical Considerations

Randomization to the two treatment arms was stratified by extent of surgical resection (EOSR) as reported during on-study registration, and the primary analyses of PFS are so stratified. All patients were analyzed as randomized. The study was designed to randomize at least 60 children with an institutional diagnosis of high-grade astrocytomas to each of the two arms. This sample size was projected to provide 80% power of detecting a 50% reduction in the estimated hazards ratio of 0.458 per year for the control arm (two-sided Mantel-Haenszel test with $\alpha = 0.10$). Because of sample size considerations for the secondary objective described below, a total of 172 children were eventually randomized. The attained sample size provides 90% (two-sided, $\alpha = 0.05$) power for detecting a difference of 20% in 2-year PFS rates (40% *v* 60%). Inference to the population of institutionally diagnosed high-grade astrocytomas was considered important because it is the institutional diagnosis that ultimately determines treatment of future children. Secondary objectives were to compare, assuming the same design variables, the two treatments in terms of distributions of PFS in the children who had centrally reviewed diagnoses of either AA or GBM and to investigate potential prognostic factors in these children. A total of 117 children with confirmed diagnoses of either AA or GBM were randomized.

Correlations among presenting clinical factors were investigated by Fisher's exact test for factors with two levels, exact Kruskal-Wallis when one factor was ordinal and the Wilcoxon's rank-sums test for quantitative variables. Exact tests were accomplished using the software package StatXact (Cytel Software Corp, Cambridge, MA).

Durations of PFS and OS were measured from the date of randomization to the date of progressive disease, death, or date of last contact as appropriate. Distributions of PFS and survival were estimated using the technique of Kaplan and Meier.[12] Standard errors of the Kaplan-Meier estimates were calculated as suggested by Peto et al[13] and appear in the text in parentheses after estimates for specific points in time. Comparisons between distributions of PFS were made using a stratified Mantel-Haenszel statistic.[14] A Cox life-table regression model[15] was used to evaluate the simultaneously prognostic importance of extent of resection, histology, sex, race, age, tumor size, and primary site of involvement within the group of children with a reviewed diagnosis of either AA or GBM. Relative risks were calculated using the variable estimates from the fitted model. Within those children with primaries in the cerebral hemispheres, the prognostic influence of polar location (ie, frontal and occipital lobes) was investigated.

Patient Population

A total of 185 patients from 60 institutions were randomized between April 1, 1985 and May 31, 1990. Thirteen patients were subsequently declared either ineligible or not assessable. Of these, nine were declared ineligible by study entry criteria after randomization for the following reasons: two had primary spinal cord tumors (one to each regimen) and seven were deemed ineligible on institutional rereview of pathology (five low-grade astrocytomas, one medulloblastoma, and one choroid plexus carcinoma). Four patients with insufficient on-study data to assess eligibility were withdrawn from the study shortly after randomization because of parental withdrawal of consent to randomization. Thus, 172 patients (92%) were considered both eligible and assessable, with 85 patients randomized to the control regimen and 87 to the experimental regimen. Only one patient was treated other than randomized, inadvertently treated on the experimental regimen after randomization to the control regimen. This patient is analyzed as randomized.

Clinical Characteristics

Clinical characteristics of the 172 eligible patients randomized on study are listed in Table 1 by treatment regimen. The median age at study entry was 10.1 years (range, 21 months to 19 years). There were no statistically significant differences between the patients ran-

Table 1. Clinical Characteristics at Study Entry

	Regimen A (control)		Regimen B (8-in-1)		Total	
	No.	%	No.	%	No.	%
Sex						
Male	46	54	44	51	90	52
Female	39	46	43	49	82	48
Race						
White	66	78	63	72	129	75
Nonwhite	19	22	24	28	43	25
Age						
1.5-2 years	4	5	2	2	6	3
3-4 years	9	11	6	7	15	9
5-9 years	23	27	40	46	63	37
≥ 10 years	49	58	39	45	88	51
Primary site						
Cerebral hemisphere	53	62	57	66	110	64
Midline	23	27	23	26	46	27
Posterior fossa	9	11	7	8	16	9
Intracranial metastases						
Present	6	7	2	2	8	5
Absent	77	91	83	95	160	93
Unknown	2	2	2	2	4	2
Spinal metastases						
Present	2	2	0	0	2	1
Absent (clinical with or without myelogram)	72	85	75	86	147	86
Unknown	11	13	12	14	23	13
Extraneural metastases						
Present	0	0	1	1	1	1
Absent	76	89	75	86	150	87
Unknown/missing data	9	11	11	13	21	12
Institutional Pathology						
AA	39	46	43	49	82	48
GBM*	30	35	27	31	57	33
Other eligible	16	19	17	20	33	19
Extent of resection (surgical report)						
Biopsy only (< 10%)	15	18	15	17	30	17.5
Partial (10-50%)	11	13	12	14	23	13.5
Subtotal (50-90%)	20	24	25	29	45	26
Near-total/total (> 90%)	39	46	35	40	74	43
Total	85		87		172	

NOTE. Because of rounding, percentages may not add up to 100%.
*Includes gliosarcoma.

domized to the two treatment regimens on the basis of sex, race, age, primary site location, or presence of intracranial, spinal, or extraneural disease at diagnosis.

Strong correlation exists between primary site of disease and the extent of surgical resection ($P < .0001$). Only 7% (three of 46) of patients with midline primary sites had more than a 90% tumor resection, compared with 56% (nine of 16) of patients with posterior fossa primaries and 56% (62 of 110) of patients with cerebral hemispheric tumors.

Correlation also exists between the extent of resection and tumor pathology ($P < .002$). Thirty-four percent (28 of 82) of the patients diagnosed with AA had more than a 90% tumor resection compared with 47% (25 of 53) of patients diagnosed with GBM. The evaluation of spinal leptomeningeal dissemination of tumor was based on clinical criteria (presence of sign and/or symptoms), evaluation of lumbar CSF cytology (performed in 59% of patients in the perioperative period), myelography (performed in 33% of patients), and spinal MRI (performed in seven patients). Of 101 patients with evaluations of lumbar CSF cytology, only two were reported as positive; in one, a myelogram was negative and in the other, no imaging of the spine was performed. Of 57 myelograms and seven spinal MRIs performed in 63 patients, only one was clearly reported as positive.

Pathology Review

Table 2 lists the degree of concordance between the institutional pathology and the central study review. The term discordant is used to indicate pathologic diagnoses determined by central review to be other than high-grade astrocytomas.

Fourteen percent of patients were considered to have discordant

Table 2. Concordance Between Institutional Pathology and Central Pathology Review

Institutional Pathology	Centralized Pathology Review					
	AA	GBM	Other	Discordant	Insufficient Tissue	Total
AA	52	13	4	11	2	82
GBM	14	38	3	2	0	57
Other eligible	9	5	7	11	1	33
Total	75	56	14	24	3	172

pathologic diagnoses on central review (seven low-grade astrocytomas not otherwise specified, six ependymomas, four juvenile pilocytic astrocytomas, three gangliogliomas, two mixed low-grade gliomas, one oligodendroglioma, and one PNET). In an additional three patients, the material was considered insufficient to classify. The centrally reviewed diagnoses of AA concurred with the institutional diagnoses in 63% (52 of 82) of patients, and of GBM in 67% (38 of 57) of patients. Other eligible tumors concurred in only 21% (seven of 33) of patients. Discordant pathologic diagnoses were determined in 13% (11 of 82) of patients called AA institutionally, in only 4% (two of 57) of patients called GBM institutionally, and in 33% (11 of 33) of patients called anaplastic mixed glial tumors institutionally.

Radiation Therapy Review

Irradiation dose was evaluated for 94% (161 of 173) of the randomized patients. In 94% (151 of 161), the delivered dose was within 5% of the dose prescribed by the protocol. Greater than 80% of the prescribed dose was delivered in all but one case. Irradiation volume was evaluated in 132 patients (77%). In 93 of 132 patients (70%), the irradiation volume was within protocol specifications. The tumor volume was believed to be included in the irradiation field, but without adequate margins in 33 cases (25%), and the tumor was believed to be shielded from the radiation beam in two cases (1.5%). In three cases (2%), the irradiation field was believed to be larger than necessary. There was no correlation between adequacy of radiation volume and treatment regimen.

Compliance With Data Submission and Follow-Up

One hundred percent of all on-study forms, neurosurgical report forms, neuropathology report forms, and pathologic materials were submitted for central review. Institutional neuroradiology report forms were received for 99% of cases, and films were received for central radiologic review as required in 90% of cases. End-of-phase report forms were submitted for review for all cycles of therapy in all but one patient (for the last four courses of therapy only).

RESULTS

Survival

Figure 2 shows estimates of PFS and OS for all eligible randomized patients. The 5-year estimates are 33% (SE = 5%) and 36% (SE = 6%), respectively. Median PFS and OS are approximately 16 and 26 months, respectively. All but three patients have follow-up data beyond the first 3 years after randomization, and no patient is censored within 2 years of randomization. Fig 3 shows estimates of survival after disease progression. One year after progression, 23% (SE = 4%) are estimated to remain alive, and 5 years after disease progression, the survival rate is 4% (SE = 3%). The median time to death for 46 patients who received no further chemotherapy after disease progression was 2 months, whereas the median time to death for 60 patients who received further retrieval chemotherapy was approximately 7 months. A Cox life-table multiple regression analysis of factors predictive of survival after progression for children on study with reviewed pathologic diagnoses of AA or GBM showed white race ($P < .002$) and older age ($P < .04$) to be independently predictive of longer survival.

Figure 4 and Table 3 show estimates of PFS for all eligible patients who were randomized to receive either control or the experimental 8-in-1 chemotherapy. The

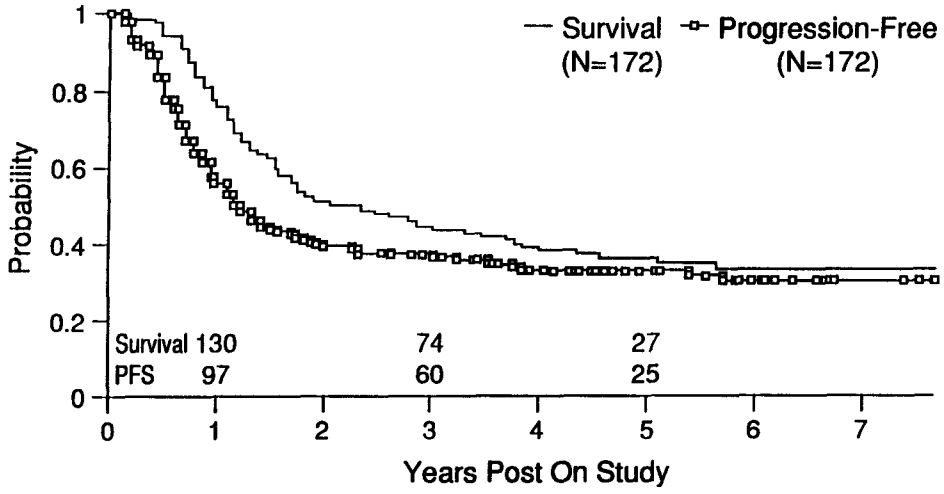

Fig 2. Kaplan-Meier estimates of survival and PFS of all eligible randomized patients with an institutional diagnosis of high-grade astrocytoma. Patients who remain at risk for treatment failure are shown above the time axis.

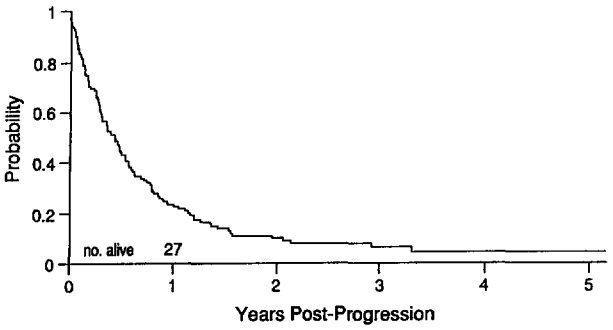

Fig 3. Kaplan-Meier estimates of postprogression survival for eligible randomized patients. Patients who remain at risk for treatment failure are shown above the time axis.

difference is not statistically significant ($P > .52$). The 5-year estimates of PFS are 26% (SE = 8%) for the control regimen and 33% (SE = 7%) for the experimental regimen. There was no difference in the median time to progression between the two regimens (14 months). When outcome by therapeutic regimen was evaluated according to reviewed pathology (AA or GBM), no significant difference was observed ($P > .6$). Additionally, evaluation of subgroups based on extent of surgical resection failed to show any difference between the two therapeutic regimens.

The possibility that inadequately delivered radiation therapy might have contributed to a poor outcome was examined. However, the PFS for patients treated with adequate margins (33%, SE = 7%) was not significantly different ($P > .5$) than that for patients treated with small margins or with disease shielded (36%, SE = 13%).

Figure 5 shows PFS for the centrally reviewed diagnoses of AA, GBM, or other eligible high-grade astrocytomas. The distributions of PFS are significantly different for the group of children with AA and GBM ($P < .02$, stratified by extent of surgical resection) and the children with other eligible diagnoses who experienced the best outcome at 5 years. Five-year PFSs for the three groups are 28% (SE = 7%), 16% (SE = 7%), and 64% (SE = 17%), respectively. Children who were reviewed as having a discordant diagnosis (data not shown) experienced a significantly improved PFS ($P < .001$) compared with the children with reviewed high-grade astrocytomas. Children with these lower-grade tumors had a 5-year PFS of 70% (SE = 17%). The remaining outcome results are restricted to patients with centrally reviewed and confirmed diagnoses of AA or GBM.

Sex, race, age at diagnosis in years, histologic diagnosis (AA *v* GBM), extent of surgical resection (≤ 90% *v* > 90% resection), tumor size, and site (midline *v* other) were investigated as potential prognostic factors in the group of children with reviewed neuropathologic diagnoses of either AA or GBM (Table 4). By univariate analysis, AA histologic diagnosis ($P < .04$), greater than 90% resection ($P = .02$), and female sex ($P < .03$) were predictive of improved PFS, whereas other factors were not statistically significant at the .05 level. A stepwise Cox life-table multiple regression analysis identified independent predictors of improved PFS as greater than 90% resection ($P < .02$), AA histologic diagnosis ($P < .01$), and female sex ($P < .01$). The most important prognostic factor was extent of surgical resection. Figures 6 and 7 show the impact of extent of surgical resection on PFS for the children with confirmed AA ($P < .04$) and GBM ($P < .04$), respectively. The median time to progression for patients with reviewed AA undergoing greater than 90% resection is 31 months compared with a median PFS of 12 months in reviewed AA patients undergoing ≤ 90% resection. Patients with reviewed diagnosis of GBM and

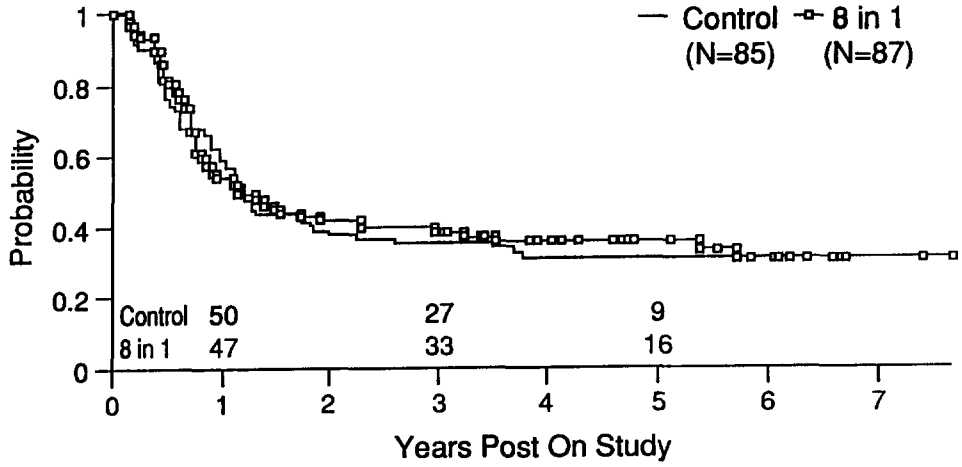

Fig 4. Kaplan-Meier estimates of PFS for eligible patients who were randomized to either control or 8-in-1 therapy. The difference is not statistically significant ($P > .5$). The numbers of children who remain at risk for treatment failure are shown above the time axis.

Table 3. Impact of Treatment Regimen on Outcome

	5-Year PFS (%)			5-Year OS (%)			Median PFS (months)		Median Survival (months)	
	Control	Experimental	P	Control	Experimental	P	Control	Experimental	Control	Experimental
Overall*	26 ± 8.4	33 ± 7.1	.52	29 ± 8.6	39 ± 7.4	.49	14	14	25	31
AA, review pathology	11 ± 6	28 ± 8.4	.6533	15 ± 7.1	38 ± 9.5	.395	13	11	22	31
GBM, review pathology	13 ± 8.8	17 ± 11	.94	18 ± 11.6	17 ± 10.8	.451	12	10	18	13

*All eligible pathologic diagnoses.

Table 4. Reviewed Neuropathology Diagnoses of AA or GBM Cox Life-Table Multiple-Regression Analysis of PFS (N = 127)

Univariate		Stepwise Multiple Regression	
Factors	P	Factors	P
Extent of resection	.018	Extent of resection	.018
Histology	.035	Histology	.003
Sex	.023	Sex	.002
Age	.7		
Race	.3		
Site	.088		

greater than 90% resection experienced only a modest prolongation of median time to progression (12 months *v* 8 months) (Tables 5 and 6). Within the group of patients with cerebral hemispheric lesions, adjusting for the impact of polar (ie, frontal and/or occipital) primary sites did not eliminate the prognostic effect of extent of resection for patients with reviewed diagnoses of AA and GBM.

Toxicity of Therapeutic Regimens

There was a substantial difference in toxicity between the two therapeutic regimens. During induction therapy, 14% of patients on the control regimen (irradiation plus weekly vincristine) experienced grade III or IV toxicities largely related to vincristine neuropathy. However, 45% of patients randomized to the experimental regimen experienced grades III or IV toxicities in induction (two cycles of 8-in-1 chemotherapy followed by irradiation) largely related to myelosuppression (56 of 76 episodes; 74%). Objective evidence of hearing loss was observed in four of 40 patients (10%) evaluated on the experimental regimen during induction.

During maintenance cycles of chemotherapy, between 9% and 22% of patients experienced grade III or IV toxicities on the control regimen because of myelosuppression (77 of 114 episodes; 68%), vincristine neuropathy (12% episodes of toxicity), and a single episode of pulmonary dysfunction recorded in one cycle of therapy only. On the experimental regimen, between 38% and 57% of maintenance cycles of chemotherapy were associated with toxicities because of myelosuppression (58% of episodes), nephrotoxicity (9% of episodes), and ototoxicity (16% of episodes). A more detailed analysis of ototoxicity in this study is currently being conducted for later publication.

There was one death in the study in a patient without disease progression treated on the control regimen who developed progressive neurologic deficits because of underlying ornithine transcarbamoylase deficiency.

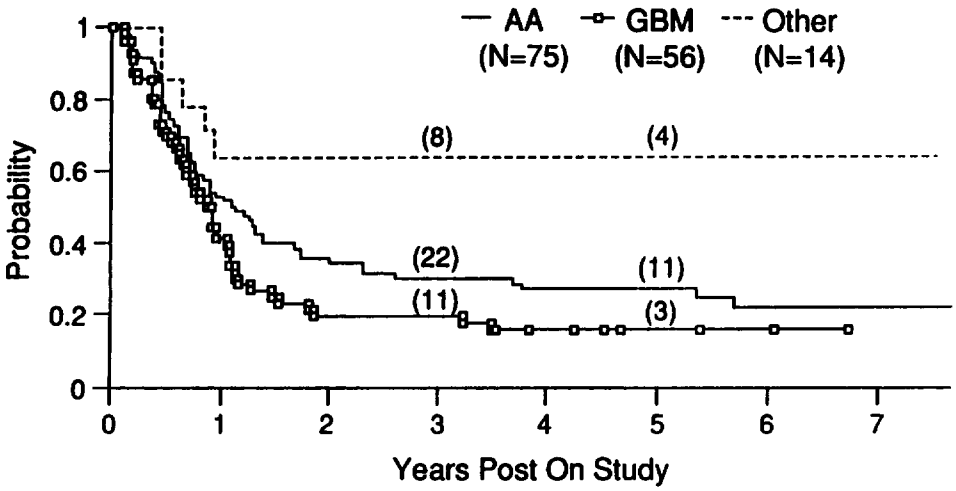

Fig 5. Kaplan-Meier estimates of PFS for children with reviewed diagnoses of AA, GBM, or other high-grade astrocytoma. The differences between AA and GBM and between AA or GBM and other high-grade astrocytomas are significant ($P < .02$). Patients who remain at risk for treatment failure are shown in parentheses.

Pattern of Failure

The overwhelming pattern of failure represented recurrence within or contiguous extension beyond the primary tumor site (107 of 110 documented patients; 97%). In 85% of patients (94 of 110), relapse occurred only within or in contiguous extension beyond the primary tumor site. In three cases, the initial site of failure was in the spinal cord, and in one, in the CSF. In total, eight patients (7%) had positive CSF cytology at first relapse, and 10 patients (9%) had positive myelograms or other evidence of spinal leptomeningeal disease. There were no cases of extraneural sites of disease at relapse. In 54 patients (49%), intracranial disease was reportedly present at initial relapse at contiguous sites other than those involved at original diagnosis.

DISCUSSION

CCG-945 is only the second randomized trial to investigate the efficacy of chemotherapy in the treatment of newly diagnosed high-grade astrocytomas in children. The earlier trial,[1] conducted between 1976 and 1981 by the CCG (CCG-943), compared irradiation alone with irradiation plus adjuvant CCNU, vincristine, and prednisone—the control arm of the present study. Only 58 eligible randomized children were assessable in the former study, and therefore factors were evaluated at somewhat limited statistical power. Nevertheless, a statistical impact of pathologic diagnosis (AA *v* GBM), primary site of disease, extent of surgical resection, and presence or absence of tumor necrosis and/or mitoses were observed both on PFS and OS. In analyzing the impact of the adjuvant chemotherapy, there was a significant advantage for chemotherapy and irradiation over irradiation alone on PFS but not on OS. Importantly, there was no benefit observed from chemotherapy in patients with AA or in any patients, irrespective of pathology, who underwent a biopsy only. In the subgroup of patients with GBM and at least a partial resection, the benefit from chemotherapy

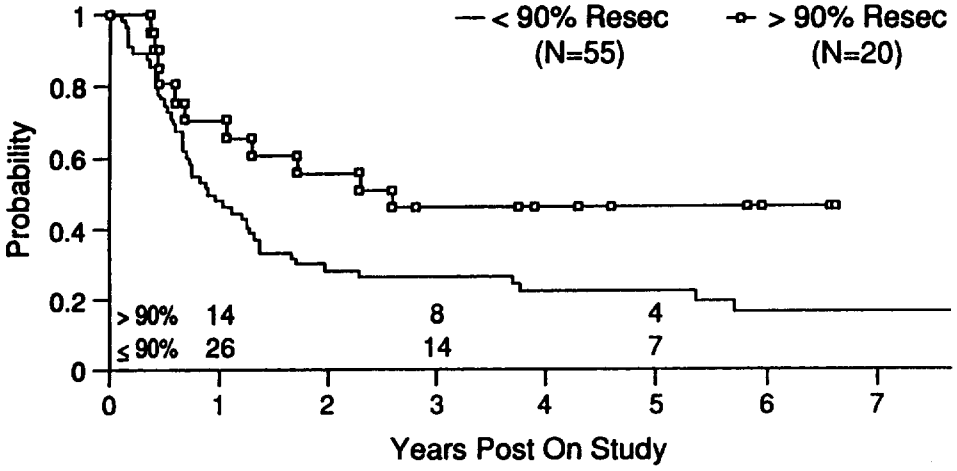

Fig 6. Kaplan-Meier estimates of PFS for patients with reviewed diagnoses of AA grouped by extent of resection. The difference is statistically significant ($P < .04$). Patients who remain at risk for treatment failure are shown above the time axis.

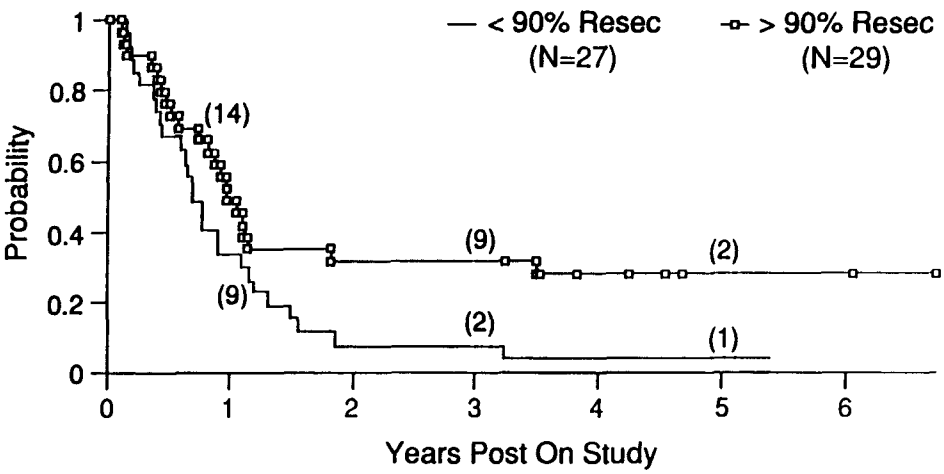

Fig 7. Kaplan-Meier estimates of PFS for children with a review neuropathology diagnosis of GBM grouped by extent of resection as reported by the neurosurgeon. The difference is statistically significant ($P < .04$). The numbers of children who remain at risk for treatment failure are shown in parentheses above the estimates.

was pronounced, with a 5-year PFS of 42% in the chemotherapy group versus 6% in the irradiation-only group ($P = .0011$). Five-year overall survival in this same subgroup was 36% for the chemotherapy-treated patients versus 5% for the irradiation-only–treated patients ($P = .04$).

In the present study, 185 patients were initially randomized, with 172 subsequently considered to be fully eligible. This larger group of patients, studied in the era of objective radiographic evaluations by computed tomography (CT) and/or MRI, permits analysis with greater statistical power of those prognostic variables deemed important in predicting outcome for children with high-grade astrocytomas at diagnosis. Ninety-five percent confidence interval (CI) estimates of 5-year PFS and OS for eligible randomized patients treated with control regimen chemotherapy in the present study are 10% to 41% and 11% to 46%, respectively. This compares with a 5-year PFS and OS on the same chemotherapy-containing arm of the earlier study of 26% to 66% and 25% to 61%, respectively. The considerable overlap of these intervals suggests that outcomes for the two studies are comparable. For example, the true, unknown 5-year PFS rate for patients treated with the control regimen is estimated to be at least 10% but less than 41% from CCG-945, and at least 26% but less than 66% from CCG-943.

The current study failed to demonstrate a statistically significant difference between the two chemotherapeutic regimens. The observed difference of 7% in PFS and 10% in OS at 5 years between the two regimens would require a much larger patient study population to affirm, and given the clearly additional toxicity of the 8-in-1 regimen, may even then not support the standard use of this more intensive chemotherapy regimen. The 8-in-1 regimen was developed at a time when the biologic heterogeneity intrinsic to malignant gliomas was just becoming recognized. The concept of assaulting the tumor with a combination of drugs, both lipid-soluble and water-soluble, cell-cycle–specific and nonspecific, and with varying (although often putative) mechanisms of cytotoxicity, was attractive and introduced at least a biologic rationale to the chemotherapy of such tumors.[9] However, many of the potentially active drugs in the 8-in-1 combination were administered at doses now recognized as inadequate; for example, procarbazine (a single dose per cycle), cyclophosphamide, and cytarabine (not clearly proven active in phase II trials at low or high dose). Additionally, hydroxyurea has only been proven of benefit in high-grade astrocytomas when given during irradiation and as yet has not been proven efficacious in phase II single-agent studies. Finally, in hindsight, if vincristine is indeed an active drug in high-grade astrocytomas, then it would have been preferable to have maintained the same dose-

Table 5. Impact of Extent of Resection on PFS

	5-Year PFS		
	> 90% Resection (%)	< 90% Resection (%)	*P*
Institutional diagnosis, all eligible pathologic diagnoses	49 ± 10.1	17 ± 5.1	.0006
Central pathology review, all eligible pathologic diagnoses	39 ± 9.6	14 ± 4.8	.0024
AA by central pathology review	42 ± 14.4	14 ± 5.4	.0279
GBM by central pathology review	27 ± 13.2	4 ± 2.6	.37

Table 6. Impact of Extent of Resection on Median PFS Time

	Median PFS (months)	
	> 90% Resection	< 90% Resection
Centrally reviewed patients, all eligible pathologic diagnoses	43	12
Centrally reviewed AA patients	31	12
Centrally reviewed GBM patients	12	8

intensity and timing of vincristine in the experimental regimen as in the control regimen. The eight weekly doses of vincristine were not administered during irradiation in the experimental regimen and were only administered on the first day of each cycle during maintenance chemotherapy. This represents a 70% decrease in dose-intensity of vincristine when compared with the control regimen. It is possible that the decrease in this agent offsets any gain from the additional agents incorporated in the 8-in-1 regimen. Further studies should address both the concerns of biologic heterogeneity and dose-intensity through the implementation of alternating cycles of limited combinations of chemotherapeutic agents used at maximal dosage, rather than repeated use of a multidrug regimen in which the optimal dose of each or several of the drugs is jeopardized.

The most significant prognostic variable on outcome is the extent of surgical resection. This was observed in the prior study (CCG-943),[1] and the findings are reaffirmed and extended in the present study, with an impact of greater or less than 90% resection observed both for patients with AA and GBM as determined by either institutional or centralized review diagnosis. Furthermore, this impact of extent of resection is not simply a reflection of primary tumor sites because it was observed within the subgroup of patients with cerebral hemispheric tumors. More recent adult studies have affirmed the benefit of radical surgical resection in patients with high-grade astrocytomas who receive postoperative irradiation and chemotherapy.[16-18] Earlier reports, particularly in adult populations, that failed to demonstrate a benefit from adjuvant chemotherapy may in part have reflected a patient population undergoing much lower radical surgical resection rates. Therefore, although chemotherapy may have some activity in the treatment of high-grade astrocytomas, it is axiomatic that such chemotherapy will work best in the context of minimal residual disease as achieved by the neurosurgeon at the outset.

There was a significant impact of pathologic diagnosis on outcome. Patients with reviewed eligible diagnoses other than AA or GBM (eg, anaplastic mixed gliomas, anaplastic oligodendrogliomas, and so on) experienced an estimated 5-year PFS of 64% and OS of 71%. Because such patients have not previously been studied in a randomized trial, it is unknown if such a favorable outcome could have been achieved with irradiation alone. Patients who, on central review, were deemed to have discordant pathologic diagnoses (ie, other than eligible, usually low-grade astrocytomas) experienced an estimated 70% 5-year PFS ($P = .0002$), irrespective of extent of resection. This finding suggests that the study neuropathologist's pathologic diagnosis was more consistent with clinical outcome than was the institutional diagnosis.

There was a statistically significant difference in outcome between patients with reviewed diagnoses of AA and GBM, consistent with previous reports both in pediatric and adult patients.[2,19] However, the estimated 28% PFS and 29% OS at 5 years for AA are not different from that reported widely in the literature for irradiation alone. This present study does not address the question directly, but fails to provide convincing evidence of a beneficial role for adjuvant chemotherapy in the treatment of newly diagnosed AA. On the other hand, patients with GBM had an estimated 16% PFS and 18% OS at 5 years. Although this finding would appear to be worse than the estimated 42% 5-year PFS observed for patients with GBM who received chemotherapy in the earlier study (CCG-943),[1] this latter study reflected a cohort of only 14 patients. Additional published studies using radiation therapy only for newly diagnosed childhood GBM, in which virtually all patients have died by 3 years, lend affirmation to the benefit of adjuvant chemotherapy for these patients, as demonstrated in this study.[20-24]

Patients with eligible reviewed pathologic diagnoses who relapsed on this study almost invariably died of disease progression within months, irrespective of therapeutic intervention. The pattern of failure was predominantly in the primary tumor site, although in almost 10% of cases there was evidence of CSF or spinal dissemination at recurrence. Additionally, the extent of disease evaluation at diagnosis showed only rare patients with positive spinal CSF cytology or myelograms. This study does not support the contention voiced elsewhere that patients with GBM should routinely undergo whole neuraxis irradiation at diagnosis.[25-27]

The outcome for children with newly diagnosed high-grade astrocytomas remains poor. Although chemotherapy seems to afford a modest survival advantage, attempts to improve the outcome with a more aggressive 8-in-1 chemotherapy regimen have been unsuccessful. The major therapeutic intervention still remains radical surgical

resection, concomitant with preservation of neurologic function. Further phase II trials are required to identify more effective chemotherapeutic agents for incorporation into subsequent phase III randomized trials.

ACKNOWLEDGMENT

The authors thank Lucia Noll and Amy Verret for manuscript preparation and Drs Leland Albright and Ruth Heyn for their detailed and constructive reviews and critique of earlier versions of this report.

APPENDIX. Participating Principal Investigators From the Childrens Cancer Group

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New York University Medical Center, New York, NY	Aaron Rausen, MD	—
Childrens Hospital of Orange County, Orange, CA	Mitchell Cairo, MD	—

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