RAPID PUBLICATION

Procarbazine, Lomustine, and Vincristine (PCV) Chemotherapy for Anaplastic Astrocytoma: A Retrospective Review of Radiation Therapy Oncology Group Protocols Comparing Survival With Carmustine or PCV Adjuvant Chemotherapy

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Purpose: **To determine any differences in outcome for patients with anaplastic astrocytoma (AA) treated with adjuvant carmustine (BCNU) versus procarbazine, lomustine, and vincristine (PCV) chemotherapy.**

Materials and Methods: **The Radiation Therapy Oncology Group (RTOG) database was reviewed for patients with newly diagnosed AA treated according to protocols that included either BCNU or PCV adjuvant chemotherapy. All patients were treated with radiation therapy. The outcome analysis included overall survival, taking into account patient age, extent of resection, Karnofsky performance status (KPS), and treatment group (BCNU *v* PCV). Stratified and nonstratified Cox proportional hazards models were used, as well as an analysis using matched cases between the groups.**

Results: **A total of 257 patients were treated with BCNU according to RTOG protocols 70-18, 83-02, and 90-06; 175 patients were treated with PCV according to RTOG protocol 94-04. All pretreatment characteristics except KPS were well balanced by treatment group; 61% of the BCNU group had a KPS of 90 to 100 compared with 73% of the PCV group ($P = .0075$). No statistically significant difference in survival was observed in any age group or by KPS or extent of surgery. The stratified analysis also showed no trends for improved survival by treatment group ($P = .40$). The Cox model identified only age, KPS, and extent of surgery as important variables influencing survival, not treatment group. Matching cases between groups using age, KPS, and surgery resulted in 133 matched pairs. No difference in survival was observed ($P = .41$). In a Cox model in which each matched pair is a strata, there was no difference between groups ($P = .20$).**

Conclusion: **Using this retrospective analysis, there does not seem to be any survival benefit to PCV chemotherapy. Future phase III studies for patients with AA may need to consider whether BCNU or PCV is used in the control arm.**

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PROCARBAZINE, lomustine, and vincristine (PCV) is one of the most commonly used combination chemotherapy regimens in neuro-oncology. This is due, in part, to a report published in 1990 that analyzed data from a Northern California Oncology Group (NCOG) randomized trial that had closed in 1983.[1] NCOG protocol 6G61 was a randomized trial that compared the effects of either carmustine (BCNU) alone or PCV combination chemotherapy after whole-brain radiation therapy. Oral hydroxyurea was used during radiation therapy in both arms of the study, which included patients with anaplastic astrocytomas (AA) and glioblastoma multiforme (GBM). The conclusion from this reanalysis was that PCV chemotherapy produced longer survival and time to progression than did BCNU, but only for patients with AA. Median survival duration was 157.1 weeks for AA patients treated with PCV compared with 82.1 weeks for AA patients treated with BCNU ($P = .021$). There was no survival benefit for patients with GBM (median survival duration, 50.4 weeks with PCV and 57.4 weeks with BCNU). After this study, the NCOG initiated a phase II trial using bromodeoxyuridine (BUdR) given during radiation therapy, followed by PCV chemotherapy. The results of the trial were promising, with 50% of AA patients alive at 4 years.[2] A phase III trial then commenced, comparing radiation therapy with or without BUdR, with all patients receiving adjuvant PCV chemotherapy. This last study originated as an NCOG trial but became an intergroup trial coordinated by the Radiation Therapy Oncology Group (RTOG). The study, RTOG 94-04, was the first trial conducted within the RTOG that used PCV chemotherapy as adjuvant treatment to radiation and excluded patients with GBM. Previously, BCNU was the most commonly used adjuvant chemotherapy used by the RTOG, and patient enrollment could include patients with GBM or AA. RTOG protocol 94-04 was closed before full enrollment because of

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a statistically strong likelihood of a lack of benefit using BUdR. A subsequent analysis of NCOG and RTOG studies was then conducted to study the influence of BUdR radiosensitization for patients with AA and GBM.[3] As part of that retrospective analysis, RTOG studies that used BCNU adjuvant chemotherapy were compared with NCOG studies that used PCV chemotherapy. Although the primary goal of the review was to study BUdR, no apparent survival differences were noted in the subset of AA patients included in the analysis, at least suggesting that PCV was possibly no more effective than BCNU.

RTOG protocol 94-04 provided an opportunity to review specifically survival outcome for AA patients treated with either BCNU or PCV within the RTOG, with much larger patient numbers than NCOG protocol 6G61. That earlier study included only 36 and 37 patients in the PCV and BCNU arms, respectively. The central goal of this current retrospective analysis is to determine if there is any difference in survival outcome for AA patients treated with adjuvant BCNU or PCV.

MATERIALS AND METHODS

The RTOG database was used to identify newly diagnosed patients with AA treated according to protocols 79-18, 83-02, 90-06, and 94-04. The first three protocols included the use of BCNU chemotherapy as an adjuvant to radiation therapy. RTOG 79-18 was a phase III randomized trial of radiation therapy with or without misonidazole used as a radiation sensitizer during radiation treatment.[4] Patients were treated with whole-brain single-fraction radiation therapy to 60 Gy and received BCNU on days 3, 4, and 5 of treatment, and then every 8 weeks. RTOG 83-02 was a phase I/II randomized dose-escalation trial of hyperfractionated (1.2 Gy two times per day) partial brain radiation and accelerated hyperfractionated (1.6 Gy two times per day) partial brain radiation.[5] Four dose levels of hyperfractionation were used: 64.8 Gy, 72.0 Gy, 76.8 Gy, and 81.6 Gy. Two dose levels of accelerated hyperfractionation were used: 48.0 Gy and 54.4 Gy. All patients were treated with BCNU using the same dose and schedule as in RTOG 79-18. RTOG 90-06 was a phase III randomized trial of partial-brain hyperfractionated radiation therapy to 72 Gy versus standard fractionated radiation treatment to 60 Gy.[6] All patients were treated with adjuvant BCNU chemotherapy in a fashion similar to the other protocols. BCNU was administered at a dose of 80 mg/m^2 on days 3, 4, and 5 of week 1 of radiation, and then for 3 days every 8 weeks beginning on day 64. Alternatively, BCNU could start on days 1, 2, and 3. RTOG 94-04 was a phase III randomized trial of standard, fractionated partial-brain radiation with or without BUdR used as a radiation sensitizer. All patients in this study received adjuvant PCV chemotherapy, which was started after the completion of radiation therapy. RTOG protocol 79-18, 83-02, and 90-06 included patients with both GBM and AA. RTOG protocol 94-04 only included patients with AA.

The database was searched for patient variables, including age, initial Karnofsky performance status (KPS), extent of surgery (biopsy *v* any other extent of resection), and pathology. Only patients classified as AA based on central pathology review were included in this analysis. Re-review of original pathology material was not performed for this study. The RTOG criteria for ''astrocytoma with anaplastic features'' required a tumor with multifocal or diffuse cellular and/or nuclear pleomorphism, increased cell density, increased mitotic features, and increased vascular prominence.[7] Tumor necrosis was not allowed. These pathologic features were used to classify patients for RTOG protocols 79-18, 83-02, and 90-06. Patients enrolled onto RTOG protocol 94-04 were classified as AA if they had focally moderate or high cellularity and at least two of the following features: high nuclear/cytoplasmic ratio, coarse nuclear chromatin, increased mitotic activity, and nuclear and/or cytoplasmic pleomorphism.[8] For the purposes of this review, all patients are called AA. If the original pathology report identified any component of oligodendroglioma in the specimen, that was also noted. Patients were considered assessable for this analysis if they had central review of pathology, conformed to eligibility criteria for the study they were on, and had available survival data. Survival was the primary outcome variable of interest.

Statistical Methods

Exact nonparametric tests were used to examine differences between the BCNU and PCV datasets with respect to patient and tumor characteristics. Survival was measured from the start of therapy to death or date of last follow-up evaluation. A modified Wilcoxon test was used to examine differences between the treatment groups with respect to survival. This retrospective study had at least 80% statistical power to detect a 28% difference in median survival between the two groups. The statistical power is less in the subsets. Univariate treatment comparisons were made within strata and a stratified analysis using age, KPS, and extent of surgery to define strata was performed. To ensure consistency, at least 10 events per stratum were needed. A stratified proportional hazards regression (Cox) model and nonstratified regression model were also used. Finally, a matched patient survival comparison was performed by matching patients based on age, KPS, and extent of surgery. Patients who did not match were not included in this analysis. A stratified Cox analysis model was then used in which each matched pair was considered a stratum.

RESULTS

From the four protocols, a total of 257 assessable patients were treated with BCNU (50 from RTOG 79-18, 133 from RTOG 83-02, and 74 from RTOG 90-06), and 175 assessable patients were treated with PCV. The pretreatment characteristics were well balanced by treatment group (Table 1). Fourteen percent of the BCNU group was $\geq$ 60 years of age compared with 10% of the PCV group. The mean age was 42 years in both groups. Approximately 38% of each treatment group were diagnosed by biopsy. KPS was not well balanced between the groups, with 61% of BCNU patients having a KPS of 90 to 100 compared with 73% of the PCV patients ($P = .0075$). A total of 29 patients treated with BCNU had an oligodendroglial component, and 41 patients treated with PCV had an oligodendroglioma component.

The BCNU group had a longer follow-up duration than the PCV group. Sixty-five percent of the patients in the BCNU group underwent complete follow-up evaluation compared with 35% in the PCV group. The censoring

Table 1. Pretreatment Patient Characteristics

	BCNU (n = 257)		PCV (n = 175)	
	No.	%	No.	%
Age				
< 30 years	49	19	25	14
30-39 years	80	31	60	34
40-49 years	44	17	47	27
50-59 years	49	19	25	14
60-69 years	33	13	12	7
70+ years	2	1	6	3
Mean, years	42.4		41.9	
Range, years	20-72		18-77	
Sex				
Male	150	58	101	58
Female	107	42	74	42
Race				
White	234	91	164	94
Black	11	4	2	1
Other/unknown	12	5	9	5
Prior surgery				
Biopsy only	95	37	67	38
Resection	160	62	107	61
Other	2	1	1	1
KPS				
40	1	0	0	
50	1	0	0	
60	15	6	0	
70	27	11	17	10
80	57	22	30	17
90	112	44	74	42
100	44	17	54	31

pattern is uniform over 13 years in the BCNU group and over 7 years in the PCV group. The median survival duration has not been reached for patients treated with PCV who are less than 50 years of age. Tables 2 to 6 show survival by patient age, grouped by decade. The 1-year survival is equal in the 18- to 29-year-old patients (Table 2), but only two deaths have occurred in the PCV group. There is no statistically significant difference in survival ($P = .19$), but it may be too early to determine. Table 3 indicates equal survival between the groups for the 30- to 39-year-old patients ($P = .93$). Patients aged 40 to 49 (Table 4) had only slightly higher survival with PCV than with BCNU, but it was not statistically significant ($P = .29$). Patients older than 50 years of age (Tables 5 and 6) fared slightly better with BCNU, but this also was not statistically significant. There does not seem to be any age relationship between treatment group and outcome.

There was no difference in survival by KPS according to treatment group when patients were grouped by KPS 70, 80, 90, or 100 (data not shown). Patients who received PCV after a resection had higher 3-year survival, but this may be a result of lack of follow-up evaluation (Table 7). There was no difference in the biopsy-only group (Table 8).

A stratified analysis using age, KPS, and extent of surgery to define strata was performed. Table 9 defines the strata. As can be seen in Table 10, there is no trend for improved survival for one treatment group over the other ($P = .40$). A stratified Cox proportional hazards model provided equivalent results (Table 11; $P = .35$). The nonstratified Cox regression model indicates that age, KPS, and extent of resection are significant factors, but not treatment group (Table 12).

Finally, cases were matched between the two groups using age, KPS, and extent of surgery. There were 133 matched patients in both groups. Patients without a match were not

Table 2. Survival for Patients Aged 18 to 29 Years

	BCNU		PCV	
	% Alive	No. at Risk	% Alive	No. at Risk
Time				
0 years	100	49	100	25
1 year	94	46	92	18
2 years	82	39	92	7
3 years	66	30	92	5
4 years	59	24	92	4
5 years	51	18	92	2
Dead/total, n	26/49		2/25	
Median time, years	5.0		Not reached	
P	.19			

Table 3. Survival for Patients Aged 30 to 39 Years

	BCNU		PCV	
	% Alive	No. at Risk	% Alive	No. at Risk
Time				
0 years	100	80	100	60
1 year	91	72	90	52
2 years	80	63	81	28
3 years	72	52	66	10
4 years	63	37	66	4
5 years	57	31	—	0
Dead/total, n	40/80		13/60	
Median time, years	7.3		Not reached	
P	.93			

Table 4. Survival for Patients Aged 40 to 49 Years

	BCNU		PCV	
	% Alive	No. at Risk	% Alive	No. at Risk
Time				
0 years	100	44	100	47
1 year	75	32	84	34
2 years	56	24	63	13
3 years	47	20	54	4
4 years	38	13	54	2
5 years	35	11	—	0
Dead/total, n	32/44		15/47	
Median time, years	2.7		Not reached	
P	.29			

Table 5. Survival for Patients Aged 50 to 59 Years

	BCNU		PCV	
	% Alive	No. at Risk	% Alive	No. at Risk
Time				
0 years	100	49	100	25
1 year	63	31	50	11
2 years	37	18	30	2
3 years	35	16	30	2
4 years	24	10	—	0
5 years	—	7	—	0
Dead/total, n	38/49		16/25	
Median time, years	1.3		1.0	
P	.18			

Table 7. Survival for Patients Who Underwent Resection

	BCNU		PCV	
	% Alive	No. at Risk	% Alive	No. at Risk
Time				
0 years	100	160	100	107
1 year	86	137	89	85
2 years	69	110	76	41
3 years	59	87	70	18
4 years	52	65	65	9
5 years	47	54	65	2
Dead/total, n	95/160		24/107	
Median time, years	4.2		Not reached	
P	.13			

included in this analysis. Table 13 presents the overall survival, indicating no difference in survival between the two groups ($P = .20$). Interestingly, the stratified analysis gave a risk ratio of 1.17 favoring of BCNU, but the matched analysis had a risk ratio of 0.74 favoring PCV (Table 14). This would indicate no difference and some variability. Figure 1 shows overall survival of all patients treated with either PCV or BCNU ($P = .546$).

Similar analyses were performed to compare the outcome of patients with a mixed high-grade oligoastrocytoma (data not shown). Of the 257 patients treated with BCNU, 29 had a reported oligodendroglial component. Of the 175 patients treated with PCV, 41 had a reported oligodendroglial component. In a stratified analysis comparing survival for patients with a mixed tumor, no difference was noted ($P = .63$). Similarly, a regression analysis was performed, again showing no difference in outcome ($P = .59$). A nonstratified Cox regression model showed no impact of treatment on survival for these patients. Finally, overall survival was similar in the PCV- and BCNU-treated patients with mixed tumors. Median survival for BCNU-treated patients was 8.5 years and was not yet reached for the PCV group ($P = .26$). In conclusion, there does not seem to be any survival benefit to the use of PCV.

Table 6. Survival for Patients Aged 60+ Years

	BCNU		PCV	
	% Alive	No. at Risk	% Alive	No. at Risk
Time				
0 months	100	35	100	18
6 months	74	26	66	11
12 months	49	17	41	6
18 months	34	12	14	2
24 months	—	7	7	1
36 months	—	6	—	0
48 months	—	4	—	—
60 months	—	3	—	—
Dead/total, n	32/35		16/18	
Median time, years	0.9		0.7	
P	.20			

DISCUSSION

The goal of this study was to determine whether there was any difference in survival for AA patients treated with either adjuvant BCNU or PCV chemotherapy. The rationale for the study was, in part, a result of concern that a definitive study has yet to be conducted to show superiority of PCV over BCNU in this subset of patients. The only comparative study conducted to address this question was the initial NCOG trial that completed enrollment in 1983. Patients with malignant glioma that included both GBM and AA were eligible for randomization to either PCV or BCNU adjuvant chemotherapy. The only stratification variable used was the initial KPS, and randomization took place before radiation therapy. Patients were enrolled onto the study between December 1977 and February 1983. The analysis of the trial in 1985 did not result in a statistically significant advantage for the use of PCV chemotherapy.[9] A subsequent reanalysis of a subset of patients resulted in the conclusion that PCV was superior to BCNU, but only in the group of patients with AA other than GBM. This reanalysis only included patients with a KPS of 70 to 100 who received radiation therapy with hydroxyurea and had at least one course of chemotherapy with either BCNU or PCV. Patients with lower KPS or those who did not complete at least one full cycle of chemotherapy were not included. Thus, the reanalysis was not performed as

Table 8. Survival for Patients Who Underwent Biopsy Only

	BCNU		PCV	
	% Alive	No. at Risk	% Alive	No. at Risk
Time				
0 years	100	95	100	67
1 year	63	59	60	35
2 years	44	40	42	10
3 years	39	36	26	3
4 years	30	22	26	1
5 years	27	16	—	0
Dead/total, n	71/95		38/67	
Median time, years	1.7		1.2	
P	.44			

Table 10. Stratified Analysis Survival

Strata	Group	No. of Patients	Median Survival (months)
1	BCNU	12	12.5
	PCV	12	19.4
2	BCNU	34	77.5
	PCV	16	Not reached
3	BCNU	38	54.0
	PCV	25	32.4
4	BCNU	81	82.1
	PCV	79	Not reached
5	BCNU	20	10.3
	PCV	13	9.3
6	BCNU	17	20.3
	PCV	5	6.2
7	BCNU	16	10.1
	PCV	17	9.2
8	BCNU	20	21.7
	PCV	7	14.2
		$P = .40$	

an intent-to-treat analysis. In addition, survival in the subset of patients with AA who were treated with BCNU (control arm) was shorter than one would expect based on current standards. Furthermore, the numbers of patients in each group was small. A sample size of less than 40 patients per group could not be expected to confidently detect a survival advantage with high power. Despite these issues of sample size and a retrospective analysis of a subset of patients, the use of PCV chemotherapy has become commonplace in the adjuvant treatment of AA patients.

The current review is also retrospective and is subject to the limitations of any such analysis. For instance, the type of irradiation and the pathologic classification of AA may have influenced the outcome. The treatment given to patients differed by protocol and included various forms of radiotherapy. Some protocols used single fractionated irradiation, whereas others used accelerated or hyperfractionated irradiation. Some protocols used whole-brain irradiation, whereas others used focal or partial-brain irradiation fields. The dose varied by protocol as well. One could argue that the most important treatment used in these protocols was radiation therapy, and any potential differences in survival outcome would be a result of radiation dose or fractionation scheme rather than the type of adjuvant chemotherapy. However, despite long years of research related to dose and fractionation, there does not seem to be a significant benefit to any scheme other than single-dose treatment to 60 Gy to a focal or partial field. It would seem unlikely that the various dose/fractionation schemes used in the protocols in this analysis would have selectively impacted survival either positively or negatively. If there were any impact, it would seem probable that the use of whole-brain irradiation would negatively affect survival. BCNU chemotherapy was used in the few protocols in which whole-brain irradiation was given, and all patients who were treated with PCV were given partial-brain irradiation. One could theoretically assume that the use of whole-brain irradiation with BCNU would negatively impact the survival outcome of that patient group. However, that fact did not seem to change the outcome of the current analysis. Finally, patients in the BCNU group had longer follow-up, but trends in the first 3 years provide no indication of future differences.

The precise pathologic diagnosis of AA is subject to some debate among neuropathologists, and other than the requirement that central review was performed by protocol design to be included in this analysis, a re-review of all pathology was not performed. A small number of patients were noted to have mixed high-grade tumors. It is possible that some patients declared as AA in earlier protocols may be considered mixed tumors today. In cases in which the tumor was

Table 11. Strata for Regression Model

Strata	Definition
1	Age < 30 yr, KPS 70-80
2	Age < 30 yr, KPS 90-100
3	Age 30 to < 40 yr, KPS 70-80
4	Age 30 to < 40 yr, KPS 90-100
5	Age 40 to < 50 yr, KPS 70-80
6	Age 40 to < 50 yr, KPS 70-100
7	Age 50 to < 60 yr, KPS 70-80
8	Age 50 to < 60 yr, KPS 70-80, resection
9	Age 50 to < 60 yr, KPS 90-100, biopsy
10	Age 50 to < 60 yr, KPS 90-100, resection
11 + 12	Age > 60 yr, KPS 70-80
13	Age > 60 yr, KPS 90-100
14	Age > 60 yr, KPS 90-100, resection

NOTE. BCNU *v* PCV risk ratio = 1.17 ($P = .35$).

Table 12. Cox Regression Model

Covariate	Risk Ratio	*P*
Age	1.05	< .001
KPS (70-80 *v* 90-100)	0.69	.013
Surgery (biopsy *v* resection)	0.57	< .001
Treatment (BCNU *v* PCV)	—	.370

Table 9. Strata Definitions for Univariate Analysis

Strata	Definitions
1	Age < 50 yr, KPS 70-80, biopsy
2	Age < 50 yr, KPS 70-80, resection
3	Age < 50 yr, KPS 90-100, biopsy
4	Age < 50 yr, KPS 90-100, resection
5	Age ≥ 50 yr, KPS 70-80, biopsy
6	Age ≥ 50 yr, KPS 70-80, resection
7	Age ≥ 50 yr, KPS 90-100, biopsy
8	Age ≥ 50 yr, KPS 90-100, resection

Table 13. Stratified Cox Analysis Using Matched Cases*

	Risk Ratio	*P*
BCNU *v* PCV	0.74	.20

*One hundred thirty-three matched pairs—each is a stratum.

considered to have an oligodendroglial component, however, no difference in survival outcome could be observed between the two treatment groups. The neuropathologist who performed central review of patients treated with PCV used pathologic criteria that differed slightly from those treated with BCNU. Thus, it is conceivable that some pathologic discordance exists in this group of patients, which may account for some differences in outcome between the PCV group and the BCNU group. In a previous study of patients with both GBM and AA treated according to NCOG and RTOG protocols, the two neuropathologists who performed the central review compared cases to assess the potential degree of discordance.[3] There was disagreement in approximately 10% of sampled cases. These same two neuropathologists reviewed cases for the current studies. Our hope is that with sufficient numbers of patients, significant differences in pathology would not be present to influence the results in one direction or the other. Other patient factors that influence outcome were well balanced between the groups, and the analysis was specifically performed to account for these factors.

There has not been a prospective phase III study conducted in the United States that has randomized patients with AA to surgery plus irradiation versus surgery plus irradiation and adjuvant chemotherapy. Previous RTOG studies included patients with both GBM and AA and suggested a benefit of chemotherapy for younger patients with tumors other than GBM. Again, sample size and protocol design did not specifically address the question of adjuvant chemotherapy for AA patients. Recent preliminary data from a Medical Research Council phase III trial

Table 14. Matched Cases

	BCNU		PCV	
	% Alive	No. at Risk	% Alive	No. at Risk
Time				
0 months	100	133	100	133
6 months	91	121	89	116
12 months	80	106	81	96
18 months	68	90	71	64
24 months	61	80	65	43
36 months	53	64	56	18
48 months	41	43	52	9
60 months	38	36	—	2
Dead/total, n	87/133		45/133	
Median time, months	38.7		Not reached	
P	.41			

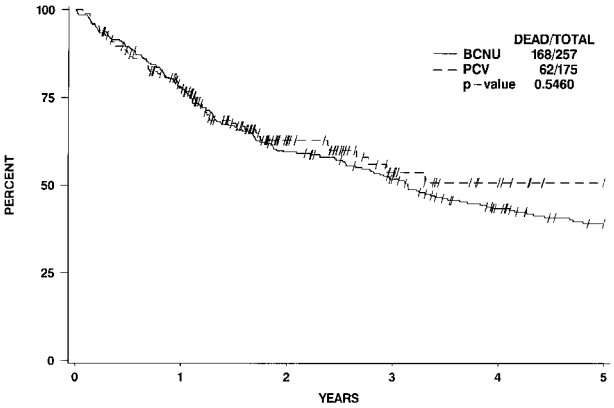

Fig 1. Overall survival of all patients treated either with BCNU or PCV chemotherapy. There was no statistical difference in survival between the two groups (*P* = .5460).

conducted in the United Kingdom, which randomized patients after surgery to irradiation alone versus irradiation plus adjuvant PCV, suggest that PCV chemotherapy offers no survival benefit for patients with either GBM or AA.[10] The final analysis of that study is still awaiting further follow-up evaluation. Thus, one cannot assume that either BCNU or PCV is the standard of care or, indeed, if any chemotherapy is of proven benefit given immediately after irradiation for this patient group. If the final analysis of the Medical Research Council phase III study is statistically compelling enough to confidently show that adjuvant PCV has no benefit for patients with AA, then future studies may want to consider irradiation alone as the control arm. Again, however, if the AA survival data from that study is substantially lower than median survival expectations reported from other large studies, the ''final'' answer concerning adjuvant chemotherapy may still await further trials.

Pertinent to this question is whether BCNU or PCV should be considered the standard form of chemotherapy to be used in the adjuvant setting, if one considers adjuvant chemotherapy to be important in improving survival. The current retrospective analysis suggests that either BCNU or PCV result in similar survival outcomes. Thus, either therapy could be considered a reasonable option after irradiation. The choice could be made based on the potential toxicity of either the single agent or the combination, or by patient or physician preference. Ideally, it would be desirable to make decisions about adjuvant chemotherapy based on well-designed, appropriately sized, prospective phase III studies. Study designs are now being considered for patients with AA. One could argue that a phase III trial of BCNU versus PCV should now be considered for such a study. However, it may be difficult to accrue patients onto such a

study because of physician or patient bias that a trial of BCNU versus PCV would not likely yield a positive result (ie, superiority of one over the other), would consume valuable patient and clinical trials resources, and is not an ''exciting'' enough study question to evaluate in 1999. Alternatively, one could consider the use of either BCNU or PCV as the control arm of a new phase III study, randomizing that therapy to a promising new chemotherapy agent. Another option would be to consider the use of BCNU alone compared with BCNU plus another agent, assuming sufficient phase II experience was available for the potential combination. Alternatively, one may consider that there is not a good phase III question to study at this point for this patient group, and further phase II trials need to be completed to identify promising new strategies.

Careful consideration needs to be given to these and other ideas before a large phase III trial is started that likely will not yield results for many years. Hopefully, as we learn from past studies and consider various options, results will be forthcoming that translate into a ''true'' standard of care.

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