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Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas

A cooperative clinical trial

MICHAEL D. WALKER, M.D., EBEN ALEXANDER, JR., M.D., WILLIAM E. HUNT, M.D., COLLIN S. MACCARTY, M.D., M. STEPHEN MAHALEY, JR., M.D., JOHN MEALEY, JR., M.D., HORACE A. NORRELL, M.D., GUY OWENS, M.D., JOSEPH RANSOHOFF, M.D., CHARLES B. WILSON, M.D., EDMUND A. GEHAN, PH.D., AND THOMAS A. STRIKE, PH.D.

The Brain Tumor Study Group and the National Cancer Institute, National Institutes of Health, Bethesda, Maryland

A controlled, prospective, randomized study evaluated the use of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and/or radiotherapy in the treatment of patients who were operated on and had histological confirmation of anaplastic glioma. A total of 303 patients were randomized into this study, of whom 222 (73%) were within the Valid Study Group (VSG), having met the protocol criteria of neuropathology, corticosteroid control, and therapeutic approach. Patients were divided into four random groups, and received BCNU (80 mg/sq m/day on 3 successive days every 6 to 8 weeks), and/or radiotherapy (5000 to 6000 rads to the whole brain through bilateral opposing ports), or best conventional care but no chemotherapy or radiotherapy. Analysis was performed on all patients who received any amount of therapy (VSG) and on the Adequately Treated Group (ATG), who had received 5000 or more rads radiotherapy, two or more courses of chemotherapy, and had a minimum survival of 8 or more weeks (the interval that would have been required to have received either the radiotherapy or chemotherapy). Median survival of patients in the VSG was, best conventional care: 14 weeks (ATG: 17.0 weeks); BCNU: 18.5 weeks (ATG: 25.0 weeks); radiotherapy: 35 weeks (ATG: 37.5 weeks); and BCNU plus radiotherapy: 34.5 weeks (ATG: 40.5 weeks). All therapeutic modalities showed some statistical superiority compared to best conventional care. There was no significant difference between the four groups in relation to age distribution, sex, location of tumor, diagnosis, tumor characteristics, signs or symptoms, or the amount of corticosteroid used. An analysis of prognostic factors indicates that the initial performance status (Karnofsky rating), age, the use of only a surgical biopsy, parietal location, the presence of seizures, or the involvement of cranial nerves II, III, IV, and VI are all of significance. Toxicity included acceptable, reversible thrombocytopenia and leukopenia.

KEY WORDS • **brain tumor** • **glioblastoma** • **chemotherapy** • **radiotherapy** • **BCNU** • **prognostic factors**

ANAPLASTIC glioma accounts for approximately one-quarter of all adult cerebral neoplasms, and includes glioblastoma multiforme, anaplastic astrocytoma (Kernohan Grade III–IV), and malignant astrocytomas.[10,11] They have a uniformly fatal course with a median survival after best conventional care of approximately 6 months and a survivorship of less than 10% at 2 years.[15] Mithramycin was the first drug evaluated in the treatment of anaplastic glioma by a multi-institutional clinical trial.[5] There was no difference in survival between patients who received mithramycin as compared to those who did not, and the median survival of all patients was 24 weeks. The importance of this study was that malignant gliomas may be studied in controlled, prospective, randomized trials, rather than the fact that mithramycin failed to prolong the lives of patients with anaplastic glioma. Using such techniques, various forms of therapy may be quantitatively as well as qualitatively evaluated and their true efficacy more clearly defined. One of the factors indicated in the mithramycin study was that patients who received radiotherapy appeared to have a longer survival than those who did not receive radiotherapy. Although the study was not designed to evaluate the efficacy of irradiation, the information provided the impetus to attempt to define more clearly its quantitative value.

The nitrosoureas are a group of antineoplastic agents possessing the appropriate pharmacological characteristics to cross the blood-brain barrier.[8] They have been demonstrated to be of value in the treatment of a wide variety of animal and human tumors.[4,14] In particular, the first of these to be developed, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), was available for clinical trial and had been demonstrated to be effective in the treatment of a variety of experimental intracranial neoplasms.[14] Phase II evaluation of BCNU in two studies indicated that it provides approximately a 50% response rate in late-stage recurrent gliomas of the brain.[17,19]

The Brain Tumor Study Group (BTSG), a cooperating group of neurosurgeons, neuropathologists, and radiotherapists working in conjunction with the National Cancer Institute, prepared a carefully designed protocol to evaluate the efficacy after surgery of 1) BCNU as a single chemotherapeutic agent, 2) radiotherapy, and 3) the combination of BCNU and radiotherapy, compared to 4) best conventional care (supportive care). In addition, a wide variety of historical, neurological, operative, and recurrence characteristics were evaluated in order to determine their interrelationship with therapy. This report concerns itself specifically with the results of the above-mentioned therapeutic trial.

Clinical Material and Methods

Ten participating neurosurgical services entered patients into the study. Patients, who in the judgment of the principal investigator met the criteria of acceptability, were randomized to one of the four treatment arms by a telephone call to the Central Office. All patients were informed of the nature of the study, the possible therapies that might be employed, the reasonably anticipated toxicity that might result from such therapy, the randomization procedure, and the availability of continued care should they decline to enter or remain in the study. Written informed consent was obtained. All data were recorded on a series of report forms, forwarded to the Central Office, verified, and coded for computer processing.

Criteria of Acceptability

The principal investigator of each institution was primarily responsible for determining the eligibility of any patient's entrance into the study. All patients must have undergone a definitive surgical resection and have had confirmation of the diagnosis by histopathological examination. Representative slides of the tumor were forwarded to the Central Office for evaluation by the Pathology Review Committee. All patients who were randomized, whether acceptable or not, were considered within the randomized population, however, inclusion in the Valid Study Group (VSG) was dependent upon subsequent fulfillment of the protocol requirements of critical pathology review, receipt of at least some of the designated treatment, control of the use of corticosteroids, and appropriate follow-up review. The patient must have been randomized within 6 weeks of definitive surgical resection and establishment of the diagnosis. It was ex-

pected that all randomized patients would have a minimal postoperative life expectancy of greater than 2 months (although none was removed from the study because of a shorter survival), and would possess a normal bone marrow reserve as indicated by a complete blood count and platelet count. Normal hepatic and renal function as well as freedom from overt infection was also required.

Treatment

Patients designated to receive BCNU* were given 80 mg/sq m intravenously on 3 successive days every 6 to 8 weeks. Body surface area was used as the unit of measure, as it provided a better method of delivering equivalent dosage among patients of varying body size. Treatment was continued at the same dose level for each course of therapy, except when patients had platelet nadirs below 50,000/cu mm or leukopenia of less than 3000/cu mm, at which time they received 75% of their former dose. All investigators were aware of the profound delayed thrombocytopenia that can accompany the use of BCNU and, therefore, followed patients closely.

Patients randomized to receive radiotherapy were initially given 5000 rads midplane tumor dose in five fractions per week (approximately 171 to 200 rads/day) over 5 to 6 weeks. Large parallel opposing lateral fields with appropriate shielding were utilized to encompass the entire cranial contents. Ten months after the initiation of the study, the dose of radiotherapy was increased from 5000 to 6000 rads midplane tumor dose, given over a course of 6 to 7 weeks. This was felt to be the maximum amount of irradiation that could be delivered within safe limits. It was anticipated that all radiotherapy would be given as one continuous course without interruption. Equipment calibration and dosage was monitored at each institution by the Radiologic Physic Center, Houston, Texas.

Evaluation

All patients were thoroughly evaluated from a neurological, hematological, general medical, and functional point of view before treatment. Those receiving BCNU had weekly complete blood counts (CBC) and platelet counts obtained, as well as frequent hepatic and renal function tests. Any patient demonstrating toxicity had more frequent monitoring as required. Appropriate neurodiagnostic tests were performed as the patient's clinical condition dictated, and all patients were evaluated at least on a monthly basis. Although patients who were randomized to the Supportive Care Arm and those who had completed their radiotherapy were not receiving additional active therapy, they were, nevertheless, evaluated routinely in order to determine the state of their disease. All patients were frequently rated on a functional scale of 0 to 100 (the Karnofsky Scale).[7] The usual standards of medical and neurosurgical care were afforded all patients but no extraordinary measures beyond those of good standard practice and appropriate therapy were undertaken to prolong the patient's life. It was anticipated that the course of the disease in the study group should be relatively similar to that experienced within the community.

It was recognized that corticosteroids might play a significant role in the prolongation of survival. Therefore, the use of corticosteroids was carefully monitored in the pre-, intra-, and postoperative periods. Steroid administration during this time was not to exceed 1 month of total use. During subsequent courses of therapy, steroids could only be given once during each course, and for not more than 1 week. The steroids of choice were either dexamethasone (3 to 4 mg every 6 hours) or methylprednisolone (30 to 40 mg every 6 hours) and their use was restricted to the control of life-threatening cerebral edema.

Statistical Methods

Data collected by the Central Office were transferred to a computer base and verified. All patients in the randomized population were included; however, protocol violations as they were identified formed the basis for the decision to exclude patients from the VSG. The major analysis of this study was made on patients in the VSG; however, nearly all analyses were performed for both VSG and randomized population, and no essential

*BCNU (NSC 409962) was supplied by the Drug Distribution Branch, National Cancer Institute, Bethesda, Maryland.

TABLE 1

Comparison of clinical characteristics of patients in the various treatment groups of the Valid Study Group

Parameter	Total	Supportive Care	BCNU	Radiotherapy	BCNU & Radiotherapy
randomized population	303	42	68	93	100
protocol violations	81 (27%)	11 (26%)	17 (25%)	25 (27%)	28 (28%)
Valid Study Group	222	31	51	68	72
male:female (%)	64:36	55:45	55:45	62:38	75:25
age (yrs)					
median	57	57	57	56	57
range	6–79	10–79	22–78	28–78	6–78
handedness (%)					
left	2.7	3.2	2.0	2.9	2.8
right	97.3	96.8	98.0	97.1	97.2
duration of symptoms (%)					
< 4 wks	34	39	37	34	31
5–8 wks	20	13	27	18	19
9–26 wks	36	38	29	38	37
27–52 wks	5	0	2	4	10
> 52 wks	5	10	4	6	3
interval from first symptom to operation (wks)					
median	8	8	6	9	9
range	1–222	1–60	0–92	0–222	0–64
location					
right:left (%)	55:45	55:45	51:49	54:46	58:42
frontal	31	26	35	32	29
temporal	33	39	22	44	29
parietal	27	29	31	16	32
occipital	6	3	10	7	4
basal ganglia/thalamus	1	0	0	0	3
other	2	3	2	1	3
operation type (%)					
subtotal resection	49	55	49	45	48
subtotal resection & lobectomy	35	23	31	44	35
"total" tumor resection	9	16	6	7	10
biopsy only	5	3	10	3	6
"total" resection & lobectomy	2	3	4	1	1
tumor characteristics (%)					
invasive	20	19	22	18	20
necrotic	19	20	15	20	19
soft	17	16	17	18	17
vascular	12	9	12	12	13
solid	10	14	9	11	8
cystic	8	8	7	9	8
friable	5	3	9	3	5
hard	4	6	3	4	5
hypovascular	3	0	2	4	3
encapsulated	2	5	3	2	1
interval from operation to randomization (days)					
median	8	5	9	9	8
range	1–42	1–27	1–38	1–42	1–29
second operation (%)	4	3	6	1	4
diagnosis (%)					
glioblastoma multiforme (9443*)	90	89	92	92	90
anaplastic astrocytoma (9442*)	9	10	8	7	10
other	1	1	0	1	0
corticosteroids used (%)	76	65	69	75	81
average no. days used	14	15	13	14	14

*Systemized nomenclature of pathology (SNOP) number.

TABLE 2

*Reasons for excluding patients from the Valid Study Group (% of patients)**

Reason	Total	Supportive Care	BCNU	Radiotherapy	BCNU & Radiotherapy
chemotherapy error	11	NA	17	NA	21
radiotherapy error	10	NA	NA	9	18
other antineoplastic treatment given	10	31	17	9	0
excess corticosteroids	36	54	39	38	26
patient lost to follow-up	1	0	4	0	0
incorrect pathology	18	15	13	19	21
inadequate records	12	0	9	25	11
other	1	0	0	0	3

*NA = Not applicable.

difference between the two groups was demonstrated.

The number of patients required for the completion of this study was based upon survival approximations from previous retrospective studies, as well as the prior experience of the BTSG.[1,5,16] The survival time of patients with anaplastic glioma is approximately exponentially distributed up to about 2 years. For the purposes of estimation, improvement was defined as an increase of 75% or more in median survival time of patients in any of the Treatment Groups as compared to those in the Control Group. A significance level of 5% with a power of test of 80% was chosen. Survival curves were calculated according to Kaplan and Meier[6] and a generalized Wilcoxon test as modified by Gehan[2] was used for obtaining a p value. Reference will be made to the median value unless otherwise specified. Chi-square tests were used to test the difference between patient characteristics in the various groups.[13]

The VSG includes all patients who received any amount of therapy no matter how small. Some patients, however, did not survive long enough to receive a significant amount of therapy, and others were only partially treated. In order to study a subset of patients who had received a significant amount of treatment, the Adequately Treated Group (ATG) was defined as those patients who had two or more courses of BCNU, 5000 or more rads of radiotherapy, and had a survival of 8 or more weeks, that being the amount of time which would have been required should the patient have been designated to receive radiotherapy or chemotherapy. Variables that might be related to an insufficient amount of therapy were thus excluded in the ATG and the chances of demonstrating therapeutic efficacy were optimized.

Results

A total of 303 patients were entered into the study between September 1, 1969, and October 1, 1972 (Table 1). There are uneven numbers of patients randomized to each therapeutic arm, as two participating institutions were unable to enter patients into the Supportive Care arm. In addition, during the last 6 months of the study, patients were randomized only to the radiotherapy or radiotherapy plus BCNU group as interim analyses indicated that these two forms of treatment were superior. An average of 27% of all the patients entered into the study had protocol violations for one or more reasons (Table 2). Overall, the protocol violations were appropriately and evenly distributed among the various treatment arms. The most common protocol violation was the excessive use of corticosteroids. This usually occurred at one of two times, either during radiotherapy when the patient was maintained on steroid for the entire 6 to 7 week period, or in association with a prolonged sequence of terminal events. The second most frequent protocol violation was due to a failure of the case to be accepted by the Neuropathology Review Committee upon final review of the permanent sections. The vast majority of these tumors were classified as being less anaplastic-appearing gliomas. Errors in therapy received were about equally divided between chemotherapy and radiotherapy; however, a higher proportion of supportive

TABLE 3

Pretreatment symptoms reported by the Valid Study Group (%)

Characteristics	Total	Supportive Care	BCNU	Radiotherapy	BCNU & Radiotherapy
initial symptom					
headache	31	33	27	35	30
seizures	18	13	14	21	19
personality change	16	6	21	18	14
motor symptoms	13	13	10	13	14
speech deficit	7	13	8	3	7
sensory symptoms	3	3	6	1	1
other	12	19	14	9	15
symptom reported any time before surgery					
headache	23	25	24	28	24
motor symptoms	20	32	18	20	23
personality change	14	13	19	13	17
seizures	11	10	10	13	12
speech deficit	10	9	10	12	12
sensory symptoms	6	9	6	4	7
CN II, III, IV, VI	3	1	2	5	3
general systemic complaints	3	1	1	5	2

care patients received some other form of antineoplastic therapy. The Valid Study Group, therefore, is made up of 222 patients who received at least a minimum amount of designated therapy and met the protocol criteria.

Clinical Characteristics

A series of pretreatment patient characteristics is shown in the remainder of Table 1. Approximately two-thirds of the patients were male, one-third female, with some degree of variation among the four treatment arms. The median age of all patients was 57 years with a range of 6 to 79 years of age. There was an even distribution of patients with different ages throughout the VSG. The vast majority of patients (90%) had a duration of symptoms of 6 months or less while in 34% symptoms were present less than 4 weeks. The median interval of time from the appearance of the first symptom to operation was only 2 months, and there was no statistically significant difference in the duration of symptoms in the various treatment groups.

The presenting symptom and subsequently developing symptoms before surgery are shown in Table 3. Headache was the initial symptom in almost one-third of the patients. Seizures heralded the onset of disease in 18%, while subtle personality changes were reported as the first symptom in 16% of patients. Only 13% indicated some motor abnormality as being the presenting symptom, and speech and sensory symptoms were rarely seen as the initial symptom.

Between the appearance of the first symptom and surgical intervention additional symptoms developed, and in most cases, these additional symptoms were the events that led to diagnostic procedures and surgery. Headache remained as the most frequent symptom reported any time before surgery; however, motor symptomatology developed in one-fifth of the patients. Personality change and seizures, if they were not the initial symptom, were not seen frequently as later symptoms. An analysis of symptom presentation and occurrence among the various therapeutic arms failed to indicate any statistically significant difference between the various groups.

Forty-five percent of the tumors were located in the left hemisphere, with 33% being found entirely or predominantly in the temporal lobe, 31% in the frontal lobe, and 27% in the parietal area. There was no statistically significant difference in hemispheric location or predominant position of the tumor between the treatment groups. All patients underwent craniotomy and surgical resection. A subtotal tumor resection was performed in

49%, while an additional 35% underwent a lobectomy as well. Only 9% of the patients were believed to have had a "gross total" tumor resection; only 5% had a biopsy. The median interval of time from operation to randomization was 8 days. There was no statistical difference in either the operative approach or interval of time to additional therapy between the various treatment groups. Only 4% of the patients underwent a second operation, those being seen slightly more frequently in the group of patients who were treated with BCNU. On an average, 76% of the patients received corticosteroid therapy at one time or another during treatment. This was prescribed for an average of 2 weeks, and there was no significant difference in its utilization among the various therapeutic groups.

TABLE 4

*Amount of therapy received by the various treatment groups of the Valid Study Group**

Therapy Delivered	BCNU	Radiotherapy	BCNU & Radiotherapy
BCNU courses (%)			
1	100	—	100
2	65	—	62
3	39	—	57
4	20	—	39
5	16	—	31
> 5	14	—	24
average doses BCNU	2.73	—	3.79
median doses BCNU	2	—	3
dose of radiotherapy (rads)			
median	—	5840	5500
mean	—	5319	5229
(± SE)	—	115	136

*The Supportive Care group received no BCNU or radiotherapy.

Neuropathology

The initial neuropathological diagnosis was made at each participating institution; however, the acceptance of a designated diagnosis was not final until representative sections had been reviewed by the Pathology Review Committee (Drs. Stephen Vogel, Peter Burger, Nitya Ghatak, and M. Stephen Mahaley, Jr.) (Table 1). Of the 303 cases in the randomized population, two did not have slides submitted for review, one was metastatic carcinoma, and 17 were considered as comparatively "benign" astrocytomas. Tumors of the VSG patients were confirmed as 90% glioblastoma multiforme, 9% anaplastic astrocytomas, and 1% other anaplastic gliomas. There was no significant difference in the distribution of histopathological types among the various treatment modalities. A more detailed review has been prepared by Mahaley, *et al.*[9]

Therapy

The amount of therapy received by the various groups was compared for adequacy and comparability of treatment and is indicated in Table 4. All patients in the VSG received the first dose of BCNU. However, just 20% of those within the BCNU only group received a fourth dose of the drug, while almost twice as many (39%) received a fourth dose in the BCNU plus radiotherapy group. In fact, after the second course those receiving combination therapy had a significantly greater number of courses of chemotherapy ($p < 0.01$). This is reflected in the fact that the average number of doses of BCNU received was 2.73 for the BCNU only group, whereas it was 3.79 for the BCNU and radiotherapy group.

Patients receiving radiotherapy alone received slightly more radiotherapy than those who received BCNU and radiotherapy (mean dose 5319 rads versus 5229 rads). However, the difference was not significant.

Toxicity

Evidence of toxicity with BCNU therapy was primarily delayed bone marrow suppression, although nausea, vomiting, and irritation at the site of injection were occasionally reported. The effect on platelet and white blood cell counts for the first dose is shown in Table 5. Not all patients could be evaluated because of either early death or inadequate reporting. There was no significant difference in the thrombocytopenia experienced by patients who received BCNU as compared to BCNU and radiotherapy. About half had a platelet count of less than 100,000/cu mm, with a median nadir for the entire group of approximately 96,000/cu mm seen on the 25th day. Approximately one-quarter of the

TABLE 5

Thrombocytopenia and leukopenia encountered during the first course of BCNU therapy with and without radiotherapy

Parameter	BCNU	BCNU and Radiotherapy
thrombocytopenia		
patients entered	51	72
percent evaluable	78	95
platelet count		
< 100 (%)	54	43
< 50 (%)	30	21
median nadir (/cu mm × 10^3)	92	98
median nadir/day (/cu mm × 10^3)	24	26
leukopenia		
patients entered	51	72
percent evaluable	80	92
white blood cell count (/cu mm × 10^3)		
< 4.0 (%)	61	68
< 2.0 (%)	18	20
median nadir (/cu mm × 10^3)	3.6	3.2
median nadir day (/cu mm × 10^3)	32	35

patients had a platelet count less than 50,000/cu mm.

Leukopenia was less pronounced, but was also seen equally distributed between the two therapeutic approaches. The median nadir white count reported was 3600/cu mm for those receiving BCNU and 3200/cu mm for those receiving BCNU and radiotherapy. Both of these were seen approximately 5 weeks from treatment. Profound anemia was not encountered. Variable elevations in liver function test enzymes were reported at different times during the course of therapy; however, the data were irregular in reporting interval and not susceptible to statistical evaluation. No pronounced lasting clinical effects, however, were noted in either hepatic or renal function.

The thrombocytopenia and leukopenia noted during the first courses of therapy were seen with approximately the same frequency during subsequent courses of treatment, although patients had their dose of BCNU appropriately reduced for profound count depressions. Serious complications, secondary to thrombocytopenia or leukopenia, were not encountered and, in general, the therapy was well tolerated. No toxicity to radiotherapy was noted.

Survival

The median survival times and percentage of patients surviving at various intervals is shown in Table 6 and the survival curve (Fig. 1). Patients who had best conventional care but no radiotherapy or BCNU had a median survival of 14 weeks, while those who had BCNU only had a median survival of 18.5 weeks. This improvement is of marginal

TABLE 6

Survival of patients treated with BCNU and/or radiotherapy

Factor	Supportive Care	BCNU	Radiotherapy	BCNU & Radiotherapy
Valid Study Group				
median survival (wks)	14.0	18.5	36.0	34.5
Wilcoxon test	—	.119	.001	.001
(p value)		—	.001	.001
			—	.408
Adequately Treated Group				
median survival (wks)	17.0	25.0	37.5	40.5
Wilcoxon test	—	.002	.001	.001
(p value)		—	.013	.006
			—	.258
percent of patients surviving				
6 mos	16	31	66	60
12 mos	3	12	24	32*
18 mos	0	4	4	19*
24 mos	0	0	1	5

*Chi square = < 0.01.

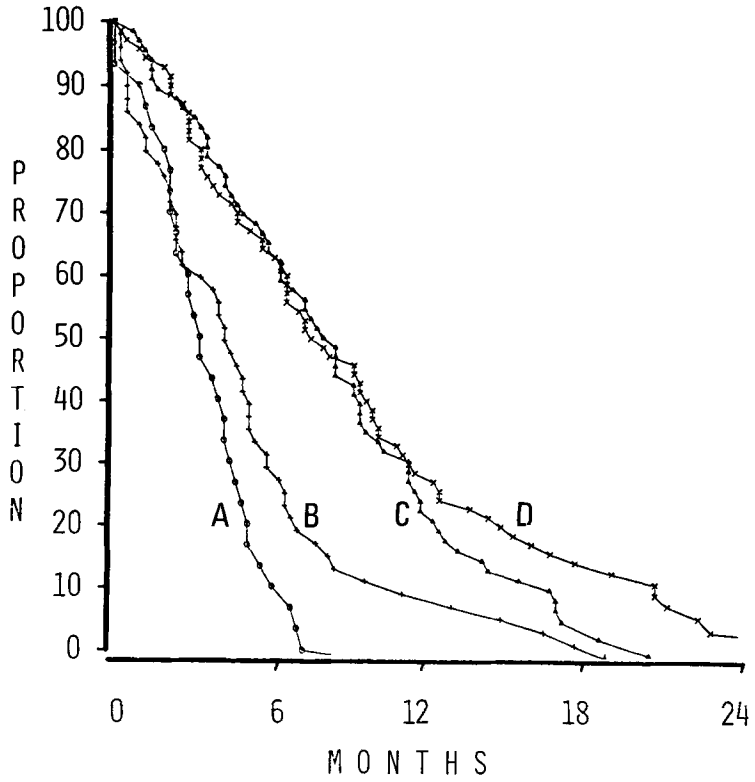

FIG. 1. Survival curves of patients who received: A) best conventional care but no radiotherapy or chemotherapy, B) BCNU, C) radiotherapy, or D) BCNU and radiotherapy.

significance ($p = 0.119$). Radiotherapy on the other hand provided a clear-cut improvement with a median survival of 36 weeks ($p = 0.001$) and radiotherapy plus BCNU had a median survival of 34.5 weeks ($p = 0.001$). There was no significant difference in this study between patients receiving BCNU and radiotherapy versus radiotherapy alone. Analysis of the ATG demonstrated changes in the survival characteristics. Patients who received a significant amount of BCNU had a modest (47%) increase in median survival time which was, however, highly significant ($p = 0.002$). The difference between BCNU and radiotherapy remained significantly different ($p = 0.013$). However, the difference between radiotherapy plus BCNU and radiotherapy alone did not change.

Prognostic Factors

The initial performance status (Karnofsky rating) of all patients was compared to survival. Those patients who were essentially well and had a high Karnofsky rating (90 to 100) had a significantly better median survival of 33 weeks as compared to those who had an intermediate Karnofsky rating of 50 to 80 whose median survival was 25 weeks ($p = 0.006$). Those patients who had a low Karnofsky rating had an even poorer median survival of 13 weeks ($p = 0.005$). The immense amount of symptomatic data, clinical characteristics, and therapeutic intervention data available has been subjected to a detailed evaluation of its correlation with the prognosis of survival. Those characteristics which seem to be negatively correlated with survival (that is, those that confer a poorer prognosis) are age, only having had a surgical biopsy as compared with a bulk resection, and a parietal location. Characteristics with a positive correlation are the presence of seizures or involvement of cranial nerves II, III, IV, and VI. A more detailed analysis of this is presented by Gehan.[3] Considering the current state of therapy and the modest value

of either drugs or radiotherapy, these prognostic factors or combinations of them may have a considerable influence upon survival.

Discussion

This study is the second in a series of prospective, controlled, randomized, cooperative clinical trials investigating the biological characteristics and treatment potential of anaplastic gliomas. It has demonstrated a modest but significant value for the lyophilic nitrosourea BCNU; that being most obvious in those patients who received an adequate amount of therapy (two or more courses). The role of radiotherapy in the treatment of anaplastic glioma was clearly demonstrated, and in this study it increases median survival by approximately 150%. The addition of BCNU to radiotherapy failed to alter median survival significantly either in those patients who were in the VSG or ATG. However, there was a significantly greater surviving fraction of patients at the end of 18 months among those who received combination therapy ($p = 0.01$). A current study evaluating BCNU and radiotherapy compared to methyl-1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (MeCCNU) alone, MeCCNU and radiotherapy, and radiotherapy alone continues to demonstrate superiority for this combination of treatments.[18]

Although the procedures of patient selection, acceptance, and randomization were similar to the mithramycin study,[16] a number of factors appear to be somewhat different in the patient population. The median age was 4 years older, and the duration of symptoms before surgery was considerably less in the second study: 90% of the patients in this study reported their first symptom within 6 months of surgery, whereas in the mithramycin study, only 31% of patients had their first symptom within 6 months of surgical resection. Despite the difference in the interval from first symptom to operation, the initial symptomatology and symptom complexes reported by this patient population are similar to those reported previously.[16] The location of tumor, both in terms of hemisphere and predominant area, was similar and the extent of resection between the two studies was not different. The distribution between glioblastoma multiforme and anaplastic astrocytoma was also similar in the two studies, therefore, there are more areas of comparability than discrepancy. The median survival of all patients in the mithramycin study was 24 weeks, thereby appearing to be better than the Supportive Care or BCNU arms in this study. However, randomization was only between receiving or not receiving mithramycin in that study and radiotherapy was permitted. The radiotherapy effect, therefore, was responsible for the seemingly superior survival noted in the mithramycin study and, in fact, was one of the observations that led to the design of this study.

The greatest number of protocol violations were due to an excessive use of corticosteroids above permitted amounts. Although the oncolytic effect on malignant glioma of corticosteroid has not been demonstrated, it was felt that the effect of these drugs is so profound as possibly to alter survival; therefore, rigid controls on their utilization were applied. A future study is addressing itself specifically to the oncolytic effect of corticosteroids in comparison with their use for the control of cerebral edema.

The amount of BCNU received by those patients treated with the drug alone was significantly less than those who received BCNU and radiotherapy. The former group received on the average of one dose less; however, with doses being given at approximately 8-week intervals, this is in keeping with the decreased survival demonstrated for patients who received drug alone. The mean and median amount of radiotherapy received between the two groups of patients who underwent radiotherapy was similar, although it was lower than the 6000 rads eventually agreed upon. Future studies will employ the 6000-rad maximum dose.

The identification of prognostic factors that relate significantly to the biology of the disease is extremely important in order to permit appropriate design and stratification of studies as well as to indicate comparability of patient populations that are studied. Studies reporting the treatment of malignant glioma should include a careful statistical analysis including at the very least factors such as age, operation, tumor location, symptom complexes (particularly the presence of seizures or involvement of cranial nerves II, III, IV, and VI), the interval from first symptom to operation, and the use of radiotherapy. Intercomparability between various studies performed in different centers may

then be carried out with reasonable assurance that factors that might modulate the outcome have been accounted for.

This study has led to the development of additional protocols designed to confirm these findings, and to evaluate them against newer modes of therapy. At the current state-of-the-art in the treatment of malignant brain tumor, it appears as though there are no alternatives other than to continue with carefully controlled, prospective, and randomized studies in order to determine the most effective forms of treatment for this disease.

References

1. Frankel SA, German WJ: Glioblastoma multiforme. Review of 219 cases with regard to natural history, pathology, diagnostic methods and treatment. **J Neurosurg 15**:489–503, 1958
2. Gehan EA: A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. **Biometrika 52**:203–223, 1965
3. Gehan EA: Prognostic factors for patients with brain tumors. **J Natl Cancer Inst** (In press)
4. Goldsmith MA, Carter SA: Glioblastoma multiforme — a review of therapy. **Cancer Treat Rev 1**:153–165, 1974
5. Jelsma R, Bucy PC: The treatment of glioblastoma multiforme of the brain. **J Neurosurg 27**:388–400, 1967
6. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. **J Am Stat Assoc 53**:457–481, 1958
7. Karnofsky DA, Burchenal JH, Armistead GC Jr, et al: Triethylene melamine in the treatment of neoplastic disease. **Arch Intern Med 87**:477–516, 1951
8. Levin VA: A pharmacologic basis for brain tumor chemotherapy. **Semin Oncol 2**:57–61, 1975
9. Mahaley MS Jr, Vogel S, Burger P, et al: Neuropathology observations on tissues from patients treated by the Brain Tumor Study Group (BTSG). **J Natl Cancer Inst** (In press)
10. Rubinstein LJ: **Tumors of the Central Nervous System.** Washington, DC: Armed Forces Institute of Pathology, Second Series, Fascicle 6, 1972
11. Russell DS, Rubinstein LJ: **Pathology of Tumours of the Nervous System, ed 3.** London: Edward Arnold, 1970
12. Schabel FM Jr, Johnston TP, McCaleb GS, et al: Experimental evaluation of potential anticancer agents. VIII. Effects of certain nitrosoureas on intracerebral L1210 leukemia. **Cancer Res 23**:725–733, 1963
13. Snedecor G, Cochran WG: **Statistical Methods, ed 6.** Ames, Iowa: Iowa State University Press, 1967, pp 215–220
14. Vendetti JM, Kline I, Goldin A: Evaluation of antileukemic agents employing advanced leukemia L1210 in mice. VIII. **Cancer Res 24 (Suppl) No. 6, Part 2**:827–879, 1964
15. Walker MD: Brain and peripheral nervous system tumors, in Holland JF, Frei E III (eds): **Cancer Medicine.** Philadelphia: Lea and Febinger, 1973, pp 1385–1407
16. Walker MD, Alexander E Jr, Hunt WE, et al: The evaluation of mithramycin in the treatment of anaplastic gliomas. **J Neurosurg 44**:655–667, 1976
17. Walker MD, Hurwitz BS: BCNU 1,3-bis(2-chloroethyl)-1-nitrosourea; (NSC-409962) in the treatment of malignant brain tumor — a preliminary report. **Cancer Chemother Rep 54**:263–271, 1970
18. Walker MD, Strike TA: An evaluation of Methyl-CCNU, BCNU and radiotherapy in the treatment of malignant glioma. **Proc Am Assoc Cancer Res 17**:163, 1976 (Abstract)
19. Wilson CB, Boldrey EB, Enot KJ: 1,bis(2-chloroethyl)-1-nitrosourea (NSC-409962) in the treatment of brain tumors. **Cancer Chemother Rep 54**:273–281, 1970

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Address reprint requests to: Michael D. Walker, M.D., National Cancer Institute, Building 31, Room 4B32, Bethesda, Maryland 20014.