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Clinical Study

Comparison between BCNU and procarbazine chemotherapy for treatment of gliomas

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Summary

We compared sequential single-agent BCNU and procarbazine (PCB) chemotherapy in 31 patients with gliomas [grade IV (10), grade III (15), grade II (6)]. Patients had failed surgical biopsy± resection and radiation therapy. All patients were treated initially with BCNU 150–300 mg/m^2 by intra-arterial or intravenous route every 6 weeks. After CT evidence of tumor progression, all patients received PCB 150 mg/m^2/day for 28 days every 8 weeks. Patient responses to BCNU were CR (0), PR (7), SD (12), progression (12), and to PCB CR (2), PR (9), SD (6), and progression (14). Kaplan-Meier estimates of median time to failure for all patients were shorter for BCNU, 5.0 months (range 1.5–20), than for PCB, 6.0 months (range 2–50+). There was a statistically significant difference (Mantel-Cox test, $p = 0.02$) in the distribution of time to disease progression between the two drugs, especially for grade III tumors ($p = 0.02$). The cumulative proportion of patients without disease progression at 6 months was 26% while on BCNU, compared to 48% while on PCB; at 12 months the cumulative proportions were 3% for BCNU compared to 35% for PCB. Although there was no formal washout period between administration of the two drugs, no carryover effect was evident. These data provide further evidence that PCB has significant activity against malignant glioma and may, in fact, be more effective than BCNU.

Introduction

Malignant gliomas are the most common primary central nervous sytem (CNS) neoplasms of adulthood and remain refractory to therapy. Despite advance in neurosurgical and radiotherapeutic techniques, median survival after these treatment modalities is only 37 weeks [1]. The addition of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) as single-agent chemotherapy after radiation therapy (RT) extends median survival to 50–51 weeks [2, 3]. BCNU remains the standard of comparison for single-agent and combination chemotherapy regimens, despite its modest efficacy [4].

Procarbazine (PCB) is an alkylating agent with activity against many neoplasms, including gliomas. In a prospective randomized trial comparing BCNU and PCB as adjunctive treatment after RT, median survival was similar [3]. Reports of the efficacy of PCB when used as a single agent after RT and nitrosourea failure vary [5, 6].

To further clarify the effectiveness of PCB against malignant glioma, we analyzed data from our previously reported patient group [6] and compared responses between sequentially administered single-agent BCNU and PCB. In this report we describe the results of this comparison.

Materials and methods

Thirty-one consecutive patients (19 male, 12 female) who had initially received BCNU and were subsequently treated with PCB were studied. The mean age at initiation of chemotherapy was 39.5 and 40.4 years, respectively, for BCNU and PCB. Twenty-five patients had complete or subtotal resections; 6 underwent only biopsy. All tumors were graded using the Kernohan classification. Six patients had low grade astrocytoma (grade II), 15 had anaplastic astrocytoma (grade III), and 10 had glioblastoma multiforme (GBM, grade IV). All patients had received 5,500–6,500 cGy of whole brain external beam radiation therapy with a focal boost to the tumor bed before BCNU.

Patients were initially treated with BCNU, 18 receiving it intra-arterially (IA, 150–200 mg/m^2 every 6 weeks), 9 intravenously (250–300 mg/m^2 every 6 weeks), 4 receiving both IA and IV treatment. After demonstration by cranial CT of tumor progression (performed every 6 weeks or as needed), all patients were placed on oral procarbazine, 150 mg/m^2/d for 28 days every 8 weeks, the standard PCB dosing regimen as described by Green *et al.* [3]. While on PCB, patients received cranial CT or MRI every 8 weeks or as needed. Three patients received and failed other chemotherapy before starting PCB

Table 1. Patient responses to therapy with BCNU and PCB

Patient	Grade	BCNU Rte	BCNU		PCB	
			Response	Duration	Response	Duration
3	II	IV	PR	12 (mo.)	PD	2 (mo.)
8	II	IA	PD	3	PR	12+
12	II	IV	PR	8	PR	13
16	II	IA/IV	PR	8	PD	2
21	II	IV	SD	7	SD	13+
23	II	IA	SD	6	PR	50+
1	III	IA	SD	5	PD	4
2	III	IV	PD	4	PD	2
4	III	IV	SD	5	CR	11
6	III	IA	SD	11	PD	2
7	III	IA	SD	5	PD	4
14	III	IA	SD	5	PD	2
18	III	IA	PD	3	SD	6
22	III	IA	PD	4	SD	12+
24	III	IA	PD	3	PR	24+
25	III	IV	PR	20	SD	44+
26	III	IA	SD	6	SD	46+
27	III	IA/IV	SD	5	CR	12+
28	III	IV	PD	5	PR	32+
29	III	IA	PD	3	PR	30
31	III	IA	PD	3	PR	10
5	IV	IA	SD	5	PD	2
9	IV	IV	PD	3	PD	2
10	IV	IA	PD	3	PR	7
11	IV	IA	PR	8	PR	6
13	IV	IV	PR	8	PD	2
15	IV	IA	PD	3	PD	4
17	IV	IA	PD	2	PD	4
19	IV	IA/IV	SD	9	SD	8
20	IV	IA	SD	5	PD	2
30	IV	IA/IV	PD	3	PD	2

(2 receiving IA cisplatin and 1 receiving IA diaziquone). Treatment with cisplatin or diaziquone was brief (1,1, and 4 months) and terminated after unequivocal CT or MRI progression.

Response criteria were as follows: Complete Response (CR), complete resolution of all abnormalities suggestive of tumor on CT scan and a stable or improved neurologic examination without steroids; Partial Response (PR), greater than a 25% decrease in tumor size on CT scan plus a stable or improved neurologic examination on a stable or reduced dose of steroids; Stable Disease (SD), no change in tumor size on CT scan, without significant change in neurologic examination while on stable or decreasing doses of steroids for at least 2 cycles of chemotherapy; Progressive Disease (PD), greater than 25% increase in tumor size on CT scan and/or progressive worsening of neurologic function directly attributable to growth of the tumor. The duration of response dated from the onset of treatment until demonstration of disease progression. For the purposes of this study, responses were considered to be Complete Response+ Partial Response+ Stable Disease.

Kaplan-Meier estimates of time to failure were calculated, and the Mantel-Cox test was used to compare the failure time distributions, ignoring the natural pairing of observations. The Wilcoxon signed-rank test for paired data also was used to compare time to progression, treating as failure times the 9 censored times of patients whose disease had not yet progressed.

Results

Patient responses to BCNU and PCB therapy are shown in Table 1. When response was defined as Complete Response+ Partial Response+ Stable Disease there was no statistically significant difference in proportion of patients responding to BCNU compared to PCB (McNemar's test, p= 0.62). Ten patients responded to both regimens, and 5 patients had PD on both regimens; nearly equal numbers had disease that progressed on one regimen but not on the other (7 with Partial Response or Stable Disease on PCB had Progressive Disease on BCNU; 9

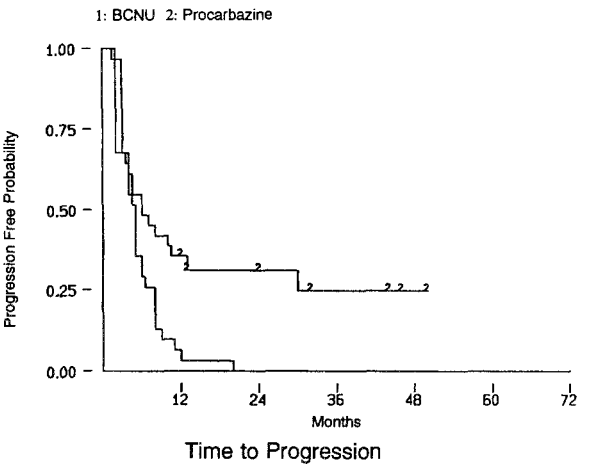

Fig. 1. Kaplan-Meier curve of time to progression for patients after receiving BCNU of PCB (p= 0.02).

with Partial Response or Stable Disease on BCNU had Progressive Disease on PCB). The conclusions are unchanged if we compare Complete Response+ Partial Response to Stable Disease+ Progressive Disease (McNemar's test, p= 0.25).

The rate of Complete Response+ Partial Response for PCB was 35% (2 CR, 9 PR) compared to 23% (0 CR, 7 PR) for BCNU. Thirty-five percent of patients (11/31) had the same or better response to PCB compared to the response to BCNU. Of the 12 patients with progressive disease on BCNU, 5 had a Partial Response and 2 had Stable Disease while on PCB.

Time to disease progression was significantly longer for the PCB regimen than for the BCNU regimen, whether a paired analysis (Wilcoxon test, p= 0.05) or an unpaired analysis (Mantel-Cox test, p= 0.02) was used (Fig. 1). The cumulative proportion of patients without disease progression at 6 months was 26% while on BCNU and 49% while on PCB; at 12 months, the cumulative proportions were 3% for BCNU and 35% for PCB. Median time to progression was 5 months (range 2–20 months) on BCNU and 6 months (range 2–50+ months) on PCB.

Twenty-six of the 31 patients in the study responded (CR, PR, or SD) to either BCNU, PCB, or both (6/6 grade II, 14/15 grade III, 6/10 grade IV). When the responders were analyzed separately, the statistical significance of the difference in survival disti-

butions was more pronounced (Wilcoxon test, p= 0.03, Mantel-Cox, p= 0.01). Median time to progression was unchanged, 5 months, for BCNU but increased to 8 months for PCB.

Although the number of patients is relatively small, we also considered whether the difference in time to progression was associated with either tumor grade or route of BCNU administration. Time to progression for patients with grade III tumors on PCB was significantly greater than time to progression for patients with grade III tumors on BCNU (Mantel-Cox test, p= 0.02; median of 4.5 months on BCNU compared to 10.5 months on PCB). There was no statistically significant difference in time to progression for patients with grade IV tumors (Mantel-Cox test, p= 0.41) or grade II tumors (Mantel-Cox test, p= 0.18). More than half of the patients in the study received IA BCNU. For these patients, time to progression was significantly longer for the PCB regimen than for the BCNU regimen (Mantel-Cox test, p= 0.03). The differences between BCNU and PCB were not statistically significant for patients who received IV BCNU (Mantel-Cox test, p= 0.38) or IA and IV BCNU (Mantel-Cox test, p= 1.0).

Toxicity was divided into nonhematologic and hematologic categories. Patients receiving BCNU developed the following nonhematologic complications: mild nausea in most patients, leukoencephalopathy (1), and retinopathy (3). There were no episodes of pulmonary fibrosis. Patients receiving PCB also developed frequent nausea, as well as fatigue (6), herpes zoster (7), and rash (1). Hematologic toxicity in patients receiving BCNU was relatively mild. The majority of patients developed mild leukopenia (<3000, >1500) and thrombocytopenia (<150,000, >50,000). One patient (#8) developed severe thrombocytopenia (<50,000) after IA BCNU and required platelet transfusions, but did not have any hemorrhagic episodes. No infectious complications were noted in the BCNU patients. The hematologic complications for patients receiving PCB were more severe. Six patients developed severe leukopenia (<1500), and 5 developed severe thrombocytopenia; there were no infectious or hemorrhagic complications.

Discussion

Many chemotherapeutic agents have been used to treat malignant gliomas. The majority of these agents, either alone or in combination, have not proved effective. Randomized trials [1–4] have demonstrated the efficacy of BCNU, and it is generally regarded as the preferred chemotherapy drug for gliomas [7]. Several reports [3, 6] suggest that single-agent PCB is also effective against malignant glioma and may be as effective as BCNU, although other studies have not been as favorable [5]. PCB demonstrated a nonsignificant trend toward longer survival at 18 and 24 months compared to BCNU in the study by Green *et al.* [3]. Rodriguez *et al.* [5] studied 83 patients with recurrent malignant glioma and had an overall response rate of only 28%. In the study by Newton *et al.* [6], 35 patients treated with PCB showed an overall response rate of 57%. PCB dosing and patient demographics were comparable in the studies of Rodriguez and Newton, except for a somewhat larger percentage of GBM patients (45% vs 34%) in the Rodriguez study. In this study, we compared responses to BCNU and PCB in a cohort of patients receiving both drugs. Time to progression was significantly longer for PCB than BCNU (p= 0.02, Fig. 1), although the two agents had nearly identical response rates: CR+ PR+ SD was 55% for PCB and 61% for BCNU, while the CR+ PR rate was 35% for PCB compared to 23% for BCNU; the differences were not statistically significant (p> 0.25). The majority of patients (68%) had the same or better response to PCB than BCNU. The difference in response was most apparant for grade III patients, who had a significantly longer time to progression (p= 0.02) while on PCB as compared to BCNU. This data provides further evidence that PCB is efficacious treatment for patients with malignant glioma and may be more effective than BCNU.

For patients receiving PCB after failure of IA BCNU, the time to disease progression was significantly longer (p= 0.03) than for those who had failed IV or IA/IV BCNU. The cause of this relationship is unclear, but does not appear to be related to the distribution of histologic types among the

routes of BCNU administration. Ten of the 15 grade III tumors (66%) and 6 of the 10 grade IV tumors (60%) received IA BCNU. The improved response duration of PCB was not related to more severe toxicity in the IA BCNU patient group, as recently reported by Shapiro *et al.* [8]. In their randomized study, grade III patients who received IA BCNU had reduced survival ($p = 0.002$) and more significant toxicity when compared to patients treated with IV BCNU. Toxicity consisted of irreversible encephalopathy, cerebral edema, and visual loss. Few of our patients demonstrated this toxicity by clinical or neuroimaging criteria and were considered BCNU failures only on the basis of enlargement of enhancing tumor mass on CT scan.

Procarbazine requires activation to intermediate forms before developing potent antineoplastic activity [9, 10]. It is first metabolized into an azo-PCB derivative, which has similar potency to PCB. Further metabolism by the cytochrome P-450 system converts azo-PCB into two seperate azoxy-PCB derivatives, which have significantly greater antitumor activity than PCB or azo-PCB. The azoxy-2-PCB derivative is the most active metabolite of PCB and causes cell death by inducing DNA strand breaks. Activated PCB, like BCNU, also derives some of its antitumor activity from alkylation of DNA, placing adducts onto the O^6 position of guanine [11, 12]. The enzyme O^6-alkylguanine-DNA alkyltransferase (AT) repairs DNA by removing the adducts of BCNU and PCB, thus reducing subsequent toxicity [11–13]. Tumor cells with high concentrations of AT are more resistant to BCNU [14] and PCB [12]. Tumors that have progressed during BCNU treatment may have developed a resistant clone of cells with high levels of AT [15]. These cells might also demonstrate cross-resistance to PCB. This scenario would theoretically militate against using PCB sequentially after BCNU. It is therefore surprising that our patients responded so well to PCB after BCNU failure. This suggests that the mechanism of BCNU resistance was not elevated concentration of AT, but instead may have been reduced cell uptake or accelerated inactivation of BCNU by cellular components such as glutathione [16].

Several newer studies utilizing PCB as part of multi-agent chemotherapy regimens for malignant glioma also suggest treatment alternatives to conventional BCNU [17, 18]. In a randomized prospective trial by Levin *et al.* [17] comparing adjuvant BCNU to procarbazine, lomustine, and vincristine (PCV), PCV was significantly more effective than BCNU in terms of overall survival ($p = 0.021$) and time to progression ($p = 0.025$) for patients with anaplastic astrocytoma. The current study corroborated some of their findings, in that single-agent PCB demonstrated significantly longer time to progression compared to BCNU ($p = 0.02$) for treatment of anaplastic astrocytoma, but not glioblastoma multiforme. In a phase II trial [18] etoposide, vincristine, and procarbazine were used against malignant glioma, with a mean time to progression of 46 weeks. Our data would suggest that PCB is the most active and important agent in these combination regimens and that the effectiveness of both regimens might be further improved with larger PCB doses. More novel approaches to chemotherapy, such as interstitial implantation of drug polymer wafers [19, 20] or hi-dose chemotherapy in combination with hematopoietic growth factors [21], also hold promise as alternative methods of treatment.

The statistical methods used to analyze the data have some limitations. Because each patient received both BCNU and PCB, paired analyses were used whenever possible. The Wilcoxon signed-rank test for paired data was used to compare time to progression, ignoring the fact that 9 patients have censored times to progression on PCB. Since none of the times to progression on BCNU are censored and all of the censored times on PCB are greater than the corresponding times to progression on BCNU, the results would be more strongly in favor of PCB if there were no censoring. No formal washout period was allowed between progression on BCNU and initiation of PCB therapy, thereby making it impossible to determine if carryover effects of BCNU affected results observed with PCB. Because of each patient's unequivocal progression during BCNU therapy, we assumed carryover effects were minimal and that time to progression following PCB was independent of residual effects of

BCNU. Carryover effects of radiation therapy might have influenced the responses noted with BCNU, but were probably of minimal significance. If present, radiation carryover effects would have biased BCNU responses to appear more significant than they actually were, making the comparison to PCB responses even more significant.

Analysis of the responding versus non-responding groups also has limitations. It is possible that unmeasured factors that affect prognosis and response to treatment may have influenced the results, unrelated to the effects of treatment. However, each patient received both BCNU and PCB sequentially, acting as his own control. This should have minimized the effects of unmeasured variables on outcome.

Single and multi-agent chemotherapy regimens have produced modest improvements in survival as adjunctive therapy for malignant gliomas. BCNU remains the standard of comparison for new chemotherapy protocols. This paper has demonstrated that PCB has significant activity in patients with malignant glioma, and may be more effective than BCNU, particularly when time to failure is compared in responders. Grade III tumors appear to be the most sensitive, but PCB also demonstrates activity against grade II and IV tumors. A randomized controlled clinical trial with drug crossover would be necessary to prove that PCB is a more effective agent than BCNU. Using this design, with time to progression as the dependent variable instead of survival, would allow for comparison of upfront activity of both drugs, as well as efficacy after progression. Interaction between drugs could also be accurately analyzed.

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