Phase II study of 6-thioguanine, procarbazine, dibromodulcitol, lomustine, and vincristine chemotherapy with radiotherapy for treating malignant glioma in children¹

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We conducted a single-arm phase II study to evaluate the efficacy and safety of radiotherapy combined with 6-thioguanine, procarbazine, dibromodulcitol, lomustine, and vincristine (TPDCV) chemotherapy for treating malignant astrocytoma in children and anaplastic ependymoma in patients of all ages. Between 1984 and 1992, 42 patients who had malignant astrocytomas (glioblastomas multiforme, anaplastic astrocytomas, or mixed anaplastic oligoastrocytomas) were treated with TPDCV chemotherapy and radiation therapy. Of these patients, 40 were younger than 18 years, but 2 were older (22 and 23 years) when treated. Cranial radiation averaged 58 Gy. TPDCV chemotherapy was given for 1 year or until progression. Between 1989 and 1991, 17 patients with malignant ependymoma were treated with TPDCV chemotherapy and craniospinal radiation. Radiation was given at an

average dose of 54 Gy to the tumor, 28 Gy to the whole brain, and 31 Gy to the spinal axis. TPDCV chemotherapy was given for 1 year or until tumor progressed. Of the patients with glioblastoma multiforme, 13 of 17 died; the median time to progression was 49 weeks, and median survival was 85 weeks. The four patients surviving at this writing were followed a median 537 weeks (range 364–635 weeks). Of the patients with nonglioblastoma malignant astrocytoma, 14 of 25 died; the median time to progression was 224 weeks. Median survival was not reached in this group. The median follow-up for those surviving was 494 weeks. For the patients with ependymoma, 11 of 17 died with a median time to progression of 141 weeks. The median follow-up for the eight who survive was 469 weeks. Nine patients died with a median survival of 183 weeks. The combination of TPDCV and radiotherapy has activity against childhood anaplastic astrocytoma, glioblastoma multiforme, and anaplastic ependymoma. The results of this study for children with glioblastoma were comparable to results in the literature, while the results for children with anaplastic astrocytoma appeared better than most reports. The combination of TPDCV chemotherapy and radiation therapy for anaplastic ependymomas appears to be active and at least as good as published reports using radiation therapy alone. *Neuro-Oncology* 2, 22–28, 2000 (Posted to *Neuro-Oncology* [serial online], Dec. 99-09, December 14, 1999. URL <neuro-oncology.mc.duke.edu>)

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³Abbreviations used are as follows: GBM, glioblastoma multiforme; PFS, progression-free survival; TPDCV, 6-thioguanine, procarbazine, dibromodulcitol, lomustine, and vincristine.

Because there is no defined treatment that produces substantial cure rates for malignant gliomas in adults and children, physicians have used a large number of chemotherapy agents alone, in combination, and in conjunction with radiation therapy (Levin et al., 1997). Because of the activity of nitrosourea combinations with other anticancer agents and the ease of administering the TPDCV³ combination to children in an outpatient setting (Prados et al., 1997), we initiated a phase II study of TPDCV chemotherapy in conjunction with radiation therapy to children. The original premise of the drug combination was that 6-thioguanine (Bodell et al., 1985; Fujimoto et al., 1982; Hunter et al., 1989), procarbazine (Levin and Wilson, 1978), and dibromodulcitol (Levin and Wheeler, 1982; Pulst et al., 1986) had been shown in cell culture and animal tumor model studies to potentiate chloroethylnitrosourea cytotoxicity. In addition, procarbazine, an active methylating agent (Weinkam and Shiba, 1978) that can compete with O⁶-alkylguanine-DNA alkyltransferase could overcome one form of chloroethylnitrosourea resistance (Meer et al., 1989; Schold et al., 1989; Valavanis et al., 1994). Vincristine was added because it would be expected to add little myelotoxicity to the combination and might damage proliferating tumor cells that began to grow after the effects of the other drugs were over.

In this report we show that TPDCV has activity against childhood malignant gliomas and, in particular, GBM and anaplastic astrocytoma. Assessment of activity against malignant ependymoma is more difficult to document because of the small number of patients treated and the lack of a substantial clinical trials literature.

Materials and Methods

Patients

All patients in this study were seen either at the University of California at San Francisco Medical Center or, when one of the authors (V.A.L.) moved, at The University of Texas M.D. Anderson Cancer Center, Houston. Eligible patients fulfilled the following criteria:

1. Histologic diagnosis of supratentorial GBM or gliosarcoma, anaplastic astrocytoma, or anaplastic oligoastrocytoma according to a modified Ringertz scale (Ringertz, 1950) or supratentorial/infratentorial anaplastic ependymoma as defined by high cell density of pleomorphic cells and the level of mitoses per high-powered microscopic field (Burger et al., 1991);
2. No prior radiation therapy or chemotherapy;
3. Normal liver function (serum glutamic-pyruvic transaminase not more than 2 times institutional normal, alkaline phosphatase levels no more than 2 times institutional normal, and bilirubin levels no more than 1.5 mg/dl), creatinine levels no more than 1.5 mg/dl, and a normal hemogram (absolute neutrophil count at least 1500/ μ l and platelet count at least 125,000/ μ l);
4. Karnofsky performance status of 60;
5. Signed informed consent form approved by the Institutional Review Board; and

6. Lack of active infection, pregnancy (adequate contraception required), any disease that would obscure toxicity or dangerously alter drug metabolism, and serious intercurrent illness.

Study Design

This was a single-arm study designed to evaluate adjuvant combination chemotherapy with TPDCV for one course prior to radiotherapy and then for 5 to 6 courses after the completion of radiotherapy. Radiotherapy was modified for age and tumor location but was always given as one fraction per day. Time to tumor progression, survival duration, and toxicity were recorded. The treatment plan is described below.

Radiation therapy. The target volume was defined by the tumor volume, as determined by an enhanced MRI or CT, with a margin of 3 cm. Beam energy was either 6 MV or 18 MV. The fraction size was 2 Gy given once a day. Treatment was given in consecutive days, Monday through Friday, until the total dose had been given. The intended dose for patients with malignant astrocytoma was 60 Gy to the primary tumor site; for patients with malignant ependymoma, the intended dose was 54 Gy to the primary tumor site and 28 Gy to the rest of the neuraxis.

TPDCV chemotherapy. After surgery and prior to radiotherapy, and beginning again approximately 2 weeks after completing radiation therapy, patients started TPDCV chemotherapy on the following schedule: 6-thioguanine, 30 mg/m² orally every 6 h for 12 doses (hours 0 to 66); procarbazine, 50 mg/m² orally every 6 h for 4 doses (hours 60 to 78); dibromodulcitol, 400 mg/m² orally for 1 dose (hour 60); lomustine, 110 mg/m² orally for 1 dose (hour 72); and vincristine, 1.4 mg/m² by i.v. on days 14 and 28. TPDCV courses were repeated at 6-to-7-week intervals for a total of 6 courses or until tumor progression.

Time to tumor progression and survival were measured from the time of histologic diagnosis (same as surgical date) until progression was documented or death occurred. At the time of progression, the patient was removed from the study and, if appropriate, offered other treatments. These patients continued to be monitored for survival data.

Evaluations

Before treatment, patients underwent a physical and neurologic examination; determination of performance status; CT or MRI scan, with and without contrast enhancement; complete blood count, differential, and platelet counts; and chemistry survey. Complete blood counts, differential, and platelet counts were obtained every week during radiotherapy and every 2 weeks during TPDCV chemotherapy; neurologic examinations, contrast-enhanced CT or MRI scans, and chemistry surveys were evaluated every 6–7 weeks during the first year. During the second year, patients in remission were evaluated with neurologic examinations and contrast-enhanced CT or MRI scans at intervals of 3 months;

Table 1. Characteristics of patients with glioblastoma multiforme or nonglioblastoma glioma receiving TPDCV chemotherapy

Feature	Total	Glioblastoma	Nonglioblastoma glioma ^a
Number	42	17	25
Sex			
Female	12 (29%)	2 (12%)	10 (40%)
Male	30 (71%)	15 (88%)	15 (60%)
Age			
Mean (SE), years	12 (0.8)	12 (1.0)	12 (1.1)
Range	2–23	5–22	2–23
Karnofsky score			
Mean (SE)	88 (1.4)	91 (1.8)	86 (1.9)
Range	60–100	80–100	60–100
Surgery			
Biopsy	7 (17%)	0	7 (28%)
Subtotal resection	24 (57%)	11 (65%)	13 (52%)
Gross total resection	11 (26%)	6 (35%)	5 (20%)

Abbreviation: TPDCV, 6-thioguanine, procarbazine, dibromodulcitol, lomustine, and vincristine.

^a23 anaplastic astrocytomas, 1 malignant glioma, 1 high-grade mixed oligoastrocytoma.

Table 2. Characteristics of patients with malignant ependymoma treated on TPDCV chemotherapy

Feature	Ependymoma ^a
Number	17
Sex	
Female	6 (35%)
Male	11 (65%)
Age	
Mean (SE), years	20 (4.1)
Range	0.8–45
Karnofsky score	
Mean (SE)	88 (1.9)
Range	70–100
Surgery	
Subtotal resection	7 (41%)
Gross total resection	10 (59%)

Abbreviation: TPDCV, see Table 1.

^a16 malignant ependymomas and 1 ependymoma with the fourth ventricle and spinal involvement.

intervals were extended to every 4 months during the third year, and to 6 months in the fourth year. Beyond this point, patients were followed every 12 months with neuroimaging studies and clinical evaluations.

Determination of Response

The primary study end points for this trial were time to tumor progression and survival. Progressive disease was defined as any increase in tumor size as determined by changes in the contrast-enhancing tumor margins of the primary lesion (Levin et al., 1977). Stable disease was defined as no change in the CT or MRI scan with the patient receiving stable or decreasing doses of glucocorticoids. A designation of tumor progression also required that the dose of glucocorticoids had not been decreased since the last evaluation period. If the glucocorticoid dose was concomitantly decreased, the response was scored stable disease for that visit, unless new lesions developed or there was unequivocal evidence of leptomeningeal spread of disease. Radiographic response to therapy was recorded but was of little value compared with time to progression, because it is difficult to distinguish resolution of postsurgical artifacts from true response to therapy and some patients had no residual disease to monitor after surgery.

Data Management and Quality Control

All patients were registered and data were kept by the Brain Tumor Research Center (University of California) Data Management Office. All relevant information was documented in the patient's medical record and/or flow sheets and computer-based MEDLOG patient database.

Results

Patient Characteristics

Between 1984 and 1992, 42 eligible malignant glioma patients were entered into this study. Two patients treated according to this study were ineligible because of age (one, aged 54, with anaplastic astrocytoma and one, aged 48, with oligoastrocytoma). The data for these two patients were not otherwise analyzed. Table 1 summarizes the characteristics of the remaining 42 eligible patients who had GBM or non-GBM malignant gliomas. Age distributions and means for the two groups were similar. The mean Karnofsky performance scores were 91 ± 1.8 (SE of the mean) and 86 ± 1.9 (SE of the mean) for the two groups. The two groups differed most in their extent of surgery, with 35% gross total resections in the GBM strata and 20% in the non-GBM strata.

Between 1989 and 1991, 17 malignant ependymoma patients were entered into this study. Table 2 summarizes the patients' characteristics for this histology. Mean age was 20 years and included children and adults with this histology. The mean Karnofsky performance scores were 88 ± 1.9 (SE). This histologic group had the highest gross total resection rate at 59%.

In addition to the patients described above, five very young children were allowed entry into the study with the intent to use only TPDCV chemotherapy and to defer radiation therapy until the tumor progressed or the child was older than 3 years. There were two children with GBM (aged 1 and 3 months) and three with anaplastic astrocytoma (aged 11 months, 14 months, and 3 years).

Table 3 summarizes the timing of radiation relative to chemotherapy, the radiation type, and the total dose for GBM and non-GBM patients. Although the intent of the study was to treat with one cycle of chemotherapy prior to radiation, there were cases in which the treating physician felt that delay of radiation could be potentially

Table 3. Radiotherapy and sequence for 42 patients with glioblastoma and nonglioblastoma glioma treated with TPDCV

Parameter	Age (years)	Radiation sequence	Radiation type	Radiation dose (Gy)
Mean ($\pm$ SD)	12.1 ($\pm$ 4.9)	After one cycle of chemotherapy, 29 Before chemotherapy, 13	41 cranial, 1 craniospinal axis	58.1 ($\pm$ 3.3)
Median	12.2			60

Abbreviation: TPDCV, see Table 1.

Table 4. Radiotherapy and sequence for 17 patients with malignant ependymoma treated with TPDCV

Parameter	Age (years)	Radiation sequence time	Radiation type	Radiation dose (Gy)		
				Tumor	Brain	Spine
Number	17			17	11	11
Mean ($\pm$ SD)	20.7 ($\pm$ 17.8)	After one cycle of chemotherapy, 16 Before chemotherapy, 1	4 cranial 13 craniospinal axis	53.6 ($\pm$ 6.9)	27.9 ($\pm$ 5.3)	30.9 ($\pm$ 9.3)
Median	19.4			54	25.2	28.8

Abbreviation: TPDCV, see Table 1.

harmful given the size and extent of postoperative tumor burden. A total of 13 patients received radiation prior to any chemotherapy. In 28 cases, one cycle of chemotherapy was given prior to radiation therapy. Table 4 summarizes similar data for the malignant ependymoma patients. The mean radiation dose to the tumor was 58 Gy for patients with malignant gliomas; in cases of malignant ependymoma, the mean dose to the primary tumor was 54 Gy, with 28 Gy to the brain and 31 Gy to the spinal cord.

Toxicity

Chemotherapy. Tables 5 and 6 summarize the worst toxicity grades for white blood cells, platelets, nausea/vomiting, and peripheral neuropathy for the three histologies. Grades 3 and 4 myelotoxicity were uncommon. Three patients had grade 3 nausea and vomiting, and one had grade 3 neuropathy. Toxicity for the five children treated with only chemotherapy showed one case of grade 4 neutropenia and no grade 3 toxicities. One patient, a 44-year-old male on protocol for 18 months, was treated at recurrence with 12 courses of carboplatin, procarbazine, and 5-fluorouracil. He later developed a myelodysplastic syndrome that led to his death 37 months after the original diagnosis of anaplastic ependymoma. The patient also was exposed to Agent Orange during the Vietnam

War and worked 20 years for a chemical company where he was probably exposed to benzene.

Radiation therapy. Obvious radiation necrosis was not observed.

Statistical Analyses

Table 7 summarizes the PFS and overall survival for the three histologies. The technique of Kaplan-Meier (1958) was used to determine the medians. Confidence intervals were computed at 95%. Figs. 1, 2, and 3 are the Kaplan-Meier (1958) curves showing PFS and overall survival for patients with GBM, with malignant astrocytoma other than GBM, and with malignant ependymoma, respectively.

Of the five children treated with chemotherapy without initial irradiation, one died with progressive disease at 15 weeks (1-month-old child with GBM) and four remain alive. Of these four patients, one progressed at 14 months and one at 3 years. Both had anaplastic astrocytoma, were treated for 6 cycles of chemotherapy, and received focal radiation therapy at relapse. Two patients remain progression-free following chemotherapy. One was a child diagnosed at 18 months of age with bifrontal anaplastic astrocytoma. She is alive and progression-free at 5-year follow-up. The final child was diagnosed at 4 months of age with a right frontal-temporal GBM. After

Table 5. Worst grade of toxicity from TPDCV treatment for 42 patients with glioblastoma and nonglioblastoma glioma

Toxicity	Number of patients with			
	Grade 1	Grade 2	Grade 3	Grade 4
White blood cells	9	13	5	2
Platelets	8	2	5	2
Nausea/vomiting	2	14	3	0
Peripheral nervous system	1	3	1	0

Abbreviation: TPDCV, see Table 1.

Table 6. Worst grade of toxicity from TPDCV treatment for 17 patients with ependymoma

Toxicity	Number of patients with			
	Grade 1	Grade 2	Grade 3	Grade 4
White blood cells	1	9	5	1
Platelets	2	4	2	2
Nausea/vomiting	2	8	1	0
Peripheral nervous system	0	2	0	0

Abbreviation: TPDCV, see Table 1.

Table 7. Progression-free and overall survival estimates

Tumor	Treatment failures/ total patients	Progression-free survival (95% CI)	Deaths/ total patients	Overall survival (95% CI)
Glioblastoma	13/17	49 wks (23, 142)	13/17	85 wks (45, 172)
Anaplastic glioma	14/25	224 wks (60, —)	10/25	NA (245, —)
Malignant ependymoma	11/17	141 wks (40, —)	9/17	183 wks (131, —)

Abbreviations: CI, confidence interval; NA, not yet attained.

6 cycles of chemotherapy, she was progression-free and remains alive 11 years after surgery.

Discussion

The past 25 years have witnessed improvements in neuroimaging, surgical technique, and anesthesia, all of which have made possible safer, more extensive tumor resections. This is reflected in the study reported here, where fully 36% of patients had gross total resections and 52% had extensive subtotal resections. Radiation therapy, notwithstanding technical advances, has led to limited improvement in survival for glioma patients. Various dose schemes and interstitial radiation sources have been either without benefit or with benefit for patients with small tumor volume at time of radiation (Berger et al., 1996; Florell et al., 1992; Levin et al., 1997; Loeffler et al., 1992). Chemotherapy is of variable benefit as measured by PFS and overall survival. Chemotherapy benefits have been most readily seen in anaplastic astrocytoma patients, much less so for GBM patients (Levin et al., 1997) and for patients with ependymal tumors at recurrence (Berger et al., 1996). As a generalization, children with gliomas appear to respond better to chemo-

therapy than adults do (Berger et al., 1996), but even this has been called into question lately for some histologies.

Although our study represented virtually a single institution's experience with combined radiation and chemotherapy for childhood and early adult GBM and anaplastic glioma, the results support the previously observed trend that survival for patients with these tumors decreases with increasing age. Typically, for adults with GBMs, median survival is between 50 and 62 weeks and between 148 and 228 weeks for patients with other anaplastic gliomas treated with postradiation combination chemotherapy protocols (Berger et al., 1996; Levin et al., 1997; Prados et al., 1998). The typical median age in these studies is the fifth decade and, in the current study, the median age is 12 years, making any meaningful comparison problematic because age is typically the strongest covariate in each of the histologic subtypes. In a more comparable childhood study, Finlay et al. (1995) reported the results of Children's Cancer Group Study No. 945, a randomized study of postradiotherapy vincristine, lomustine, and prednisone (arm A) versus an eight-drugs-in-1-day protocol (arm B) for patients with GBM and anaplastic astrocytoma. For GBM, the researchers found a median PFS of 52 (arm A) and 43 (arm B) weeks and median overall survival of 78

Fig. 1. Unadjusted time to tumor progression (---) and survival (—) for patients with glioblastoma multiforme.

Fig. 2. Unadjusted time to tumor progression (---) and survival (—) for patients with anaplastic astrocytoma.

Fig. 3. Unadjusted time to tumor progression (—) and survival (—) for patients with malignant ependymoma.

and 56 weeks for the two arms, respectively. For anaplastic astrocytoma, the median PFS was 56 (arm A) and 48 (arm B) weeks and for median overall survival 95 and 134 weeks, respectively. Our current study results are comparable for GBM with a median overall survival of 85 weeks and, at 245 weeks, better than the reported series for anaplastic astrocytoma.

In contrast to the many combination trials of radiation and chemotherapy in GBM and anaplastic glioma, the clinical trials literature is limited for malignant ependymal tumors. Most historical series combined surgery and radiation for ependymal tumors without distinction for grade of malignancy. Studies reported between 1980 and 1992 indicated a weighted mean 5-year survival of 43% (Berger et al., 1996; Levin et al., 1997) for ependymoma, and Shaw et al. (1987) reported a 29% 5-year survival in 7 patients irradiated for anaplastic ependymoma. Some researchers argue that the diagnosis of anaplastic ependymoma is problematic. Schiffer et al. (1991) reviewed 298 cases of ependymoma and paid special attention to many histologic features. They concluded that the anaplastic variant is indeed discernible and that cell density and mitotic frequency may be pivotal features. Kovalic et al. (1993) reported that, compared with more differentiated ependymoma, patients with anaplastic ependymoma were 50% as

likely to be free of tumor progression and be alive at 10 years. They also found that local field radiotherapy may be superior to whole-brain irradiation. In our study, histology was considered to be frankly malignant based on focal pleomorphic high cell density and mitotic activity criteria. We aggressively treated this group of 17 patients with a mean age of 20 years with preradiation chemotherapy and postradiation chemotherapy, yet our median PFS was only 141 weeks, median survival 183 weeks (3.5 years), 5-year PFS 37%, and 5-year overall survival 47%. The literature contains very few studies of anaplastic ependymoma treatment with which to compare our results. Goldwein et al. (1990) presented a retrospective analysis that included a subset of 13 patients with anaplastic ependymoma who had a 31% 5-year PFS. Robertson et al. (1998) reported on a Children's Cancer Group 945 subset of 12 patients treated with postradiation chemotherapy vincristine, lomustine, and prednisone or eight-drugs-in-1-day. They found a 46% 5-year PFS when the two arms were combined and analyzed. Lastly, Lyons and Kelly (1991), in a retrospective analysis that included eight patients with anaplastic ependymoma, found a 3.7-year median survival. The conclusion drawn from our study of anaplastic ependymoma is that, while our study is larger and more focused on radiation and chemotherapy combined, the results with respect to PFS and overall survival do not differ substantially from those in the literature.

In conclusion, TPDCV chemotherapy as an adjuvant therapy to surgery and radiotherapy was shown to have activity against GBM, anaplastic astrocytoma, and anaplastic ependymoma. Compared with other chemotherapy regimens, it appears to offer no advantage to children with GBM. The data suggest that TPDCV may be superior to current treatment regimens for children with anaplastic astrocytoma, based on the median survival and potential for a long-term remission with the ease of a primarily oral well-tolerated therapy. A controlled phase III trial would be the best way to determine whether TPDCV or a similar treatment should be used in place of other current treatments for childhood anaplastic astrocytoma. Although the combination of postsurgical chemotherapy with TPDCV and radiotherapy appears to have activity against anaplastic ependymoma and is easy to administer to children, the results do not justify further trials with TPDCV or similar programs. Clearly, what is needed are new and better treatment paradigms for these patients.

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