A phase I trial of temozolomide and lomustine in newly diagnosed high-grade gliomas of childhood

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A phase I trial was conducted to determine the maximum tolerated dose (MTD) of temozolomide given in combination with lomustine in newly diagnosed pediatric patients with high-grade gliomas. Response was assessed following two courses of therapy at the MTD. Temozolomide was administered to cohorts of patients at doses of 100, 125, 160, or 200 mg/m² on days 1–5, along with 90 mg/m² lomustine on day 1. Two courses of lomustine/temozolomide were given prior to radiation therapy (RT) and up to six courses were administered afterward. Thirty-two patients were enrolled. Dose-limiting myelosuppression was seen in two of three patients enrolled at the 200 mg/m² dose level. One of 14 patients in the expanded MTD cohort (160 mg/m²) experienced dose-limiting thrombocytopenia. After two courses at the MTD, one patient with a 5-mm enhancing nodule postoperatively had a complete response, one patient with a large residual temporal lobe glioblastoma had a partial response, and eight patients had stable disease. Several patients developed transient radiographic worsening after completing RT. Median 1- and 2-year overall survivals at the MTD were 60% ± 13% and 40% ± 13% with a median of 17.6 months. Thirteen of

20 patients (65%) who underwent MRI scans within 6 months prior to death developed metastatic disease. In conclusion, when administered with 90 mg/m² lomustine on day 1, the MTD of temozolomide is 160 mg/m²/day × 5. Radiographic changes following RT make determination of early tumor progression difficult. Metastatic disease is common prior to death. *Neuro-Oncology* 10, 569–576, 2008 (Posted to *Neuro-Oncology* [serial online], Doc. D07-00110, May 22, 2008. URL <http://neuro-oncology.dukejournals.org>; DOI: 10.1215/15228517-2008-019)

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Patients with high-grade gliomas (HGGs) continue to have a poor prognosis despite the use of multimodality therapy including surgery, radiation therapy (RT), and chemotherapy. RT clearly prolongs survival time,¹ and several clinical trials have found adjuvant chemotherapy to be of benefit,^{1–4} yet long-term survival remains poor.

The nitrosoureas, initially utilized because of their lipid solubility and ability to cross the blood-brain barrier, have long been the backbone of chemotherapy against HGG. The first pediatric cooperative group HGG study (CCG-943) showed a survival benefit when lomustine (1-[2-chloro-ethyl]-3-cyclohexyl-1-nitrosourea, CCNU) and vincristine were administered following RT.² Although a subsequent histopathology consen-

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sus review found a significant percentage of low-grade gliomas in the survivors of cooperative group HGG trials,⁵ a subset analysis of patients with centrally reviewed malignant gliomas on CCG-943 confirmed that there was a significant improvement in both progression-free survival (PFS) and overall survival (OS) for those treated with adjuvant chemotherapy (R. Spoto, personal communication, March 2004).

Temozolomide, an oral alkylating agent with good CNS penetration, is now considered an important component of frontline treatment for adults with HGG. A randomized trial of RT plus concurrent and adjuvant temozolomide versus RT alone in patients with newly diagnosed glioblastoma (GBM) revealed a significant survival benefit for those receiving chemoradiotherapy.⁴ Although the response rate to temozolomide in pediatric HGG appears to be less impressive than in adults,^{6,7} xenograft studies have shown synergistic antitumor activity when temozolomide is combined with a nitrosourea.⁸ Thus, in this phase I study, we sought to determine the maximum tolerated dose (MTD) and estimate the preliminary response rate for the combination of temozolomide with a fixed dose of lomustine in newly diagnosed pediatric patients with unresectable HGG.

Materials and Methods

Eligibility

Patients ≥ 3 and < 22 years of age at the time of diagnosis of a nonbrainstem, non-spinal cord, nondisseminated, histologically confirmed HGG with measurable postoperative residual were eligible. All specimens were centrally reviewed by a neuropathologist blinded to the outcome or response data (A.Y.). Patients could not have received prior treatment other than surgery or corticosteroids. Other eligibility criteria included enrollment within 31 days of surgery, a Karnofsky or Lansky score $\geq 50\%$, and adequate bone marrow, renal, hepatic, and pulmonary function. Patients could not be receiving phenobarbital or cimetidine because of the potential interaction with lomustine. Other exclusion criteria included pregnancy and uncontrolled infection. Informed consent was obtained from patients, parents, or guardians at the time of enrollment. The protocol was approved by the institutional review board (IRB) of participating institutions.

Study Design

Following recovery from surgery and prior to RT, patients received two courses of temozolomide and lomustine. All patients received 90 mg/m² lomustine on day 1 and temozolomide on days 1–5 of each course. The starting temozolomide dose was 100 mg/m²/dose with subsequent cohort escalations to 125, 160, and 200 mg/m²/dose. The second course of chemotherapy was given 4 weeks after the first course or when counts recovered. An MRI scan to assess response was performed after recovery from the second course, prior to starting RT.

Four weeks following completion of RT, patients who had at least stable disease (SD) after the first two courses of chemotherapy received up to six additional courses of lomustine and temozolomide at the same dose they received prior to RT. Courses were given no closer than 4 weeks apart, following post-nadir recovery of absolute neutrophil count (ANC) to $\geq 1,000/\mu\text{l}$ and platelet count to $\geq 100,000/\mu\text{l}$.

Determination of the MTD

A minimum of three patients were treated at each dose level. If no unacceptable toxicity was experienced, the dose was escalated in subsequent patients. If one patient experienced dose-limiting toxicity (DLT), three additional patients were accrued. If two or more patients experienced DLT, then the MTD was exceeded and three more patients were treated at the next lower dose level. The MTD was defined as the maximum dose level at which no more than one of six patients experienced DLT and above which two or more patients encountered DLT.

DLT was evaluated during course 1 and defined as grade 4 neutropenia or thrombocytopenia that persisted for ≥ 7 days, failure of counts to recover to ANC $\geq 1,000/\mu\text{l}$ and platelet count $\geq 100,000/\mu\text{l}$ by day 42, and grade 3 or 4 nonhematologic toxicity (NHT; excluding nausea and vomiting, infection, fever, or grade 3 hepatic toxicity that returned to grade 2 or less by day 42). If patients required platelet transfusions for more than 7 days, they were considered to have grade 4 thrombocytopenia. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

Toxicity Evaluations and Dose Modifications

Patients were seen weekly during the first two courses of chemotherapy and then prior to each post-RT course of chemotherapy. Complete blood counts were performed at least weekly. Chemistries and liver function tests were performed weekly during the first two courses of chemotherapy and every other week thereafter. No dose modifications were allowed during pre-RT chemotherapy. Patients who experienced a DLT during course 1 proceeded directly to RT and were allowed to receive post-RT chemotherapy at the next lower dose level. During post-RT chemotherapy, the temozolomide and lomustine doses were reduced by 25% if platelets did not recover to $\geq 100,000/\mu\text{l}$ or ANC to $\geq 1,000/\mu\text{l}$ by day 56 of that course. If the counts did not recover by day 56 after the dose reduction, the lomustine dose was decreased by an additional 25%.

Response Evaluation

All patients receiving two courses of chemotherapy or who experienced progressive disease (PD) prior to the start of RT were considered evaluable for response. A patient was declared to have a complete response (CR) if all evidence of tumor (enhancing and nonenhancing)

disappeared; a partial response (PR) if there was a $>50\%$ decrease in the product of the greatest tumor diameter and its perpendicular diameter on MRI scan; and a minor response (MR) if there was a $\geq 25\%$ but $\leq 50\%$ reduction in the product of the greatest tumor diameter and its perpendicular diameter. A response required the patient to be on a stable or decreasing dose of steroids and needed to be confirmed by central review by a pediatric neuroradiologist (L.F.). PD was defined as a $>25\%$ increase in tumor size, the emergence of new lesions, or a positive cerebrospinal fluid (CSF) cytology. All other patients were considered to have SD.

A total of 15 evaluable patients were to be enrolled at the MTD in order to assess response to the combination of temozolomide and lomustine. Survival curves of patients treated at the MTD were computed using the product limit (Kaplan-Meier) estimates, with standard error via the Greenwood formula.⁹

Radiation Therapy

Radiotherapy targets included gross tumor volumes (GTV), clinical target volumes (CTV), and planning treatment volumes (PTV) based on CT or CT/MRI fusion. GTV1 included the gross disease at planning plus presurgical tumor. This target was expanded by 2–3 cm along contiguous white matter tracts to form CTV1, and that by 0.3–0.5 cm to form PTV1. A boost target was also defined as GTV2, corresponding to the extent of gross tumor at treatment planning. GTV2 was expanded by 1 cm to form CTV2 and again by 0.3–0.5 cm to form PTV2. Required dose prescription delivered 45 Gy for PTV1 and an additional 14.4 Gy for PTV2 (total, 59.4 Gy in 33 fractions). The protocol placed limits on dose to the dense optic pathways and the cervical spinal cord. Intensity-modulated RT, proton beam, and cobalt-60 were not allowed.

Results

Patient Characteristics

Thirty-two patients (age, 4–21 years; median, 12 years) from 19 institutions were enrolled (Table 1). One patient never started treatment when consent was withdrawn by the family, and three patients were determined to be ineligible: one had signed an expired version of the IRB consent, one had an ineligible diagnosis on central pathology review, and one had multifocal (i.e., disseminated) disease at the time of diagnosis. Of the 28 eligible patients who received treatment, two were not fully evaluable for toxicity: one patient progressed within 2 weeks of starting therapy and underwent reoperation, and the other received incorrect doses of chemotherapy during course 1.

Central Review of Pathology

Upon central review, one anaplastic astrocytoma (AA) was called an anaplastic ganglioglioma, three AAs were called GBMs, and one GBM was called an AA.

Toxicity

No DLTs were seen at the first three dose levels (Table 2). Two of three patients treated at a temozolomide dose of 200 mg/m²/day developed hematologic DLT (neutropenia, thrombocytopenia). None of six patients developed DLT at a temozolomide dose of 160 mg/m²/day, which therefore defined the MTD. One of 14 patients in the expanded MTD cohort experienced a hematologic DLT (failure to recover platelets to $>100,000$ by day 42). For the group as a whole, 4 of 27 (15%) patients received platelet transfusions, and one received a red blood cell transfusion during the first course.

Nine of the 15 patients treated at the MTD did not receive post-RT chemotherapy, either because of PD following pre-RT chemotherapy ($n = 4$) or during or after RT ($n = 3$), or because of parental ($n = 1$) or physician choice ($n = 1$). In those receiving post-RT chemotherapy, myelosuppression was cumulative, as expected. A box plot of course lengths of patients treated at the MTD is shown in Fig. 1. The fifth and sixth post-RT courses were administered at a median (range) of 46 (28–62) days apart versus 28.5 (27–47) days between courses 1 and 2. Counts recovered at a median of 77 (28–119) days in the four patients receiving post-RT course 6. Regression analysis of course length for patients treated at the MTD showed a significant increase in course duration with increase in course number ($p = 0.001$). There were two hospital admissions for infection (bacteremia without neutropenia, herpes zoster) and one for fever and neutropenia with negative cultures.

Grade 3 NHT was minimal, and no grade 4 NHT was encountered. One patient developed uncomplicated appendicitis after the second post-RT course. One patient at dose level 1 developed grade 3 elevation of serum glutamic pyruvic transaminase during course 4, which did not recur.

Responses

Twenty-seven of the 28 eligible patients who received treatment were evaluable for response. Central review diagnoses included GBM ($n = 16$) and AA ($n = 11$). All responses were confirmed by central review. Following the first two courses, 1 patient had CR, 1 PR, 2 MR, and 12 SD. Eleven patients progressed during pre-RT chemotherapy, eight during the first few weeks. Of the 14 evaluable patients treated at the MTD (eight GBM and six AA), one showed CR, one PR, and eight SD. The CR occurred in a patient who had undergone near gross total resection, with a 5-mm residual area of nodular enhancement on postoperative MRI that was no longer visible after two courses of chemotherapy. The PR occurred in a patient who underwent partial resection of a 7 × 5 cm right temporal lobe GBM, leaving a 3 × 3 cm residual tumor. Following two courses of chemotherapy, MRI showed only a small amount of abnormal signal without mass effect or enhancement.

Table 1. Summary of eligible patients receiving protocol therapy

Patient	Temozolomide		Sex	Location	Extent of Resection	Dx, Institution	Dx, Central	Response to		Metastases	TTD (years)
	Dose (mg/m ²)	Age (years)						Pre-RT Courses	Pre-RT Chemotherapy		
1	100	12.2	M	Cerebellar peduncle	Bx	AA	GBM	2	SD	4	3.3
3	100	10.1	M	Temporal/thalamic	Bx	AA	AA	2	SD	2	2.7
4	100	16.1	F	Thalamus	Bx	GBM	GBM	2	MR	6	1.9
5	125	5.6	M	Thalamus	Bx	AA	AA	2	SD	2	2.3
6 ^a	125	8.8	M	Frontotemporal	NGTR	GBM	GBM	1	PD	0	0.5
7	125	18	F	Pineal to occipital	STR	GBM	GBM	2	PD	0	0.6
8	125	9.5	F	Frontotemporal	Partial	AA	GBM	2	PD	0	1.5
9	125	6.1	F	Bithalamic	Bx	AA	AA	2 ^a	MR	2	1.3
10	125	11	F	Thalamus	STR	GBM	GBM	2	PD	0	0.5
11	125	15.4	F	Frontoparietal	STR	GBM	GBM	1	PD	0	2.1
12	160	17	F	Bithalamic	Bx	AA	AA	2	SD	2	Alive
13	160	4	M	Occipital	NGTR	AA	GBM	2	CR	6	Alive
14	160	4.4	M	Tectum/pineal	STR	GBM	AA	2	SD	0	0.4
15	200	9.6	F	Thalamus	Bx	GBM	AA	1	PD	0	1.2
16	200	17.3	F	Thalamus	Bx	AA	AA	2	SD	0	0.9
17	200	7.5	M	Parietal	STR	GBM	GBM	2	PD	0	2.5
18	160	15.5	M	Temporal/thalamic	STR	AA	AA	2	SD	0	Alive
19	160	3.7	M	Temporal/thalamic	NGTR	GBM	GBM	1	PD	0	0.5
20	160	8.5	M	Temporal/parietal	NGTR	GBM	GBM	2	SD	6	1.5
21 ^a	160	5.7	M	Thalamus	Bx	AA	AA	2	PD	0	0.6
24	160	21.4	M	Temporal	Partial	GBM	GBM	2	PR	0	1.0
25	160	17.8	F	Bifrontal	STR	AA	AA	2	SD	6	Alive
26	160	16.2	F	Thalamus	NGTR	GBM	GBM	2	PD	0	0.8
28	160	18.6	M	Frontal	STR	GBM	GBM	2	SD	0	1.5
29	160	5.6	M	Frontal	NGTR	AA	AA	1—DLT	Not evaluable ^b	0	Alive
30	160	11.5	M	Brachium pontis	STR	AA	AA	2	SD	5	1.5
31	160	12.2	F	Thalamus	Bx	GBM	GBM	1	PD	0	0.8
32	160	7.6	F	Frontal	STR	GBM	GBM	2	SD	6	Alive

Dx, diagnosis; RT, radiation therapy; TTD, time to death; M, male; Bx, biopsy (<10% removal); AA, anaplastic astrocytoma; GBM, glioblastoma; SD, stable disease; P, parenchymal; F, female; MR, mixed response; NGTR, near gross total resection (>90% resection with visible residual disease); PD, progressive disease; STR, subtotal resection (50%–89% resection); LM, leptomeningeal; partial, partial resection (10%–49% removal); CSF, cerebrospinal fluid; V, ventricle; CR, complete response; PR, partial response; DLT, dose-limiting toxicity.

^aNot evaluable for toxicity.

^bPatient did not have an MRI following pre-RT chemotherapy.

Table 2. Course 1 hematologic toxicity (grade 3 or 4)

Temozolomide Dose (mg/m ²)	No. Patients Entered	No. Evaluable Patients	WBC		ANC		Hemoglobin		Platelets	
			Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 4
100	3	3	0	0	1	0	0	0	1	0
125	7	6	0	0	0	0	0	0	1	0
160 ^a	15	14	0	0	3	1	0	1	2	0
200	3	3	1	0	1	1 ^b	0	1	1 ^b	1

Abbreviations: WBC, white blood cell count; ANC, absolute neutrophil count; Gr, grade.

^aOne patient in the expanded cohort had grade 2 thrombocytopenia that was dose limiting, i.e., failure to recover to >100,000/mm³ by day 42.^bDose-limiting toxicity.

Progressive Disease

Several patients developed increased enhancement and/or edema at the primary site and/or new areas of enhancement within 4 months of completing RT. Most of these patients were deemed to have PD and taken off the study. Five patients provide noteworthy illustrations of the difficulty in determining true tumor progression during this time period. Patient 28 was felt to have PD 1 month after completing RT and lived for 13 months without further intervention. Patient 17 was called PD 1 month after completing RT and lived for 2 years without further therapy other than debulking surgery; pathology showed some residual tumor with markedly variable morphology and reactive changes. Patient 12 was called PD 3 months after RT on the basis of increasing size and enhancement at the primary site and is a long-term survivor. Two additional patients developed new areas of enhancement consistent with metastatic lesions 1–3 months after completing RT. In patient 3, these lesions disappeared over the next year on oral etoposide (VP-16); patient 15 remained stable until the time of the last follow-up scan 6 months later and survived for more than a year without further therapy.

Sites of Recurrence

Thirteen of 20 patients (65%) who had MRI scans done within 6 months prior to death developed metastatic disease, nine of which were leptomeningeal and/or ventricular. Three patients developed metastatic disease within a few weeks of surgery, either in the ventricle that was opened at surgery or along the operative tract.

Survival

One- and 2-year OS for all evaluable patients was 64 ± 9% and 39% ± 9%, respectively, with a median of 17.6 months. For the group treated at the MTD, 1- and 2-year OS was 60% ± 13% and 40% ± 13% (see Fig. 2). Six of the 15 patients treated at the MTD remained alive with a median follow-up time of 32 months.

Discussion

The role of adjuvant chemotherapy in the treatment of pediatric HGGs was established in the 1980s, based on the results of a randomized Children's Cancer Group study using lomustine and vincristine.² Although subsequent studies have all utilized chemotherapy, further improvements in outcome have not been realized.^{10–13} With the advent of temozolomide, there was renewed hope that outcome could be improved. The benefit of temozolomide for adults with newly diagnosed HGGs was established in a randomized study by Stupp et al.,⁴ who showed a significant improvement in OS and PFS in newly diagnosed adults with glioblastomas treated with temozolomide during and after RT compared to those treated with RT alone. The results of a single-arm Children's Oncology Group trial in children with HGGs using the same schedule of temozolomide are not

Fig. 1. Box plot of course duration for patients treated at maximum tolerated dose, excluding course 3 (radiation therapy course). The data from course 1 of patient 21 and course 8 of patient 30 were not included due to incorrect dosing and withdrawal from study due to surgery after 18 days, respectively.

Fig. 2. Overall survival (OS) for patients treated at maximum tolerated dose (MTD) ($n = 15$).

yet available, although even with the adult study there remains much room for improvement.

The combination of a nitrosourea and temozolomide is a logical next step. A phase II study in adult patients with recurrent glioblastomas evaluated the combination of a nitrosourea (BCNU) followed 2 h later by a single oral dose of temozolomide. The results did not appear different from what was seen in patients treated with the standard 5-day regimen of temozolomide alone.¹⁴ However, since temozolomide exhibits marked schedule dependency,¹⁵ with a greater therapeutic effect and a higher response rate when given over 5 days compared to 1 day,¹⁶ the lack of benefit of the combination regimen in this study may in part reflect the use of a less active temozolomide schedule. There has only been one published study evaluating the combination of a nitrosourea (BCNU) with the 5-day regimen of temozolomide. This phase I trial in adults with recurrent solid tumors included seven patients with recurrent HGGs. Of these, two patients had prolonged SD, and one patient with a recurrent glioblastoma had an 83% decrease in the size of his tumor for 19 months before he died of an unrelated cause.¹⁷

Several chemotherapy regimens have been evaluated in pediatric patients with HGG using the “window” design to assess response by administering chemotherapy prior to RT.^{12,13,18} The Children’s Cancer Group 9933 (CCG-9933) study evaluated the combinations of “high-dose” carboplatin/VP-16, cyclophosphamide/VP-16, and ifosfamide/VP-16 prior to RT.¹¹ More than half of the patients either progressed during chemotherapy or did not complete chemotherapy because of toxicity, and 21% of the patients never received RT. In contrast, the combination of lomustine/temozolomide at the MTD was generally well tolerated, and only one patient

came off the study by parental request after developing thrombocytopenia during the first course. There were few hospitalizations for toxicity, and all patients went on to receive RT. Our response rate of 14% at the MTD is similar to other combination regimens studied in the cooperative group setting. Although the CR should be interpreted with caution as the lesion prior to therapy measured less than 1 cm in longest diameter, the PR was readily documented. CCG-9933 had a 0%, 9%, and 21% response rate for ifosfamide/VP-16, carboplatin/VP-16, and cyclophosphamide/VP-16, respectively.¹¹ The German Pediatric Oncology Group found a 20% response rate after 8 weeks of chemotherapy with ifosfamide, VP-16, methotrexate, cytosine arabinoside, and cisplatin.¹² One of 13 patients had a PR to procarbazine, and there were no responses in 14 patients treated with topotecan.¹³

We found that imaging studies performed within a few months of completing RT were very difficult to interpret. At least five patients who were deemed to have progressed within 1–3 months after RT had prolonged survival (median, 20 months following “progression”), either without further intervention or with palliative oral chemotherapy. In contrast, the median time to death for patients treated on study CCG-945 who received no further chemotherapy after disease progression was 2 months, versus 7 months for those who received retrieval chemotherapy.¹⁰ It is possible that administration of chemotherapy prior to or during RT acts as a radiosensitizer and increases the likelihood of radiation swelling. The nitrosoureas are reported to potentiate the effects of RT through inhibition of sublethal damage repair,¹⁸ and even chemotherapy given after RT has been reported to increase the risk of radiation necrosis.¹⁹ This observation of post-RT radiographic worsening followed by improve-

ment without a change in tumor-specific treatment is becoming increasingly recognized.²⁰ It is typically impossible to distinguish between RT changes and tumor progression on radiographic studies performed during the first few months following completion of RT. Metabolic imaging with PET scans has a high false-positive and false-negative rate after radiotherapy.²¹ Surgical confirmation of necrosis is the only definitive means of distinguishing between tumor and necrosis. This approach was undertaken in adult patients with glioblastoma treated with chemoradiotherapy at a single institution.²² Fifteen of 51 patients (29%) developed a >25% enlargement of the residual mass on MRI scan in conjunction with clinical worsening shortly after the completion of chemoradiotherapy. Seven of these patients were found to have treatment-related necrosis without tumor at the time of reoperation. As chemoradiotherapy is being used with increasing frequency, with what appears to be an increased incidence of early necrosis,²⁰ OS rather than PFS may be a more accurate primary outcome measure in clinical trials in HGG patients receiving RT. Indeed, OS at 12 months was found to be a more accurate trial endpoint than PFS at 6 months in an evaluation of pooled data from 11 cooperative group phase II trials in adults with newly diagnosed glioblastomas.²³ Furthermore, PD occurring within 3–4 months of completing radiotherapy should be interpreted cautiously, as should responses in “recurrent” patients who were enrolled in clinical trials after developing “progression” within 3–4 months of completing RT.

The high incidence of metastatic disease developing at some point during the course of the disease is noteworthy. A review of pediatric patients with HGGs treated on cooperative group studies over 10 years found that only 3% had evidence of CNS dissemination at the time of initial presentation.²⁴ The incidence dramatically increases following diagnosis, 26%–41% from series largely done in the CT/early MRI era.^{25–27} Grabb et al. found that 11 of 34 children with HGG developed disseminated disease at a median of 8 months (range, 1 week to 59 months) from diagnosis.²⁷ Ventricular entry during surgery was a significant risk factor. Interestingly, an analysis of patients with pontine gliomas, who do not routinely undergo biopsy, reported a 17% incidence of dissemination, with a much longer median time to onset (15 months; range, 3–96 months).²⁸ This suggests that surgery may increase the risk of dissemination early in the course of treatment, although many tumors will eventually disseminate regardless of treatment.

Consistent with this, some patients in this study developed dissemination in the ventricle or along the operative tract within a few weeks of surgical entry, while other patients developed metastatic lesions much later in the course of the disease. Similarly, a recent report from England found a 46% incidence of leptomeningeal and/or parenchymal metastases.²⁹ In our study population, four patients developed parenchymal metastatic lesions distant from the primary tumor site without evidence of leptomeningeal dissemination; in two of these patients, the metastatic nodules were contralateral to the primary tumor. It would seem unlikely that these new lesions represented areas of local recurrence in an extensive infiltrating tumor, although even if these cases were not considered true metastases, the overall incidence of leptomeningeal or ventricular metastases is substantial (50% of those with MRI scans done within 6 months prior to death). Since most patients with HGG eventually progress at the primary site, it is unclear whether craniospinal RT would provide any benefit, and it would clearly limit the amount of post-RT chemotherapy that could be administered.

In conclusion, the MTD for this regimen is 160 mg/m²/day of temozolomide × 5 with 90 mg/m²/day lomustine on day 1. Given the tolerability of the regimen, the number of long-term survivors, and the confirmed responses, a phase II study evaluating RT and concurrent temozolomide followed by lomustine and temozolomide is ongoing within the Children’s Oncology Group. In this trial, patients will receive six courses of maintenance chemotherapy rather than eight in order to mitigate cumulative myelosuppression. This larger trial will evaluate the impact of known prognostic variables such as extent of resection,³⁰ as well as biologic correlates such as O⁶-methylguanine DNA methyltransferase expression.³¹

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