A phase I study of topotecan as a radiosensitizer for brainstem glioma of childhood: First report of the Children's Cancer Group-0952[1]

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Our purpose was to establish the maximum tolerated dosage (MTD) of daily i.v. topotecan with conventionally fractionated radiotherapy (XRT) for patients with intrinsic pontine glioma of childhood. Topotecan was given as a 30-min i.v. infusion 30–60 min before each XRT treatment given daily for 33 days. Total XRT dose was 59.4 Gy. Dose escalation of topotecan was carried out using a standard phase I design. Dose limiting toxicity (DLT) was defined as an absolute neutrophil count (ANC) of ≤500/mm^3 for ≥7 days; platelets of ≤50,000/mm^3 for ≥7 days; >7 days platelet transfusions; fever and neutropenia (ANC ≤500/mm^3 for ≥7 days); and/or any ≥ grade 3 nonhematologic toxicity. In this multi-institutional phase I study, 17 patients <21 years with intrinsic pontine glioma were enrolled. Sixteen patients completed treatment. An ANC ≤500/mm^3 for ≥7 days occurred in 2/5 patients at 0.50 mg/m^2 of topotecan, which was the DLT. The remaining 14 patients received topotecan without experiencing DLT. One patient at 0.40 mg/m^2 died of disease progression while on treatment. There were 6 other grade 4 hematologic events (5 ANCs <500/mm^3, 1 hemoglobin <6. 5 g/dl) not meeting DLT criteria. No significant nonhematologic toxicities were seen. The actuarial median survival time is 15 months (95% confidence interval, 9.6–19 months); 1-year survival is 53%. DLT of daily topotecan with cranial XRT is grade 4 neutropenia for ≥7 days at 0.50 mg/m^2 x 33 (total dosage = 16.5 mg/m^2); the recommended safe MTD of daily topotecan for further phase II testing is 0.40 mg/m^2 x 33 (total dosage = 13.2 mg/m^2). *Neuro-Oncology 5, 8–13, 2003 (Posted to Neuro-Oncology [serial online], Doc. 02-010, November 27, 2002. URL http://neuro-oncology.mc.duke.edu)*

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[3]Abbreviations used are as follows: DLT, dose-limiting toxicity; MTD, maximum tolerated dosage.

Intrinsic pediatric pontine gliomas have a dismal prognosis, and treatment strategies continue to be unrewarding. When treated with conventionally fractionated radiation to doses of 60 Gy, these patients have a median survival of 9 months, and long-term survivors are rare (Berger et al., 1983; Freeman et al., 1993; Stroink et al., 1986). Aggressive surgical resection is restricted by the location and infiltrative nature of these tumors. Systemic chemotherapy has not produced significant benefits (Allen et al., 1996; Jenkin et al., 1987). Hyperfractionated radiotherapy has been explored; a recent randomized trial demonstrated no survival advantage from this approach (Freeman et al., 1993; Linstadt et al., 1991; Mandell et al, 1999; Packer et al., 1993; Prados et al., 1995).

Radiosensitization affords a potentially useful investigational avenue for this disease because of the almost complete absence of metastatic dissemination; the high local failure; and the surrounding, slowly proliferating parenchyma. Topotecan, a topoisomerase I inhibitor, is known as a radiosensitizer in addition to having modest antitumor activity. Previous in vitro and in vivo studies have shown that topotecan converts repairable radiation-induced sublethal DNA damage to lethal double-strand DNA breaks (Boothman et al., 1989, 1992; Chabner, 1992; Kim et al, 1992; Lamond et al., 1996a, 1996b; Mattern et al., 1991; Rowinsky et al., 1992; Schiller et al., 1994). Topotecan, as a radiosensitizer in conjunction with conventional radiotherapy, may provide a local control advantage for children with intrinsic brainstem gliomas. Particularly relevant to this issue are the preclinical data from Lamond et al. (1996a, 1996b) demonstrating synergy/sensitization between topotecan and radiation in glioma cell lines in vitro. To determine the MTD[3] of topotecan with radiation for children with brainstem gliomas, a multi-institutional phase I study was undertaken with daily topotecan and conventional radiation therapy. Survival, as measured in the limited context of a phase I trial, was a secondary endpoint.

Materials and Methods

Eligibility criteria included clinical and radiographic (MRI) evidence of tumors that intrinsically (greater than 50% intra-axial) involved the pons, the pons and medulla, the pons and midbrain, the entire brainstem, or tumors that contiguously involved the thalamus or upper cervical cord. Histologic verification was not required. Patients were required to be less than 21 years of age at enrollment, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, and have a life expectancy of more than 8 weeks. History, physical exam, and contrast-enhanced MRI of the brain, as well as adequate hematologic, renal, and liver function, were required for enrollment. Other eligibility requirements were adequate bone marrow function including peripheral absolute neutrophil count $\geq$1000/mm^3, platelet count $\geq$100,000/mm^3 (transfusion independent), and hemoglobin >10.0 g/dl (transfusion allowed); adequate renal function including serum creatinine $\leq$1.5 x normal, creatinine clearance, or radioisotope glomerular filtration rate $\geq$70 ml/min/1.73 m^2; and adequate liver function including total bilirubin $\leq$1.5 x normal and aspartate transaminase or alanine transaminase <2.5 x normal. All patients and/or their parents or legal guardians were required to sign an informed consent according to Children's Cancer Group guidelines. Patients with neurofibromatosis or pregnant patients were not eligible for the study.

Radiotherapy

All patients were to receive 50.4 Gy to the initial tumor volume with a 1.5-cm margin followed by a 9-Gy boost to the tumor volume plus a 1-cm margin. External beam radiotherapy was administered in a 1.8-Gy/fraction (to the prescription point along the central axis where the treatment fields intersected). All patients were treated with a linear accelerator with 4-to-10-MV photons. Patients were treated once a day, 5 days a week. The spinal cord was excluded from the tumor boost, and the spinal cord dose was limited to 46 Gy. A body mold, head positioning devices, and a treatment-planning CT scan were strongly recommended. Patients were simulated in the same position as the CT setup. Radiation therapy was delivered within 30–60 min after completion of the topotecan infusion.

Radiosensitizer

Topotecan was administered on the days of planned radiotherapy. It was given as a 30-min i.v. infusion and was completed within 30–60 min before initiation of radiotherapy. The starting dosage of topotecan was 0.30 mg/m^2/day i.v., which was <60% of the MTD reported in a recent publication of a phase I trial of topotecan given as a low-dose, 21-day continuous infusion (Hochster et al., 1994).

Dose Escalation

The primary study objective was to determine the MTD of i.v. topotecan with conventional radiotherapy for childhood intrinsic pediatric pontine gliomas. The MTD was defined as the dosage at which fewer than one-third of the patients experienced a DLT. Dose-limiting toxicity was defined as absolute neutrophil count $\leq$500/mm^3 for $\geq$7days, platelets $\leq$50,000/mm^3 for $\geq$7 days, >7 days platelet transfusions, fever and neutropenia (absolute neutrophil count) $\leq$500/mm^3 for $\geq$7 days, and $\geq$grade 3 nonhematologic toxicity, except for grade 3 nausea and vomiting, for $\leq$7 days.

Dose escalation was conducted according to the following scheme. The first 3 eligible patients were entered at dose level 1 and were followed for a minimum of 15 weeks before further accrual. If none of the 3 patients experienced DLT, then the dose was escalated to the next higher level in 3 subsequent patients. If 1 of these 3 patients experienced DLT at that dose level, then up to 3 more patients were accrued at the same level. If none of these additional patients experienced DLT, then the dose was escalated in subsequent patients; if 1 or more of these 3 additional patients experienced DLT, then patient entry at that dose level was stopped, MTD had been exceeded, and dose escalation was not continued. Three more patients were treated at the next lower dose, provided that only 3 patients were previously evaluated at that dose level. If 2 or more patients experienced DLT, then the MTD had been exceeded and dose escalation was stopped. Three more patients were treated at the next lower dose level, provided that only 3 patients were previously evaluated at that dose level. The MTD was the dose level at which 0/6 or 1/6 patients experienced a DLT with at least 2/3 or 2/6 patients encountering a DLT at the next higher dose. The protocol allowed for the enrollment of a fourth patient at a dose level if none of the patients enrolled at that level had experienced DLT and 3 patients had not completed evaluation for DLT.

Evaluation and Supportive Care During Treatment

Patients were examined weekly for 7 weeks and had blood work done, which included a complete blood count with differential and platelet count drawn 3 x/week for 7 weeks, as well as blood urea nitrogen, creatinine, aspartate transaminase, alanine transaminase, alkaline phosphatase, lactate dehydrogenase, bilirubin, total protein, and albumin at 2 and 5 weeks. Initiation of broad-spectrum antibiotics for febrile and neutropenic patients was required. Prophylactic use of antibiotics such as TMP-SMX for *Pneumocystis carinii* prophylaxis was at the investigator's discretion. Packed red blood cell transfusion to maintain hemoglobin ≥10 g/dl and platelet transfusion to maintain platelet count ≥50,000/ml were required. Antiemetics, fluids, electrolytes, and general supportive care were used when necessary. Corticosteroid use was permissible only for treatment of increased intracranial pressure. No other chemotherapy or immunomodulating agents could be used.

Follow-up

Patients underwent physical exams at 8 weeks, at 3, 6, 9, 12, 15, 18, 24, 30, and 36 months, and then annually. MRI of the brain with gadolinium-diethyltriaminepentaacetic acid enhancement was conducted at 3, 6, 9, 12, 15, 18, 24, 30, and 36 months. Blood work, including complete blood count, creatinine, blood urea nitrogen, aspartate transaminase, alanine transaminase, alkaline phosphatase, lactate dehydrogenase, bilirubin, total protein, and albumin, was required at 3 months. Survival was defined to be the time from study entry until death or last patient contact, whichever came first. If the patient died, an event was considered to have occurred. Otherwise, the patient was censored at the date of last contact. Survival probability was estimated by the method of Kaplan and Meier (Kalbfleisch et al., 1980).

Results

Patient Characteristics

A total of 17 patients were enrolled on this study between August 1995 and February 1998, and 16 patients completed protocol treatment. Outcome data current to November 2000 were used for this analysis. Patient characteristics at the time of study enrollment are listed in Table 1. Patient age ranged from <1 to 14, with a median age of 5 years. Ten patients were male and 7 were female. Most patients were Caucasian (14), 2 were African American, and 1 was Native American. Median time from diagnosis to study entry was 1 week, ranging from <1 to 2 weeks. Median time to diagnosis from onset of symptoms was 3 weeks, ranging from <2 to 52 weeks. Eleven patients were on steroids at the time of enrollment.

Table 1. Patient characteristics at the time of study enrollment

Age (years)	
Median	5
Range	<1–14
Sex (No. of patients)	
Female	7
Male	10
Race (No. of patients)	
Caucasian	14
African-American	2
Native American	1
Temporal relationships (weeks)	
Median time from symptom onset to diagnosis	<4 (<2–52)
Median time from diagnosis to study entry	1 (<1–2)

Radiotherapy

Nine patients were treated at a dose of 50.4 Gy and were boosted to a total dose of 59.4 Gy. Four additional patients were treated at a total dose of 59.4 Gy, but the boost field was started at 45 Gy in 3 cases and at 48.6 Gy in 1 case. One patient was treated at 59 Gy, which included a 3.2-Gy tumor bed boost given with a fractionated stereotactic scheme. One patient was treated at a total lower dose of 57.6 Gy due to young age (2.7 years). One patient was treated at 60 Gy in 2.0 Gy/fraction, and finally, 1 patient received <10 Gy and progressed. All other patients were treated with 1.8 Gy/fraction. The maximum dose to the optic chasm was ≤50.4 Gy, and all but 1 patient had the spinal cord dose limited to 50.4 Gy. One patient had a major radiotherapy protocol deviation by treatment of the spinal cord at the C-2 level at a total dose of 60 Gy.

Topotecan

Four patients received topotecan at 0.30 mg/m^2, 8 patients at 0.40 mg/m^2, and 5 patients at 0.50 mg/m^2. Topotecan was given as a 30-min i.v. infusion before each daily radiation treatment. Table 2 illustrates the various topotecan dose cohorts.

Table 2. Dose escalation and DLT frequency

Level (mg/m^2/day)	No. with DLT	No. of patients	Description
0.3	0	4	None
0.4	0	8[a]	None
0.5	2	5	One prolonged neutropenia; one prolonged neutropenia with sepsis

[a]One patient was not evaluable for toxicity because of death from disease progression in week 1.

Table 3. Dose-limiting toxicities

Toxicity	Topotecan dose (No. of patients)		
	0.30 mg/m^2	0.40 mg/m^2 [a]	0.50 mg/m^2
ANC ≤500/mm^3 ≥7 days	0/4	0/8	1/5
Platelets ≤50,000/mm^3 for ≥7 days	0/4	0/8	0/5
>7 days of platelet transfusions	0/4	0/8	0/5
Fever and ANC≤500/mm^3 for ≥7 days	0/4	0/8	1/5
≥Grade 3 nonhematologic toxicity[b]	0/4	0/8	0/5

Abbreviation: ANC, absolute neutrophil count.

[a]One patient died of disease progression while on treatment.

[b]This category is applicable for all investigational drug-related nonhematologic toxicities except grade 3 or grade 4 nausea and vomiting that could be controlled within 7 days.

Toxicities

DLTs. Two of 5 patients at the 0.50 mg/m^2 dose experienced a DLT. One patient had prolonged (7 days or longer) neutropenia, and the other had prolonged neutropenia and sepsis. The dose of topotecan was reduced in 4/16 patients due to toxicity at higher dose levels. The protocol allowed for dose reduction for patients who had grade 4 neutropenia or thrombocytopenia, but less than 7 days' duration was not considered dose limiting. Two dose reductions occurred in the 2 patients with dose-limiting neutropenia as described above. Two other reductions occurred in patients enrolled at the 0.40 mg/m^2 dose level and followed delays for neutropenia/thrombocytopenia of 4 days for each patient; thus they were not considered DLTs. The remaining 14 patients did not experience a DLT. One patient at 0.40 mg/m^2 died of disease progression while on treatment. This patient is not included in the assessment of toxicity of the 0.40 mg/m^2 dose level. The DLTs are listed in Table 3.

Grade 3/4 hematologic toxicities related to topotecan. Seven patients experienced grade 3 or grade 4 neutropenia, 8 patients experienced non-dose-limiting grade 3 or grade 4 leukopenia, and 12 patients had grade 3 or grade 4 lymphopenia. One patient had radiation treatments disrupted secondary to neutropenia; although the protocol did not require this, 1 patient received growth factor by the investigator's choice; 7 patients received oral antibiotics (all of whom received TMP-SMX, probably for *P. carinii* pneumonia prophylaxis); and 3 required parenteral antibiotics. The median white blood cell nadir (per mm^2) was 1,850 with a range of 200–9,000. Four patients had grade 3 or 4 anemia. Four patients required 1 red blood cell transfusion and 3 required >1 red blood cell transfusion. The median hemoglobin nadir (g/dl) was 8.7 with a range of 6.2–10.2. Two patients experienced nadir platelet counts that were less than 50,000/mm^3. One patient received a platelet transfusion while on protocol therapy. These did not meet DLT criteria. The median platelet nadir was 169,000 with a range of 34,000–296,000. Grade 3/4 hematologic toxicities related to topotecan are listed in Table 4.

Grade 3/4 nonhematologic toxicities related to topotecan. One patient experienced grade 3 nausea, and 1 had grade 3 total bilirubin elevation. The latter's association with topotecan was not established, and it was therefore not possible to regard this toxicity as even possibly related to topotecan administration. There were no other major nonhematologic toxicities observed, including skin toxicity, stomatitis, vomiting, or diarrhea. Additionally, 1 patient required central venous nutrition, and 15 patients were given steroids during treatment, of whom 11 were on steroids at enrollment. The median number of days of steroid administration for those who received steroids was 44 (range 18–56).

Grade 3/4 toxicities related to radiation therapy. No specific severe enhancement of acute or long-term radiation toxicities was observed. Specifically, no potentiation of skin reactions or late necrosis was observed.

Survival and Response

This was a secondary endpoint in the context of this phase I trial. The estimated median survival time for patients evaluable for toxicity was 15 months (95% confidence interval, 9.6–19 months). The estimated 1-year probability of survival was 53%. Radiographic response was not assessed centrally because precise delineation of these tumors would be necessary to have an accurate estimate of response. Unfortunately, these tumors typically are highly infiltrative in the substance of the brainstem, and their borders cannot be reliably and reproducibly outlined with any degree of precision. These tumors typically have highly heterogeneous enhancement patterns and often can be poorly to completely nonenhancing, further complicating the reliability of response assessment. Finally, previous studies have demonstrated a post treatment effect in which the enhancement pattern is altered after radiotherapy, and this too makes response assessment inaccurate in this tumor.

Discussion

Intrinsic pontine gliomas represent between 10% and 20% of all pediatric brain tumors (Albright et al., 1986). Survival in these children is generally dismal; 5-year survival is usually around 5%, with most patients dying within 1 year of diagnosis (Epstein et al., 1996; Panitch et al., 1970).

Table 4. Nadir hematologic profile related to topotecan

Patient No.	Dose level (mg/m^3/day)	Nadir hematologic values		
		WBC	Hgb	Platelets
1	0.3	1300	9.4	248,000
2	0.3	4600	9.7	225,000
3	0.3	5400	10.2	170,000
4	0.3	1800	7.6	240,000
Median		3200	9.6	232,500
Range		1300–5400	7.6–10.2	170,000–248,000
5	0.4	200	8.7	168,000
6	0.4	4600	9.3	235,000
7	0.4	9000	6.4	106,000
8	0.4	1300	8.7	41,000
9	0.4	2800	9.2	194,000
10	0.4	3200	8.2	296,000
11	0.4	3200	8.4	257,000
12	0.4	N/E	N/E	N/E
Median		3200	8.7	194,000
Range		200–9000	6.4–9.3	41,000–296,000
13	0.5	1700	7.7	71,000
14	0.5	1900	9.6	118,000
15	0.5	900	6.2	34,000
16	0.5	1000	8.9	91,000
17	0.5	1400	7.7	79,000
Median		1400	7.7	79,000
Range		900–1900	6.2–9.6	34,000–118,000
Overall median		1850	8.7	169,000
Overall range		200–9000	6.2–10.2	34,000–296,000

Abbreviations: WBC, white blood count; Hgb, hemoglobin.

Radiation therapy has been the mainstay of treatment for pediatric brainstem gliomas for the past 30 years. Conventional external beam radiotherapy with doses of 54–60 Gy minimally improves survival (Greenberger et al., 1977). Death typically occurs secondary to local progression within the field of irradiation. To try to improve local control and, ultimately, survival, investigators have recently studied hyperfractionation as a means of dose escalation (Freeman et al., 1993; Linstadt et al., 1991; Mandell et al., 1999; Packer et al., 1993; Prados et al., 1995). Although doses as high as 78 Gy were delivered, overall survival remained unchanged for the diffuse brainstem glioma patients.

Systemic chemotherapy has proven equally disappointing. In a randomized trial, overall survival rate at 5 years was unchanged at 20% with the addition of lomustine, vincristine, and prednisone to conventional radiation (Jenkin et al., 1987). With consistently negative results from various approaches, it is reasonable to consider these tumors for phase I trials of innovative approaches. It is not anticipated that such phase I studies will produce a dramatic improvement in survival, but they will allow the determination of the MTD for agents that can subsequently be tested in definitive phase II and III trials for supratentorial as well as infratentorial gliomas.

In this multi-institutional study, 16/17 patients completed the study and were included in the analysis. The MTD was 0.4 mg/m^2 of i.v. topotecan given before daily conventional radiation therapy for pediatric brainstem glioma patients for 33 doses. DLT was encountered in 2 patients at 0.5 mg/m^2 of daily i.v. topotecan. One patient developed prolonged neutropenia for >7 days, and another patient experienced prolonged neutropenia and sepsis. After reaching the DLT, 4 additional patients received 0.4 mg/m^2 daily doses of i.v. topotecan, confirming the MTD of 0.4 mg/m^2.

Most of the patients had some type of non-dose-limiting leukopenia, and 4 patients developed grade 3/4 anemia. Antibiotics were given to 10 patients, and red blood cell transfusions were required for 7. Significant thrombocytopenia was rarely encountered in this study. For the most part, nonhematologic problems were rare. There were only 2 other significant nonhematologic toxicities due to topotecan in this study: 1 patient developed nausea, and 1 patient had an elevation of total bilirubin. Side effects from the radiation itself were all less than grade 3.

Overall survival for the current study is comparable to studies of radiation therapy alone. This study was not designed to detect a survival advantage. Only 13 patients were treated at or above the MTD. Therefore, no significant conclusions regarding efficacy can be made on the

basis of this phase I trial. However, a 15-month median survival and 53% 1-year survival are encouraging. These numbers deserve particular attention because recent MRI-based selection criteria for intrinsic pediatric pontine gliomas have in fact demonstrated that there are 2 distinct tumor categories. Patients with dorsally exophytic tumors usually fare better, whereas those with predominantly intrinsic disease, as in this study, do much worse. In fact, older clinical trials that did not exclude the dorsally exophytic tumors often reported a better survival rate (Fischbein et al., 1996). Modern MRI-based trials have typically reported median survival of ≤10 months, and although our 95% confidence intervals overlap, this outcome is noteworthy.

In summary, the MTD of daily i.v. topotecan was 0.4 mg/m^2 for 33 doses (13.2 mg/m^2), with the DLT being prolonged neutropenia. Further randomized investigations of topotecan as a radiosensitizer in conjunction with radiotherapy appear to be reasonable and should be pursued in future trials.

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