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Clinical Study

Recurrent brainstem gliomas treated with oral VP-16*

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Abstract

12 patients: (7 males and 5 females) with recurrent brainstem gliomas were treated with the oral topoisomerase inhibitor VP-16 (Etoposide). Patients ranged in age from 3 to 49 years with a median age of 7 years. All patients had been previously treated with radiation therapy (conventional fractionation: 4; hyperfractionation: 8) and 5 had received prior nitrosourea-based chemotherapy at time of tumor recurrence. Tumor recurrence was documented by radiographic tumor enlargement utilizing brain MRI with gadolinium enhancement (12) and clinical neurologic deterioration (9). Two patients underwent biopsy pathologically documenting tumor recurrence. Each cycle of therapy consisted of 21 days of VP-16 (50 mg/m^2/day) followed by a 14 day rest followed by an additional 21 days of VP-16 (50 mg/m^2 day). Complete blood counts were followed bi-weekly and a neurologic examination and brain MRI scan with contrast were performed prior to initiation of each cycle of therapy. Treatment related complications included: partial alopecia (5); diarrhea (5); weight loss (4); neutropenia (2); and thrombocytopenia (4). No patient required transfusion or antibiotic treatment of neutropenic fever. There were no treatment related deaths. 12 patients were evaluable of whom 6 demonstrated a radiographic response (1 complete; 3 partial; 2 stable disease) with a median duration of response of 8 months. In summary; oral VP-16 is a well tolerated and relatively non-toxic chemotherapeutic agent with apparent activity in this small cohort of patients with recurrent brainstem gliomas.

Introduction

Malignant gliomas involving the brainstem account for 10–20% of pediatric and 1–2% of adult brain tumors [1, 2]. These tumors produce disproportionate neurological dysfunction for their size. While these tumors vary from well differentiated astrocytomas to glioblastomas multiforme, most tumors of the brainstem are ultimately lethal regardless of histology [3, 4].

Surgery is of limited value except in cases of cystic or exophytic lesions or when the diagnosis is in question [5–7]. Histological grading of tumors from surgical biopsy specimens is not always fruitful because of limited sampling which necessarily results when the surgeon operates on intra-axial lesions of the brainstem. Radiation therapy for malignant gliomas of the brainstem is of proven therapeutic value and the most effective therapy [8]. Reported series indicate that 5 year survivals of 20–30% are to be expected following radiation therapy [8]. Radiation therapy improve symptoms and signs in 75–90% of patients. More modern diagnostic imaging (i.e. multiplanar contrast enhanced brain MR imaging) have reduced the likelihood of misdiagnosis accounting for lower 5 year survival rates (5–15%) in more recent series [9–12]. In 2 large published series, hyperfractionated radiation therapy appears to offer meaningful improvement in survival of patients with malignant gliomas

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of the brainstem [10, 12]. This therapy has increasingly become the standard adjuvant treatment. By contrast, the place of adjuvant chemotherapy for brainstem gliomas is of unproven value and similarly the use of pre-radiation chemotherapy for malignant brainstem tumors does not appear to offer benefit over radiation therapy [13, 14].

Treatment of recurrent brainstem gliomas remains problematic in that only partially effective therapeutic modalities are available. These include re-operation (an unusual circumstance as for example with cystic brainstem lesions), radiation therapy and chemotherapy. The role of radiosurgery in the treatment of recurrent brain stem gliomas is as of yet, unexplored. Because of concerns of radiation necrosis and it's consequent neurological morbidity and frequent requirement for re-operation, high activity radioactive seed implants are impractical for recurrent brainstem gliomas [15]. Therefore chemotherapy remains the primary treatment of recurrent brainstem gliomas, though unfortunately response is of limited duration. Multiple drugs appear to have modest activity against brainstem gliomas including nitrosoureas, procarbazine, cyclophosphamide, β-interferon, AZQ, and platinum compounds [16–22].

VP-16 or Etoposide is an important anti-neoplastic agent used against several types of tumors (i.e. small cell lung cancer, germ cell tumors, Kaposi sarcoma) [23–28]. VP-16 has been used most often in combination chemotherapy as salvage therapy for recurrent gliomas, though it's role in the treatment of gliomas as demonstrated by single agent trials is less certain [29–39].

Methods

Study population

12 patients (7 male; 5 female) were seen at the University California, San Diego Gildred Cancer Center between January 1988 and October 1991 with neuroradiographic documentation of recur-

Table 1. Brainstem gliomas: salvage therapy with VP-16

Patient	Gender/Age (yrs)	Prior therapy		VP-16 therapy Response/duration (MNS)
		Radiation	Chemotherapy	
1	F/1	H	–	PD
2	M/3	C	CENU	PR/8
3	M/4	H	–	CR/20
4	F/4	H	–	SD/6
5	F/5	H	–	PD
6	M/6	H	–	PD
7	M/8	H	–	PD
8	M/9	C	CENU	SD/8
9	M/18	H	–	PD
10	F/27	H	CENU	PD
11	F/29	C	CENU	PR/4
12	M/49	H	CENU	PR/12

M	Male
F	Female
C	Conventional fractionation
H	Hyperfractionation
CENU	Nitrosourea-based chemotherapy
PR	Partial response
CR	Complete response
PD	Progressive disease
SD	Stable disease

rent brainstem gliomas. These patients or their parents were asked to participate in a institutional review board approved study of chronic oral VP-16. Patients ranged in age from 3–49 years with a median age of 7 years. 75% (9/12) of patients were less than 18 years of age. Karnofsky performance status ranged from 60–100% with a median of 80%. Neurological examination at time of recurrence included the following: ophthalmoplegia (6/12); facial paresis (4/12); bulbar paresis (2/12); spasticity (11/12); hemiparesis (4/12); limb ataxia (6/12); gait ataxia (6/12); and hyperreflexia (9/12). 3 patients, aside from complaints of headache, had normal neurological examinations.

Prior therapy (see Table 1) included radiation therapy in all patients and 5 patients had previously been treated at recurrence with a nitrosourea (BCNU in 4; CCNU in 1). 25% of patients (3/12) were treated following diagnosis of a brainstem tumor with conventional once per day radiotherapy (dose: range 55–60 Gy; median 60 Gy). 75% of patients (9/12) were treated with hyperfractionation radiotherapy given as 100 cGy twice per day to a total dose of 72 Gy. The median time to tumor recurrence following initial diagnosis was 8 months with a range of 5–24 months.

33% of patients (4/12) underwent biopsy (stereotactic 3; open 1) following initial diagnosis of a brainstem tumor by clinical and neuroradiographic criteria. Neuropathologic diagnosis were as follows: well differentiated glioma (1); anaplastic astrocytoma (2); and glioblastoma multiforme (1). 2 patients (17%) without pathology at time of diagnosis, underwent biopsy at time of recurrence and were found pathologically to have the following: anaplastic astrocytoma (1); glioblastoma multiforme (1).

Imaging

Cranial MR examinations were performed on a 1.5-tesla superconducting magnet (Signa; General Electric, Milwaukee, WI). Using a spin-echo pulse sequence, axial T_2-weighted (T_2W; TR3000 msec/TE80 msec) proton density-weighted (PDW: TR3000 msec/TE30 msec) images were initially acquired. Subsequently, both sagittal and axial or coronal T_1-weighted (T_1W: TR600 msec/TE25 msec) images were acquired. Slice thickness was 5 mm, with a 2.5 mm interval between successive slices in all instances; a 256 × 256 matrix was utilized. After intravenous administration of 0.1 mmol/kg gadolinium/DTPA Dimeglumine (Berlex Laboratories, Cedar Knolls, NJ), coronal, axial, and sagittal T_1W sequences (TR600 msec/TE25 msec) were obtained. All post contrast images were obtained within 30 minutes of gadolinium infusion.

Drug schedule

All 12 patients were treated with escalating doses of dexamethasone (range 6–30 mg; median 10 mg) for 4–8 weeks at time of clinical and neuroradiographic recurrence. Follow-up contrast enhanced cranial MR and neurological examination documented tumor progression despite dexamethasone treatment. The dexamethasone trial was an empiric attempt to differentiate radiation neucrosis of the brainstem from tumor recurrence. In 3 patients, ^{201}Th SPECT studies were performed in an attempt to differentiate radiation necrosis from tumor recurrence. In all 3 instances, imaging of the brainstem was unsuccesful.

VP-16 was given orally as 50 mg/m^2/day for 21 consecutive days (A subcycle) followed by a 14 day break and then an additional 21 days (B subcycle) of oral VP-16 at 50 mg/m^2/day. All doses were given as single daily drug administrations in the morning. In small children the dose administered was either 25 or 50 mg per day.

Dexamethasone was used concurrently in 8/12 patients treated with VP-16 and was maintained as either a stable dose (3/12) or a tapering dose (5/12) as patient clinical status permitted.

VP-16 dose modifications were as follows:

Granulocytes/ul	Platelets/ul	VP-16
≥ 1500	≥ 100,000	100%
1000–1499	99,999–75,000	50%
< 1000	< 75,000	0%

Method of evaluation

Blood counts were obtained weekly, neurological examination was performed monthly and contrast enhanced cranial MR was performed every 8–9 weeks following a cycle of VP-16 and prior to initiating the next cycle of chemotherapy.

Neuroradiographic response criteria were as follows: a complete response (CR) required disappearance of all lesion(s). A partial response (PR) required a greater than 50% decrease in the product of greatest orthagonal diameters of each measurable lesion on cranial enhanced MR. In addition, dose of steroids, if any, must have been stable or decreased, and the neurological examination must have been stable or improved to warrant a complete or partial response. Stable disease (SD) required less than 50% decrease in the product of greatest orthagonal diameters of each measurable lesion or demonstrated no significant change on enhanced cranial MR imaging. Progressive disease (PD) required a 25% increase in the greatest product of orthagonal diameters of any measurable lesion, the appearance of a new lesion, or deterioration of the neurological examination not explained by other causes. The time to tumor progression was measured as the interval from entry on study until documentation of PD.

In patients with SD, PR or CR, an additional cycle of VP-16 was initiated following which patients were assessed again as described above. Patients with PD were removed from study.

Results

50% (6/12) of patients responded to chronic oral VP-16 including: 1 CR; 3 PR and 2 SD. Response duration range from 4–20 months with a median of 8 months. Excluding patients with SD, 33% (4/12) of patients demonstrated complete or partial responses with a median duration of response of 10 months. In responding or stable patients, Karnofsky performance status changed no more than 10% of initial score at time of VP-16 initiation. 82% (10/12) patients have died as a result of progressive tumor. Following clinical or radiographic documentation of PD, median survival was 7 weeks with a range of 3–10 weeks.

Treatment-related toxicity included: partial alopecia (5/12); diarrhea (5/12); weight loss (4/12); thrombocytopenia (4/12); neutropenia (2/12). Diarrhea was managed with oral anti-diarrheals. Weight loss amounted to no more than 15% of pre-treatment weight and may have been mitigated by concurrent dexamethasone use. Thrombocytopenia (range 25–80,000/mm^3; median 40,000/mm^3) and neutropenia (1,200–3,000/mm^3, median 2,100/mm^3) were sufficiently mild and transient so as not to result in a delay of therapy or require parenteral support (i.e. platelet transfusion or antibiotic treatment of neutropenic fever). No treatment-related deaths occurred.

Discussion

The rationale for investigating the use of VP-16 beyond the 3–5 day standard intravenous dosage schedule is based on 3 major considerations: the mechanism of action, pre-clinical studies and clinical data [40–44].

VP-16 appears to be a relatively phase specific agent that inhibits cells in the G_2 phase of the cell cycle [23, 24, 27, 40]. Even at low concentrations, VP-16 induces single strand and double strand DNA breaks. Recently, VP-16 has been shown to damage DNA by interacting with the enzyme topoisomerase II [23, 27]. This enzyme normally catalyzes DNA form interconversions by introducing a transient enzyme bridged, double strand break on one or two crossing DNA segments. By stabilizing the DNA-topoisomerase II complex, VP-16 prevents DNA strands from rejoining, resulting in double strand breaks. Topoisomerase II is most active during the G_2 phase of the cell cycle, thus accounting for cell cycle specificity of VP-16. It appears that the interaction of VP-16 with topoisomerase II is reversible once the VP-16 concentration falls below a critical level. Reversal of the topoisomerase II ● VP-16 complex would allow subsequent DNA repair and decreased cytotoxic-

ity. It would follow that prolonged exposure to a critical VP-16 concentration would enhance the anti-neoplastic activity of the drug both by the cell cycle specific mechanism of action and by prolonging it's interaction with topoisomerase II [26, 27, 44].

Several years ago, the schedule dependency of VP-16 was demonstrated in the treatment of L1210 ascites tumors in mice [23, 24, 27]. Several schedules were investigated and intermittent schedules with dosing intervals of 2–5 days were found superior to a single dosing schedule. Despite the fact that VP-16 is active against many neoplastic diseases, most clinical data supporting schedule dependency involve small cell lung cancer patients. Greco performed a phase I study to determine the maximum tolerated dose of VP-16 administered orally for 21 consecutive days [44]. In these heavily pre-treated patients, the maximum tolerated etoposide dose was 50 mg/m^2/day. Myelosuppression was the dose-limiting toxicity. Leukocyte count nadirs occurred between days 22 and 29 and most patients were able to resume VP-16 by day 36. No evidence of cumulative toxicity were seen in patients receiving multiple courses. The only other common side effect was alopecia. Phase II studies are presently in progress evaluating chronic oral etoposide administration in the treatment of lymphoma, germ cell tumors, small cell lung cancer, ovarian carcinoma, relapsed acute leukemia and renal cell carcinoma [26].

There is a limited experience in the use of topoisomerase inhibitors in the treatment of malignant brain tumors. VP-16 appears to be modestly active as evaluated in a single uncontrolled study by Garbino and Gorgon Fiery in 1984 [36]. In this study VP-16 was compared with historic controls and believed to be an effective single agent. Two controlled trials utilized VM-26, another topoisomerate inhibitor (Seiler in 1980 and the EORTC consortium in 1981), comparing VM-26 and CCNU as a chemotherapy regimen treatment with radiation therapy only, and no statistical advantage could be shown in median time to tumor progression [29, 35]. However, both studies suffer from relatively small sample size. Skylanski *et al.* in 1974 studied VP-16 in a pediatric patient population, although only a single patient was eligible for evaluation by brain scan criteria and was believed to have a response [30]. The largest study of VP-16 in recurrent malignant brain tumors was a phase II study reported by Terelli in 1984 [32]. 22 consecutive patients with recurrent malignant brain tumors after failing prior radiation therapy and systemic combination chemotherapy with BCNU and vincristine were treated with intravenous VP-16 on an escalated dose schedule given daily for 5 consecutive days every 3 weeks. Response was seen in 17% of patients; an additional 17% of patients manifested stable disease. Overall median survival from start of therapy was 4.5 months whereas patients with either responding or stable disease had a median survival of 8 months.

In 1989 Finlay utilized dose intensive VP-16 and thio-TEPA followed by autologous bone marrow transplantation for recurrent previously treated primary brain tumors and a response rate of 60% was reported [45]. A similar experience with VM-26 for recurrent brain tumors was reported by Giannone in 1983 [46]. This study used dose intensive hydroxyurea and VM-26 followed by autologous bone marrow transplantation, a 17% response rate was reported. Four other studies are reported in abstract form and suggest VP-16 when used in combination with other chemotherapeutic agents may be efficacious in patients both with recurrent primary brain tumors and in an adjuvant setting. These studies have utilized cis-platin and VP-16 (Kovnar, 1989); cytosine arabinoside and VP-16 (Corden, 1989); VP-16 and carboplatin (Don Francesco, 1989); and vincristine and VP-16 (Pons, 1990) [33, 34, 47, 48]. A total of 54 patients have been studied and demonstrated an overall response plus disease stabilization rate of approximately 40%. Assessing the contribution of VP-16 to this observed response rate is difficult in that all 4 studies employed combination chemotherapy.

The present small study suggests activity of VP-16 as a single agent when used with a chronic oral dosing schedule in recurrent brainstem gliomas. Further substantiation of the activity of VP-16 against recurrent brainstem tumors will require a

larger patient study group. The modest myelosuppression observed with daily oral VP-16 may allow combination therapy with agents demonstrating synergy and independent anti-neoplastic activity against glial tumors.

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