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Phase II Study of Daily Oral Etoposide in Children With Recurrent Brain Tumors and Other Solid Tumors

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Pre-clinical data and adult experience suggests that topoisomerase targeted anti-cancer agents may be highly schedule dependent, and efficacy may improve with prolonged exposure. To investigate this hypothesis, 28 children with recurrent brain and solid tumors were enrolled in a phase II study of oral etoposide (ETP).

Patients were prescribed ETP at 50 mg/m^2/day for 21 consecutive days. Courses were repeated every 28 days pending bone marrow recovery. Evaluation of response was initially performed after 8 weeks and then every 12 weeks either by CT or MRI.

Three of 4 patients with PNET (primitive neuroectodermal tumor)/medulloblastora achieved a partial response (PR). Two of 5 with ependymoma responded, one with a complete response and one with a PR. Toxicity was manageable with only 1 admission for fever and neutropenia in 120 cycles of therapy. Five patients had grade 3 or 4 neutropenia. One had grade 4 thrombocytopenia and one grade 2 mucositis and withdrew as a result. One patient had grade 2 diarrhea. Two patients who achieved a PR had received ETP as part of prior combination chemotherapy regimens.

Daily oral etoposide is active in recurrent PNET/medulloblastoma and ependymoma. Toxicity is manageable and rarely requires intervention. Daily oral etoposide in combination with crosslinking agents should be considered in future phase III trials. Determination of activity in glioma and solid tumors is not complete. Med. Pediatr. Oncol. 29:28–32, 1997.
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Key words: etoposide; children; medulloblastoma; ependymoma; glioma; brain tumor

INTRODUCTION

Etoposide is a semisynthetic glycosidic derivative of the extract from the roots and rhizomes of the May apple or mandrake plant, *Podophyllum peltatum.* The cytotoxic activity of the parent compound, epipodophyllotoxin, was recognized in the early 1940s, but its clinical utility was limited by toxicity. Two glycosidic derivatives, etoposide and teniposide, have demonstrated high levels of clinical activity, with acceptable toxicity, in a wide range of malignancies, including leukemias, Ewing's tumor, lymphoma, and small-cell lung carcinoma [1].

Initially, the mechanism of action of etoposide and teniposide was thought to be mitotic arrest through binding to tubulin, at a distinct site from the vinca alkaloids [2]. Subsequent data clarified the target as the topoisomerase II-DNA reaction intermediate, referred to as the cleavable complex [3]. The nuclear enzyme topoisomerase II binds to DNA and forms rapidly reversible DNA strand breaks which reduce torsional strain during DNA unwinding and facilitate strand segregation following DNA replication [4]. The presence of etoposide serves to stabilize the reaction intermediate, converting the cleavable complex into a double-stranded DNA break [5]. The double-stranded breaks, if not repaired, lead to cell death [6]. It is important to note that the bond between etoposide and the cleavable complex is noncovalent and rapidly reversible [7]. Therefore, if etoposide is removed prior to an irreversible commitment to cell death, fewer cleavable complexes will remain and the cytotoxic effect will be reduced. Based on the pro-

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posed mechanism of action, it was reasonable to speculate that etoposide cytotoxic activity would be increased by prolonged drug exposure.

Schedule-dependent cytotoxicity for etoposide has been the subject of considerable laboratory and clinical investigation. In a comprehensive study of etoposide dose and schedule efficacy in a murine L1210 subcutaneous tumor model, Dombernowsky and Nissen observed that prolonged treatment (e.g., daily × 5 days) was superior to brief treatment (e.g., single parenteral bolus) when a *single* course of etoposide was administered. However, *continuous* treatment with etoposide (i.e., single bolus every 4 days × 5 courses) was superior to all single course schedules, yielding the greatest percentage of ''cured'' animals [8]. Sixteen years later, Slevin and co-workers demonstrated the superior clinical activity of 5-day consecutive treatment over 1-day treatment in patients with small-cell lung cancer [9]. Toxicity was comparable in the two treatment arms.

Recent studies in adult cancer patients suggest that daily oral administration of etoposide for prolonged intervals, e.g., 21 days, may be an effective schedule. Response rates of 60% have been reported in adult patients with recurrent non-Hodgkin's lymphoma, even in patients who were refractory to higher doses of etoposide administered over 1 to 3 days [10]. These findings led investigators to conclude that additional clinical studies of etoposide antitumor activity after prolonged intravenous or daily oral administration are warranted in other tumors, including those for which intermittent parenteral etoposide dose schedules yielded low tumor response rates.

Although etoposide has been incorporated into a number of treatment protocols for pediatric brain tumors, there is little data regarding the objective response rate for single agent i.v. bolus etoposide in childhood brain or solid tumors. However, published experience with other tumors suggests that etoposide cytotoxicity may be more schedule-dependent than dose-dependent. To address this question, we conducted a phase II clinical trial of daily oral etoposide in children with recurrent or progressive brain and solid tumors. The starting etoposide dose used in this study, 50 mg/m^2/day × 21 days, was lower than the phase I maximum tolerated dose (60 mg/m^2/day) for daily oral etoposide in children reported by Mathew and colleagues at St. Jude Children's Research Hospital [11]. In the St. Jude study, patients with refractory solid tumors were given escalating doses of oral etoposide daily for 21 days on a t.i.d. schedule. The small individual doses required the use of the intravenous injection diluted 1:2 for oral administration [12]. For the present study, patients were given the total daily dose of 50 mg/m^2/day in a single daily oral administration, usually using the 50-mg capsules.

METHODS

Twenty-nine patients with recurrent brain or other solid tumors from two pediatric cancer centers were entered on study from October 1993 until May 1995. Study entry criteria included: age less than 21 at original diagnosis, normal bone marrow, hepatic and renal function, life expectancy greater than 8 weeks, ECOG performance scale 0–2 (in bed less than 50% of the day or better), and histologically proven tumor which had recurred following standard therapy. All children with PNET/medulloblastoma and ependymoma had failed external beam irradiation and combination chemotherapy either as part of initial therapy or as part of a prior salvage regimen. The patients with optic pathway glioma all had prior treatment with at least carboplatin and vincristine. The patients with brainstem glioma were all previously treated with involved field irradiation. The patients with malignant solid tumors had all had prior treatment with at least 2 regimens of combination chemotherapy and (excepting osteosarcoma) irradiation. Histologic verification was waived for patients with neuroimaging evidence characteristic for optic pathway and diffuse pontine tumors. All patients had measurable disease on MRI. No patient received any concurrent adjuvant therapy. No patient had neurofibromatosis. All patients had an informed consent approved by the institutional review board of the treating institution signed by a parent or guardian.

The starting dose of etoposide was 50 mg/m^2 administered as a single daily oral dose for 21 days followed by a 7-day rest. In an attempt to treat as many patients as possible with the 50-mg capsules, patients whose body surface area was not within 12.5% of 1 or 2 m^2 were given discontinuous dosing, resulting in an approximation of the 50 mg/m^2 dose. For example a patient who was 1.5 m^2 was given 100 mg alternating with 50 mg on a daily basis. Small children who could not swallow capsules were given the solution for injection by mouth. For these children, the dose was calculated exactly. Patients with stable or improving disease who had hematologic recovery (ANC >1,000/mm^3, platelet count >100,000/mm^3) on day 28 began a second course. Patients whose ANC remained >1,000/mm^3 and whose platelet count remained >100,000/mm^3 throughout the first course had their dose increased by 25% for subsequent cycles. Patients who experienced grade 4 hematologic toxicity at any time during a course of therapy had a dose reduction of 25% for the subsequent course. Patients continued on etoposide for 52 weeks or until tumor progression.

Patients were monitored carefully for response and toxicity. To identify tumor responses, computed tomography (CT) or magnetic resonance imaging (MRI) was performed after the second course of therapy and every 12 weeks thereafter. Brain tumor patients were followed

TABLE I. Response Data[a]

Disease (n = 28)	Number	CR	PR	SD	PD
PNET/medulloblastoma	4	0	3	0	1
Ependymoma	5	1	1	2	1
Optic pathway	3	0	0	3	0
Malignant glioma	3	0	0	0	3
Brainstem glioma	3	0	0	1	2
Ewing's sarcoma	4	0	0	0	4
Osteosarcoma	2	0	0	1	1
Other	4	0	0	0	4

[a]Other includes one patient each with ganglioglioma, neuroblastoma, rhabdomyosarcoma, and schwannoma.

exclusively with MRI. Patients were initially seen weekly for a physical exam and complete blood count. A chemistry profile was performed at the start of each cycle. Once a pattern of mild myelosuppression (≤grade 2) was established in an individual patient, CBC could be performed on alternate weeks. Toxicity was graded using the common toxicity criteria of the National Cancer Institute.

Standard response criteria were used. Complete response (CR) was defined as disappearance of all tumor on CT or MRI. Partial response (PR) was defined as at least 50% decrease in the product of the two greatest diameters on CT or MRI. Stable disease was defined as <50% decrease in the product of the two greatest diameters on MRI but no evidence of an increase in tumor size and no new tumor foci distant from the primary tumor. Progressive disease was defined as any evidence of an increase in the product of the two greatest diameters on MRI or evidence of new tumor foci distant from the primary tumor. To qualify as an objective response, patients on corticosteroids had to be on a stable or decreasing dose of steroid. For patients with optic pathway glioma only, all of whom were progressing at the time of study entry, the duration of stable disease (growth arrest) was also recorded since use of chemotherapy to delay the start of radiation therapy may represent an important therapeutic benefit for these children.

RESULTS

Twenty-nine patients were entered on study during an 18-month period and are evaluable for toxicity. One boy with medulloblastoma was taken off study at 1 month and went on to autologous bone marrow transplantation. Of the 28 patients evaluable for response, there were 9 girls and 19 boys. Mean age was 11.5 years (range 2–20). Twenty patients had primary brain tumors and 9 had extraneural solid tumors. Histologic diagnosis and objective response data are reported in Table I. Of the four evaluable patients with PNET/medulloblastoma, three achieved a partial response, two lasting for 6 months, and the third had radiotherapy implants to the tumor bed after achieving a PR. Of the five patients with ependymoma, one achieved a CR (Fig. 1), which failed to progress for 14 months, and another a PR lasting for 5 months. There were no responders in brainstem glioma, supratentorial malignant glioma, or the limited number of patients with solid tumors. Although none of the patients with progressive optic pathway glioma had an objective response to etoposide, all three had stable disease. Two have been stable for over 2 years and the third was stable at 3 months when he was removed from study secondary to severe mucositis. This patient proceeded directly to radiation therapy.

Five patients responded to oral etoposide and two of these had prior exposure to intravenous etoposide. One of five patients with medulloblastoma had prior exposure to etoposide and that patient responded to oral etoposide. Four of five patients with ependymoma received prior etoposide, one of whom responded to oral etoposide on this study.

Toxicity was manageable with only one patient requesting to be removed from study due to grade 2 mucositis (Table II). Most patients had little or no toxicity. In 120 courses of chemotherapy given to 29 patients, only 4 patients had a platelet count drop below 100,000/mm^3, 1 patient had a platelet count drop below 25,000/mm^3, and only 3 patients had an ANC drop below 500/mm^3. Complete blood counts were obtained weekly and it is possible that the true nadir was missed. There was one admission for fever and neutropenia and no episodes of bacteremia. One patient had grade 2 diarrhea.

DISCUSSION

Etoposide is an active agent in the treatment of various malignancies. Unfortunately the optimal dose and schedule remain unsettled, and may depend on the tumor studied. Prolonged administration of etoposide may improve its therapeutic index. For example, Hainsworth and colleagues demonstrated a 60% response rate in patients with recurrent non-Hodgkin's lymphoma regardless of prior exposure to short course etoposide [10]. This response rate is nearly twice that demonstrated for short-term therapy. In small-cell lung cancer, the response rate of oral etoposide has been reported to be 45% compared to response rates of 10% in short course administration [13]. These studies indicate that the optimal dose and schedule have not been systematically evaluated.

The earliest studies of etoposide in childhood cancer observed responses in leukemia and various solid tumors. Chard and colleagues in the Children's Cancer Study Group treated 126 children with recurrent cancer with 75–125 mg/m^2/day i.v. for 5 days [14]. Responses were noted in 8 of 78 leukemia patients, all but one in acute non-lymphoblastic leukemia. Ten of 48 patients with solid tumors responded including lymphoma, neuroblastoma, Wilms' tumor, rhabdomyosarcoma, and Ewing's sarcoma. Rivera and colleagues at St. Jude Children's

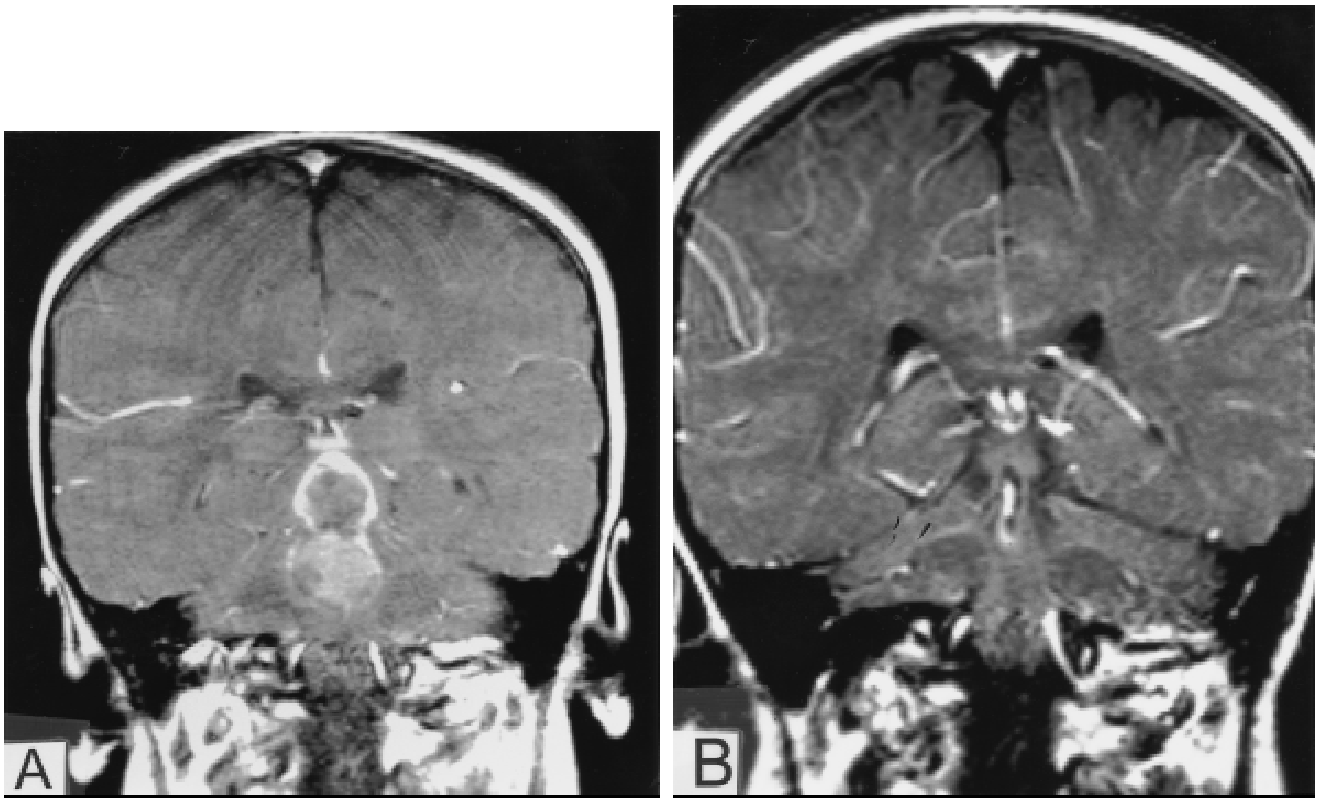

Fig. 1. Enhanced T1 weighted magnetic resonance images of patient with a recurrent ependymoma immediately following partial resection **(a).** The residual tumor, with enhancement at the periphery, is seen superior to the operative cavity. After 12 cycles of oral etoposide **(b)** the residual tumor is no longer evident.

TABLE II. Toxicity Data

	Grade		
Toxicity (n = 29)	2	3	4
Neutropenia	3	2	3
Thrombocytopenia	4	0	1
Mucositis	1	0	0
Diarrhea	1	0	0

Research Hospital studied 39 children with either etoposide, teniposide, or both given on a twice weekly schedule [15]. Patients were randomly assigned to receive one agent, and if after 2 to 4 weeks were unresponsive, were given the alternate agent. Five patients with leukemia responded to etoposide. None of 10 patients with a solid tumor responded to either agent. No patient with a brain tumor was treated on either study.

The subsequent pediatric experience with etoposide for brain tumors remains limited. Pons and associates treated 20 children with etoposide (100 mg/m^2 daily × 5) and vincristine for low-grade glioma [16]. One patient had an objective (partial) response. The Children's Cancer Group evaluated the activity of Etoposide (100 mg/m^2 i.v. daily × 5) with or without mannitol disruption of the blood brain barrier for children with recurrent brain tumors. Objective responses (CR + PR) for the two treatment groups combined were observed in 6 of 35 patients with medulloblastoma, 2 of 14 with low-grade glioma, 2 of 18 with high-grade glioma, and 2 of 20 with brain stem glioma (Kobrinsky, personal communication). By contrast, Chamberlain reported more encouraging results in children with recurrent optic pathway tumors or brain stem glioma treated with daily oral etoposide. Objective responses were noted in 5 of 14 children with recurrent chaismatic-hypothalamic glioma; three additional patients had stable disease for at least 6 months [17]. For children with recurrent brain stem glioma, 4 of 12 had an objective response [18].

In the present study three patients with PNET/medulloblastoma responded to daily oral etoposide with greater than 50% tumor shrinkage. The duration of these responses exceeded 6 months. Two patients with ependymoma responded, one had a complete response lasting more than 1 year. Although the number of patients in this study does not allow an accurate estimate of the true response rate, our results in medulloblastoma and ependymoma suggest that daily oral etoposide has clinically significant activity for these primary brain tumors. Furthermore, our responses to oral etoposide in patients who were previously treated with intravenous etoposide, demonstrates that resistance to short course (5 day) intrave-

nous etoposide does not preclude response to daily oral etoposide.

In contrast to published reports of objective responses in patients with brain stem gliomas and optic pathway tumors treated with daily oral etoposide [17,18], we did not observe responses in either of these tumors. In addition, no responses were noted in any solid tumors outside the brain. The lack of response in brainstem glioma, though discouraging, remains an all-too-common result. However, our finding of prolonged clinical stability in patients with optic pathway tumor deserves further comment. In the young patient with optic pathway glioma, a major goal of chemotherapy often is the delay of radiation therapy to the developing brain [19]. Daily oral etoposide may have clinical benefit in achieving this goal with manageable acute toxicity. However, treatment of optic pathway/hypothalamic low-grade gliomas with carboplatin and vincristine has shown significant objective response rates in addition to achieving the goal of delaying radiation therapy [20].

Bioavailability after oral administration is a function of dose, and at doses higher than 50 mg/m^2 bioavailability decreases. At the dose used in this study, bioavailability can be estimated to be 76% [21]. There is, however, 3-fold interpatient variability. The standard dose for children is often 100 mg/m^2 i.v. daily for 5 days, for a total of 500 mg/m^2 every 28 days. In the present study patients received 50 mg/m^2/day p.o. for 21 days yielding a net effective dose of approximately 800 mg/m^2 every 28 days (50 × 0.76 × 21). The estimated 50% increase in the dose intensity of etoposide did not result in unmanageable toxicity. An assessment of long-term risks is beyond the scope of this study. The primary risk factors associated with etoposide related secondary acute myelogenous leukemia, (11q23 translocation), remains unclear. However, the risk of secondary AML is an important issue, especially in patients with low-grade tumors where long-term survival is expected.

In summary, daily oral etoposide, at the dose of 50 mg/m^2/day for 21 consecutive days followed by a 7-day rest is well tolerated and active in medulloblastoma/PNET and in ependymoma. An interesting approach for further study would be the replacement of short course etoposide for daily oral etoposide in a randomized study, perhaps for high-risk PNET. Such a study would allow a direct assessment of etoposide schedule dependent activity in a childhood brain tumor demonstrated to be etoposide responsive.

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