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Treatment of Patients With Pineoblastoma With High Dose Cyclophosphamide

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The outcome for patients with pineoblastoma has historically been very poor, with most patients dying of disseminated disease despite irradiation. Furthermore, the low incidence of this tumor has hindered progress toward defining better treatment strategies. Here we report the activity and toxicity of cyclophosphamide administered as a single agent at a dose schedule of 2 g/m^2/day for 2 successive days at monthly intervals for a maximum of four courses. Eight patients were evaluated, six newly diagnosed and two recurrent. Amongst the six newly diagnosed patients, there were three patients demonstrating partial responses, and three had stable disease throughout the cyclophosphamide treatment period. All six patients are alive and disease free after further therapy. One patient with recurrent disease demonstrated tumor progression on cyclophosphamide, and the other had stable disease throughout the cyclophosphamide treatment period. Both patients subsequently died of progressive disease. The major toxicity of high dose cyclophosphamide was hematopoietic, with one patient requiring a dose reduction after three courses due to prolonged thrombocytopenia. One patient was also withdrawn from treatment with cyclophosphamide due to impaired pulmonary function. This study demonstrates the activity of high dose cyclophosphamide in the treatment of pineoblastoma and may serve as basis for the design of future studies of this tumor.

Key words: pineoblastoma, cyclophosphamide, neoadjuvant chemotherapy

INTRODUCTION

Tumors of the pineal region are rare, accounting for only 2% of all primary central nervous system (CNS) tumors in children, and pineoblastomas account for only 9% of all the malignancies encountered in this location [1,2]. This tumor displays histologic features and biological behaviour, such as local invasion and leptomeningeal dissemination, similar to medulloblastoma, although it is associated in young children with a worse prognosis [3]. Thus, it is considered by many a member of the primitive neuroectodermal tumor family of CNS malignancies [2,4].

The management of patients with this rare tumor is evolving. Historically, irradiation was the mainstay of therapy and when used alone was associated with a dismal outcome, with only 25% or less of patients surviving [1]. Whilst few reports of the treatment of this tumor exist, more recently a multimodal approach to therapy has been described, with patients undergoing combinations of resection, neoadjuvant or adjuvant chemotherapy, and irradiation [4–10]. The scarcity of pineoblastoma makes large clinical trials evaluating phase 2 or 3 chemotherapeutic approaches an impractical task. Thus, in order to precisely define agents with activity in these tumors, it is important to consider experience with single drugs in trials with small cohorts of patients.

Alkylating agents have been demonstrated to have activity in a wide variety of pediatric CNS malignancies in both laboratory and clinical studies [5,11–13]. Cyclophosphamide displays activity against medulloblastoma

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in phase 2 trials of patients with recurrent or newly diagnosed disease [5,12,14]. Furthermore, treatment of patients with recurrent medulloblastoma with high dose cyclophosphamide (2 g/m^2/day for 2 days) administered with GM-CSF or G-CSF resulted in responses in 9 of 11 patients [15], suggesting the capacity to overcome alkylator resistance in these tumors through dose escalation. In this report we describe the activity and toxicity of high dose cyclophosphamide in the treatment of eight patients with newly diagnosed or recurrent pineoblastoma.

CLINICAL MATERIALS AND METHODS

Patient Sample

All patients reported here, other than patient 5, were a subset from a larger population treated on one of two studies: a phase 1 dose escalation study of cyclophosphamide and GM-CSF in patients with recurrent or persistent primary CNS neoplasms or a phase II trial of cyclophosphamide and GM-CSF in the treatment of recurrent, progressive, or persistent childhood brain tumors. All patients on study were enrolled after written informed consent and under the supervision of the Duke University Medical Center institutional review board. All eight patients reported had histological confirmation of pineoblastoma with central review (R.M.), and seven patients had magnetic resonance imaging (MRI) documentation of measurable tumor. One patient had computerized tomographic (CT) imaging. All patients had spinal axis evaluation, seven with MRI and one with myelography. The life expectancy of all eight patients was at least 8 weeks, and their Karnofsky or Lansky score at least 60%. Minimal hematological values prior to therapy included a hemoglobin over 8.0 g/dl, an absolute neutrophil count (ANC) over 1,500/ml, and a platelet count over 100,000 cells/ml. Patients enrolled on these two studies were required to have serum creatinine less than 2.0 mg/dl, SGOT and a bilirubin less than 1.5 × normal values, adequate pulmonary function as measured by diffusing capacity (DLCO, $\geq$75% predicted), resting cardiac ejection fraction >55% with normal wall motion on gated nuclear angiography scan, and recovery from the acute toxicity of any recent therapy. Prior treatment with radiation must have been completed at least 12 weeks prior to this evaluation.

Treatment Schedule

The objective was to evaluate patients treated with cyclophosphamide administered in a dose of 2 g/m^2/day for two successive days at monthly intervals for a total of four courses. Cyclophosphamide was administered over a 1 hour period with high volume intravenous fluids (2× maintenance) and Mesna protection of the urogenital tract. Patients received growth factor support with either GM-CSF or G-CSF to ameliorate neutropenia. GM-CSF was administered subcutaneously at a dosage of 2.50mg/m^2 per dose twice daily and beginning on day 3 of each cycle of therapy. G-CSF was administered subcutaneously at a dose of 10 mg/kg daily beginning on day 3, and patient 5 received only 5 mg/kg daily of G-CSF. Treatment with GM-CSF or G-CSF continued until the ANC exceeded 1,000 cells/ml on two consecutive determinations after the chemotherapy-associated nadir. Cycles of chemotherapy were repeated every 4 weeks, provided that hematological recovery had occurred (ANC >1,000 cells/ml, platelets >100,000 cells/ml).

Response Evaluation

Patients were evaluated by neurological examination prior to each course of therapy. MRI or (CT) scan of the brain and spine if indicated was performed following cycles 2 and 4. MRI scans were performed pre- and post-gadolinium contrast.

Responses were defined by previously described standard radiographic criteria: Complete response (CR) was defined as complete resolution of all lesions and no clinical progression. Partial response (PR) was defined as greater than 50% reduction in the product of the maximum perpendicular diameters of all lesions and no clinical progression. Stable disease (SD) was defined as a less than 50% reduction and a less than 25% increase in size with no clinical deterioration, and progressive disease (PD) was defined as greater than 25% increases in such dimensions.

Toxicity Evaluation

Complete blood counts, including differential leukocyte counts, and platelet counts were performed twice weekly, or more frequently if indicated. Renal function, hepatic enzymes, and serum electrolytes were checked prior to each course to assess nonhematological toxicity. For those patients enrolled on study, pulmonary function tests were performed prior to each course, and a gated angiography scan was performed prior to every other course and at the completion of therapy.

RESULTS

Patient Characteristics

Eight patients were treated with cyclophosphamide, six patients with newly diagnosed disease and two patients with recurrent tumors (Table I). The patients consisted of six males and two females, with ages ranging from 3 to 23 years (median 21 years). The six patients with newly diagnosed disease were treated prior to cyclophosphamide, with surgery consisting of partial resection confirmed radiographically within 3 days of craniotomy. Metastatic workup was positive for a subarachnoid lesion

TABLE I. Summary of Patient Demographics

Patient no.	Disease status	Age/sex	Previous therapy	Sites of disease
1	Newly diagnosed	F/23	Biopsy	Pineal/C2 metastasis
2	Newly diagnosed	M/23	Partial resection	Pineal
3	Newly diagnosed	M/19	Partial resection	Pineal
4	Newly diagnosed	M/21	Partial resection	Pineal
5	Newly diagnosed	F/22	Partial resection	Pineal
6	Newly diagnosed	M/21	Partial resection	Pineal
7	Recurrent	M/3	Biopsy/RT	Pineal
8	Recurrent	M/17	Partial resection/RT/ CBDCA & VP-16; VCR & CTX	Pineal/leptomeningeal/C2/T9

RT = craniospinal irradiation with tumor boost; CTX = cyclophosphamide; CBDCA = carboplatin; VCR = vincristine.

TABLE II. Summary of Treatment and Response

Patient no.	Disease status	Treatment	Response after 2 courses	Response after 4 courses
1	Newly diagnosed	(2.0 g/m^2/day CTX × 2) × 3 (1.5 g/m^2/day CTX × 2) × 1	PR[a]	PR[a]
2	Newly diagnosed	(2.0 g/m^2/day CTX × 2) × 4	PR	PR
3	Newly diagnosed	(2.0 g/m^2/day CTX × 2) × 2	PR[b]	
4	Newly diagnosed	(2.0 g/m^2/day CTX × 2) × 4	SD	SD
5	Newly diagnosed	(2.0 g/m^2/day CTX × 2) × 4	SD	SD
6	Newly diagnosed	(2.0 g/m^2/day CTX × 2) × 3	SD[c]	
7	Recurrent	(2.5 g/m^2/day CTX × 2) × 1	PD[d]	
8	Recurrent	(2.0 g/m^2/day CTX × 2) × 4	SD	SD

CTX = cyclophosphamide; SD = stable disease; PR = partial response; PD = progressive disease.
[a]Complete resolution of C2 lesion after four courses, PR of pineal tumor.
[b]Proceeded to radiotherapy at patient's request.
[c]Decreased pulmonary function after three courses.
[d]Clinically and radiographically progressed after one course and removed from therapy.

TABLE III. Summary of Subsequent Treatment and Outcome

Patient no.	Disease status	Subsequent treatment	Weeks	Outcome
1	Newly diagnosed	RT/ABMT	131+	Alive: no evidence of disease
2	Newly diagnosed	RT/ABMT	78+	Alive: no evidence of disease
3	Newly diagnosed	RT/ABMT	63+	Alive: no evidence of disease
4	Newly diagnosed	RT/ABMT	113+	Alive: no evidence of disease
5	Newly diagnosed	RT/stereotactic RT	56+	Alive: no evidence of disease
6	Newly diagnosed	RT/CCNU/VCR/Pred.	97+	Alive: no evidence of disease
7	Recurrent	None	19	Dead
8	Recurrent	IT 4HC	38	Dead

RT = Craniospinal irradiation with tumor boost; ABMT = autologous bone marrow transplant; CCNU = lomustine; VCR = vincristine; Pred. = prednisolone; IT 4HC = intrathecal 4 HC.

at C2 in one newly diagnosed patient, and one patient with recurrent disease had widespread leptomeningeal, C2, and T9 metastases.

Treatment Response

All of the six newly diagnosed patients were evaluated after the first two courses of cyclophosphamide (Table II), with three patients demonstrating partial responses and three patients demonstrating stable disease. Three of these six patients completed the full four courses of high dose cyclophosphamide as planned. Patient 6 received only two courses due to pulmonary toxicity, (see later). Patient 3 demonstrated a PR after only two courses and proceeded to radiotherapy at parental request. Patient 1 received three full courses and one further course, which was dose reduced in response to prolonged thrombocytopenia after course 3.

Evaluation after the fourth course in the three patients completing therapy revealed a continuing response in one patient and continued stable disease in the remaining two.

Patient 1 demonstrated a further partial response after the fourth course of cyclophosphamide, which was given at a reduced dose. This response included complete resolution of the C2 metastasis (Fig. 1).

Two patients received cyclophosphamide after failing prior irradiation or chemotherapy (Table II). Patient 7 was demonstrated to have progressive disease after a single course of 2.5 g/m^2 of cyclophosphamide daily for two doses and was withdrawn from further treatment. Patient 8 received a full four courses of high dose cyclophosphamide and demonstrated stable disease through this treatment period.

Modifications to Therapy and Toxicity

A total of 24 courses of cyclophosphamide were administered to these eight patients. Four patients (patients 2, 4, 5, and 8) received all four courses of high dose cyclophosphamide without modification. The most common toxicity was hematological. Grade 4 granulocytopenia (ANC <200 cells/ul) occurred following 18 courses requiring hospital admission for fever and neutropenia on 10 occasions. Specific infections during therapy included two episodes of pseudomonas bacteremia, one shunt infection, and one cellulitis of the finger. There was 16 episodes of grade 4 thrombocytopenia (platelet count <20,000 cells/ul) requiring platelet transfusion, and the patients required a total of 12 transfusions of packed cells. After three courses of high dose cyclophosphamide, patient 1 had prolonged thrombocytopenia requiring transfusion. Thus, a fourth course of only 1.5 g/m^2 × 2 was administered. Patient 6 was found to have reduced pulmonary function after three courses of high dose cyclophosphamide were administered. This patient had no prior history of pulmonary disease, however, was a heavy cigarette smoker prior to therapy. He showed a reduction in functional residual capacity from 95% to 64% and of DLCO from 163% to 51%. Thus, no further cyclophosphamide was administered to this patient. In the remainder of patients pulmonary function remained normal. No patients had evidence of cardiotoxicity or hematuria.

Subsequent Treatment and Outcome

The six patients with newly diagnosed tumors were treated with craniospinal irradiation and a boost to the primary site; patient 5 has also received stereotactic radiosurgery. Four patients received autologous bone marrow rescue with cyclophosphamide and melphalan (three patients), or with busulphan and melphalan (one patient). One patient did not proceed to bone marrow rescue due to insurance difficulties and has received adjuvant chemotherapy. All patients are alive with no evidence of disease. Both patients who were treated for recurrent disease have died of progressive tumor (Table III).

DISCUSSION

Tumors of the pineal region represent a number of different histological variants with diverse clinical behaviour. Due to technical limitations, until recently these tumors were usually managed with a course of empiric radiotherapy without prior biopsy. This historical approach, along with the scarcity of pineoblastomas, has limited the acquisition of useful clinical data. Analysis of published retrospective reports during the era of such treatment suggests that radiotherapy alone offers a very slim chance of survival to patients suffering from pineoblastoma, with the vast majority of patients dying within 2 years from diagnosis [16–18]. Of seven patients reported by the Children's Cancer Group treated with mainly local irradiation, six have died, two with disseminated disease [17]. Linggood and Chapman reported only one survivor at 6 years from diagnosis of four patients treated with radiotherapy, three of whom had craniospinal treatment [18].

Most recently the potential role of chemotherapy has emerged in several reports, albeit with very small patient numbers (4, 6, 7, 9, 10, and 16). The use of adjuvant chemotherapy was reported by Packer et al., in that series of five patients reported, four received chemotherapy and two were alive at 2 years [1]. Several groups have reported the use of preirradiation chemotherapy in small numbers of patients with objective responses reported [4,10,19]. Kovnar et al. [10] reported two patients with lasting responses to preirradiation cisplatin and etoposide, and Ghim et al. [4] reported similar results in two of three patients treated with neoadjuvant etoposide, cisplatin, and vincristine.

Unfortunately the use of adjuvant chemotherapy has not resulted in increased survival [1,7,20], in children less than 3 years old, who have a uniformly dismal prognosis [3,8]. The only promising, although preliminary, results using adjuvant chemotherapy were conducted by the Children's Cancer Group, who reported 76% progression-free survival at 3 years [8]. However, further advances in the chemotherapy of patients with pineoblastoma are essential.

The current study was designed to build on prior studies demonstrating cyclophosphamide activity against medulloblastoma [5,12,14,15] germinoma [21] and astrocytoma of both high and low grade [13]. Furthermore, it builds on previous studies confirming both acceptable toxicity [22] and increased activity against medulloblastoma [15] associated with growth factor supported dose escalation of cyclophosphamide. Treatment of patients with recurrent medulloblastoma with high dose cyclophosphamide treated on the same study with (2 g/m^2/day for 2 days) administered with GM-CSF or G-CSF resulted in responses in 9 of 11 patients [15]. The numbers of supratentorial primitive neuroectodermal tumors

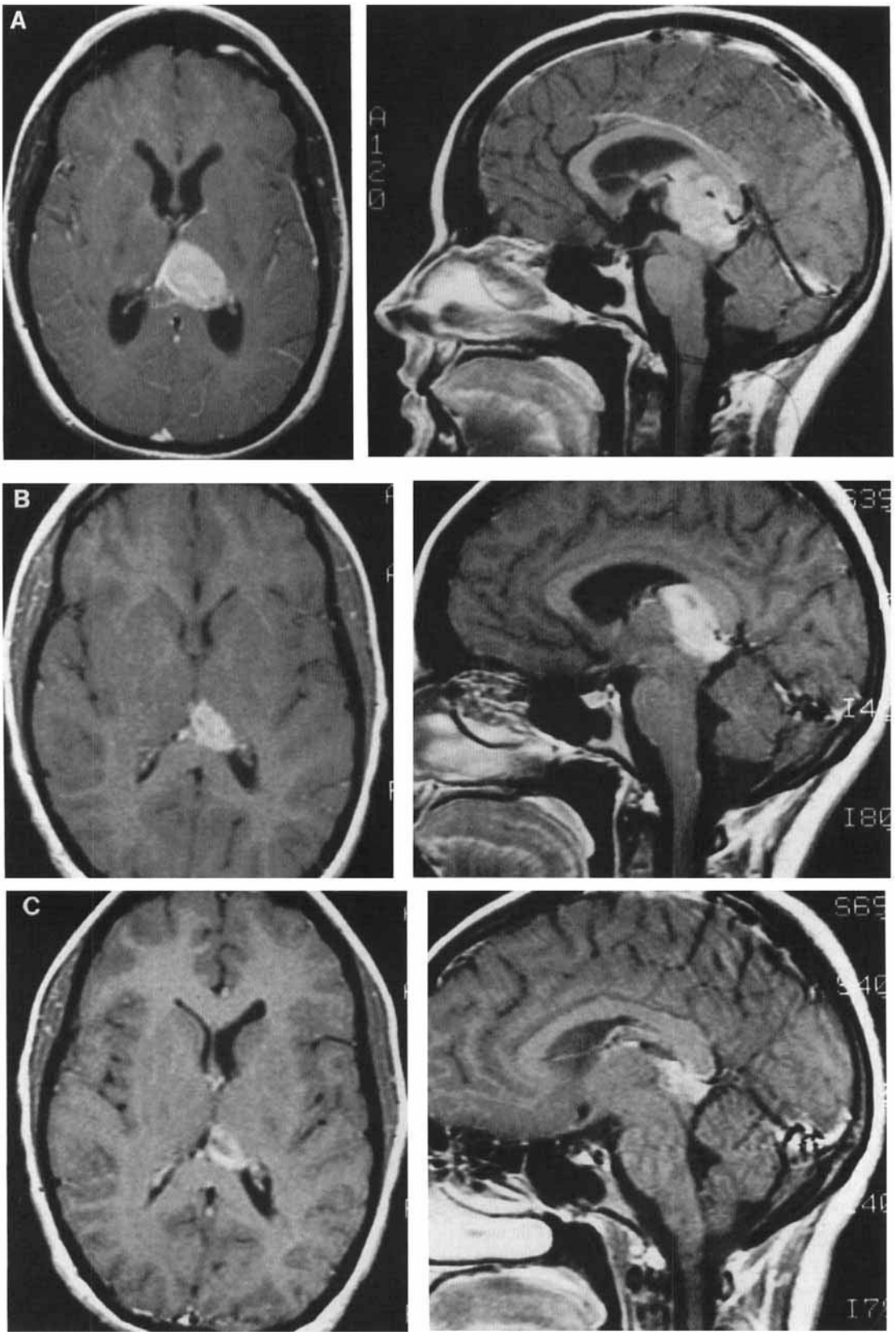

Fig. 1. **A:** (Oct/92) Sagittal **(right)** and axial **(left)** post contrast T1-weighted MRI (TR/TE/NEX,500/20/1) demonstrated a large, lobulated enhancing tumor in the pineal region. **B** (Dec/92) and **C** (Feb/93): Two follow-up studies at the same level showed continuing resolution of the pineal region mass. The mass effect on the aqueduct was also reduced.

(PNETs) and cerebral neuroblastoma treated with this approach remains too small to draw any meaningful conclusions. Of the six patients with newly diagnosed pineoblastoma, we observed good responses in three patients, including the complete resolution of a cervical metastases, with no patients demonstrating progressive disease. As the normal pineal gland will enhance with contrast, it is difficult to distinguish between residual tumor, normal gland, and postsurgical scar. Interestingly, none of the newly diagnosed patients with residual enhancement after completing cyclophosphamide treatment have progressed to date.

Not surprisingly, no activity was seen in the two patients with recurrent disease, although this small number of patients renders the evaluation of the activity of cyclophosphamide in the setting of recurrent disease yet to be determined. In summary, high dose cyclophosphamide is active in the treatment of pineoblastoma and warrants further studies to define its potential role in improving survival in patients with this tumor.

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