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Short communication

Postoperative chemotherapy without radiation in young children with malignant non-astrocytic brain tumours

A Report from the Australia and New Zealand Childhood Cancer Study Group (ANZCCSG)

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Abstract. Young children with malignant brain tumours have particularly poor survival and manifest severe sequelae of radiation therapy. A multi-institutional pilot study of post-operative primary chemotherapy for children under 3 years with primitive neuroectodermal tumours (PNET) or ependymoma was initiated in 1987. The chemotherapy protocol comprised carboplatin, vincristine and the "eight drugs in 1 day" regimen. Radiation was recommended only if tumour progression or recurrence was documented. A total of 14 patients between 5 and 36 months of age were enrolled. Seven had supratentorial tumours (PNET, pinealoblastoma, intracranial retinoblastoma) with multiple predictors of adverse outcome. Four of these responded to initial chemotherapy but subsequently progressed and all had died by 16 months from diagnosis. The seven patients with infratentorial tumours (three medulloblastomas, four ependymomas) had more favourable predictors of outcome: no meningeal dissemination and gross macroscopic resection in six of the seven cases. One patient progressed rapidly and died within 5 months. The other six are alive at 37–57 months from diagnosis. Four are in continuous complete remission at 57, 51, 41 and 37 months, respectively from the time of their tumour resection. One is described as having stable disease with a persistent radiographic lesion at 41 months from diagnosis. One has relapsed on two occasions and is the only surviving patient to have been irradiated. Intelligence scores for the six long-term survivors have thus for remained within the normal range. It is suggested that some infants with standard-risk ependymoma and, possibly, medulloblastoma may be cured without radiation therapy.

Introduction

It is widely acknowledged that young children with malignant brain tumours have particularly poor survival [5, 8, 10, 11]. Furthermore, the long-term sequelae of radiation therapy tend to be more severe and often disabling in patients less than 3 years of age [4, 10, 14, 18]. From the mid- to the late 1980s, the large North American multi-institutional groups initiated strategies of postponement of radiation therapy and introduction of interval chemotherapy in these patients [6, 7, 9]. At that time, limited institutional data were emerging supporting the feasibility of primary chemotherapy and avoidance of radiation [21]. In 1987, the Australia and New Zealand Childhood Cancer Study Group (ANZCCSG) initiated a pilot study that utilised post-operative chemotherapy and avoided radiation therapy unless there was disease progression or recurrence. We now report the long-term outcomes of this pilot cohort of patients.

Patients and methods

A total of 14 patients with medulloblastoma/PNET or ependymoma, aged between 5 and 36 months, were entered on the pilot study between April 1988 and December 1989. Of the seven who had supratentorial primary sites (Table 1), two had pineal tumours in conjunction with bilateral retinoblastoma. The other seven had infratentorial tumours (three medulloblastomas, four ependymomas) and none had proven meningeal dissemination at diagnosis (Table 2).

The chemotherapy regimen is outlined in Fig. 1. The initial phase comprised two cycles of carboplatin and vincristine given weekly for 4 consecutive weeks, followed by 3 weeks of rest. Continuation therapy comprised three cycles of 15 weeks, starting with the "eight drugs in 1 day" regimen [16] (methylprednisolone, 300 mg/m^2 vincristine, 1.5 mg/m^2; lomustine 75 mg/m^2; procarbazine, 75 mg/m^2; hydroxyurea,

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Table 1. Supratentorial brain tumours

Age[a]	Site/diagnosis	Operation	Outcome[a]
24	Parietal ependymoma	GMR	Prog 7, RT, d 10
6	Parietal PNET	GMR	Prog 3, d 5
21	Pinealoblastoma	Partial	Prog 5, d 7
5	Pinealoblastoma	Bx	Resp, Prog 4[b], d 5
24	Frontal PNET[b]	Bx	Resp, Prog 12, d 16
6	Intracranial RB	Bx	CR 3[c], Prog 11, d 13
36	Intracranial RB	Bx	Resp, Prog 7[b], d 9

[a] All ages and intervals are expressed in months
[b] Includes meningeal dissemination
[c] Intraocular response also documented
GMR, Gross macroscopic resection; Prog, tumour progression; RT, radiation therapy; d, death; PNET, primitive neuroectodermal tumour; Bx, biopsy only; Resp, tumour response; RB, retinoblastoma; CR, complete response

Table 2. Infratentorial brain tumours

Age[a]	Diagnosis	Operation	Toxicity	Outcome[a]
25	Epend	GMR	Auditory	CCR 57
12	Medullo	GMR	–	CCR 51
23	Epend	GMR	Auditory	CCR 41
10	Epend	GMR	Auditory	CCR 37
17	Epend	Partial	–	Prog 7, Resect[b] V & C 18[b], SD 41
25	Medullo	GMR	Auditory	CR, Prog 14, RT: CR, Prog 36[c]
30	Medullo	GMR	Seizures	Prog 3[c], RT, d 5

[a] All ages and intervals are expressed in months
[b] Second-look partial resection and second-line chemotherapy
[c] Includes meningeal dissemination
Epend, Ependymoma; GMR, gross macroscopic resection; CCR, continuous complete remission; Medullo, medulloblastoma; CR, complete tumour response; Prog, tumour progression; RT, radiation therapy; SD, stable disease; V, vincristine; C, cyclophosphamide, d, death

1500 mg/m^2 cisplatin, 90 mg/m^2; cytosine arabinoside, 300 mg/m^2; cyclophosphamide, 300 mg/m^2) given on weeks 1 and 5, followed by a repeat of the initial phase schedule from weeks 9 to 15. Evaluations of disease status included a computer-assisted tomographic (CT) scan of the brain (repeated within 3 days of operation), myelography and cerebrospinal fluid (CSF) cytocentrifuge. The CT was repeated after each cycle of initial therapy and twice during each cycle of continuation therapy (weeks 1 and 9). Myelography and CSF were repeated only if there were initial abnormalities or if progression had been documented at the primary site. In the presence of radiological evidence of disease progression, the patient was deemed ineligible for continuation of this chemotherapy protocol and rescue radiation guidelines were recommended. Evaluations for toxicity comprised regular full blood counts, chemistry profiles (including determinations of electrolytes, calcium, magnesium, urea, creatinine and liver function), chest radiography and audiology. In patients surviving for 1 or more years from diagnosis, annual neuropsychological evaluations were conducted using the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R).

Results

The extent of initial resection, toxic effects of therapy and patient outcomes are outlined in Tables 1 and 2. In the supratentorial group (Table 1), four of the five evaluable patients responded to chemotherapy, including a complete response at the intracranial site in a patient with retinoblastoma. However, all patients showed disease progression (five at original sites only and two with meningeal dissemination also) at between 3 and 12 months from diagnosis and all had died by 16 months. Radiation therapy was given as rescue in one patient with no demonstrable benefit.

Six of the seven patients with infratentorial tumours (Table 2) had gross macroscopic resection prior to chemotherapy. The only patient to have died showed rapid progression at 3 months and had no response to rescue radiation. The remaining six patients are alive at 37–57 months from diagnosis and four of them are in continuous complete remission (CCR). One patient has a persistent radiographic lesion at 41 months from diagnosis. She had local progression at 7 months, was further but incompletely resected, then received 18 months of second-line chemotherapy (vincristine and cyclophosphamide) without radiation, and has been off all treatment for a further 16 months. These five long-term survivors have not received radiation therapy. The remaining patient received rescue neuraxis radiation for local relapse at 14 months, then had a second (local and meningeal) relapse at 36 months and is now responding to intensive experimental chemotherapy at 42 months from diagnosis.

The chemotherapy regimen of the pilot protocol was well tolerated and did not produce delays in the schedule. Four of the six survivors show high-frequency hearing loss and the patient who received rescue radiation requires hearing aids. The neuropsychological evaluations are shown in Table 3. All of the scores fall within the normal range of intelligence. No clinical neurological defect developed during or after chemotherapy. No other organ dysfunction has been observed in long-term follow-up of the six survivors.

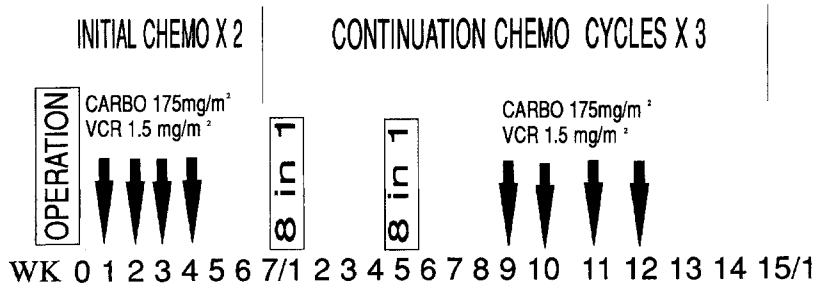

Fig. 1. Schema of chemotherapy for young children with malignant non-astrocytic brain tumours

Table 3. Current neuropsychological evaluations in the surviving cohort of patients with infratentorial tumours

Age at Dx	Status	WPPSI-R scores		
		Verbal	Performance	Age[a]
25 months	CCR 57 months	85	81	76 months
12 months	CCR 51 months	109	93	61 months
23 months	CCR 41 months	105	104	59 months
10 months	CCR 37 months	[b]	100	55 months
17 months	SD 41 months	94	84	48 months
25 months	Post-RT	94	106	55 months

[a] Age at the time of the most recent testing

[b] Variable scores in a child from a non-English-speaking (Vietnamese) family

Dx, Diagnosis; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence-Revised; CCR, continuous complete remission; RT, radiation therapy; SD, stable disease

Discussion

At the time of commencement of this study, it was considered controversial to omit radiation therapy in the management of childhood brain tumours [11]. Although the Paediatric Oncology Group (POG) and the Children's Cancer Study Group (CCSG) in the United States had initiated studies incorporating a strategy of delayed radiation therapy in young children, there was little experience regarding the efficacy of chemotherapy used alone. In particular, long-term survival of patients treated without radiation therapy was considered unlikely. Limited data from the M. D. Anderson Hospital (MDAH), utilising a regimen of nitrogen mustard, oncovine, procarbazine and prednisone (MOPP) for infants with medulloblastoma/PNET, gave credence to the proposal to reserve radiation for documented tumour progression or recurrence [21].

Our results were markedly different in the supratentorial and infratentorial tumours sites. In the supratentorial group, each of the patients had one or more adverse prognostic predictors (Table 1). Three had large cortical tumours, two had pinealoblastomas, and two had intracranial retinoblastomas (trilateral). The age range was 5–36 months, with six of the seven patients being 24 or less months of age at the time of diagnosis. The surgical procedures were gross macroscopic resection in two patients, partial resection in one subject and biopsy only in four patients. Meningeal disease was documented in one patient. In keeping with current experience with either radiation or chemotherapy protocols [15, 17, 20], these patients did very poorly. The initial responses in four of the five evaluable patients were short-lived.

In the seven patients with infratentorial tumours the outcomes were markedly different. These patients had more favourable prognostic predictors, including an age range of 10–30 months, conventional histopathology, gross macroscopic resection in six of the seven patients and no evidence of meningeal involvement at presentation. Four (three ependymomas, one medulloblastoma) of the seven patients are in CCR at 57, 51, 41 and 37 months from diagnosis, respectively. These patients completed their chemotherapy regimen and have received no radiation therapy. The fifth survivor (ependymoma) is described as having stable disease at 41 months from diagnosis, has been off all chemotherapy for 16 months and has received no radiation, and no third-look operation has been attempted. The sixth surviving patient (medulloblastoma), although continuing to respond to experimental intensive chemotherapy, is unlikely to survive in the long term.

The chemotherapy schedule used in our protocol incorporated what was, at that time, a combination of the best available published regimens. Allen et al. [1] had obtained encouraging results utilising carboplatin weekly for 4 weeks at a dose of 175 mg/m^2. We added vincristine to this regimen. The "eight drugs in 1 day" regimen was being hailed as a new strategy with promising early results [16]. The emphasis since that time has shifted to more dose-intensive regimens, particularly in tumours with adverse prognostic factors. The limited responses we obtained in the evaluable supratentorial tumours confirm the suboptimal intensity and efficacy of this pilot protocol. In subsequent studies we have made the following modifications: the chemotherapy has been intensified, particularly in the initial phase of the protocol; cyclophosphamide has been given particular emphasis; and the eligibility criteria have been broadened to include patients up to 4 years of age with all types of malignant brain tumours.

The neuropsychological monitoring of our long-term survivors suggest a benefit by comparison with studies using radiation therapy [4, 10, 14, 18]. The WPPSI-R scores are encouraging, but larger numbers of patients and longer follow-ups are needed. Although we do not have adequate baseline measures, other series have found scores significantly below expectations for age after the initial surgery alone (Duffner, personal communication; [10, 13, 19]). Several investigators have suggested diminished adverse effects of chemotherapy as compared with radiation in young patients [3, 10, 12, 19].

Despite the limitation of small numbers, this small cohort of survivors represent a group probably cured by a combination of gross macroscopic resection and subsequent chemotherapy. The four CCR patients are highly unlikely to relapse at this time; all have been followed for a minimum of 37 months and the two with the shortest follow-up of 37 and 41 months presented at ages of 10 and 23 months, respectively. The patient with the persistent radiographic lesion may also be cured.

Although the studies by the United States cooperative groups (POG 8633, CCG 945, CCG 921) were not designed to address omission of radiation therapy, the reported (but not yet published) progression-free intervals for infants with medulloblastoma/PNET and ependymoma indicate a majority of chemotherapy failures to have occurred within the 1st year of therapy [7, 9]. Furthermore, contrary to the protocol design, most infants in the CCSG series did not receive radiation therapy and no relapse has been observed after 2 years from diagnosis [9]. Similarly, the follow-up of the original MDAH series did not find any relapse beyond 20 months [3].

Our findings, supported by those of other investigators [2, 3, 9, 19], suggest that a subcategory of infants with well-resected, non-metastatic (standard-risk) ependymoma and, possibly, medulloblastoma may be cured without

radiation. The important questions now being addressed are whether these numbers can be increased by more intensive chemotherapy, whether the benefits may apply to older patients and whether those eligible can be better defined. In young children at least, the strategy of primary post-operative chemotherapy alone is worthy of continuing study and patients who subsequently progress may be salvageable by rescue radiation therapy [2, 6, 7].

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