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Treatment of Standard Risk Medulloblastoma With Craniospinal Irradiation, Carboplatin, and Vincristine

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Background. Improved outcome for children with medulloblastoma requires new treatment protocols which incorporate chemotherapeutic agents that are capable of eradicating minimal residual disease in the primary posterior fossa site and in the leptomeninges and whose toxicities are tolerable.

Procedure. We treated 25 children with nondisseminated medulloblastoma with complete or near complete surgical resection of the posterior fossa tumor, 3,600 cGy craniospinal irradiation (CSRT) and 5,400 cGy posterior fossa irradiation followed by adjuvant chemotherapy with carboplatin and vincristine.

Results. The estimated 3-year progression-free survival (PFS) was 0.73 (S.E. ± 0.09) compared with a 3-year PFS of 0.69 in historical controls treated with surgical resection and CSRT but without chemotherapy. Six relapses occurred outside the posterior fossa and one relapse occurred both in the posterior fossa and in the lateral ventricle. The major acute toxicities were myelosuppression, anorexia and neuropathy.

Conclusions. Our experience with this adjuvant chemotherapy regimen with carboplatin and vincristine, as used by us, does not encourage its adoption in future clinical trials. Med. Pediatr. Oncol. 29:563–567, 1997.

Key words: medulloblastoma; chemotherapy; carboplatin; vincristine

INTRODUCTION

Medulloblastoma is a midline tumor of the cerebellum that occurs predominantly in children less than 15 years of age [1,2]. The tumor frequently disseminates throughout the cerebrospinal fluid (CSF) pathways and cannot be cured by surgical resection alone. Surgical removal of the tumor followed by radiotherapy with 3,600 cGy to the craniospinal axis (standard dose craniospinal irradiation [CSRT]) and 5,400 cGy to the posterior fossa results in a 5-year progression-free survival (PFS) of 50–60% [1,2]. Higher doses of CSRT may improve survival but are associated with a high risk of major cognitive decline [3]. Lower doses of CSRT without adjuvant chemotherapy result in a high rate of early relapse [4]. Chemotherapy can produce measurable shrinkage of tumor in newly diagnosed patients prior to the administration of CSRT and in patients with recurrent disease [5–9] and some adjuvant regimens have produced excellent survival results.

The best treatment results reported to data have consisted of surgical resection and standard dose CSRT followed by chemotherapy with lomustine (1-(2-chloroethyl)-3 cyclohexyl-1-nitrosourea, CCNU), cisplatin, and vincristine [10]. Five-year PFS for high risk patients, defined as those with a subtotal resection, evidence of metastatic disease and/or brainstem involvement, was 85%. Although these survival results are excellent, toxicities from the chemotherapeutic regimen in the 63 patients included hearing loss that required cisplatin dose reduction (30 patients), permanent hearing loss requiring a hearing aid (two patients), hematologic toxicity requiring CCNU dose reduction (nine patients), transient grade 3 to 4 renal toxicity (13 patients) and second malignancies (three patients).

This study attempted to design an effective treatment for standard risk cerebellar medulloblastoma utilizing carboplatin rather than cisplatin and CCNU in the hopes of decreasing morbidity without compromising efficacy. Carboplatin causes predictable hematologic toxicity but is not associated with the dose-limiting ototoxicity and renal toxicity of cisplatin or the pulmonary fibrosis of CCNU. By avoiding these toxicities we planned a dose intensification of platinum delivery to the tumor. The study hypotheses were that adjuvant chemotherapy with carboplatin and vincristine (VCR) would prolong progression-free survival in patients with standard risk medulloblastoma compared with historical controls treated with surgical resection and CSRT alone and that the chemotherapy would be well tolerated.

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MATERIALS AND METHODS

Patients were enrolled from a number of participating institutions including the authors' and those listed in the acknowledgments.

Eligibility

Criteria for inclusion into the study included age above 3 years; histologically proven cerebellar medulloblastoma; no prior treatment other than surgery; postoperative imaging and cytology demonstrating absence of tumor metastases and $\leqslant 1.5$ cm^2 of residual tumor at the primary site.

Treatment

Radiation therapy (RT) was administered according to previously published guidelines [1] at a dose of 3,600 cGy to the craniospinal axis and an 1,800-cGy boost to the posterior fossa for children $\geqslant$ 6 years old. Children 3 to 5 years old received 2,400 cGy to the craniospinal axis and a 3,000-cGy boost to the posterior fossa. Vincristine (1.5 mg/m^2 i.v. push, maximum dose 2 mg) was given weekly during RT for a total of eight doses. Chemotherapy was begun 4 weeks following the completion of RT. Eight courses were planned. Each course lasted 6 weeks and consisted of carboplatin (560 mg/m^2) given week 1 and vincristine (1.5 mg/m^2 i.v. push, maximum dose 2 mg) given weeks 1, 2, and 3.

Patients were evaluated frequently by physical examination, blood counts and chemistries, hearing tests and neuroimaging. Chemotherapeutic doses were adjusted according to protocol guidelines if toxicity was encountered.

Statistical Methods

The study hypothesis was that postsurgery treatment with CSRT and chemotherapy with carboplatin and vincristine would produce a 3-year progression-free survival probability greater than the 0.65 which was found in historical controls treated with CSRT alone [1]. The maximum number of patients to be accrued onto the trial was 35. A patient was defined as a failure if he/she died or had progression of disease. A stopping rule allowed for the early termination of the trial at the time when the seventh treatment failure was observed. At the seventh failure, the 95% upper confidence bound for the probability of treatment failure crossed above 0.35, meaning we could not be confident that the treatment results would be an improvement over historical controls. Progression-free survival was estimated using the method of Kaplan-Meier.

Each individual institution adopting this treatment in a research protocol setting obtained approval by the appropriate Human Rights Committee in accordance with the Institutional Assurance Policies of the U.S. Department of Health and Human Services. No such approval was obtained at Memorial Sloan Kettering Cancer Center or by two individual physicians who considered this therapy to be the treatment of choice and not investigational. Informed consent was obtained from the parents or guardians of every child and also, if possible, from the patients themselves.

RESULTS

Demographics and Surgical Outcome

Twenty-five patients were enrolled on the study. There were 21 males and four females with a median age of 10 years (range 4 to 21 years). Twenty patients had complete surgical resections of their tumors with no radiographically visible residual tumor; four patients had less than 1.5 cm^2 of residual tumor and one patient was unassessable because of postoperative hemorrhage. The only significant surgical complication was the cerebellar mutism syndrome which occurred in five patients and which clinically resolved in four of them.

Dose of CSRT and Chemotherapy

Nineteen patients received standard dose RT with 5,400 cGy to the posterior fossa and 3,600 cGy to the brain and spinal cord. One 4-year-old received reduced dose CSRT of 2,340 cGy as planned. Five patients received modification of the planned CSRT dose per institutional preference. One 4.5-year-old received CSRT at 3,060 cGy and one older patient received reduced CSRT at 2,340 cGy. Three patients received increased RT to the posterior fossa at 5,920 to 6,000 cGy. The median number of cycles of maintenance chemotherapy was seven per patient. The median dosage of chemotherapy actually received was 75% of the intended VCR dose and 81% of the intended carboplatin dose.

Outcome

The estimated 3-year PFS in this study was 0.73 (S.E. $\pm$ 0.09) (Fig. 1). The study was halted after the seventh treatment failure because this protocol showed no significant improvement compared with historical controls treated with surgery and CSRT alone. To date, seven of the 25 eligible patients have suffered relapse of their tumor 8 to 65 months following initiation of treatment (median 24 months). One additional patient died of probable cervical cord necrosis or possibly a cervical leptomeningeal metastasis 16 months following treatment. All patients with recurrent tumor had leptomeningeal dissemination outside of the primary site and only one patient also had disease at the primary site. One patient developed rapidly progressive LM metastases while receiving chemotherapy. Seventeen patients are alive and

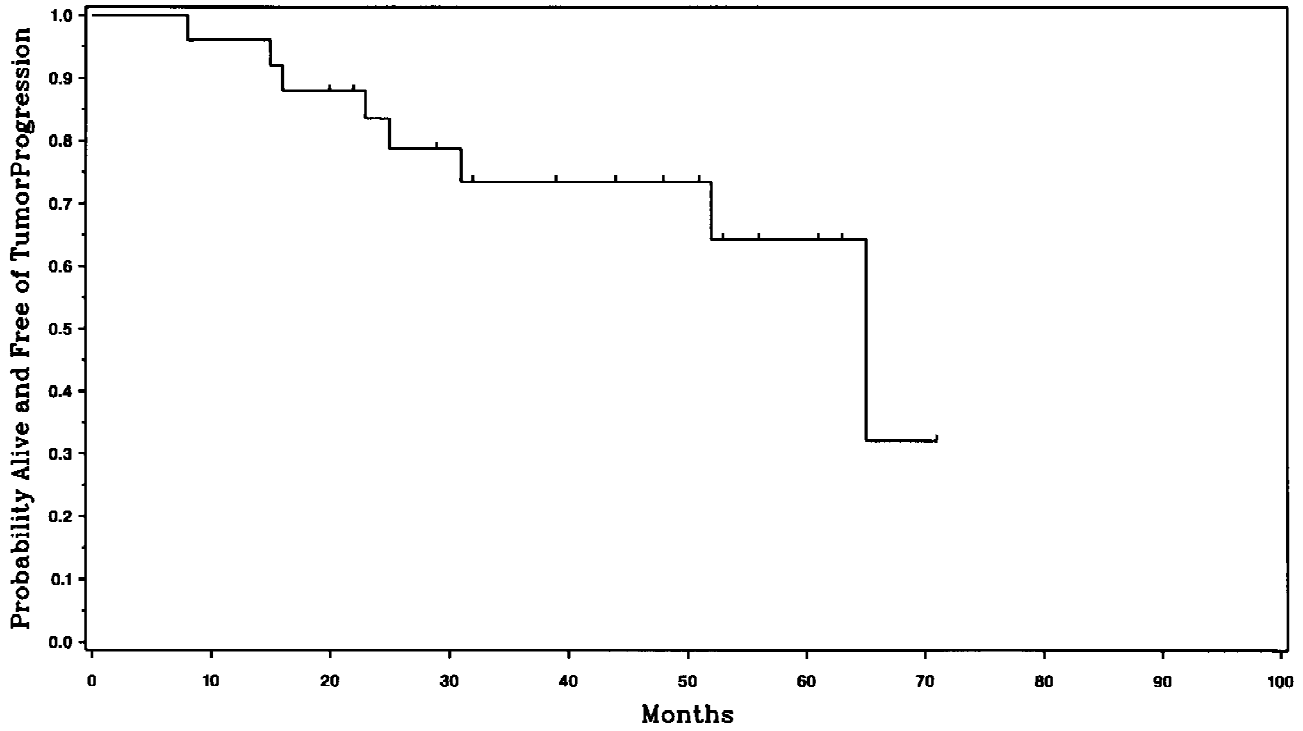

Fig. 1. The probability of progression-free survival for all patients in the study (n = 25).

disease-free from 20 months to 71 months following the onset of therapy (median = 44 months).

Toxicity

The major toxicities from chemotherapy were myelosuppression, anorexia and neuropathy. Complete toxicity information for every course of chemotherapy was available for 21 patients. Neutropenia with absolute neutrophil count (ANC) less than 500/mm^3 was noted in 44% of courses and less than 200/mm^3 in 17%. However, febrile neutropenia occurred in only seven of 25 patients (6.5% of courses). There were three episodes of bacteremia, one in conjunction with a wound infection. Other infections during chemotherapy included localized herpes zoster infection in five patients, chickenpox in one, perioral herpes simplex in one, pneumocystis carinii pneumonia in one, sinusitis in two, and otitis media in two. All infections resolved with treatment. Thrombocytopenia with platelet count less than 50,000/mm^3 was noted in 64% of courses and less than 20,000/mm^3 in 32%. Platelet transfusions were required in 16 of 25 patients and 51% of courses. Red blood cell transfusions were required in 14 of 25 patients and 36% of courses. Reductions in carboplatin doses because of hematologic toxicity were necessary in nine of 25 patients. One patient received 50% carboplatin doses from the onset of chemotherapy because of myelosuppression during CSRT. Despite these reductions, there was a trend for hematologic toxicity to be associated with *improved* outcome. There were four treatment failures among 16 patients who required at least one platelet transfusion (25%) compared with four failures among nine patients who did not require platelet transfusion (44.4%). More strikingly, treatment failures occurred in 2/14 (14.3%) patients who required platelet transfusions during more than one course of chemotherapy compared with 6/11 (55%) treatment failures among patients who did not require platelet transfusions or required them during only one chemotherapy course. Statistical analysis could not be performed because of the small number of patients and the possibility of unobserved confounding factors.

Severe anorexia developed in 12 patients (48%) and five (20%) required supplemental feedings via gastrostomy or intravenous hyperalimentation. The median weight loss during maintenance chemotherapy was 10.8% of initial body weight (range 33% loss to 26% gain). Vincristine toxicity manifested by distal weakness, pain and constipation as well as nausea and vomiting necessitated dose reductions or deletions in 12 (48%) patients. Neuropathy was prolonged in some patients but resolved in all. None of the patients developed nephropathy. Chemotherapy courses had to be delayed in nine (36%) patients for a median of 2 weeks (range 1 to 14 weeks). One patient stopped chemotherapy after four courses because of severe unilateral sensorineural hearing loss. There were no other permanent toxicities from chemotherapy.

DISCUSSION

The results of this treatment protocol utilizing adjuvant carboplatin and VCR following CSRT for standard risk medulloblastoma was disappointing. The estimated progression-free survival at 3 years was 0.73 (S.E. ± 0.09) which was no better than historical controls treated with surgical resection and CSRT alone [1]. In addition, this chemotherapy was associated with significant short-term toxicity including severe anorexia, neuropathy, and myelosuppression with transfusion requirements.

All patients with recurrent tumor had leptomeningeal dissemination outside of the primary site and only one patient also had disease at the primary site. Most previous studies utilizing similar doses of RT to the posterior fossa with or without adjuvant chemotherapy have found that 37% to 73% of relapses involved the posterior fossa [1,10,11]. It is possible that more aggressive surgical resections combined with current radiotherapy techniques are yielding better tumor control at the primary site and the efficacy of adjuvant chemotherapy is reflected primarily by the frequency of leptomeningeal metastases.

There is a striking discrepancy between the excellent results achieved with the use of CCNU, cisplatin and VCR in the treatment of high risk medulloblastoma and the failure of carboplatin, VCR to improve outcome for standard risk disease in this study [10]. VCR was used in both protocols but gave no apparent benefit in this study. The relative efficacy of carboplatin, cisplatin, and CCNU in the treatment of medulloblastoma remains uncertain. Although carboplatin has, in general, a similar spectrum of anti-neoplastic activity as cisplatin [12] and is apparently better able to penetrate the blood brain barrier from plasma to CSF [13], the therapeutic results from carboplatin as a single agent in the treatment of medulloblastoma have varied [9,14,15]. This study protocol delivered more than twice as much platinum to the patient than the CCNU, cisplatin, VCR regimen but no benefit from chemotherapy was demonstrated. There are several possible explanations. Cisplatin may be a more effective agent to treat medulloblastoma than carboplatin for reasons that are unidentified at present. Alternatively, carboplatin may be effective only when dosing is calculated using the glomerular filtration rate to maximize carboplatin area under the curve (AUC). The present study indirectly supports this suggestion. There was a trend for hematologic toxicity, which is known to correlate with carboplatin AUC [16], to be associated with improved outcome. Patients requiring platelet transfusions in two or more chemotherapy courses had a relapse rate of 14.3% compared with 55% in patients requiring less platelet transfusions. Finally, CCNU may be the key agent that sets apart the successful protocol from the unsuccessful one [1,10,17,18]. The efficacy of CCNU may result from its excellent penetration of the blood brain barrier and ability to achieve high cytotoxic levels in the CSF [19].

Several recent studies provide evidence that the dose of CSRT can be reduced from 3,600 cGy to 2,400 cGy without compromising efficacy when treatment also includes preirradiation or postirradiation chemotherapy [3,8,10]. Reduction of the CSRT dose is essential to the goal of avoiding the cognitive decline associated with the current therapy of medulloblastoma. Future studies could compare the CCNU, cisplatin and VCR protocol with less toxic regimens that utilize agents with demonstrated activity against newly diagnosed medulloblastoma such as cyclophosphamide or etoposide [5–7,12] as is planned by the Children's Cancer Group. Carboplatin, as administered in this study, appears to be a less suitable candidate.

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