Brain-stem tumors in childhood: a prospective randomized trial of irradiation with and without adjuvant CCNU, VCR, and prednisone

A report of the Childrens Cancer Study Group

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Seventy-four children with a brain-stem tumor diagnosed between 1977 and 1980 were entered into a prospective study in which exploration and assessment for resection were optional, radiation treatment using standard methods was required, and randomization occurred with regard to the use of adjuvant chemotherapy (1-(2-chloroethyl)-1-nitrosourea, vincristine, and prednisone) or no further treatment. The overall 5-year survival rate was 20% and was not improved by the adjuvant chemotherapy program. An increased risk of infection was associated with the adjuvant therapy.

KEY WORDS • brain-stem neoplasm • children • radiation therapy • chemotherapy • astrocytoma • glioblastoma

In 1977, Childrens Cancer Study Group (CCSG) investigators elected to study the treatment of brain-stem tumors because few children survived the disease, because important questions regarding surgical and radiation practice remained unanswered, and because response rates to systemic agents in patients who relapsed seemed to justify a formal evaluation of adjuvant chemotherapy. Data presented mainly within the last decade indicated that the 5-year survival rate for a child with a brain-stem tumor located in the pons or medulla was poor but uncertain, varying between 0% and 38%. Although the lower end of this range reflected usual practice. A histological diagnosis was therefore made in 0% to 58% of cases in reported studies, even when autopsy data were included. Although most tumors were astrocytomas, it was unclear whether high-grade or low-grade tumors predominated at diagnosis. Low-grade cystic astrocytomas or resectable exophytic tumors filling the fourth ventricle were exceptional.

Children with brain-stem tumors were treated by irradiation prior to our study. Many patients (33% to 87%) obtained symptomatic improvement, but relapse and death in the 1st year was common. Radiation doses of less than 5000 cGy appeared to produce poorer results than doses greater than 5000 cGy, although dose-response data for brain-stem tumors were meager. The conclusion that high doses were superior was based chiefly on the poor results with low doses, the observation that failure is nearly always due to recurrence at the primary site, and a mass lesion, and exploration was not undertaken. In the last decade exploration of the primary tumor became more common and was performed in 14% to 92% of patients, although the lower end of this range reflected usual practice. A histological diagnosis was therefore made in 0% to 58% of cases in reported studies, even when autopsy data were included.

Usually, the diagnosis of a brain-stem tumor was based on the clinical symptoms and signs combined with neuroradiological investigations that demonstrated
by analogy with brain-tumor response to irradiation for other tumor sites and types. There was no advantage to whole-brain irradiation.9

In general the chemotherapy of brain tumors has been disappointing,4,16,27 and to date this has also been true for the chemotherapy of brain-stem tumors.1,6,16,22,24 The reported clinical data were either anecdotal or the summation of small single-institution series. In 1977, the investigators of the CCSG (see Appendix) considered that the nitrosoureas and vincristine (VCR) were as efficacious against tumors as any agents then in use, and prospective randomized studies were set up to assess the value of these agents as adjuvant therapy for certain common childhood brain tumors, including medulloblastoma and ependymoma,6 cerebral hemisphere malignant astrocytoma,2 and brain-stem tumors. The intent of these three studies was to utilize standard surgical and radiation practice and introduce adjuvant chemotherapy as the study variable. The chemotherapy drugs selected for all three studies were 1-(2-chloroethyl)-1-(2-chloroethyl)-1-nitrosourea (CCNU) and VCR, together with prednisone. Results of the first two investigations were published in 19826 and 1984,5 respectively. The primary objective of the present prospective trial was to determine whether adjuvant chemotherapy would decrease the local recurrence rate and increase the survival rate in patients with brain-stem tumors.

Clinical Material and Methods

Selection of Patients

All children whose diagnosis of brain-stem tumor had been made during the 3 weeks prior to commencement of the study were eligible for inclusion provided that: 1) there had been no prior treatment except steroids and the surgical procedure(s), if any; 2) the children were in the age range of 2 to 21 years; and 3) the tumor site was either the pons or medulla. Extension cephalad from the pons or caudal from the medulla did not exclude the patient provided that the tumor bulk was associated with either the pons or medulla. Patients with tumors at mid-brain sites were excluded, due to their more favorable response to radiation treatment. Diagnosis of brain-stem tumors was based either on the clinical findings and radiological investigation alone or on findings at exploration, with or without histological confirmation.

The neuroradiological studies utilized were the choice of the investigators; however, they were required to submit the reports of these investigations for central review regardless of whether the investigations were undertaken at diagnosis or during subsequent evaluations. Operative reports, if any, were also evaluated centrally. Histological material was reviewed by one of us (C.B.).

The eligible patients were randomly assigned to treatment with either radiation alone (Regimen II) or radiation plus systemic chemotherapy with CCNU, VCR, and prednisone (Regimen I). Patients in the study who either developed progressive disease or who relapsed were eligible for a further study of systemic treatment. Patients who failed after treatment with radiation alone were to receive CCNU, VCR, and prednisone (Regimen IV), as in the adjuvant program (Regimen I), and those who had a recurrence following adjuvant treatment were to receive procarbazine alone (Regimen III).

Assessment of Disease Progression

Progression of disease or relapse, the end-point of this study, was to be determined by the unanimous opinion of the treatment team comprised of the neurosurgeon, radiation oncologist, and pediatric oncologist, who based their decision on the clinical symptoms and signs supported by neuroradiological and other studies. Specifically, steroid withdrawal, shunt complications, meningitis, hemorrhage, and postirradiation encephalopathy were to be excluded as a cause of neurological deterioration. Because tissue confirmation of relapse was usually absent and the differential diagnosis sometimes difficult, the treatment team was conservative in diagnosing relapse. When there was doubt, a period of observation and repeat investigation were indicated.

Radiation Treatment

Radiation therapy was to start as soon as possible following diagnosis or postoperative recovery. The intent of the protocol was that the radiation oncologist would continue to use standard treatment. However, it was suggested that the radiation dose be 5000 to 6000 cGy, given at the rate of 800 to 900 cGy/week in five daily fractions. The tumor dose was the midline dose on the central axis for parallel opposed beams. The irradiated volume was to include a margin of normal tissue of not less than 3.0 cm around the tumor. The lower limit of the field was to be at the lower border of the C-2 vertebra, provided that this did not contravene the 3.0-cm constraint. The institution's radiation treatment sheet and a summary sheet were submitted for central review. The appropriateness of the treatment volume could not be assessed centrally since, in this study, neuroradiological diagnostic material and follow-up radiation films were not centrally reviewed.

Adjuvant Chemotherapy

The adjuvant chemotherapy program included VCR given weekly by intravenous injection (1.5 mg/sq m, maximum 2.0 mg) for eight doses concurrently with radiation treatment. This was supplemented by cycles of CCNU, VCR, and prednisone ("maintenance therapy"), which were initiated 12 weeks following the commencement of irradiation. Each 42-day cycle comprised CCNU (100 mg/sq m orally) on Day 1, prednisone (40 mg/sq m orally) on Days 1 to 14, and VCR (1.5 mg/sq m to a maximum of 2.0 mg intravenously) on Days 1, 8, and 15. The duration of maintenance therapy was planned to be eight cycles (48 weeks).
Results

From January, 1977, to October, 1980, 80 patients were entered into the study. Six of these patients were not eligible: in five patients the anatomical location of the tumor was inappropriate and in one patient the diagnosis was incorrect. Therefore there were 74 eligible patients (36 boys and 38 girls); 17 patients were less than 5 years old, 43 were aged 5 to 9 years, seven were aged 10 to 13 years, and seven were more than 15 years old. Fifty-three patients were white, 11 black, and nine were of other races. There were two postoperative deaths prior to the start of radiation treatment, and two patients did not complete radiation treatment due to parents' refusal, one prior to and one during radiation treatment.

One patient was lost to follow-up evaluation from the day of study entry. Overall, 35 patients were treated or were scheduled to be treated with radiation alone (Regimen II) and 39 with radiation plus adjuvant chemotherapy (Regimen I). Four patients were treated without randomization (two patients in Regimen I and two in Regimen II), and two patients randomly assigned to Regimen II were treated with Regimen I. The principal analyses relate to the 70 randomly assigned patients who were classified as "randomized." Analysis with randomized patients classified as treated and including non-randomized patients yielded equivalent results. Data are updated to March, 1985.

Survival Rate

The 5-year survival rate for patients randomized to irradiation alone (Regimen II) was 17% and for patients randomized to irradiation and adjuvant chemotherapy (Regimen I) was 23% (Fig. 1 left). The respective rates at 18 months were 26% and 35% (Fig. 1 left). These differences were not significant (p = 0.56, log-rank test2). Five-year relapse-free survival rates were 17% for both regimens (Fig. 1 right). The median times to relapse were 8 months for Regimen I and 7 months for Regimen II. Neither age nor sex influenced survival rate.

Of the 74 eligible patients, one was lost to follow-up review on Day 1, 14 were alive at 28+ to 90+ months (median 76+ months), and 59 were dead 0 to 14 months (median 2.6 months) from the time of relapse or from study entry when disease control was not obtained. Two patients died prior to the start of radiation treatment. There were no deaths due to toxicity. The other 57 deaths were tumor-related. Thirteen of the 14 survivors were in a first remission, and one was alive in remission after treatment for relapse. These surviving patients are described below in more detail.

Neuroradiological Investigation

At diagnosis, the relative frequency of neuroradiological investigations among the 73 patients were: computerized tomography (CT) in 70 cases (96%), air studies in 33 cases (45%), and angiography in 28 cases (38%). Reevaluation of the primary tumor, either for progressive symptoms or electively, was undertaken by CT scanning alone in all patients.

Surgical Treatment

Surgical reports were available on 73 patients. Forty-one patients (56%) did not undergo surgical exploration, 28 (38%) were explored with or without a biopsy
procedure, and four (5%) underwent exploration and a partial resection of their tumor. Thus, only four (12%) of the 32 patients surgically explored underwent a limited resection. The survival rate was 20% (eight of 41) in the patients not explored, 11% (three of 28) in the patients explored but not undergoing resection, and 75% (three of four) in the patients undergoing partial resection. These latter patients had lived 44+, 67+, and 80+ months by the time of the March 1985, update in this study.

In addition, 18 (72%) of 25 patients noted to have hydrocephalus had a shunt placed. A shunt was utilized in three (7%) of the 41 patients who did not undergo exploration and in 15 (47%) of the 32 patients who did undergo exploration, including three of the four patients who underwent partial resection.

Histological Data

Tissue specimens were obtained in 32 patients at exploration but were diagnostic in only 23. Of the 23 patients, the histological finding was low-grade astrocytoma in 11 patients, high-grade astrocytoma in nine, and “other tumors” in three. These latter three tumors included probable ganglioglioma in one patient; mixed neoplasm, with elements of ependymoma, medulloblastoma, and astrocytoma, in one patient; and a tumor classified only as “other” in one patient because the tissue was inadequate to differentiate between medulloblastoma and anaplastic astrocytoma. Survival rates were 27% (three of 11) for patients with low-grade astrocytoma, 8% (one of 12), for those with high-grade astrocytoma and other histologies, and 20% (10 of 50) for patients with no histological diagnosis.

Tumor Location

In 47 patients the site of the primary tumor was in the pons with or without caudal extension (pons alone in 21 patients and pons plus medulla in 26 patients); four (9%) of these patients are alive. In 11 patients the tumor was in the pons with cephalad extension; four (36%) of these patients are alive. The tumor was in the medulla in 14 patients (medulla alone in four patients, medulla plus cervical cord in four patients, medulla and pons in three patients, and medulla, pons, and cervical cord in three patients); five (36%) of these patients are alive. Adequate data on the location of the tumor were not available for two patients, one of whom has survived.

Radiation Treatment

Of the 74 eligible study patients, four received no radiation treatment. Two of the four died postoperatively, one refused treatment, and one was lost to follow-up review after registration. Six patients stopped radiation treatment early, due to progressive disease in three (after 2366, 3360, and 3600 cGy), shunt sepsis in two (after 4816 and 4955 cGy), and parents’ refusal in one case (after 2300 cGy). Two patients completed a course of radiation treatment, but no data were available for analysis. Only one of these patients survived, living 52+ months. This was the patient whose parents refused further irradiation after the child had received 2300 cGy. In this patient there was no histological diagnosis and no chemotherapy was given. Treatment parameters were analyzed for the remaining 62 patients who completed radiation treatment. Fifty-nine patients were treated by localized parallel opposed fields and three patients by a three-field technique.

Radiation Volume. Four (31%) of 13 patients who were treated with fields less than 80 sq cm in size are alive; 18 (25%) of 32 patients treated with fields of 80 to 109 sq cm are alive; and one (7%) of 14 treated with fields equal to or greater than 110 sq cm is alive. The minimum field size in a shrinking-field technique was used for this analysis. No data were available for three patients.

Radiation Dose. A tumor dose in the range of 5000 to 5499 cGy was administered to 33 patients, of whom eight (24%) survived. A higher tumor dose of 5500 to 5999 cGy was given to 21 patients, of whom five (24%) survived. Two patients received less than 5000 cGy (4500 and 4200 cGy), and six patients received doses in the range of 6000 to 6199 rads. None of these survived.

Daily Dose Fraction. The protocol required daily doses of 160 to 180 cGy for 5 days/week. Investigators elected on average to use rather higher daily dose fractions. Fractions of less than 175 cGy were used in 16 patients and four (25%) are alive; 175- to 185-cGy fractions were used in 19 patients, two (11%) of whom are alive; and fractions greater than 185 cGy were used in 24 patients, seven (29%) of whom are alive. No data were available for three patients.

Adjuvant Chemotherapy

Vincristine. Thirty-seven patients commenced adjuvant chemotherapy with VCR, and 35 completed the program. Two patients developed progressive disease while receiving VCR, and the drug was discontinued. Twenty-seven patients completed eight doses of VCR without need for a dose reduction greater than 15%, and eight patients tolerated only a reduced dose. Of these eight, total dose reductions were 15% (one patient), 20% (two patients), 25% (two patients), 33% (two patients), and 50% (one patient). Dose reductions were indicated because of the gastrointestinal and neurological side effects of VCR, none of which were life-threatening.

Maintenance Therapy. Three patients developed progressive disease after beginning VCR chemotherapy but earlier than 12 weeks from the commencement of irradiation and thus did not receive maintenance therapy with CCNU, VCR, and prednisone. An additional patient did not start maintenance therapy because of episodes of meningitis. Therefore, 31 patients commenced maintenance therapy. Eighteen patients discontinued maintenance treatment due to progressive...
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disease. Twelve patients completed eight cycles of mainte-
nance therapy, and one patient stopped treatment af-
after seven cycles due to an episode of herpes zoster.

One patient with familial thrombocytopenia received 
CCNU at 40% of the protocol dose in the first cycle.
Due to a fall in platelet count from 180,000 to 8000 
cu mm, CCNU was omitted in subsequent cycles. 
The dose of CCNU was reduced in six other patients 
without moderate hematological toxicity. Their dose 
reduction was required in the third cycle (one patient), 
the fourth cycle (three patients), the fifth cycle (one pa-
tient), and the seventh cycle (one patient). The VCR 
and prednisone were well tolerated, although one pa-
tient developed a personality disorder attributed to pred-

Infectious complications were seen more often in 
patients receiving adjuvant chemotherapy. Respiratory 
infections occurred in five patients, shunt infections in 
two, chicken pox in two, herpes zoster in three, mast-
toiditis in two, mediastinal abscess in one, and septic 
iepis in one, for a total of 16 infectious episodes among 
37 patients. In comparison, among 30 patients who 
completed radiation treatment alone, there were three 
episodes of otitis media, one respiratory infection, and 
one episode of shunt infection, for a total of five infect-
ious episodes. Overall, there were no infectious compli-
cations that resulted in death.

Two patients who completed eight cycles of mainte-
nance therapy did not stop at that point, as 
required by protocol, but continued with this treatment 
for 14 and 17 cycles, respectively. These patients con-
tinue in complete remission at 81+ and 89+ months 
from diagnosis, respectively. The first patient developed 
anemia requiring blood transfusion and became hypo-

The high rate of surgical exploration may reflect 
investigator interest in a detailed evaluation within the 
context of this study. The resection rate in explored 
patients confirmed that resection is rarely possible. The 
fragmentary data indicating that three of the four pa-
tients who underwent resection continue in a first re-
mission would support the use of resection when fea-
sible. There was no evidence that these were tumors of 
the favorable exophytic type described by Hoffman, et 

Chemotherapy for Relapse

Six patients who relapsed after radiation treatment 
alone were given CCNU, VCR, and prednisone (Regi-
men III) according to the same schedule and dosage as 
for adjuvant treatment. Two patients responded and 
were maintained on this treatment for two and five 
cycles, respectively, until the development of further 
progressive disease. Four patients received only one 
cyclus and were then judged to have progressive disease. 
These four patients survived 1, 2, 3, and 5 months from 
relapse compared with 5 and 12 months for those who 
responded to treatment.

Procarbazine, 100 mg/sq m, administered daily for 
14 days every 28 days (Regimen IV), was given to five
tients in this study demonstrated recurrent tumor at the primary site; that is, centrally in the irradiated tissue. With radiation doses in the range of 5000 to 6000 cGy there was no evidence for a dose-response relationship. For brain-stem tumors we continue to recommend a dose of 5250 to 5500 cGy given in daily fractions five times a week, with a total weekly dose of 800 to 1000 cGy. The smaller daily dose fraction and total doses are utilized for younger children.

The CCNU, VCR, and prednisone chemotherapy program used in this study proved to be well tolerated. There was no known added toxicity within the irradiated tissue volume. The principal morbidity associated with adjuvant chemotherapy was an increased risk of infection. None of the infections were fatal. The appearance of chicken pox (two cases) and herpes zoster (three cases) among the patients given adjuvant chemotherapy may be a consequence of the immunosuppression associated with systemic chemotherapy.

The majority of patients who relapsed in this study were treated symptomatically. A small subset of patients were selected by the investigators, using unknown criteria, for a trial of chemotherapy after progression or relapse. The results were disappointing. Other CCSG studies have indicated that this adjuvant chemotherapy program does indeed have value in childhood malignant astrocytomas of the cerebral hemisphere and in poor-risk patients with medulloblastoma.

We have no adequate explanation of why this adjuvant program should be helpful for malignant astrocytomas of the cerebral hemispheres, but not for apparently identical, often smaller tumors in the brain stem. Clearly, new effective methods are needed for treatment of brain-stem tumors in childhood.

APPENDIX

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