Ann Natl Acad Med Sci (India), **44(2)**: 111-117, 2008

Craniospinal Irradiation and Carboplatin and Etoposide combination chemotherapy in Medulloblastoma : AIIMS experience

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Abstract

The management of medulloblastoma includes surgery and craniospinal irradiation (CSI). Additionally, different chemotherapy schedules have been tried with an aim to improve survival. The outcome in patients with medulloblastoma treated with surgery, CSI and chemotherapy with carboplatin and etoposide was studied. The records of 50 patients with medulloblastoma treated at AIIMS from May 2001 to May 2005 were reviewed. After surgery, CSI was given to all patients. All patients were planned for 6 cycles of chemotherapy with carboplatin and etoposide after completing CSI, except in patients under 5 years of age who were given chemotherapy upfront. Patients were followed with clinical examination every 3 months and MRI of brain and spine every 6 months. At last follow up, 34 (68%) patients were disease-free, 3 (6%) had local progression, 1 (2%) had residual disease. Disease status was not available for 12 (24%) patients. No grade 3 or 4 chemotherapy or radiotherapy induced toxicities were seen. Chemotherapy with carboplatin and etoposide is an effective combination to be used in the adjuvant treatment of medulloblastoma following surgery and CSI.

Key words: Medulloblastoma, craniospinal irradiation, chemotherapy, carboplatin, etoposide

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Introduction

Medulloblastoma is the most common childhood malignant brain tumor, accounting for 16% of all pediatric brain tumors (1). The peak incidence of medulloblastoma is between 3 and 4 years of age, and the tumor is rare in adults. For adult medulloblastoma the peak age is between 20 and 35 years, after which the incidence steadily declines (2).

Medulloblastoma was first identified in Bailey and Cushing's classification of CNS tumors in 1925(3). The efficacy of radiation therapy was reported within a decade of Cushing's initial report of the tumor. The seminal report documenting the cure of medulloblastoma with CSI was published by Bloom in 1969, citing 32% survival at 5 years and 25% disease free survival at 10 years, with CSI(4).

The first randomized trials incorporating the role of chemotherapy in medulloblastoma were by SIOP (5) and CCG (6) in 1990, which established the role of chemotherapy in high risk patients. A range of alkylating agents and platinum-based regimens has been used in various studies. These have been used with reduced doses of radiotherapy in standard risk patients and with standard doses of radiotherapy in high risk patients.

We present here the outcome of 50 patients with medulloblastoma who were treated with surgery followed by adjuvant CSI and 6 cycles of chemotherapy with carboplatin and etoposide.

Materials and methods

We retrospectively reviewed the records of 50 patients with histopathologically proven medulloblastoma who were treated at our institution from May 2001 to May 2005. Staging work up included MRI of brain and spine and CSF analysis. All patients underwent a maximal safe resection with a histopathological analysis of the operative specimen. Adjuvant management comprised of CSI and chemotherapy.

All patients received CSI with a dose of 36 Gray in 20 fractions to whole brain and 30 Gray in 20 fractions to spine over 4 weeks, followed by a posterior fossa boost of 20 Gray in 10 fractions over 2 weeks (total dose 56 Gray). This was followed 3-4 weeks later by 6 cycles of adjuvant chemotherapy, which consisted of a combination of Carboplatin (AUC 5 iv D1) and Etoposide (100 mg/m^2 iv D1-D3) given every 3 weeks.

In children less than 5 years of age chemotherapy was started upfront after surgery in order to delay initiation of radiotherapy, which was instituted after completion of chemotherapy.

Blood counts were monitored twice weekly during radiotherapy. Additionally, complete blood counts, electrolyte levels, renal and liver function tests were performed before each cycle of chemotherapy. Chemotherapy was initiated only if these were within normal limits. Common toxicity criteria (CTCAE v 3.0) were used for recording treatment related toxicity.

After completion of the planned treatment regimen, patients were followed up longitudinally with a complete clinical evaluation including neurologic examination every 3 months and surveillance magnetic resonance imaging scans of the brain and spine every 6 months.

Results

Patient and disease characteristics

50 patients with medulloblastoma were treated at our institution between May 2001 and May 2005. Mean age was16.22± 11.83 years with a median age of 11.5 years (range 3-55 years). The main characteristics of patients and presenting features are described in Table 1.

Treatment

All patients were staged with MRI of brain and spine and CSF analysis. Surgery comprised maximal safe resection. The extent of resection and postoperative histology are described in Table 2.

Table 1

Age group (years)	Number (%)
0-10	23 (46)
10-20	14 (28)
20-30	6 (12)
30-40	5 (10)
40-50	1 (2)
50-60	1 (2)
Gender	
Male	35 (70)
Female	15 (30)
Presenting features	
Headache	38 (76)
Vomiting	6 (12)
Ataxia	6 (12)
Tumor location	
Midline	33 (66)
Lateralized	17 (34)

Table 2

Parameter	Number (%)
Extent of resection	
Gross total excision	30 (60)
Near total excision	12 (24)
Tumor decompression	8 (16)
Histology	
Classic	41 (82)
Desmoplastic	7 (14)
Anaplastic	2 (14)

All patients completed CSI as per the planned protocol. A total of 242 cycles of chemotherapy were given, the

median number of cycles per patient being 6 (range 0-6). Thirty nine (78%) patients completed 6 cycles of prescribed chemotherapy. Eight (16%) patients did not receive any chemotherapy. No grade 3 or 4 toxicities were observed with either radiotherapy or chemotherapy.

Follow up

Patients were followed up for a median duration of 59 weeks (range 13-230 weeks). At last follow up, 34 (68%) patients showed no evidence of disease, 1 (2%) showed residual local disease on imaging, and 3 (6%) patients showed local progression. Twelve (24%) patients were lost to follow up.

Discussion

Surgery followed by CSI is an accepted standard of care for management of medulloblastoma. Chemotherapy has been used in various studies with an improvement in outcome. With the identification of risk factors, i.e., age, extent of resection and presence or absence of metastases, a number of investigators are now using a risk-adapted approach for medulloblastoma (7) (Table 3) .

Table 3

Factor	Standard risk	High risk
Age at diagnosis	>3 years	=3 years
Extent of surgical resection	<1.5 cm^2 residual	≥1.5 cm^2 residual
Stage	M0	=M1

In standard risk cases, chemotherapy has been tried with the intention of reducing the craniospinal radiotherapy dose and thus the attendant neurocognitive and endocrine effects, while preserving or improving the survival rates. Packer *et al* first proved the efficacy of this concept in 65 patients in a CCG study in 1999(8). They reduced the craniospinal radiotherapy dose from the standard 36 Gray to 23.4 Gray, while maintaining the posterior fossa dose of 55.8 Gray, and added adjuvant chemotherapy comprising of vincristine, cisplatin and lomustine. A progression-free survival (PFS) of 79% at 5 years was observed, which compared favourably with historical controls.

A larger study randomized 421 patients aged 3 to 21 years to treatment with reduced dose CSI (23.4 Gray) and posterior fossa boost of 55.8 Gray, followed by adjuvant chemotherapy with either of two combination regimens; vincristine, cisplatin and lomustine or vincristine, cisplatin and cyclophoshamide(9). 379 patients were available for analysis. Five-year event free survival (EFS) and overall survival (OS) rates were 81% and 86% respectively for the entire cohort. EFS was unaffected by sex, race, age, treatment regimen, brainstem involvement or anaplasia. Patients in the lomustine arm experienced electrolyte imbalances more frequently while those in the cyclophosphamide arm had higher infection rates.

European studies such as the SIOP III study(10) have compared pre-radiation chemotherapy with vincristine, carboplatin and cyclophosphamide followed by standard dose CSI with CSI alone, and showed significant improvement in event free survival at 5 years with pre-radiation chemotherapy (74% vs 60%; p=0.036).

Reduced dose CSI in combination with chemotherapy, as opposed to conventional CSI schedules, has also shown some degree of intellectual preservation in prospective studies (11).

High risk medulloblastoma, especially if metastatic at diagnosis, has a particularly poor prognosis, despite use of standard CSI and chemotherapy. Addition of chemotherapy improves survival by 15-20% compared with historical controls administering radiotherapy alone (12). Pre-radiation chemotherapy has been seen to be inferior to post-radiation regimens in high risk patients, possibly by delaying radiotherapy, which might be responsible for the worse outcome (13).

Chemotherapy has not been able to improve outcomes for adult medulloblastoma patients, and its role in treatment of adult medulloblastoma in first remission is uncertain at present (14).

Our study included all age groups of patients treated for medulloblastoma at our institution from 2001 to 2005. The extent of disease and completeness of resection were noted but were not used for risk stratification of varying treatment regimens. All patients were offered surgery followed by standard dose CSI, the dose to whole brain being 36 Gray and the posterior fossa boosted to 56 Gray. The spine was treated to a dose of 30 Gray. The timing of chemotherapy was determined by the age of the patient. Patients older than 5 years were given CSI first followed by chemotherapy. In younger patients, where it was desirable to delay radiotherapy, chemotherapy followed surgery.

Both carboplatin and etoposide have been seen to be effective chemotherapeutic agents in medulloblastoma. A combination of the two has not been used earlier for the treatment of newly diagnosed medulloblastoma. A phase II study by SFOP evaluated the antitumor efficacy of this combination in 26 patients with measurable disease (residual or recurrent) following surgery, chemotherapy and/or radiotherapy (15). Two courses of carboplatin (160 mg/m^2/day D1-5) and etoposide (100 mg/m^2/day D1-5) were given. 36 courses were evaluated for efficacy and toxicity. Response rate, as assessed by CT, MRI, or myelogram and CSF, was 72%, with 6 patients developing progressive disease. Median duration of grade 4 neutropenia was 8 days. 6 patients developed life-threatening septicemias. Severe toxicity was encountered mainly in heavily pretreated patients.

We used the carboplatin-etoposide combination at lower doses compared with the SFOP study, and found this schedule to be both feasible and effective. No grade 3 or 4 adverse events were noted. Our follow up duration was short, the median duration being 59 weeks. 68% patients were disease-free at last follow up. It remains to be seen how these patients fare on long term follow up, in order to be able to compare our results with those of other studies.

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