Outcomes of adult medulloblastoma treated with a multimodality approach: A tertiary cancer center experience

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Abstract

Objectives: Adult medulloblastoma (AMB) is a rare central nervous system tumor. We aimed to analyze the treatment outcomes of AMB treated at our institute with surgery followed by craniospinal irradiation (CSI) and adjuvant chemotherapy. **Methods:** We retrospectively evaluated the treatment charts of 31 patients of AMB treated from 2003-2011. The patient demography, treatment details and survival data were collected in a predesigned proforma. Kaplan Meier method was used to analyze disease free survival (DFS) and the impact of prognostic factors was determined by univariate analysis (log rank test). **Results:** Male: Female ratio was 21:10. Cerebrospinal fluid dissemination was noted in 16% cases. CSI (36 Gray at 1.8 Gray/fraction to entire neuraxis and 20 Gray at 2 Gray/fraction boost to posterior fossa) was used in all cases. 26 patients received adjuvant chemotherapy (carboplatin plus etoposide). Median follows up was 26.85 months (9.47-119.73 months). The estimated 3 and 5 years DFS was found to be 84.9% and 50.7% respectively. On univariate analysis, tumor located laterally had a trend towards better DFS (HR 3.04; 95%CI 0.722 to 12.812; $P = 0.07$) compared to midline tumors. Other factors like adjuvant chemotherapy, age, gender, surgical extent had no statistically significant impact on survival. **Conclusion:** The results of our study (largest series from India) show that the regimen of surgery, adjuvant CSI and chemotherapy is feasible and confers descent survival. AMB patients should be treated with a multimodality approach in a tertiary care centre.

Key words: Adult medulloblastoma, chemotherapy, radiation

Introduction

Medulloblastoma (MB) is the most common brain tumor in children, accounting for 15–30% of all pediatric cancers of the central nervous system (CNS).[1] In adults, medulloblastoma (AMB) is rare, accounting for only 1–3% of all primary brain tumors.[2] AMB, compared to the pediatric counterpart, has been found to have a distinct demography, morphology and molecular characteristics.[1,3] However, the rarity of AMB precludes randomized trials to optimize the therapeutic approach. Hence, treatment decisions are based upon information derived from case series[4,5] and retrospective studies with considerable heterogeneity.

Maximal safe resection and adjuvant radiotherapy (RT) to the cranio-spinal axis has been considered optimum in many institutes.[1] The 5 years overall survival (OS) and disease-free survival (DFS) has been reported to be approximately 60–85% and 50–75% respectively in large series of AMB.[1] Adjuvant chemotherapy (AdCT) has been found to improve survival[5,6] however the role remains controversial.[4]

Treatment protocols are variable across institutes[6] and there is little consensus on this. Ours being a tertiary referral center registers the larger number of CNS cases. Hence in this report, we intended to present our experience of treating patients of AMB with adjuvant cranio spinal irradiation (CSI) followed by chemotherapy.

Materials and Methods

A total of 1487 brain tumor patients were registered in our institute from January 2003 to December 2011. We performed a retrospective analysis of AMB (≥18 years of age) patients undergoing adjuvant treatment in our institute. 45 patients were found to have AMB, constituting 3.02% of all CNS cases. 3 patients did not receive adjuvant RT because of poor performance status and follow-up data was missing in 11 cases and these cases were excluded from analysis. Demographic features, clinical characteristics including radiological findings, surgical details and histopathological features were recorded in a predesigned proforma. The study was approved by institutional review board and all the patients signed the informed consent form prior to initiation of treatment.

The patients underwent maximal safe surgical resection (gross total excision [GTE] [>90% resection], sub-total excision [<90% resection] or decompression only) along with placement of a ventriculo-peritoneal shunt prior to surgery. This was followed by CSI and AdCT. Postoperative magnetic resonance imaging (MRI) of the entire neuraxis and cerbro-spinal fluid (CSF) cytology was done for all cases for risk categorization. The risk stratification was done according the Changs criteria.[7] The presurgical extent of the disease was documented from the diagnostic contrast-enhanced MRI of the brain.

Adjuvant radiation was delivered within 4–6 weeks of surgery. RT was delivered by either Co-60 tele-therapy machine (Theratron 780 C, Canada) or with a linear accelerator (Varian Medical System, Palo Alto, California, United States). The patients were immobilized in a prone position with a customized thermoplastic head cast with the appropriate prone head rest. The curvature of the vertebral column was neutralized with a Styrofoam block. The patients treated on telecobalt unit were planned by two-dimensional fluro-simulation. In patients planned with three-dimensional conformal radiation therapies, the clinical target volume (CTV) consisted of the entire brain and spinal axis extending at least 1 cm beyond the thecal sac (as determined from MRI images). 5 mm margin was given around CTV to delineate planning target volume. The planning was done using Eclipse treatment planning system Version 6.5 (Varian Medical Systems, Palo Alto, CA). The whole cranium received a dose of 36 Gray in 20 fractions over 4 weeks, followed by 20 Gray in 10 fractions over 2 weeks boost to the posterior fossa. The dose to the spinal axis was 36 Gray at 1.8 Gray per fraction, followed by a boost dose of 5.4–9 Gray at 1.8 Gray per fraction (for isolated spinal drop metastasis).

Adjuvant chemotherapy schedule consisted of 6 cycles of carboplatin and etoposide (injection carboplatin area under curve 5 [intravenous] on D1 plus injection etoposide 100 mg/m^2 [day 1–3] repeated every 3 weeks). Patients with CSF dissemination or spinal drop metastasis received injection vincristine (1.4 mg/m^2; maximum 2 mg intravenous weekly)

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and intra-thecal methotrexate (15 mg once a week till three consecutive CSF are negative for tumor cells) in addition to the standard chemotherapy.

Complete blood count, liver function test and renal function test was repeated once a week during radiation and before each cycle of AdCT. The chemotherapy toxicity was graded according to the common terminology criteria for adverse events criteria version 3.0 (National Cancer Institute, USA). Patients presenting with features of raised intracranial tension or any grade 3 or higher hematological or nonhematological toxicities were managed indoors with intravenous antibiotics, growth factors, transfusion of blood products and supportive care as required.

After completion of treatment, the patients were evaluated with periodic clinical and radiological examination. The patients were followed 1-month after completion of radiation and subsequently every 3 months for first 2 years, every 6 months for next 3 years and yearly thereafter. A contrast-enhanced MRI of the brain and spine was ordered, starting from second follow-up visit and repeated subsequently. Response evaluation was done by Mac Donald's criteria.[8]

The recurrences were worked up with contrast-enhanced MRI of brain and spine as well as CSF cytology. For a localized recurrence, surgical salvage was considered, followed by consolidation with re-irradiation or chemotherapy. In patients with a disseminated recurrence, chemotherapy alone was considered. The chemotherapy schedule for salvage consisted of VEC (injection vincristine 1.5 mg/m^2 [Max 2 mg], injection etoposide 100 mg/m^2 [intravenous day 1–3] and injection carboplatin area under curve 5 [intravenous day 1]) with or without intrathecal methotrexate.

Disease free survival was calculated from the date of surgery till the date of documented disease progression or death and Kaplan–Meier method was used for survival analysis. Univariate analysis (log-rank test) was used to assess the impact of age (</>30 years), gender, laterality of tumor, extent of surgery, chang's stage and AdCT on DFS. The statistical analysis was performed using SPSS version 21.0. $P < 0.05$ was taken as significant and SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis.

Results

Patient characteristics have been summarized in Table 1. 10 patients aged more than 30 years. The median time gap between surgery and initiation of RT was 30 days (range: 21–35 days). Five patients had CSF dissemination at presentation. The distribution as perchang's stage was M3 (Gross nodular seeding in spinal subarachnoid spaces) in 4 patients and M2 (Intracranial tumor beyond primary site) in one patient.

Surgery was contemplated in all patients. Medium pressure ventriculo peritoneal shunt was placed in all cases prior to surgery. 24 patients underwent a GTE and 7 patients underwent subtotal resection (STR).

Cranio-spinal irradiation was delivered in all cases. The dose to the spinal axis was 36 Gray and the cranial dose was 56 Gray. The compliance to radiation was excellent, and all patients completed the stipulated treatment. Median duration of RT treatment was 49 days (range 42–58 days).

Totally 26 patients received adjuvant CE based chemotherapy. Remaining 5 patients received radiation alone. Median number of chemotherapy cycles was 6 (range - 3–6). Of note 20 patients received the planned 6 cycles of chemotherapy whereas 6 patients received <6 cycles. 10 (33%) patients developed grade III or higher hematological toxicity and 6 patients developed febrile neutropenia. 3 patients developed Grade IV hematological toxicity. However, there was no treatment-related mortality. 1 patient developed Grade 2 gastrointestinal toxicity and 2 patients developed grade 3 gastrointestinal toxicity. Grade I skin toxicity was seen in 10 patients and 1 patient developed grade II skin toxicity during RT.

Median follows-up 26.85 months (RANGE: 9.47–119.73 months). The median DFS for the entire cohort was not reached. The estimated 3 and 5 years DFS was 84.9% and 50.7%. At the last follow-up 22 patients were found disease free. Disease free survival of the entire cohort has been depicted in Figure 1. Median DFS was better [Figure 2] for patients with gross total resection (GTR) (not reached) compared to STR group (40.16 months); with a hazard ratio (HR) of 2.4301 (95% confidence interval [CI]: 0.4280–13.7994; $P = 0.0703$). 66% of patients in the present series had lateralized disease. The median DFS was not reached for the laterally located tumors compared to 35.08 months for centrally located tumors with a HR of 3.04 (95% prognostic factors did not show CI - 0.7221–12.8129; $P = 0.0703$). Other prognostic factors did not show the statistically significant impact on DFS as summarized in Table 2.

The most common site of failure was the posterior fossa (7 patients). Only one patient developed isolated spinal metastasis, and one had a local failure with CSF dissemination. One patient underwent re-excision and salvage chemotherapy was used in all cases. However, all but one patient progressed after salvage therapy.

Table 1: Patient characteristics

Patient attributes	Factors
Median age (years) (range)	26 (18-49)
Symptoms* (number of patients)	
Headache	25
Vomiting	13
Ataxia	06
Vision disturbance	02
Pain in neck/back	02
Median symptom duration (months) (range)	2 (1-24)
Median KPS (range)	80 (70-90)
Male: female	20:11
Tumor location (number of patients)	
Lateralized	21
Midline	10

*Symptoms add more than 31 (total number of patients) because of multiple symptoms at presentation. KPS=Karnofsky performance status

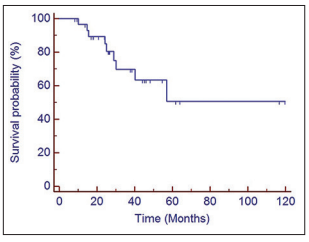

Figure 1: Disease free survival of entire cohort

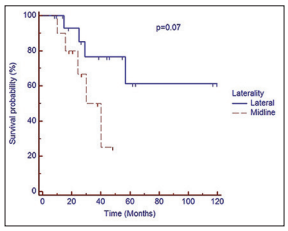

Figure 2: Disease free survival in lateral and midline located tumors

Discussion

Medulloblastoma has been recognized to hold a major share in the spectrum of small blue round cell brain tumors. Origin from the transient undifferentiated neuroepithelial cells of the developing cerebellum explains the high incidence of MB in pediatric age group. It has been reported that 75% of all MB cases occur in < 15 years and only 20–25% cases are diagnosed in the adult population.[1] It is interesting to note that AMB constituted 3% of total CNS cases registered in our institute. This figure may be higher compared to true incidence because of the referral bias.

Medulloblastoma are known as a highly aggressive tumor with predominantly neuronal differentiation. AMB has a lesser propensity to metastasize, however late recurrence has often been reported. The extra CNS metastasis is limited to the bone in both pediatric medulloblastoma (PMB) and AMB, however, lung metastasis is more frequent in AMB and liver metastasis in PMB.[6] In our study, there were no patients with extra-neuraxis metastasis.

Histology of AMB has been reported to be desmoplastic in 50–70% cases whereas PMB is more frequently of the classical variety.[9-11] Even, the molecular classification of four distinct types of PMB does not hold true for its adult counterpart. Recently, gene expression profile has revealed three distinct classes of AMB compared to four classes in PMB. The group C tumors which comprise a robust group in PMB are seen exceptionally in the adult age group. Note should be made that even the WNT/wingless and the group D tumors fare worse compared to the pediatric counterpart leaving enough space to search for the cause of such results.[3] The deletion of 10q, which was restricted to SHH and Group C hardly made any prognostic impact in PMB but is associated with worse outcome in the adult subgroup. This clearly shows the heterogeneity of MB across age group. Therefore, extrapolation of information from the pediatric group to adult patients may have several limitations.[12,13]

Several prognostic factors have been implicated to influence the survival of AMB like gender, CSF dissemination, Chang staging, laterality of tumor location, etc., Weil *et al*.[14] in their experience of 109 consecutive patients of PMB treated with multimodality approach found female sex to be independently associated with favorable survival (HR 0.52; 95% CI, 0.29–0.92; P = 0.03). However, studies in AMB[4] and also other PMB failed to suggest any gender preference in survival outcome including our present study.

Cerbro-spinal fluid dissemination and spinal metastasis makes the back bone of Chang's prognostic criteria.[7] As high as 36% cases of AMB has been reported to have positive CSF cytology in AMB or has drop metastasis.[6] Brandes *et al*.[15] in their study of 36 AMB patients reported significantly better outcome in patients with no CSF dissemination (5 years progression-free survival: 75% vs. 45%; P = 0.01). Interestingly, 13 patients (36%) in this study had CSF dissemination at presentation, and this could be the reason for this statistical difference. In the present study, there was no statistically significant difference in DFS (3 years DFS in nonmetastatic vs. metastatic: 72.9% vs. 60%; P = 0.36). This could be because of small number of metastatic patients in our study (16%) (0.3616). Similarly, no difference has been reported in other studies[4,11] as well and this likely have been masked due to the small patient number.

Table 2: Impact of prognostic variables on DFS

Univariate analysis			
Factor	***P***	**HR**	**95% CI of HR**
Age (<30 years vs. ≥30 years)	0.8979	1.0947	0.2677-4.4759
Adjuvant chemotherapy (yes vs. no)	0.3572	1.6740	0.580-10.2559
Gender (female vs. male)	0.6605	0.5774	0.1558-2.1402
Surgery (STR versus GTR)	0.1848	2.4301	0.4280-13.7994
Laterality (midline versus lateral)	0.0703	3.0418	0.7221-12.8129
Stage (M+vs. M0)	0.3616	2.0337	0.2786-14.8464

HR=Hazard ratio, CI=Confidence interval, STR=Subtotal resection, GTR=Gross total resection, M+ =Metastatic, M0=Nonmetastatic, DFS=Disease free survival

Location of tumor varies between adult and pediatric patients with approximately 50% lateralized tumor in the adult subgroup compared to < 10% in the pediatric patients.[12,13] The nonvermian location predicts a complete resection, which may translates into better survival. In our study, 66% patients had disease localized laterally and patients with lateralized disease showed a trend toward improved DFS (HR: 3.5 years DFS in completely resected vs., incomplete: 57.8% vs. 28.6%; P = 0.07).

Surgical resection has been established as the cornerstone of therapy. Several recently published series have established complete surgical excision as the most important prognostic factor.[4] Chan *et al*.[13] in their study of 32 patients with AMB found STR to be adversely associated with posterior fossa control (P = 0.02) and DFS (P = 0.02). In the present report also patients with a GTR found to have better survival than those with a STR (median DFS: Not reached vs. 40.16 months), however may be due to small sample size it could not reach statistical significance (P = 0.1848).

Surgery alone produces unacceptable high recurrence and dismal survival in AMB necessitating adjuvant radiation.[16,17] Adjuvant radiation therapy has been considered an integral part in the management of patients with MB. The high propensity for CSF dissemination makes it necessary to treat the entire neuraxis with an adequate dose of radiation followed by a boost to the posterior fossa. Early initiation of radiation, preferably within 4–6 weeks after surgery has been reported to confer better long-term disease control. del Charco *et al*.[18] in their study of 53 patients showed posterior fossa control to be detrimental when RT duration was >45 days (5 years control rates: 68% vs. 89%; P = 0.01). Median duration of RT treatment in our study was 49 days and this might have caused some detrimental effect on survival.

Dose-response has also been established and there is enough data to advocate a posterior fossa dose in the range of 50–56 Gray for a prolonged disease control and survival.[19,20] Adequate dose to the spinal axis has been shown to provide better prolonged disease control. The spinal axis dose reduction from 36 Gray to 23.4 Gray was attempted in the pediatric population but resulted in excessive recurrence.[21] However, the dose reduction was possible only when concurrent and AdCT was added to CSI. Packer *et al*.[22] in a phase III trial showed the addition of a multi-agent chemotherapy with a lower dose of radiation to the spinal axis resulted in excellent results but at the cost of significantly higher toxicity. In AMB there is a little inhibition to use a higher dose to the spinal axis because of a rare chance of growth retardation. However, there is some suggestion to reduce CSI dose in adults (particularly in standard risk patients) based on the

Table 3: Summary of published series of adult medulloblastoma treated with craniospinal irradiation and chemotherapy

Author, year (reference)	Number of patients	Extent of resection	Number of patients (chemotherapy regimen)	Survival outcome	Pattern of recurrence (number of patient)
Kunschner *et al*., 2001[24]	28	GTR-53%	4 (CVP) 2 (others)	3, 5 years OS - 91%, 88% 3, 5 years PFS - 68%, 62%	PF - 6 Bone - 2
Brandes *et al*., 2003[15]	36	GTR-44%	6 (MOPP) 16 (CECy)	5 years PFS - 76% (low risk); 61% (high risk) Median OS - 8.15 years	PF - 5 Bone - 1 Bone marrow - 1
Padovani *et al*., 2007[4]	253	GTR-58%	252 (regimen NR)	5, 10 years DFS - 65%, 55%	PF - 35 Extra CNS - 9
Menon *et al*., 2008[25]	18 (>16 years)	GTR-72%	14	5 years 55% PFS-NR	11 - PF
Rikesh Gandhi *et al*., 2013[26]	669	GTR-47.7%	NR	Median OS - 155 months	NR
Present study	31	GTR-77%	26 (CE)	3, 5 years DFS - 84.9%, 50.7%	PF - 7

GTR=Gross total resection, CVP=Cyclophosphamide, etoposide, cisplatin, OS=Overall survival, PFS=Progression free survival, PF=Posterior fossa, MOPP=Nitrogen mustard, vincristine, oral prednisolone and procarbazine, CECy=Cisplatin, etoposide, cyclophosphamide, DFS=Disease free survival, CNS=Central nervous system, CE=Carboplatin and etoposide, NR=Not reported

results reported by Padovani *et al*.[4] In this multicentric retrospective study of 253 adults, patients of standard risk MB treated with low spinal dose (<34 Gray) with chemotherapy had noninferior outcomes as compared to those treated with spinal doses >34 Gray (P = 0.7). We in our institute have been following a spinal dose of 36 gray and has been well tolerated over the period of time. However, the dose reduction with chemotherapy (with extrapolation from pediatric population) seems reasonable and needs testing in a clinical trial setting.

Chemotherapy in average risk PMB has helped to reduce the dose of radiation to the Cranio-spinal axis. However, spinal dose is of little concern and it's difficult to find place for chemotherapy in AMB. There is little agreement about the magnitude of true benefit of adding AdCT in AMB. But, some institutes do continue to use chemotherapy for prolonging disease control. A combination chemotherapy regimen[22] has long been considered most appropriate for MBs. However, these regimens are associated with considerable grade III and Grade IV toxicity. Silvani *et al*.[23] recently published their experience of treating AMB patients with CSI and chemotherapy with cisplatin and etoposide (regimen similar to our regimen). The authors reported 5 years PFS and OS 57.6% and 80% respectively with 16% grade II and IV hematological toxicity. Table 3 summarizes the studies adopting adjuvant CSI and chemotherapy with an aim to improve survival. However, point should be made that there is little consensus regarding the chemotherapy regimen in these studies which makes it difficult to reach a meaningful conclusion. In this study, we have reported a series of AMB uniformly treated with surgery followed by adjuvant CSI and adjuvant cisplatin and etoposide based chemotherapy. The 3 and 5 years DFS was 84.9% and 50.7%, respectively.

Our data have several limitations owing to the retrospective nature of the study, which brings into question various sources of bias. However, it appears difficult to conduct randomized trial for this rare disease. It is noteworthy that after recurrence many patients are deemed nonsalvageable and the poverty in developing countries precludes regular follow-up. The effectiveness of this combined modality approach in an unselected patient population outside a clinical trial simulating a real world scenario and can be considered as strength of the data. This is the largest series of AMB patients reported from India and would act as comparative benchmark for reports from other institutes as well.

Conclusion

Maximal safe surgical resection remains the cornerstone of therapy for AMB. In our experience of 31 patients, adjuvant CSI, followed by chemotherapy is well tolerated with minimal morbidity and descent survival outcomes. Tumors with lateral location tend to have a better outcome than centrally located tumors. The role of AdCT in AMB needs to be tested in a multicentric trial.

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