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Original Article

Treatment Refusal and Abandonment Remain Major Concerns Despite Good Outcomes with Multi-Modality Management in Pediatric Medulloblastoma: Experience from a Cancer Center in Eastern India

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Abstract

Context: Survival in medulloblastoma, the most common pediatric brain tumor, has lagged behind in developing countries in comparison to the West. **Aim:** The aim of this study was to analyze the clinical profile and outcome in a cancer center in Eastern India. **Methods:** Twenty-nine children were retrospectively analyzed over 6 years. **Results:** Vomiting (79%), headache (69%), and unsteadiness (55%) were the presenting complaints. The majority (67%) had classical histology. High-risk (HR) disease (61.6%) exceeded average-risk (AR) (38.4%) disease in numbers. Treatment-refusal (27.6%) and abandonment (6.9%) were major concerns. Four-year EFS was 81% and 52%, excluding and including refusal/abandonment, respectively. There was no relapse/progression among AR patients. Four-year EFS in HR was 63%. Posterior fossa syndrome (37.5%), febrile neutropenia (29%), and ototoxicity (16.7%) were the main treatment-related morbidities. **Implications:** Following this audit, patient tracking to reduce abandonment, coordination to limit delay in postsurgical referral, developing strategies for molecular subgrouping, and reducing cumulative cisplatin exposure were measures adopted to improve outcome in the unit.

Keywords: *Brain tumor, defaulter, ototoxicity, posterior fossa*

Introduction

Central nervous system tumors are second only to hematological malignancies among childhood cancers. Medulloblastoma is the most frequent brain tumor in children.[1] Cure rates with multimodality treatment approaches 85% for average-risk (AR) and 75% for high-risk (HR) patients.[2] Data from India are limited.[3-7] The aim of the study was to analyze the clinical profile and outcome in a referral oncology center in Eastern India over the last 6 years.

Materials and Methods

All children, <18-years at diagnosis, were retrospectively included between May 2011 and April 2017. Patients were referred, after surgery from different neurosurgical centers in the region, for adjuvant radiation and chemotherapy. Diagnosis was confirmed on histopathology after procuring blocks and slides, if available. Staging investigations included magnetic resonance imaging (MRI) of the spine, postoperative MRI of the brain (for assessing residual disease), and analysis of the cerebrospinal fluid (CSF). Children >3-years at diagnosis, with postoperative residual <1.5-cm^2, normal CSF, and a nonlarge cell/anaplastic (non-LCA) histopathology were classified as AR. They received craniospinal irradiation with 23.4 Gy in 13-fractions, while children >3-years with HR disease received 36 Gy in 20-fractions. All children >3-years received boost to the posterior fossa/tumor bed with a dose of 55.8 Gy in 31-fractions. None received concurrent chemotherapy with radiation. Children <3-years were candidates for radiation-sparing or delaying strategies using chemotherapy. Adjuvant chemotherapy for AR included cisplatin, vincristine and lomustine, and for HR included cisplatin, vincristine and cyclophosphamide, both for eight cycles, lasting 6 weeks each, with each cycle starting following recovery of blood counts. Survival analysis was performed using the Kaplan–Meier method.

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Results

Twenty-nine children were included in this study. Median age was 7 years (range: 0.9–14). Sixteen (55%) were male. Median symptom-interval was 3.7 months (range: 1–12). Clinical features at diagnosis included vomiting (23, 79%), headache (20; 69%), unsteadiness of gait (16; 55%), and cranial nerve palsy (3; 10%). On the preoperative MRI (n = 25), the location of the tumor was in the midline cerebellum (10; 40%), roof of the 4th ventricle (10; 40%), and lateral cerebellum (5; 20%). Surgical data were available in 19; 9 (47%) had gross tumor excision, 4 (21%) had near total removal, and 6 (31.5%) had subtotal resection. A ventriculoperitoneal shunt had been inserted in 14/23 (61%). Pathological subtype was documented in the reports of 12 patients: classical (8; 67%), desmoplastic/nodular (2; 16.5%), and LCA (2; 16.5%). Staging (n = 25) revealed 12 (48%) with localized disease, 3 (12%) with malignant cells in the CSF, 7 (28%) with disease in the spine, and 3 (12%) with distant metastasis in the liver and bones. Sixteen had HR (61.6%) and 10 (38.4%) had AR disease. Out of the 16 children with HR disease, 13, including two children <3-years, had metastatic disease; among the rest, two had residual disease >1.5 cm^2, and one was 1.7 years old. Data were incomplete in three children.

Among the 29 children, 8 (27.6%) refused treatment and 2 (6.9%) abandoned care. All had HR disease. One child (3.4%) opted for palliative care in view of metastatic disease. Three (10.3%) had recurrence/progressive disease on follow-up. The remaining 15 (51.7%) children are well on follow-up. Median follow-up duration for the entire cohort was 54 months. The median 4-year event-free survival (EFS) was 81.4% ± 0.1% and 51.2% ± 0.1%, excluding and including refusal/abandonment, respectively. There were no relapses/progressive disease, or refusal/abandonment among AR patients (EFS = 100%). Among HR patients, EFS, excluding refusal/abandonment was 63.4% ± 0.1% [Figure 1] and including refusal/abandonment was 31.1% ± 1.2%.

Data related to treatment-related toxicity was available in 24 children. About 9 (37.5%) had posterior fossa syndrome, 7 (29%) needed admissions for febrile neutropenia, 1 (4%) had a shunt block, and 4 (16.7%) had hearing loss. All needed nutritional support. There was no death related to treatment toxicity.

Discussion

With the rapid introduction of molecular profiling in clinical classification, management of pediatric brain tumors, including medulloblastoma, is likely to undergo a paradigm change.[1] However, the developing countries are struggling with providing optimal care to children with potentially curable brain tumors. Access to care and treatment refusal/abandonment remain important concerns. This has been highlighted in previous studies from Asia, Africa, and Latin America.[8-10] The index series reports 35% refusing/abandoning care. The retrospective nature of the audit precluded detailed analysis of the possible reasons for default. However, patient tracking over telephone has been prospectively activated in our center to counter this menace, using workforce, and financial support from government and voluntary groups.

Despite limited numbers, the protocol-based standardized management for the AR patients produced satisfactory results. The higher proportion of HR patients was plausibly due to referral bias. The previous studies from India have

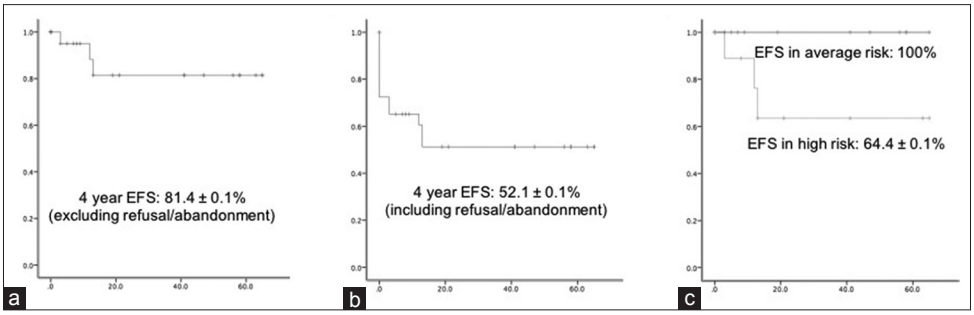

Figure 1: Event free survival in children with medulloblastoma: (a) excluding refusal and abandonment; (b) including refusal and abandonment as events; (c) event-free survival in children with average and high-risk disease at median follow-up of 54 months (cases with refusal/abandonment were censored)

Table 1: Published reports on pediatric medulloblastoma from India

Author	Center	Year	n	Survival
Muzumdar *et al*.[4]	Mumbai	2011	365	5-year progression free survival: 73% (average risk), 34% (high risk)
Menon *et al*.[3]	Trivandrum	2006	79	5-year overall survival: 24%
Kumar *et al*.[6]	Hyderabad	2015	31	3-year overall survival: 40%
Das *et al*. (current study)	Kolkata	2018	26	4-year event-free survival: 100% (average risk), 63% (high risk)
Gupta *et al*.[5]	Mumbai	2012	20	3-years relapse-free survival: 83% (average risk, age >5 years)

reported the survival in the AR group varies between 73% and 83% and among HR, between 34% and 63%, similar to the index study [Table1].[3-6] Lack of molecular subgrouping is recognized as a lacuna in most of these studies. An additional limitation was that there were only three children below 3 years of age, one of whom had progressive disease, and the other two had defaulted. It is well established that this challenging subgroup of patients need a dedicated approach different from that for older children.

Measures adopted in the unit following this audit included developing better coordination with referral centers to reduce delay, developing an electronic database, molecular studies for better subgrouping, and limiting the cumulative cisplatin exposure to reduce ototoxicity by adapting from results of international collaborative studies.[11] We hope that the recently published guidelines of the Indian Society of Neuro-Oncology and collaborative studies under the Indian Pediatric Oncology Group will help standardize management and improve outcomes in Indian children with medulloblastoma.[1]

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Conflicts of interest

There are no conflicts of interest.

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