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M1 Medulloblastoma: High Risk at any Age

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Abstract

Background—The prognosis for children with M1 medulloblastoma (positive CSF cytology) has not been well-defined.

Methods—We retrospectively reviewed the records of 285 newly diagnosed medulloblastoma patients treated between 1984 and 2006. Older children received post-operative craniospinal and tumor bed irradiation; radiotherapy for younger children depended on treatment era and physician/family preference.

Results—55 patients were <3 years old and 230 patients were ≥ 3 years old at diagnosis. We detected significant ($p < 0.0001$) associations between M1 disease and EFS for the entire cohort and for both younger and older patients. Among younger children, M1 patients had lower EFS than M0 ($p = 0.0044$).

Conclusions—Children <3 years old with M1 medulloblastoma fared poorly in our small series. Survival for older children with M1 disease treated with higher-dose CSI was better than that of M2/M3 patients, but still less than optimal; our findings do not support reduction in therapy for either cohort.

Keywords

medulloblastoma; cytology; infant; survival; metastatic; prognosis

Background

Metastatic (M) stage has, in general, been shown to be an important marker of poor prognosis for children with medulloblastoma, [1-5] but the significance of M1 disease (metastatic tumor detected by cerebrospinal fluid [CSF] cytology only) has not been as clearly defined. For children less than three years of age, the prognostic value of M1 disease has not been specifically evaluated in published clinical trials [2-6]. Children older than three years of age with metastatic medulloblastoma have had improved survival rates with current therapy including at least 35 Gy craniospinal irradiation and dose intensive chemotherapy. [7,8] In the

setting of such intensive therapy, some investigators have suggested that M1 medulloblastoma is not an adverse prognostic factor. [8] We retrospectively reviewed the records of all medulloblastoma patients treated at our institution between 1984 and 2006 in order to compare rates of event-free survival (EFS) and overall survival (OS) for children with M1 medulloblastoma to those of children with localized (M0) and macroscopic metastatic (M2/3) disease. We then examined the prognostic impact of M1 disease in children of different ages ($<$ or ≥ 3 years).

Methods

After obtaining approval from the Institutional Review Board, we retrospectively reviewed the records of all newly diagnosed medulloblastoma patients treated at St. Jude Children's Research Hospital between 1984 and 2006. Metastatic stage was defined as follows: M0, no evidence of metastasis; M1, tumor cells identified by CSF cytology; M2, intracranial metastatic tumor detectable by computed tomography (CT) or magnetic resonance imaging (MRI); M3, spinal metastatic tumor detectable by CT myelography or spine MRI. Treatment generally included maximal safe resection and chemotherapy. For children < 3 years of age at diagnosis, the timing and extent of radiotherapy (RT) depended on the treatment era and physician/family preference; in general, patients diagnosed prior to 1998 received treatment based on the Pediatric Oncology Group Baby-POG 1 study, [2,9] in which neoadjuvant chemotherapy was followed by craniospinal irradiation (CSI) at the time of disease progression or after a delay of 12 to 24 months. Children < 3 years of age with localized medulloblastoma diagnosed in 1998 or later received post-resection chemotherapy followed by focal conformal RT to the primary tumor site, while children with metastatic medulloblastoma treated during this era either received CSI at the time of disease progression or were never irradiated. All children ≥ 3 years of age received post-operative CSI and tumor bed RT. Since 1996, children ≥ 3 years of age at diagnosis have been treated on two successive protocols (SJMB96 and SJMB03) which employ risk-adapted RT followed by 4 cycles of high-dose chemotherapy with autologous stem cell rescue as previously described. [7] EFS was measured from the date of initial treatment to the earliest date of disease progression, second malignancy or death for patients who failed; and to the date of last contact for patients who remained at risk for failure. OS was measured from the date of initial treatment to the date of death or the date of last contact. Analysis of EFS and OS was performed using the Kaplan-Meier curves and log-rank tests; survival rates are presented as percentages followed by 95% confidence intervals in parentheses. [10] Due to the retrospective nature of the study and the small cohort sizes involved, the p-values provided for the various log-rank tests have not been adjusted for multiple testing.

Results

During the study interval, 285 patients with newly diagnosed medulloblastoma were treated at our institution. Patient demographic and clinical features are presented in Table 1. Median follow-up was 4.5 years (range 0.2–23 years). Five-year OS and EFS rates are presented in Table 2. Five-year OS for all patients was 73.1% (65.7%–78.9%), and 5-year EFS for all patients was 63.4% (55.2%–69.6%). Patients with M1 medulloblastoma ($n=18$) had significantly diminished OS (Figure 1A, p -value=0.00852) and EFS (Figure 1B, p -value=0.0060) compared to patients with M0 disease.

During the study interval, we treated 55 children < 3 years of age at diagnosis, including 5 patients with M1 disease. M1 disease was diagnosed by lumbar CSF cytology in all 5 patients. CSF samples were obtained at least 13 days postoperatively in 4 patients; in a single patient initial staging was based on a perioperative sample, but this patient had persistently positive CSF cytology two months after the start of therapy. The patients with M1 disease were treated

on the POG 8633 (Baby POG-1, n=2), St. Jude CNS-3 (n=2), and PBTC-001 (n=1) trials; details of these treatment regimens have been published previously.[9,11-12] The CNS-3 trial consisted of an upfront thiotepa window preceding Baby POG-1 therapy; neither patient treated on this trial experienced disease progression during window therapy. While the small cohort size hinders the generalizability of our observation, EFS for M1 patients in this younger cohort was significantly worse than that of M0 patients, and similar to that of M2/M3 patients (Figure 1C, p-value=0.0044). All patients with M1 disease ultimately received CSI to a dose of > 35.0 Gy. Four patients received CSI after disease progression (one with recurrence of positive CSF cytology after initially clearing and three with primary site recurrences); all four patients subsequently died of disease. One patient never experienced disease progression; he was treated with chemotherapy for one year as per the Baby POG-1 protocol, [9] followed by 35.2 Gy CSI, and was alive at last follow-up, more than 16 years after initial diagnosis.

For the 230 children = 3 years of age (Figure 1D), there was likewise a significant difference in EFS by M-stage (p-value<0.0001). EFS for M1 patients appeared to be better than for M2/3 patients (p-value=0.147), but less than that of M0 patients (p-value=0.105); the comparisons among subgroups failed to reach statistical significance in this cohort.

Discussion

In this retrospective review of 285 children with medulloblastoma treated at a single institution, we found that patients with M1 disease have reduced rates of EFS and OS compared to those with M0 disease. When survival results were analyzed by age at diagnosis, we found that children younger than three years of age with M1 medulloblastoma had significantly diminished EFS compared to those with localized (M0) disease, and in fact fared as poorly as those with macroscopic metastatic (M2/M3 disease). The impact of M1 disease on OS and EFS, particularly in patients =3 years of age, has not been published previously. M1 medulloblastoma patients three years of age or older were treated with postoperative CSI and had better outcomes than younger children with the same stage of disease, but EFS was still less than optimal. Interpretation of our results is limited by the small number of patients in each subgroup, the retrospective nature of the study, and the heterogeneity of treatment plans. Nevertheless, we believe our findings provide important insights for the design of clinical trials.

The impact of M1 disease on EFS has not been defined previously for infants and toddlers with medulloblastoma. In most clinical trials for these children, patients with M1 disease have been grouped with those with M2/3 disease. [3,5,6,9,13] In the German cooperative group HITSKK92 trial, however, patients with M1 disease were not distinguished from those with M0 disease. Notably, this trial produced the best survival results to date for children less than three years of age with medulloblastoma. On the HITSKK92 trial and most of the other published trials, patients received the same initial treatment regardless of M-stage, but current and future trials will treat children differently based on the presence of metastatic disease. The prognosis associated with M1 disease in children younger than three years of age is therefore an important consideration in the design of these clinical trials. Our results suggest that children less than three years of age with M1 disease are at very high risk of disease progression, and should be treated similarly to those with M2 or M3 disease.

The survival results we report for patients ≥ 3 years of age are consistent with those reported by Zeltzer, et al. [1] from the Children's Cancer Group CCG921 trial, which ran from 1986 to 1992. In that series the five year rates of progression-free survival (PFS) were 70±5%, 57±10%, and 40±8% for patients with M0, M1, and M2/3 medulloblastoma, respectively. Similarly, Kortmann, et al. reported that in the German cooperative group HIT '91 trial, 3-year PFS was 72±4%, 65±12%, and 30±15% for patients with M0, M1, and M2/3 disease, respectively. [8] The difference in PFS between M0 and M1 patients was not statistically significant, prompting

the authors to suggest that risk stratification be modified for future trials. Our results suggest that M1 patients have lower EFS than M0 patients despite receiving full dose CSI (>35 Gy). We would therefore not consider M1 patients to be candidates for reduced-intensity therapy, and recommend that they continue to be considered high-risk in future trials.

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Figure 1.
OS and EFS by M-Stage

Table 1

Patient Characteristics

Patient Demographic and Clinical Features										
		ALL PATIENTS (N=285)			< 3 YEARS OLD (N=55)			> 3 YEARS OLD (N=230)		
Age at diagnosis (years)		Median	Range		Median	Range		Median	Range	
		6.9	0.2–20.3		1.7	0.2–2.9		8.2	3.0–20.3	
Sex		n	%		n	%		n	%	
Male		188	66		34	62		154	67	
Female		97	34		21	38		76	33	
Maximum Extent of Resection Prior to Adjuvant Treatment										
Gross Total		n	%		n	%		n	%	
		198	69		31	56		167	73	
Near Total		27	9		7	13		20	9	
Subtotal		55	19		16	29		39	17	
Biopsy		5	2		1	2		4	2	
M Stage										
M0		n	%		n	%		n	%	
		186	65		32	58		154	67	
M1		18	6		5	9		13	6	
M2		19	7		5	9		14	6	
M3		62	22		13	24		49	21	

Table 2**OS and EFS by Age and Metastatic Stage**

Category	5-Year OS (95% CI)	5-Year EFS (95% CI)
All Children	73.1% (65.7%–78.9%)	63.4% (55.2%–69.6%)
<i>M0</i>	84.4% (77.2%–90.3%)	76.2% (68.2%–82.9%)
<i>M1</i>	59.8% (12.2%–88.1%)	49.4% (5.7%–79.3%)
<i>M2/M3</i>	51.5% (30.0%–64.5%)	37.6% (16.5%–50.6%)
Children < 3 years of age	58.1% (40.2%–73.4%)	41.4% (25.4%–56.8%)
<i>M0</i>	65.2% (42.3%–86.1%)	55.3% (36.3%–75.9%)
<i>M1</i>	40.0% (1.2%–100.0%)	20.0% (0.0%–100.0%)
<i>M2/M3</i>	50.0% (21.9%–79.4%)	22.2% (2.5%–52.7%)
Children ≥ 3 years of age	76.7% (68.9%–82.9%)	68.7% (60.3%–75.4%)
<i>M0</i>	88.4% (81.5%–94.2%)	80.5% (72.5%–87.5%)
<i>M1</i>	67.7% (13.7%–99.7%)	60.6% (8.5%–94.7%)
<i>M2/M3</i>	51.5% (27.0%–66.7%)	41.8% (17.9%–57.1%)