Published in final edited form as:

J Pediatr Hematol Oncol. 2019 March ; 41(2): 152–154. doi:10.1097/MPH.0000000000001166.

Central nervous system involvement of rhabdomyosarcoma: A single institution experience

Daniel C. Moreira, MD¹, Margaret E. Macy, MD¹, Carrye R. Cost, MD¹, Brian S. Greffe, MD¹, and Timothy P. Garrington, MD¹

¹Department of Pediatric Oncology, University of Colorado Denver School of Medicine and Children's Hospital Colorado, Aurora, CO, USA.

Abstract

The incidence of central nervous system (CNS) involvement in patients with rhabdomyosarcoma is low, and the outcome is dismal. We present a single institution analysis of CNS involvement of pediatric rhabdomyosarcoma. In 59 patients, the prevalence of CNS involvement was 11.9% (seven patients), higher than prior reports. Of the six deaths from disease, all had rapid progression, with a median survival of 14 days. The higher incidence could be secondary to treatment modifications or more sensitive detection. These findings are useful for decisions at the time of CNS involvement and could lead to modifications for future rhabdomyosarcoma clinical trials.

Keywords

rhabdomyosarcoma; CNS involvement; CNS metastasis; leptomeningeal enhancement

Introduction

Central nervous systemic (CNS) involvement of pediatric rhabdomyosarcoma (RMS) is infrequent, even in patients with metastatic or parameningeal disease. Although primary CNS rhabdomyosarcoma exists, it is exceedingly rare and CNS disease is typically secondary to hematogenous metastasis [1]. Metastatic disease to the CNS in RMS has a low prevalence, reported to be approximately 3% (TABLE 1) [2–6]. However, postmortem analyses of tumor-related deaths have shown a prevalence of CNS disease of 14% to 20% [7, 8]. This higher prevalence probably reflects the natural course of fatal RMS. CNS involvement of RMS has a very poor prognosis with rapid progression [2, 5, 8, 9]. In this study, we present a single institution experience regarding CNS involvement of pediatric RMS over a ten-year period.

Correspondence: Timothy P. Garrington, Children's Hospital Colorado, 13123 E 16th Ave, B115 Aurora, CO 80045; Phone: 720-777-8365; Fax: 720-777-7279; timothy.garrington@childrenscolorado.org.

No funding acknowledgements are necessary for this submission.

Conflict of Interest

The authors declare that there is no conflict of interest.

Methods

After Internal Review Board approval, we performed a retrospective review of children diagnosed with RMS between June 2006 and June 2016 at Children's Hospital Colorado, a tertiary referral center. Patients were included in the study if they had pathologic confirmation of RMS at diagnosis or relapse, and received therapy and follow up at the institution. Intracranial involvement was defined as any disease that crossed the dura mater, therefore leptomeningeal disease and parenchymal brain lesions were included. Imaging or pathologic studies were a requirement to confirm CNS involvement.

Results

Over the ten-year period, 64 patients with RMS were treated and 59 met inclusion criteria. Of those 59 patients, CNS involvement was documented in seven (11.9%) (TABLE 2). No patient had CNS disease at diagnosis. The mean age at diagnosis was 11.5 years (range: 2 to 26 years). Four had alveolar RMS (57.1%) and three had embryonal RMS (42.9%). Of the four patients with alveolar RMS, three had a PAX3-FKHR translocation. Of the three patients that had parameningeal primary tumors, one had intracranial extension (ICE) at diagnosis. Five (71.4%) had metastatic disease at presentation. All patients with metastatic disease had bony metastases, while three also had lung metastases. Based on the Children's Oncology Group (COG) risk stratification, five patients (71.4%) were classified as high risk while two were intermediate risk (28.6%). All patients were treated according to COG protocols with cyclophosphamide dosed at 1.2 g/m²/cycle. Cyclophosphamide Equivalent Dose (CED) was used to quantify total alkylating agent exposure [10]. All patients achieved radiographic complete remission prior to CNS relapse. Four patients (57.1%) developed CNS progression during first-line therapy, while one occurred immediately after finishing first-line therapy completion. Two patients had previous relapses.

All patients had neurologic symptoms that led to the diagnosis of CNS metastasis. No patient was found to have CNS disease on routine surveillance imaging. Four patients (57.1%) had other sites of progression or metastasis. The median time to diagnosis of CNS involvement following initial diagnosis or diagnosis of relapse was 336 days. The symptoms were characteristic of increased intracranial pressure or cortical damage, including altered mental status, headaches, somnolence and seizures. When initial evaluation of neurologic symptoms was performed with a head CT, ventriculomegaly was the most frequent abnormality. Of note, Patient 3 had a head CT performed due to headaches with no abnormalities 10 days prior to the diagnosis of CNS relapse, when an extra-axial mass was found on repeat head CT. For the five patients with ventriculomegaly on CT who had a subsequent MRI performed, leptomeningeal enhancement was present in all cases. In three of these patients, parenchymal lesions were also found (42.9%). All patients with leptomeningeal enhancement had diagnostic lumbar punctures and malignant cells were found in four of these five patients. Patient 4 presented with seizures and was found to have an isolated parenchymal lesion on head CT with associated uncal and cerebellar herniation. He underwent emergent neurosurgical decompression and complete resection, with subsequent tumor bed radiation and chemotherapy. He is the only patient who had total

resection of his CNS disease, and he remains alive almost 16 months after his CNS relapse. The six patients who died of disease had a median survival of 14 days (mean of 34.5 days).

Discussion

Consistent with prior reports, this study confirms that CNS involvement of RMS not only has a dismal prognosis, but that the time from progression to death is often extremely rapid. All patients had symptoms that led to the diagnosis of CNS disease, indicating that CNS symptoms must be considered a harbinger of RMS involvement and further evaluation should be contemplated urgently. However, given the associated symptoms and the rapidity of progression, the addition of routine surveillance of the CNS is unlikely to prove beneficial.

Compared to prior reports, we present a higher incidence of CNS relapse in patients with RMS. Due to the fact that our analysis is more recent, it could reflect a change in the natural history of RMS with current therapeutic regimens or an improvement in our capability to detect CNS disease. It is clear that a larger study population is needed to confirm our finding.

RMS treatment has evolved over recent decades with a new focus on risk stratification and decreased toxicity. These changes may have altered the pattern of CNS involvement in patients with RMS. Vincristine, actinomycin and cyclophosphamide have remained the backbone of treatment in the United States. Of these agents, cyclophosphamide is the only agent with CNS penetration [11–13]. Since the time of the first consortium trials, the dosing of cyclophosphamide has decrease from 2.2gm/m² to 1.2gm/m² and the total dose has decreased significantly, 30.8gm/m² on IRS-IV compared to 8.4 gm/m² on ARST0531 [14]. While the majority of prior reports of CNS involvement in RMS are from the time of higher dose of cyclophosphamide, all our patients received 1.2gm/m². Cyclophosphamide doses have been replaced with other agents known to be active in RMS, such as ifosfamide, doxorubicin, irinotecan, and etoposide. Of these agents, doxorubicin does not readily penetrate the CNS [15]. Irinotecan, etoposide and ifosfamide penetrate the blood brain barrier, though their efficacy compared to cyclophosphamide in treating RMS involving the CNS is unknown [16–18]. Further analysis of the effects of chemotherapy dosing and agents on the incidence and timing of CNS involvement in newer treatment regimens is necessary, as this would impact future trial design.

Another reason for our finding of an increased incidence of CNS disease may be more sensitive diagnostic techniques. With the more widespread use of MRI, CNS disease may be diagnosed more frequently [19]. This is supported by the increased incidence of patients with parameningeal RMS and ICE at diagnosis over the last decades: 19% on IRS-II and 46% on D9803 [20]. In addition, our observation that four patients had ventriculomegaly on CT scan, but MRI was needed to detect masses in two patients and all leptomeningeal enhancement points to the importance of this imaging modality. Thus, imaging with MRI should be considered if CT scans are inconclusive and clinical concerns persist.

Knowledge of the poor prognosis and rapid progression to death of CNS relapse in RMS must be considered when counseling patients and families, and in the planning of therapeutic or palliative interventions. Studies of a larger cohort of patients to further analyze the incidence and characteristics of patients with RMS who develop CNS disease may help to identify patients who are at highest risk. Alternative strategies for treatment must be developed to improve survival for this group of patients in the future.

References

1. Bradford R, Crockard HA, Isaacson PG. Primary rhabdomyosarcoma of the central nervous system: case report. *Neurosurgery*. 1985; 17(1):101–4. [PubMed: 3895025]
2. Parasuraman S, et al. Brain metastases in pediatric Ewing sarcoma and rhabdomyosarcoma: the St. Jude Children's Research Hospital experience. *J Pediatr Hematol Oncol*. 1999; 21(5):370–7. [PubMed: 10524449]
3. Wiens AL, Hattab EM. The pathological spectrum of solid CNS metastases in the pediatric population. *J Neurosurg Pediatr*. 2014; 14(2):129–35. [PubMed: 24926970]
4. Hauser P, et al. Incidence and survival of central nervous system involvement in childhood malignancies: Hungarian experience. *J Pediatr Hematol Oncol*. 2005; 27(3):125–8. [PubMed: 15750442]
5. Kebudi R, et al. Brain metastasis in pediatric extracranial solid tumors: survey and literature review. *J Neurooncol*. 2005; 71(1):43–8. [PubMed: 15719274]
6. Paulino AC, Nguyen TX, Barker JL Jr. Brain metastasis in children with sarcoma, neuroblastoma, and Wilms' tumor. *Int J Radiat Oncol Biol Phys*. 2003; 57(1):177–83. [PubMed: 12909231]
7. Shimada H, et al. Pathology of fatal rhabdomyosarcoma. Report from Intergroup Rhabdomyosarcoma Study (IRS-I and IRS-II). *Cancer*. 1987; 59(3):459–65. [PubMed: 3791156]
8. Graus F, Walker RW, Allen JC. Brain metastases in children. *J Pediatr*. 1983; 103(4):558–61. [PubMed: 6620015]
9. De B, et al. Central nervous system relapse of rhabdomyosarcoma. *Pediatr Blood Cancer*. 2017
10. Green DM, et al. The cyclophosphamide equivalent dose as an approach for quantifying alkylating agent exposure: a report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer*. 2014; 61(1):53–67. [PubMed: 23940101]
11. Kellie SJ, et al. Cerebrospinal fluid concentrations of vincristine after bolus intravenous dosing: a surrogate marker of brain penetration. *Cancer*. 2002; 94(6):1815–20. [PubMed: 11920545]
12. Tattersall MH, et al. Pharmacokinetics of actinomycin D in patients with malignant melanoma. *Clin Pharmacol Ther*. 1975; 17(6):701–8. [PubMed: 1139861]
13. Wiebe VJ, et al. Pharmacology of agents used in bone marrow transplant conditioning regimens. *Crit Rev Oncol Hematol*. 1992; 13(3):241–70. [PubMed: 1476655]
14. Malempati S, Hawkins DS. Rhabdomyosarcoma: review of the Children's Oncology Group (COG) Soft-Tissue Sarcoma Committee experience and rationale for current COG studies. *Pediatr Blood Cancer*. 2012; 59(1):5–10. [PubMed: 22378628]
15. Sardi I, et al. Pharmacological modulation of blood-brain barrier increases permeability of doxorubicin into the rat brain. *Am J Cancer Res*. 2013; 3(4):424–32. [PubMed: 23977451]
16. Kreisl TN, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol*. 2009; 27(5):740–5. [PubMed: 19114704]
17. Kaijser GP, et al. Ifosfamide metabolism and pharmacokinetics (review). *Anticancer Res*. 1994; 14(2A):517–31. [PubMed: 8017856]
18. Relling MV, et al. Etoposide achieves potentially cytotoxic concentrations in CSF of children with acute lymphoblastic leukemia. *J Clin Oncol*. 1996; 14(2):399–404. [PubMed: 8636749]
19. Smith-Bindman R, et al. Use of diagnostic imaging studies and associated radiation exposure for patients enrolled in large integrated health care systems, 1996–2010. *JAMA*. 2012; 307(22):2400–9. [PubMed: 22692172]

20. Spalding AC, et al. The effect of radiation timing on patients with high-risk features of parameningeal rhabdomyosarcoma: an analysis of IRS-IV and D9803. *Int J Radiat Oncol Biol Phys.* 2013; 87(3):512–6. [PubMed: 24074925]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

TABLE 1

Reports of the incidence of CNS involvement in RMS

Reference	CNS Involvement Patients (%)	Years of Analysis	Age of Patients Analyzed
Parasuraman, S et al [2] *	10/419 (2.4)	1962–1998	N/A **
Wiens, AL & Hattab, EM [3]	2/161 (1.2)	1981–2011	Less than 21 years
Hauser, P et al [4]	2/50 (4)	1989–2002	Less than 18 years
Kebudi, R et al [5]	3/115 (2.6)	1989–2002	Less than 16 years
Paulino, AC et al [6] *	7/104 (6.7)	1965–2000	Less than 21 years
Total	24/809 (2.8)	1962–2011	Less than 21

* Only included brain parenchymal lesions for analysis.

** Age limit for analysis was not mentioned, but oldest patient in report was 18 years-old.

TABLE 2

Clinical characteristics of patients with RMS and CNS involvement

Patient	1	2	3	4	5	6	7
Sex	M	M	F	M	M	M	F
Age at Diagnosis (years)	3	15	26	14	2	16	5
Histologic Variant	Embryonal	Alveolar	Alveolar	Alveolar	Embryonal	Alveolar	Embryonal
Molecular Status	-	PAX3-FKHR	PAX3-FKHR	Variant FKHR rearrangement and amplification	-	PAX3-FKHR	-
Stage, Group	4,4	4,4	4,4	3,1	3,3	4,4	4,4
Primary Tumor	PM	Foot	Pelvis	Rib	PM	Sacral	PM
Locations of metastases at diagnosis	Lung, bone, LN	Bone	Lung, bone, LN	None	None	Bone	Lung, bone
COG Risk Stratification	High	High	High	Intermediate	Intermediate	High	High
Upfront Therapy	VDC/IE/VI/VAC	VDC/IE/VI/VAC	VDC/IE/VI/VAC	VAC/VI	VAC/VI	VDC/IE/VI/VAC	VDC/IE/VI/VAC
Radiation (Gy)	50.4, weeks 21–25	50.4, weeks 21–25	50.4, weeks 22–26	36, weeks 5–10	50.4, weeks 4–9	50.4, weeks 1–5	50.4, weeks 3–9
First Relapse Therapy	-	-	VinoCT	VinoCT	-	-	-
Total CED Received (g/m ²)	16.98	22.98	34.98	13.2	4.8	13.28	7.88
Time of CNS relapse	Upfront therapy, week 34	2 weeks off therapy	On relapse therapy	1 year off relapse therapy	Upfront therapy, week 24	Upfront therapy, week 29	Upfront therapy, week 26
Time to CNS relapse (from diagnosis; from relapse, days)	336	390	1081; 403	1031; 613	182	280	234
Symptoms at relapse	Status epilepticus	AMS, seizure	AMS, somnolence	AMS, seizure	AMS, headache	Headache, somnolence	Headache, diplopia
Head CT	VM	VM	Extra-axial mass	VM, isolated mass, herniation	VM	VM	Not done
Brain MRI	LM enhancement and parenchymal masses	LM enhancement and frontal mass	Not done	Done after tumor resection. No LM enhancement	LM enhancement	LM enhancement	LM, thalamus and midbrain enhancement
Malignant cells in CSF	0%	12%	Not done	Not done	81%	29%	6%
Additional metastatic sites at time of CNS relapse	Spine, lung	None	Paraspinal	None	None	None	Spine
Time to death after CNS relapse (days)	37	124	10	Alive	15	13	8

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

PM=parameningeal; LN=lymph nodes; VDC =vincristine, doxorubicin, cyclophosphamide; IE=ifosfamide, etoposide; VI= vincristine, irinotecan, actinomycin, cyclophosphamide; VAC=vincristine, actinomycin, cyclophosphamide; VM=ventriculomegaly; LM=leptomeningeal