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Orbital Sarcoma with Metastases at Diagnosis: A Report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group

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Abstract

We reviewed clinicopathologic features and treatment outcomes in 7 patients diagnosed with Stage 4/Group IV orbital sarcoma and treated on IRSG protocols I-III. Three patients had embryonal rhabdomyosarcoma (RMS), and 2 patients each had alveolar RMS or unclassified sarcoma. Median age at diagnosis was 1.8 years (range 0.2 – 6.9 years). All patients had bone marrow involvement, including 6 with normal CBC at diagnosis. Cerebrospinal fluid (CSF) was normal in 6 patients. Three patients survived > 5 years, including one with local recurrence.

Conclusion—Further study is needed to determine necessity of bone marrow and CSF examination in orbital sarcoma patients.

Keywords

orbit; rhabdomyosarcoma; sarcoma; metastasis; pediatric

Introduction

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma of childhood, and RMS of the orbit constitutes approximately 10% of all RMS cases.¹⁻² Fortunately, most patients with orbital RMS (ORMS) present with localized disease, and the overall prognosis for localized ORMS is excellent.²⁻⁶ However, ORMS patients with metastases at diagnosis do occur, and the clinical features and outcomes of these patients are not well described.

The Intergroup Rhabdomyosarcoma Study Group (IRSG) was formed in 1972 to investigate the biology of RMS and to improve treatment. The treatment protocols were sequentially designated IRS – I through IRS – IV.³⁻⁶ The primary objective of this study was to review the clinical and pathologic characteristics and treatment outcomes of patients with metastatic (Stage 4/Group IV) orbital sarcoma at time of initial diagnosis.

Methods

Medical records were reviewed for those patients diagnosed with Stage 4/Group IV orbital rhabdomyosarcoma or undifferentiated sarcoma and enrolled on IRSG treatment protocols - I, - II, and - III, conducted from 1972-1991. No patients with metastatic orbital sarcoma were registered on the subsequent IRS-IV Pilot or IRS-IV protocols. Patient characteristics reviewed included age at diagnosis, gender, histology, and disease extent. Treatment characteristics included treatment received, time to treatment failure, site(s) of treatment failure, and overall duration of survival. Treatment failure was defined as being discovery of new disease during primary treatment or disease recurrence following completion of primary therapy. Since the IRSG protocols I through IV included patients with unclassified soft-tissue sarcoma, patients with this histologic diagnosis were included in this analysis. Statistics were descriptive in nature.

Results

Nine patients of 330 eligible patients enrolled onto IRSG studies IRS-I through IRS-IV with primary orbital sarcoma were initially registered with Stage 4/Group IV orbital disease. However, 2 patients were excluded from analysis, leaving 7 patients with metastases at diagnosis out of 330 enrolled (2%). One of the excluded patients was subsequently determined to have neuroblastoma following biopsy of a new bone metastasis and discovery of elevated catecholamines. Secondary review of another patient determined that the primary site of disease was the nasopharynx, rather than the orbit. Of the 7 evaluated patients (Table 1), there were 5 females, and the median age at diagnosis was 1.8 years (range 0.2 - 6.9 years). Three patients had embryonal RMS, 2 patients had unclassified sarcoma, one patient had pure alveolar RMS, and another patient had a mixed tumor which was 60% alveolar and 40% embryonal RMS (classified as alveolar histopathologically).

Tumor size was recorded for 5 patients, and 2 patients had tumors at least 5 cm in greatest diameter. Four patients had local extension of their disease into the ethmoid and maxillary sinuses, including 2 patients with extension into the infratemporal fossa. The largest amount of bulk tumor was in the orbit, and these 4 patients, like the other 3, presented with orbital swelling. One patient had direct intracranial extension (Table 1). The cerebrospinal fluid (CSF) was examined in 6 patients and was negative for malignant cells in each. The bone marrow was involved in all 7 patients, and 3 patients had metastatic involvement of more than one organ system. Although the bone marrow was involved in all patients, only one patient (with unclassified sarcoma) had cytopenias in the complete blood count (CBC) at presentation.

Treatment and follow-up data are detailed in Table 2. Six patients received chemotherapy with vincristine, dactinomycin, and cyclophosphamide (VAC), and one patient received vincristine and dactinomycin only. Another patient received doxorubicin, cisplatin and etoposide in addition to VAC. Five patients (71%) had dose reductions of chemotherapy, with vincristine being most commonly decreased. All patients received radiation therapy; the median dose was 44 Gray (Gy; range 13 – 50 Gy). The patient with intracranial extension also received 34 Gy to the whole brain. Complete response to therapy was documented in 3 patients; 2 other patients experienced progression of disease during initial treatment.

Overall, 5 patients developed recurrent disease; 3 developed bone metastases and 1 developed spread into the meninges. The fifth patient had an isolated local recurrence. Median time to treatment failure was 0.4 years (range 0.17 – 0.75 years). Four of the 7 patients (57%) survived at least 3 years from initial diagnosis, and 3 patients (43%) were

alive at 5.8, 14.6 and 18.5 years. Two of the 3 surviving patients had initially achieved a complete response. Two patients had ERMS, and one patient had mixed ARMS-ERMS tumor with 60% of the tumor exhibiting ARMS histology.

Discussion

The orbit is one of the more common sites for RMS, and based on previous IRSG studies, the orbit is considered a favorable anatomic site due to excellent outcome rates. The great majority of patients with orbital sarcoma present with localized disease. Yet for those uncommon patients who present with metastatic disease, the data are unclear about whether there are common clinical characteristics or prognostic features.

Embryonal RMS is the most common histology encountered in patients with non-metastatic orbital sarcoma and occurs in approximately 90% of cases, but in Stage 4/Group IV cases, embryonal RMS was found in just about half of the cases.⁷ Also, due to the low incidence of orbital sarcoma presenting with metastases, two concerns would be [1] whether the primary tumor had originated from a non-orbital parameningeal site with orbital extension, and [2] whether the orbit was actually a metastatic site. However, all patients were centrally reviewed, and the primary sites were determined to be in the orbit. Also, orbital metastases are quite rare and are usually seen in patients with significantly advanced, recurrent disease.⁸ Review of our patient group demonstrated only one patient with another tumor in a separate soft-tissue site. That patient presented with concurrent orbital swelling, and the extremity lesion, discovered after diagnosis and before initiation of chemotherapy, was the same size (5 cm) as the orbital lesion. The remaining patients had involvement of bony sites and/or bone marrow. Interestingly, no Stage 4 orbital sarcoma patients were identified from the IRS -IV pilot and IRS -IV studies. However, those studies excluded orbital sarcoma patients with parameningeal extension from being included in the orbital primary tumor category. Thus, those patients were either designated as having parameningeal disease, or were included in the group with other head/neck sites and parameningeal extension.

A complete metastatic evaluation in orbital sarcoma patients currently includes a lumbar puncture for CSF cytologic analysis. The reasoning for this evaluation is largely precautionary, because many tumors present adjacent to the optic nerve, which is a direct extension of the central nervous system. Despite evidence of hematogenous spread to the bone marrow, the CSF was unremarkable in the 6 of the 7 patients examined, including the one with direct intracranial extension of the primary tumor. Thus, the need for initial diagnostic lumbar punctures in orbital sarcoma patients deserves further study.

All 7 patients had bone marrow involvement at diagnosis, but only one presented with blood cell cytopenias. Overall the prevalence of bone marrow involvement for all patients diagnosed with orbital sarcoma was only 2.1% (7 of 330 patients). However, 5 of the 7 patients had additional clinical findings including bone metastasis or extension into adjacent sinuses or the infratemporal fossa. Thus, bone marrow examination may be required only in those patients with evidence of disease extending beyond the orbital compartment. Nevertheless, further study and more data are required.

Previous studies of Stage 4/Group IV RMS patients have demonstrated that bone and/or bone marrow involvement represents a significant predictor for poor long-term prognosis.⁹⁻¹⁰ However, 4 of the Stage 4 orbital sarcoma patients survived for at least 3 years from initial diagnosis. Due to the small number of patients, it was not possible to perform subset analysis for significant clinical characteristics. However, all 3 patients with complete response to initial therapy were among the patients who survived at least 3 years. Also, the 3 patients with the longest survival durations had tumors with embryonal histology, although

one patient had a tumor with mixed histology (60% ARMS/40% ERMS). The patients who had either pure alveolar RMS or unclassified sarcoma eventually died of disease. Further follow-up and results from other large studies are needed to determine (1) whether patients with primary orbital sarcoma and metastases represent a distinct subset of patients with an improved chance for survival, and (2) whether bone marrow and CSF examinations at diagnosis may be omitted for certain subgroups of orbital sarcoma patients.

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TABLE I
Seven IRSG Patients With 1° Orbital Sarcoma And Metastases At Diagnosis: Characteristics Of Patients And Tumors*

Patient Number	Age in Years, Gender	1° Site	Size (cm)	Pathology	Metastatic Sites at Diagnosis	Extent of Disease at Diagnosis
1	4.3, M	R	?	ALV	Marrow	1° invaded ethmoid, maxillary sinus; normal complete blood count (CBC) and cerebrospinal fluid (CSF)
2	1.7, F	L	1	Sarc NOS	Marrow, Skull	Hemoglobin 7.6, ANC 1100; platelets 11,000 at diagnosis; normal CSF; marrow still + at relapse
3	1.8, F	L	4	Sarc NOS	Marrow	1° extended into infratemporal fossa, nasopharynx, ethmoid, maxillary sinus; normal CBC and CSF; marrow still + on day 61
4	0.22, M	R	?	EMB	Marrow, Bones	1° extended to maxillary sinus; scapula biopsy +; normal CBC and CSF; marrow still + on day 45
5	1.0, F	R	5	EMB	Marrow	Normal CBC and CSF
6	5.0, F	R	5	60% ALV; 40% EMB	Marrow, L thigh, ICE	1° extended to infratemporal fossa. Normal CBC and CSF; marrow cleared on day 28.
7	6.9, F	R	2	EMB	Marrow	Normal CBC; CSF not examined

* Abbreviations: 1°, primary; R, right; ALV, alveolar rhabdomyosarcoma (RMS); L, left; Sarc NOS, sarcoma not otherwise specified;?, unknown; +, positive (involved by tumor); EMB, embryonal RMS; ANC, absolute neutrophil count; ICE, direct intracranial extension from 1° site; N1, regional (cervical) LN contained tumor

TABLE II
Treatment, Response, and Outcome Of 7 Patients With 1° Orbital Sarcoma And Metastases At Diagnosis*

Patient Number	RT Dose, in Gray	Chemotherapy, % Drugs Given Prior to Relapse	Best Response Achieved, Years from Diagnosis	Site(s) of Failure	Time to Failure (or to Off-Study), in Years	Survival in Years, + = Alive
1	50	VAC, 100%	CR, 0.21	Meninges	0.75	3.33
2	20, low 2° to PD	V 83%; AC 100%	PD	Extremity + Pelvic Bones	0.17	0.84
3	38, low	VAC, 100%	Improved, < PR	Bones, L cervical LN	0.41	0.49
4	13, low 2° to PD	V 83%; AC, 100%	PD	Bones	0.18	0.22
5	45	VA, 68%; C, 71%	CR, 0.10	Off Study due to hematologic toxicity; no failure	(0.34)	18.5+
6	44, orbit; 41, thigh; 34, whole brain	V, 49%; A, 87%; C, Dox, 81%; CPT, 82%; Etop, 100%	CR, 0.41	0	Not Applicable	14.6+
7	45.5	V, 79%; A, 100%	No information	Local	0.55	5.8+

* Abbreviations: RT, radiation therapy; VAC, vincristine, dactinomycin, cyclophosphamide; Dox, doxorubicin; CPT, cisplatin; Etop, etoposide; CR, complete response (no evident disease at any site), 2°, secondary; PD, progressive disease; L, left; LN, lymph nodes; < PR, less than partial response (PR = 50-99% smaller)