Combination Therapy for Unresectable Primitive Myxoid Mesenchymal Tumor of Infancy: A Story of Cure

Trevor Memmott[1], Jessica Hass Alfonso[1], Unni Udayasankar[1], and Holly Pariury[1]

[1]Banner University Medical Center Tuscon

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Abstract

Primitive myxoid mesenchymal tumor of infancy is a rare, locally aggressive, chemotherapy-refractory pediatric sarcoma with a high morbidity and mortality rate. Surgical resection is the gold standard of treatment, but a significant number of cases are initially unresectable due to tumor location. For these individuals, traditional first-line chemotherapy with vincristine, actinomycin, and cyclophosphamide has yielded no benefit. Alternatively, therapy with doxorubicin and ifosphamide-based regimens have shown success in several cases. We present a case of a pediatric patient with unresectable PMMTI successfully cured after receiving a combination of ifosphamide and doxorubicin followed by surgery and adjunctive proton beam radiation.

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Trevor Memmott[1], Jessica Hass Alfonso[1], Unni Udayasankar[3,4], Holly Pariury[1,2,3]

[1] Department of Pediatrics, University of Arizona, Tucson, AZ, USA

[2] The University of Arizona Cancer Center, Tucson, AZ, USA

[3] Banner University Medical Center, Tucson, AZ, USA

[4] Department of Radiology, University of Arizona, Tucson, AZ, USA

Address all correspondence to: Holly Pariury D.O., Department of Pediatrics, 1501 N. Campbell Ave., PO Box 245073, Tucson, AZ 85724-5073

Tel: (520) 626-7053; Fax: (520) 6986

hpariury@peds.arizona.edu

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Abbreviations

Primitive mesenchymal myxoid tumor of infancy	PMMTI
Gross total resection	GTR
Proton beam radiation	PBT
Non-rhabdomyosarcoma soft tissue sarcomas	NRSTS
Vincristine, actinomycin, plus/minus cyclophosphamide or ifosphamide	VA/VAC/VAI

Primitive mesenchymal myxoid tumor of infancy	PMMTI
Vincristine, doxorubicin, cyclophosphamide	VDC
Ifosphamide and Doxorubicin	ID
Vincristine, cyclophosphamide, and topotecan	VCT

ABSTRACT

Primitive myxoid mesenchymal tumor of infancy is a rare, locally aggressive, chemotherapy-refractory pediatric sarcoma with a high morbidity and mortality rate. Surgical resection is the gold standard of treatment, but a significant number of cases are initially unresectable due to tumor location. For these individuals, traditional first-line chemotherapy with vincristine, actinomycin, and cyclophosphamide has yielded no benefit. Alternatively, therapy with doxorubicin and ifosphamide-based regimens have shown success in several cases. We present a case of a pediatric patient with unresectable PMMTI successfully cured after receiving a combination of ifosphamide and doxorubicin followed by surgery and adjunctive proton beam radiation.

Introduction

Primitive myxoid mesenchymal tumor of infancy (PMMTI) is a locally aggressive, treatment refractory soft-tissue sarcoma initially reported in 2006[1]. Treatment is primarily surgical with more than two-thirds of the approximately 30 reported cases having undergone surgery alone. For those individuals in which a complete surgical resection is not feasible up front, morbidity is high, and event free survival is poor.[2] Here we present the case of an infant with an unresectable PMMTI who is in remission and off therapy greater than two years following a combination of systemic chemotherapy, surgery and adjunctive proton beam radiation. Taken in conjunction with the eight previously reported cases for which systemic therapy was attempted, we propose an initial treatment strategy for patients with initially unresectable PMMTI.

Case Report

A 9-month-old term female presented with a one-month history of a rapidly enlarging left trapezius mass. Family history was unremarkable. Magnetic resonance imaging (MRI) showed a 3-4 cm mass involving the left trapezius and paraspinal muscles with extension into the left neural foramen at T2-3 and an epidural component at T1 (Fig 1). Staging work up was consistent with a single lesion localized to the back and spine. An excisional tumor biopsy was performed.

Pathology revealed primitive-appearing small round blue cells in a background of myxoid matrix. Immunohistochemistry showed patchy positivity for BCL-6 and NTRK, and diffuse nuclear immunoreactivity for BCOR. Tumor tissue was negative for desmin, Oscar, CD99, S100, and myogenin. Testing was negative for a NTRK gene fusion and rearrangement of ETV6. A comprehensive solid tumor molecular profiling panel was remarkable for a single variant of unknown significance at RASA1 p.Y528c. Collectively these findings were consistent with the diagnosis of PMMTI.

Given the tumor extension into the neural foramen and epidural space, complete resection of her disease was not feasible up front. She was initially treated with two cycles of vincristine (days 1,8, 15), dactinomycin (day 1) and cyclophosphamide (day 1) based on historical practice. Due to rapid, localized, progression of disease, her therapy was then changed to ifosphamide (2500mg/m2/dose; days 1-3) and doxorubicin (37.5mg/m2/dose; days 1-2), which she received for 4 cycles. Her tumor demonstrated a significant partial response, allowing for a gross total resection (GTR) of the mass. Surgical pathology demonstrated diffuse fibrosclerosis of the tumor which extended beyond the resection margins, however no signs of residual malignancy were seen. Given the previously aggressive nature of patient's disease, good response to current therapy, and chemotherapy refractory nature of recurrent disease, she then received consolidation therapy with localized proton beam radiation (PBT) and two concurrent cycles of ifosphamide. The patient is now 34 months from initial diagnosis and continues to be in remission 27 months following the completion of her multidisciplinary therapy. Late effects include ifosphamide-induced Fanconi syndrome for which she receives oral bicarbonate supplementation.

Discussion

PMMTI is a unique and locally aggressive soft-tissue sarcoma seen only in the pediatric population, with 30 cases published in PubMed to date. It has a mean age of onset of 6.5 months (range 0 to 36 mo) and there are no reported cases of metastatic disease at presentation. Since PMMTI's discovery, there has been a growing body of genetic and immunohistochemical data to aid in the diagnosis. Key diagnostic features include nuclear positivity for BCOR and BCL6, BCOR internal tandem duplication, and ETV6-NTRK3 rearrangement negativity.[2,3] While the clinical and pathologic characteristics of this disease have become better understood in recent years, optimal frontline therapy remains less clear.

Like patients with low-grade non-rhabdomyosarcoma soft tissue sarcomas (NRSTS), the standard of care for PMMTI is surgery alone when a GTR with negative margins can be acheived.[2,4] If this cannot be achieved, systemic therapy should be considered given the high rate of recurrence combined with the morbidity and psychosocial impact of multiple non-curative surgeries over time. Of the 19 cases of PMMTI with published treatment and outcome data, all but 2 underwent surgical resection upfront and 60% had disease progression or recurrence, with a median time to recurrence of less than 6 months. Among those that did undergo surgery as initial treatment, half went on to require additional tumor resections, the majority of which were also not curative.[2]

While a PMMTI is currently described as a chemo-resistant malignancy, to date, a total of only 9 cases, including this one, have been described in which systemic chemotherapy was attempted.[1-3,5-8.]Of those 9 cases, two received unspecified chemotherapy regimens; one of which was alive with disease at time of publication, the other of which was in remission at 4-year follow up.[1] Of the 7 patients with both chemotherapy treatment and outcome data (Table 1), 6 received vincristine and actinomycin (VA) as their initial systemic regimen, 4 of which concurrently received cyclophosphamide (VAC) and 1 of which concurrently received ifosphamide (VAI). The seventh patient received a similar regimen of vincristine, doxorubicin and cyclophosphamide (VDC).[2-3,5-8] Progression of disease or short-duration recurrence was seen in 100% of cases, making a strong case against the use of a VA/VAC backbone in the treatment of PMMTI.

Six of the 7 patients went on to receive subsequent chemotherapy, with a wide variation in the regimens used. Two-thirds of these individuals received one additional chemotherapy regimen, with the remaining 2 patients undergoing 3 or more chemotherapy regimens.[2,5-8] Partial or complete response was seen with three treatment regimens including ifosphamide/doxorubicin (ID; N= 4/4), VDC with ifosphamide and etoposide (N = 1/1) and vincristine, cyclophosphamide, and topotecan (VCT; N = 1/1). With the exception of the individual who received VCT, sustained treatment response was only seen in patients who received ID-containing regimens.[6-8] Of note, the individual who received VCT, was already demonstrating a good response to ID, however their treatment course had to be changed due to receiving a maximum cumulative dose of anthracyclines.[7] Those patients who received ifosphamide or doxorubicin alone or paired with alternative agents, did not show a response.[2,5,7] While these numbers are small, these outcomes encourage the utilization of ifosphamide and doxorubicin together as first line chemotherapy for unresectable disease over other previously attempted anti-neoplastic agents. Given the risk of anthracycline-induced cardiomyopathy with this regimen, the utilization of concurrent dexrazoxane for cardio protection is warranted. This combination is highly active and widely utilized in the treatment of soft tissue sarcomas and is the standard chemotherapy backbone in conjunction with surgical resection and adjunctive radiotherapy for pediatric patients with non-targetable, advanced NRSTS in the United States.[9]

The question of whether to provide consolidation therapy with localized radiation for patients with unresectable PMMTI is a difficult one, particularly given the very young age at disease onset. Two patients, including our own, underwent consolidation therapy with proton irradiation and both were in remission greater than 2 years off therapy with limited long-term toxicities to date.[8] Although both PBT and conventional photon-based radiotherapy are similarly efficacious, the increased precision of proton irradiation significantly reduces the risk of adverse events including secondary cancers.[10] While not appropriate in many situations, it should be considered a potential component of multidisciplinary PMMTI care in the setting of unresectable disease or positive surgical margins.

In summary, PMMTI is a rare and aggressive disease associated with a high rate of recurrence after surgery alone. For those unable to achieve complete surgical resection at a microscopic level, event-free survival is dismal, and morbidity is high. Here we demonstrated the efficacy and tolerance of multidisciplinary treatment with ID chemotherapy followed by delayed GTR and adjunctive PBT in an infant with unresectable PMMTI. Taken in conjunction with the previously reported cases for which systemic therapy was attempted, this combination should be considered for patients unable to negative surgical margins upfront. Further study in a larger cohort of patients in needed. Additionally, while our patient did not demonstrate targetable findings on genomic sequencing, very little data has been reported on this, and targeted solid tumor genomic sequencing, may prove beneficial for this rare disease.

Conflict of Interest Statement: No conflicts of interest to declare

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Figure Legend:

Figure 1

A) Axial T2 weighted MR image shows a uniformly hyperintense, lobulated, posterior paraspinal mass (Black arrows) that extends to the intraspinal epidural space through the left neural foramen (white arrows). **B)** Axial fat suppressed T1 weighted MR image acquired following intravenous administration of gadolinium contrast agent demonstrates intense, nearly homogeneous enhancement of the lobulated lesion (black arrows) with an enhancing intraspinal, epidural component (white arrow). Irregular enhancement is also seen extending to the left lateral chest wall and axilla.

Table 1

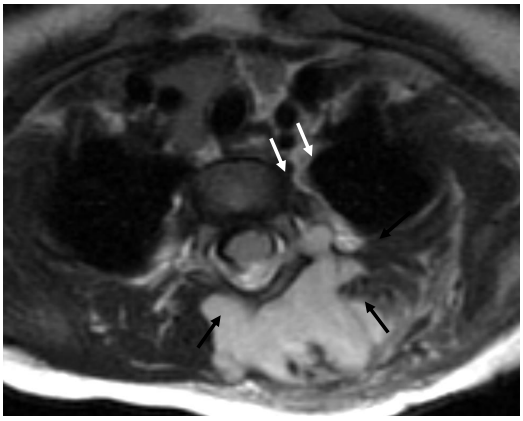
PMMTI Chemotherapy Treatment and Outcome Data

Hosted file

PMMTI Table 1.docx available at https://authorea.com/users/734942/articles/711615-combination-therapy-for-unresectable-primitive-myxoid-mesenchymal-tumor-of-infancy-a-story-of-cure

Figure 1

A



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