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Excessive treatment failures in patients with parameningeal rhabdomyosarcoma with reduced-dose cyclophosphamide and delayed radiotherapy.

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Abstract

Pediatric patients with parameningeal rhabdomyosarcoma and high risk features are recommended to receive radiotherapy at initiation of protocol therapy due to concerns about the increased risk of local and leptomeningeal failure from treatment delay. We report our early experience on a multi-institutional prospective trial incorporating delayed primary site radiation and reduced dose cyclophosphamide in all patients with parameningeal tumors. We observed an excessive number of loco-regional treatment failures following this approach and have subsequently amended our trial to move radiation therapy upfront for those patients with high risk features. We suggest that investigators should be vigilant for treatment failure given our early prospective experience with delayed radiotherapy and reduced dose cyclophosphamide.

Keywords

rhabdomyosarcoma; parameningeal tumors; cyclophosphamide; radiotherapy

Introduction

Pediatric patients with parameningeal rhabdomyosarcoma with high risk features (intracranial extension, cranial nerve palsies, etc.) are recommended to undergo radiotherapy at initiation of protocol therapy due to concerns about the increased risk of failure from treatment delay¹². Several smaller studies have successfully delayed radiotherapy with the use of more intensive chemotherapy³⁴. The most recent Children's Oncology Group trial for intermediate risk disease (ARST 1431) also now employs delayed radiation therapy for all

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patients with parameningeal rhabdomyosarcoma, regardless of risk features, in conjunction with standard Vincristine, Actinomycin, Cyclophosphamide (1.2 grams/m²) / Vincristine, Irinotecan chemotherapy. The current Children's Oncology Group trial, ARST 1431, employs both reduced dose cyclophosphamide and delayed radiotherapy in all intermediate risk patients regardless of primary site.

In 2013 we initiated a prospective multi-institutional study in children with newly diagnosed rhabdomyosarcoma evaluating the use of combination chemotherapy, proton beam radiation therapy, upfront or delayed primary surgical resection and maintenance anti-angiogenic therapy. The study incorporated delayed radiation therapy (week 12) for all patients requiring radiation including all patients with Parameningeal primary sites of disease in order to reduce the late effects associated with irradiation of large volumes of the head and neck region in young children⁵ that have not had the benefit of chemo-reduction of their disease. During this study we identified an excessive risk of loco-regional failure (primary site recurrence or leptomeningeal spread) requiring a return to early initiation of radiation therapy in patients with parameningeal primary tumors and high risk features. We report these findings and outcomes for subsequent patients with PM primaries in this ongoing trial.

Methods and Materials

RMS13 is a risk adapted multimodality therapeutic trial which treats patients with newly diagnosed rhabdomyosarcoma according to their initial risk assignment. Initially low and intermediate risk patients were enrolled and receive 12 weeks of (Vincristine (1.5 mg/m²), Actinomycin (0.045mg/kg) and Cyclophosphamide (1.2 grams/m²) (VAC) chemotherapy followed by 12 weeks of VA chemotherapy (Low risk subset 1) or 42 weeks of VAC chemotherapy (low risk subset 2 and intermediate risk patients). High risk patients, added to the trial in 2015, receive 54 weeks of interval compressed chemotherapy (vincristine, dactinomycin, cyclophosphamide, irinotecan, ifosfamide, etoposide, and doxorubicin). Intermediate and high risk patients receive additional maintenance therapy (anti-angiogenic chemotherapy incorporating bevacizumab, sorafenib and low-dose cyclophosphamide) after completion of cytotoxic chemotherapy.

At the initiation of the trial all patients, including all patients with parameningeal disease regardless of parameningeal features, received radiation therapy at week 13 for involved margins or an unresected primary tumor. The residual post chemotherapy gross disease is targeted with a 0.5cm margin and this volume, plus tissue that initially harbored gross disease (specifically bone or other "infiltrated" tissues) is treated to a dose of 36 CGE with proton beam. A "cone-down" is utilized to treat residual post chemotherapy gross disease to doses of 50.4 CGE (tumors ≤5cm at diagnosis) or 59.4 CGE (tumors >5cm at diagnosis).

Results

The characteristics and outcomes of all parameningeal patients currently enrolled are shown in Table 1. As of (October 2017) there are 13 patients with intermediate or high risk disease and PM primaries whose age ranged from 3 to 21 years. Four patients were treated prior to amending the study and changing the timing of radiation therapy and nine have been treated

since the amendment (median follow-up on study of 9.9 mo. and 9.3 mo., respectively). The first three patients with PM primary sites of disease that were treated on this trial either progressed locally prior to RT or recurred with leptomeningeal disease following delayed RT at 1.6, 7.2 and 12.5 months from start of therapy. A fourth patient that was under treatment had RT moved earlier and received it at week 6 and is alive without recurrence. These 4 patients all had high risk features of parameningeal disease including large tumor size, cranial base and bone erosion or intracranial extension. Following this initial experience on this trial we amended the protocol to move radiation therapy upfront (day 21) for patients with parameningeal disease with high risk features ² including any of the following: 1) intracranial extension or evidence of meningeal impingement, cranial nerve palsies or base of skull erosion, 2) tumor location in an unfavorable parameningeal site (infratemporal fossae, pterygopalatine fossae or paranasal sinuses), 3) primary tumor > 5 cm in one dimension, or 4) age < 1 year at diagnosis. Since that change in protocol therapy we have accrued an additional nine intermediate and high risk patients with parameningeal RMS, seven of which had high risk PM features necessitating RT upfront, and have documented 2 regional recurrences in the leptomeninges (2.9 and 6.4 months from initiation of therapy) and no local recurrences.

Discussion

The vast majority of rhabdomyosarcoma trials that have been conducted by the Children's Oncology Group have prescribed RT to the primary site by week 13 unless the patient had a PM primary tumor site with high risk features in which case RT would be initiated early. The criteria for selecting PM patients for early RT has mostly been based on criteria that adversely increase the risk of failure such as age < 1 year, CNP, CBBPE, ICE, size > 5 cm and unfavorable site.^{2,6,7} Others have proposed response to chemotherapy as a modifying factor for target volume reductions,⁸ although this strategy for altering radiotherapy timing is untested.⁹ Smaller studies have successfully delayed or omitted radiotherapy with adequate local control rates when patients received more intensive chemotherapies.^{3,4,10}

Our findings suggest that local control rates may be compromised in selected patients with PM tumors when RT is delayed and given with lower doses of cyclophosphamide (1.2 g/m²). Reduced doses of cyclophosphamide have been recently implicated as a factor that contributes to higher local failure rates in children with Group III vaginal and orbital rhabdomyosarcoma^{11,12} thought to play a role in the s been attributed to an increased risk of local failure in recent studies in lower risk subsets of rhabdomyosarcoma¹¹. The contribution of limited radiotherapy target margins cannot be excluded⁸ but prior studies have demonstrated no decrement with reductions in target volume with leptomeningeal failure rate.¹ By starting at a delayed time point, a larger proportion of the at risk tumor bed from diagnosis gets treated to a lower dose (36CGE) prior to cone down. Reduced dose primary site radiotherapy has not been shown to result in an increased failure rate following adequate chemotherapy response¹³. While this could potentially contribute to an increased local failure rate in a parameningeal primary patient, it does not explain the observed increase in the risk for leptomeningeal failure⁸. Physicians employing a delayed radiotherapy approach in patients with Parameningeal primaries with high risk features should use caution as our

observations raise the possibility that reduce cyclophosphamide and delayed RT may compromise local control in children with PM RMS.

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Figure 1a. Pre-Treatment Disease Extent and Radiotherapy Plan

T2 FLAIR post-contrast MRI at the time of planning demonstrating an expansive nasopharyngeal primary with intracranial extension.

Figure 1b. Failure MRI with Radiotherapy Plan Overlay.

T2 FLAIR post-contrast MRI with multiple areas of hyper-intense T2 signal corresponding to diffuse leptomeningeal disease.

Figure 2.
Progression Free Survival

Table 1.**RMS13 Patients With Parameningeal Primary Tumors**

Age (yrs)	Location	Pre / Post Amend	RT Timing	Risk Group	Primary Tumor Size	PM Risk Factors	Progression / Recurrence	Time to Progression / Recurrence (mo.)	Current Status
2.3	Infratemporal Fossa	Pre	Delayed	Intermediate Risk	> 5 cm	CN Palsy, CBBE	Progression, Primary Site	1.6	Alive at 42.4 mo.
6.1	Nasopharynx	Pre	Delayed	Intermediate Risk	> 5 cm	CN Palsy, CBBE, ICE	Leptomeningeal Recurrence	7.2	Dead at 15 mo.
3.8	Infratemporal Fossa	Pre	Delayed	Intermediate Risk	> 5 cm	CBBE	NED	-	Alive at 36.3 mo.
14.1	Paranasal Sinus	Pre	Delayed	Intermediate Risk	> 5 cm	CN Palsy, CBBE, ICE	Leptomeningeal Recurrence	12.5	Dead at 25.8 mo.
3.4	Middle Ear	Post	Delayed	Intermediate Risk	5 cm	None	NED	-	Alive at 20.1 mo.
10.7	Nasopharynx	Post	Delayed	Intermediate Risk	5 cm	None	NED	-	Alive at 7.7 mo.
3	Nasopharynx	Post	Early	Intermediate Risk	> 5 cm	None	NED	-	Alive at 20.3 mo.
8.7	Infratemporal Fossa	Post	Early	High Risk	> 5 cm	CBBE	NED	-	Alive at 20.3 mo.
3.6	Middle Ear	Post	Early	High Risk	5 cm	CN Palsy, CBBE	Leptomeningeal Recurrence	6.4	Dead at 6.4 mo.
9.8	Parapharyngeal Space	Post	Early	Intermediate Risk	> 5 cm	CBBE	NED	-	Alive at 13.3 mo.
5.5	Infratemporal Fossa	Post	Early	High Risk	> 5 cm	CN Palsy, CBBE, ICE	NED	-	Alive at 9.3 mo.
11.2	Paranasal Sinus	Post	Early	Intermediate Risk	> 5 cm	CN Palsy, CBBE, ICE	Leptomeningeal Recurrence	2.9	Alive with disease at 4.2 mo.
21.4	Parapharyngeal Space	Post	Early	Intermediate Risk	> 5 cm	CBBE	NED	-	Alive and 3.6 mo.

Pre = Pre-Amendment, Post = Post-Amendment, PM = Parameningeal, NED = No evidence of disease, mo = months, CN = Cranial nerve, CBBE = Cranial Base Bony Erosion, ICE = Intracranial Extension