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Optimal Dosing of Cyclophosphamide in Rhabdomyosarcoma: It's Complicated

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Rhabdomyosarcoma is the most common soft-tissue sarcoma in children in the United States with an incidence of 4.5 per million, which translates into approximately 350 new diagnoses per year. The use of risk-based multimodal therapies developed by cooperative groups has been largely responsible for improving the 5-year survival rates for this disease, which now exceed 70%.[1]

Despite marked improvements in the outcomes of most children with rhabdomyosarcoma, survival rates for patients with metastatic disease and select patients with intermediate-risk disease, such as those with unresectable stage 2/3 tumors, have not significantly improved over the past 30 years. The Children's Oncology Group Soft Tissue Sarcoma Committee (COG-STS) has used vincristine, actinomycin, and cyclophosphamide (VAC) as the main backbone for treating rhabdomyosarcoma. To improve the survival of patients with intermediate-risk disease, the COG-STS conducted a series of clinical trials in which doses of active agents were intensified or novel agents such as camptothecins were incorporated. Promising activity was found in phase 2 window trials of patients with metastatic rhabdomyosarcomas.[2,3] For example, in a prospective single-arm trial of 115 patients with intermediate-risk rhabdomyosarcoma, dose escalation of cyclophosphamide to 4.5 g/m^2 did not result in improved outcomes and was associated with significant gastrointestinal toxicity.[4] In the prospective randomized trial D9803, 516 patients with intermediate-risk rhabdomyosarcoma were randomly assigned to receive VAC chemotherapy with a cyclophosphamide dose of 2.2 g/m^2 or VAC alternating with vincristine, cyclophosphamide, and topotecan (VTC; Table 1). The estimated 4-year failure-free survival and overall survival rates were similar for the 2 arms.[6] In the most recent trial ARST0531, which is the subject of this report, 448 patients with intermediate-risk rhabdomyosarcoma were randomized to receive VAC chemotherapy or VAC alternating with vincristine and irinotecan (VI). The 4-year event-free survival and overall survival rates were similar for both arms, but the VAC/VI arm had fewer hematologic toxicities and more gastrointestinal toxicities than the VAC arm.[7] On the basis of these results, the COG-STS adopted VAC/VI as the new

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backbone for therapy for patients with intermediate-risk disease in the ongoing study ARST1431.

In a study published in *Cancer*,[8] Casey and investigators of the COG-STS report increased local failure rates in patients with intermediate-risk rhabdomyosarcoma enrolled in ARST0531. Eligibility criteria for this trial included a diagnosis of nonmetastatic alveolar rhabdomyosarcoma or incompletely resected embryonal rhabdomyosarcoma arising at unfavorable sites (stage 2/3, group III). Chemotherapy consisted of VAC at a dose of 1.2 g/m^2 or VAC alternating with VI. Local control started at week 4, and radiation therapy (RT) doses were tailored to the volume of the residual tumor. Patients with node-negative group I/II alveolar tumors received 36 Gy, whereas those with nodal disease received 41.4 Gy. Patients with gross residual disease (group III) received a total cumulative dose of 50.4 Gy to a response-adjusted volume after chemotherapy. The 2 randomized groups were well balanced with respect to baseline patient characteristics. Group III embryonal tumors were present in 54%, 33% had group III alveolar tumors, and 13% had group I/II alveolar tumors. The most common primary site was the parameningeal region (45%), which was followed by the genitourinary tract (13%) and extremities (13%). The local failure rate for patients with group I/II alveolar tumors was 14.4%, which was similar to the rate of 8.6% reported in the previous COG-STS D9803 trial. In the 369 patients with group III disease, the incidence of local failure at 5 years was 25.4%, with higher local failure rates in patients with embryonal tumors (28.4% vs 20.2%). A tumor size >5 cm was associated with a higher local failure rate (32.3% vs 16.7%). Local failures rates were similar in patients who received VAC (21.3%) or VAC/VI (26.1%), and the modality of RT used, which included proton-beam RT in 12% of patients, did not influence local failure rates. The event-free survival and overall survival rates for patients in ARST0531 were inferior to those for patients in D9803. These differences were most apparent for patients with embryonal stage 2/3, group III tumors, who made up 54% of the patients enrolled in ARST0531.

Therefore, what were the differences between this trial and previous trials that could explain these inferior outcomes?

In D9803, patients received a cyclophosphamide dose of 2.2 g/m^2 per cycle, with cumulative doses ranging from 25.1 to 30.1 g/m^2 (Table 1). In ARST0531, the cyclophosphamide dose was reduced by approximately 45% to 1.2 g/m^2 per cycle, and the total cumulative dose of the VAC arm was decreased by approximately 45% to 16.8 g/m^2. Furthermore, for patients randomized to the VAC/VI arm, the total cumulative dose was further reduced by 66% to a total dose of only 8.4 g/m^2 in comparison with the VAC/VTC arm of D9803. The reasons for decreasing cyclophosphamide doses in ARST0531 are not entirely clear but were likely based on observations from the Intergroup Rhabdomyosarcoma Study IV (IRS-IV) trial, which showed that higher doses of cyclophosphamide (2.2 g/m^2) per cycle did not appear to improve the outcomes of patients with stage 2/3, group III tumors in comparison with the IRS-III trial.[9] Notably, however, although the cyclophosphamide dose per cycle in IRS-III was only 900 mg/m^2, most patients with group III disease received repeated pulsed doses of VAC or VAC alternating with Doxorubicin for 2 years (weeks 20-104), and this resulted in cumulative cyclophosphamide doses as high as 18 g/m.[2,10] Thus, the total cumulative dose of cyclophosphamide in ARST0531 was significantly lower than that used in IRS-IV,

D9803, and IRS-III. There were also subtle differences in the populations and criteria used to diagnose alveolar tumors in ARST0531 and D9803. However, patients with group III embryonal rhabdomyosarcoma, who had the highest rates of local recurrence, were expected to be very similar in the 2 studies. In ARST0531, group III patients represented 87% of the patient population and had an overall 5-year cumulative incidence of local failure of 25.4% versus 13% in IRS-IV and 19% in D9803 (Table 1). Furthermore, local failure rates were significantly higher for patients with group III embryonal tumors in ARST0531 than for patients in D9803 (27.9% vs 19.4%; $P = .03$), and a larger tumor size was associated with the highest local failure rate (32%) in ARST0531, which was higher than the local failure rate of 25% reported in D9803.[11] Unfortunately, these higher local failure rates translated into poorer clinical outcomes for patients with stage 2/3, group III embryonal tumors.

It is possible that there is a threshold of alkylating agents needed to optimize the outcomes of select patients with intermediate-risk rhabdomyosarcoma, but the optimal dose is unknown. However, there is a precedent to suggest that a minimal dose of cyclophosphamide is required to achieve favorable clinical outcomes. In D9803, patients with stage 2/3, group II/III alveolar disease randomized to the VAC/VTC arm and receiving a total cumulative cyclophosphamide dose of 25.1 g/m^2 had poorer outcomes than those receiving higher cumulative doses of VAC (Table 1). Similarly, failure-free survival rates were suboptimal for girls with genital tract embryonal rhabdomyosarcoma when the total cyclophosphamide cumulative dose was reduced to 4.8 g/m^2 and RT was eliminated.[12] More recently, we and others reported an increased risk of locoregional failure in patients with head and neck rhabdomyosarcoma treated with lower cyclophosphamide doses and definitive RT (Table 1).[13,14] In contrast, the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) Rhabdomyosarcoma 2005 (RMS 2005) study reported improved outcomes for patients with intermediate-risk rhabdomyosarcoma who received 9 courses of ifosfamide, vincristine, and actinomycin D followed by 6 cycles of maintenance therapy with vinorelbine and cyclophosphamide with a total cumulative cyclophosphamide dose of 17.7 g/m^2. This trial used a longer cyclophosphamide exposure and higher cumulative doses of alkylators than ARST0531, and this suggests that a minimal threshold of cyclophosphamide is necessary to yield favorable outcomes in this population. The total cumulative cyclophosphamide doses for the VAC and VAC/VI arms in ARST0531 were lower than those in EpSSG RMS 2005 (Table 1). It remains unclear whether the dose per cycle (intensity), total cumulative dose, or prolonged administration (sustained exposure) led to improved outcomes in EpSSG RMS 2005. However, on the basis of these findings, the COG-STS has adopted maintenance therapy identical to that used in EpSSG RMS 2005 in ARST1431 for intermediate- risk patients but has retained the VAC/VI backbone arm, which, when combined with maintenance therapy, will deliver a total cumulative cyclophosphamide dose of only 12.6 g/m^2. This trial will clarify the role of the cyclophosphamide dose and schedule in treating intermediate-risk rhabdomyosarcoma.

The rationale for the early introduction of RT at week 4 in ARST0531 was to potentially improve local control, which accounts for the majority of local failures in rhabdomyosarcoma. Unfortunately, because up to 43% of patients having parameningeal tumors with intracranial extension received early RT in D9803, interpreting the potential effect of early RT versus delayed RT on rates of local control is problematic (Table 1).[11]

Prior analyses of data from IRS-II to IRS-IV suggested that the presence of meningeal impingement increased the risk of local failure if RT was not started within 2 weeks of the diagnosis, and this indicates that the timing of RT is still relevant, although the confounding factor of cyclophosphamide doses precludes definitive conclusions.[15]

The different targeting strategies used among studies further complicate inferences on the factor that potentially influenced local failure rates. ARST0531 used a response-adjusted RT volumetric targeting strategy that differentially dosed regions of group III tumors according to the radiographic response following induction chemotherapy, whereas D9803 did not allow for a reduction in the target volume less than the original extent of the disease at diagnosis. However, the authors state that most patients did not have a significant reduction in tumor volume at week 4, and this suggests that this intervention is likely not the cause of increased local failure rates in ARST0531. Similarly, rates of delayed primary excision, which allows for reductions in RT doses, were lower in ARST0531 than D9803 (Table 1). However, the use of this intervention did not appear to compromise local control rates in comparison with treatment with conventional RT doses. Although advances in imaging and RT delivery techniques have made it possible to treat smaller volumes with the goal of mitigating late effects, it remains unclear whether new techniques such as proton-beam RT, which was used in only 12% of the patients in ARST0531, will significantly affect the long-term outcomes of these patients.[16,17]

The study by Casey et al[8] clearly delineates the potential role of cyclophosphamide dosing in the local control of group III rhabdomyosarcoma, although defining a potential threshold for the cumulative dose or dose intensity and ruling out other potential contributors such as timing remain a challenge. Future trials should be cognizant of the potential contribution of systemic therapy to local control and consider augmented local therapy strategies for patients with poor prognostic factors for local failure.

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REFERENCES

1. Skapek SX, Ferrari A, Gupta AA, et al. Rhabdomyosarcoma. Nat Rev Dis Primers. 2019;5:1. [PubMed: 30617281]
2. Pappo AS, Lyden E, Breneman J, et al. Up-front window trial of topotecan in previously untreated children and adolescents with metastatic rhabdomyosarcoma: an Intergroup Rhabdomyosarcoma Study. J Clin Oncol. 2001;19:213–219. [PubMed: 11134215]
3. Pappo AS, Lyden E, Breitfeld P, et al. Two consecutive phase II win-dow trials of irinotecan alone or in combination with vincristine for the treatment of metastatic rhabdomyosarcoma: the Children's Oncology Group. J Clin Oncol. 2007;25:362–369. [PubMed: 17264331]
4. Spunt SL, Smith LM, Ruymann FB, et al. Cyclophosphamide dose intensification during induction therapy for intermediate-risk pediatric rhabdomyosarcoma is feasible but does not improve outcome: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. Clin Cancer Res. 2004;10:6072–6079. [PubMed: 15447992]

5. Donaldson SS, Meza J, Breneman JC, et al. Results from the IRS-IV randomized trial of hyperfractionated radiotherapy in children with rhabdomyosarcoma—a report from the IRSG. Int J Radiat Oncol Biol Phys. 2001;51:718–728. [PubMed: 11597814]

6. Arndt CA, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: Children's Oncology Group study D9803. J Clin Oncol. 2009;27:5182–5188. [PubMed: 19770373]

7. Hawkins DS, Chi YY, Anderson JR, et al. Addition of vincristine and irinotecan to vincristine, dactinomycin, and cyclophosphamide does not improve outcome for intermediate-risk rhabdomyosarcoma: a report from the Children's Oncology Group. J Clin Oncol. 2018;36:2770–2777. [PubMed: 30091945]

8. Casey DL, Chi YY, Donaldson SS, et al. Increased local failure for patients with intermediate-risk rhabdomyosarcoma on ARST0531: a report from the Children's Oncology Group. Cancer. 2019;125.

9. Crist WM, Anderson JR, Meza JL, et al. Intergroup Rhabdomyos-arcoma Study-IV: results for patients with nonmetastatic disease. J Clin Oncol. 2001;19:3091–3102. [PubMed: 11408506]

10. Crist W, Gehan EA, Ragab AH, et al. The Third Intergroup Rhabdomyosarcoma Study. J Clin Oncol. 1995;13:610–630. [PubMed: 7884423]

11. Wolden SL, Lyden ER, Arndt CA, et al. Local control for interme-diate-risk rhabdomyosarcoma: results from D9803 according to histology, group, site, and size: a report from the Children's Oncology Group. Int J Radiat Oncol Biol Phys. 2015;93:1071–1076. [PubMed: 26581144]

12. Walterhouse DO, Pappo AS, Meza JL, et al. Reduction of cyclophosphamide dose for patients with subset 2 low-risk rhabdomyosarcoma is associated with an increased risk of recurrence: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. Cancer. 2017;123:2368–2375. [PubMed: 28211936]

13. Lucas JT Jr, Pappo AS, Wu J, Indelicato DJ, Krasin MJ. Excessive treatment failures in patients with parameningeal rhabdomyosarcoma with reduced-dose cyclophosphamide and delayed radiotherapy. J Pediatr Hematol Oncol. 2018;40:387–390. [PubMed: 29683960]

14. Casey DL, Wexler LH, Wolden SL. Worse outcomes for head and neck rhabdomyosarcoma secondary to reduced-dose cyclophosphamide. Int J Radiat Oncol Biol Phys. 2019;103:1151–1157. [PubMed: 30508617]

15. Michalski JM, Meza J, Breneman JC, et al. Influence of radiation therapy parameters on outcome in children treated with radiation therapy for localized parameningeal rhabdomyosarcoma in Intergroup Rhabdomyosarcoma Study Group trials II through IV. Int J Radiat Oncol Biol Phys. 2004;59:1027–1038. [PubMed: 15234036]

16. Hayes-Jordan A, Doherty DK, West SD, et al. Outcome after surgical resection of recurrent rhabdomyosarcoma. J Pediatr Surg. 2006; 41:633–638; discussion 633-638. [PubMed: 16567168]

17. Donaldson SS, Anderson JR. Rhabdomyosarcoma: many similarities, a few philosophical differences. J Clin Oncol. 2005;23:2586–2587. [PubMed: 15728222]

TABLE 1.

Comparison of Cyclophosphamide Doses, Local Therapies, Local Failure Rates, and Patient Outcomes in Trials on Rhabdomyosarcoma

Study	Cyclophosphamide Dose, g/m^2		Local Therapy Characteristics		Local Failure Rate, %			Outcomes: FFS/EFS and OS
	Per Cycle	Cumulative Dose	Timing, wk	DPE, % Group III	PM >5 cm		Group III Emb/Alv	
IRSG-IV[5]	2.2	26.4	9	0.8	16	34	13	5-y FFS: 70% 5-y OS: 75%
D9803[6]	2.2	25.1-30.8	12	45	19.5	25	19.4/17.7	4-y EFS: 68%-73% 5-y OS: 79%
ARST0531[7]	1.2	8.4-16.8	4	16	27.7	32.3	27.9/20.2	4-y EFS: 59%-63% 4-y OS: 72%-73%
MSKCC	1.2-2.2	10-24	13	NR	12.5	NR	10.6/6.8	2-y EFS: 74.6% 2-y OS: 84.1%
RMS 2005	≈1.5 + maint	≈17.7	13	NR	NR	NR	NR	3-y EFS: 78.4% (maint) vs 72.3%3-y OS: 87.3% (maint) vs 77.4%
ARST1431	1.2 + maint	12.6	13	—	—	—	—	—

Abbreviations: DPE, delayed primary excision; EFS, event-free survival; Emb/Alv, embryonal/alveolar; FFS, failure-free survival; IRSG-IV, Intergroup Rhabdomyosarcoma Study Group IV; maint, maintenance; MSKCC, Memorial Sloan Kettering Cancer Center; NR, not reported; PM, parameningeal; OS overall survival; RMS 2005, Rhabdomyosarcoma 2005.