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VIncristine, irinotecan, and temozolomide in children and adolescents with relapsed rhabdomyosarcoma

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Abstract

Background—The combination of vincristine, irinotecan, and temozolomide (VIT) is often used to treat children and adolescents with relapsed rhabdomyosarcoma (RMS); however, the outcome of these patients has not been previously described.

Procedures—We sought to determine the response rate (RR) and progression-free survival (PFS) for patients with relapsed RMS treated with VIT by retrospective review of patients treated at five tertiary care hospitals. Prior treatment with irinotecan was permitted.

Results—Among 19 patients with a median age of 8 years (range 2–17 years), 12 (63%) were males and 12 (63%) had embryonal histology. Median time to relapse from initial diagnosis was 16 months (range 2.8–45 months). VIT was used as first, second, third, or fourth line of therapy in four (21%), seven (37%), six (32%), and two (10%) patients, respectively. Four patients received VIT as adjuvant therapy following radiation and/or surgery. Therefore, among 15 evaluable patients, the best response to VIT was 0 (complete response, CR), 0 (partial response, PR), 4 (stable disease, SD), and 11 (progressive disease, PD) for an overall clinical benefit rate (CR + PR + SD) of 26.7% (95% CI: 7.8–55.1%). After a median follow-up of 8 months, 2 (10%) patients were alive without disease, 3 (16%) were alive with disease, and 14 (74%) patients died of PD. PFS at 3 months was 23% (95% CI: 5.7–46.7%).

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Conclusions—VIT therapy in combination with adequate local control is associated with some disease control in patients with first relapse RMS and may be another reasonable option to offer patients as salvage therapy.

Keywords

chemotherapy; irinotecan; pediatric soft tissue sarcoma; rhabdomyosarcoma; relapse; temozolomide

1 | INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children and adolescents with approximately 250 children diagnosed annually in the United States.[1,2] Currently, more than 70% of children with localized RMS can be cured of their disease.[2] Improvements in outcome have been attributed to the use of intensive combination chemotherapy, better staging, and more effective local therapy with surgery and radiation. However, relapsed disease is still extremely difficult to salvage with only 10% chance of patients surviving at 5 years.[3]

The combination of vincristine and irinotecan (VI) has been previously investigated in patients with first relapse RMS at high risk for poor outcome.[4] Further, among patients with treatment naïve high-risk RMS, response rates (RRs) to VI combination and single agent irinotecan was 70% and 42%, respectively.[5] Dose-limiting toxicities of VI are primarily gastrointestinal (diarrhea).[4] Temozolomide as a single agent is of limited benefit in patients with RMS[6] however, the addition of temozolomide to VI (vincristine, irinotecan, and temozolomide [VIT]) has previously been evaluated in patients with relapsed Ewing sarcoma, with an RR of 50–68%.[7–9] Two small series of included patients with relapsed RMS, which documented an RR of 25% and 43% among four and seven patients, respectively[10,11] The synergy of these two agents has shown to be due to temozolomide-induced methylation of DNA causing localization and enhancement of topoisomerase I cleavage complexes, allowing irinotecan to effectively stabilize the DNA-enzyme complex that leads to cytotoxicity of the tumor cells.[12] Herein, we describe the progression-free survival (PFS) of patients with relapsed RMS in the largest series to date, compiling data on 19 patients from five tertiary care centers.

2 | METHODS

We conducted a multicenter retrospective review from the following centers: Nationwide Children's Hospital (Columbus, OH), Hospital for Sick Children (Toronto, Canada), Children's Hospital of Philadelphia, Texas Children's Hospital and Children's Hospital of Los Angeles. Eligibility criteria for this study were as follows: Primary diagnosis of RMS from 2000 to 2013, which had received VIT at the time of first or subsequent relapse; patients who had previously received irinotecan were not excluded. The following data were collected: age at initial diagnosis, location of initial tumor, prior chemotherapy, number of relapses, time to recurrence after initial treatment, local control strategy used at relapse, status at last follow-up, and time to follow-up. RR was recorded as was assessed by the treating institution according to RECIST 1.1. Toxicity data were not collected. Approval

from Institutional Review Board was obtained at each site prior to accrual of data. A RedCAP database[13] was established to securely transfer data across institutions. Data were analyzed with descriptive statistics. PFS distributions were estimated using the Kaplan–Meier method[14] and were compared using the log-rank test.[15] Statistical significance was determined at the 0.05 level.

3 | RESULTS

Demographics

The median age of 19 enrolled patients was 8 years (range 2–17 years) at primary diagnosis. Twelve (63%) were males and 12 (63%) had embryonal histology. Metastatic disease was present in three (16%) patients at initial diagnosis. Median time to relapse from initial diagnosis was 16 months (range 2.8–45 months). VIT was used as first, second, third, or fourth line of therapy in four (21%), seven (37%), six (32%), and two (10%) patients, respectively. Sites of relapse were as follows: seven (37%), local; nine (47%), distant, and three (16%), combined.

Treatment

Therapy at initial diagnosis included doxorubicin-based 4 (20%) and vincristine, dactinomycin, and cyclophosphamide 15 (75%). Of these, three (57%) received an irinotecan-based regimen, in whom VIT was used as first, second, and fourth line after relapse. At relapse, VIT was administered every 21 days as follows: vincristine, 1.5 mg/m^2 intravenously (IV) on day 1; irinotecan, 50 mg/m^2 IV or 70–100 mg/m^2 orally, days 1–5; temozolomide 100–150 mg/m^2 orally, days 1–5. Local control was administered to 11 (58%) patients and included radiation for 8 (42%), and surgery for 5 (26%) patients (Table 1).

Outcome

Four patients who received adjuvant VIT chemotherapy postsurgery for local control are not included in the response analysis. Among the 15 evaluable patients, the best response to VIT was as follows: 0 (complete response, CR), 0 (partial response, PR), 4 (stable disease, SD), and 11 (progressive disease, PD) for an overall clinical benefit rate (CR + PR + SD) of 26.7% (95% CI: 7.8–55.1%). One patient with SD had received prior irinotecan. Two (13%) patients remain alive with disease at 8.6 and 14.8 months. Thirteen (87%) patients had died of PD at a median time of 4.9 months (range: 1.2–23 months). PFS at 3 months was 23% (95% CI: 5.7–46.7%; Fig. 1). All three patients who are alive without disease had had only local recurrence, had local therapy with surgery, RT or both, and received adjuvant VIT chemo.

4 | DISCUSSION

Collecting information on disease outcome outside a clinical trial is challenging despite multicenter involvement. Moreover, retrospective analyses such as this one are inherently limited by quality of information documented and collected, with no central radiology or pathology review and interpatient variability in dosing of chemotherapy agents. In the current series, toxicity information was not collected. Nonetheless, herein, we describe the

largest series to date of children and adolescents treated with VIT for relapsed RMS. Best response to VIT was SD, however, this was achieved in a quarter of patients. Notably, all patients alive at last follow-up had only a local recurrence and received adjuvant VIT.

Almost half of the patients in our series had local relapses, and local control was offered at the time of relapse with surgery, radiation, or both to over half of all patients. This study was not equipped to analyze the overall impact of local control in addition to chemotherapy on outcome, although surgery has been previously demonstrated to play an important role in patients with relapsed RMS.[16] In our dataset, the three patients who were alive at last follow-up underwent aggressive local control with surgery and/or radiation therapy.

Irinotecan has been incorporated into front-line therapy of patients with newly diagnosed RMS in the two most recently closed studies through the Children's Oncology Group (COG). ARST0431 utilized a dose-intensive multiagent regimen that includes vincristine, doxorubicin, cyclophosphamide/ifosfamide and etoposide alternating with vincristine, actinomycin, cyclophosphamide/VI (VAC/VI) for the treatment of high-risk RMS.[17] Unfortunately, the reported 3-year eventfree survival of 38% was similar to prior studies, and so it remains unclear whether VI will be used in future studies of high-risk patients. Conversely, when patients with intermediate-risk disease enrolled on ARST0531 were randomized to receiving either VAC alone or alternating with VI, patients on both arms had similar favorable outcome.[18] Due to the decreased toxicity associated with VAC alternating with VI, this has been chosen to be the new standard backbone for the current study in patients with intermediate-risk RMS. Thus, moving forward, many patients will likely have received irinotecan in upfront therapy. In the current study, one of the four who derived clinical benefit from VIT received prior irinotecan.

Another commonly used treatment regimen for relapsed RMS includes cyclophosphamide and topotecan for which a window phase II study demonstrated an RR of 47% in patients with newly diagnosed RMS.[19] In 15 patients with relapsed RMS, PR and SD was 67% and 20%, respectively.[20] However, this study limited inclusion to those who had ≤2 prior lines of therapy. Our data highlight the importance of number of prior lines of therapy when evaluating response to novel treatments. Due to the small sample size, there was no significant statistical difference when comparing patients who received VIT after varied number of prior cycles of therapy. The outcome of those who received VIT as second-line therapy was poorer than when VIT was administered as first-line therapy. Despite these limitations, the role of VIT at first relapse in patients previously exposed to irinotecan deserves consideration.

The clinical trial sponsored by Centre Oscar Lambret randomizing patients to VI versus VIT has completed accrual, and although prior irinotecan was not permitted, there was no restriction to prior lines of therapy.[21] Most early-phase studies within pediatric oncology also do not limit number of prior lines of therapy, which may impact overall responses when evaluating new agents. Interestingly, the most recently completed COG trial ARST0921 enrolled patients with first relapse RMS, with no prior therapy for relapsed disease. This study was informative and actually demonstrated a difference in PFS in those receiving a combination of vinorelbine, cyclophosphamide, and temsirolimus over those receiving the

same backbone chemotherapy and bevacizumab.[18] The results of this study have helped with the inclusion of temsirolimus in the currently open study for intermediate-risk RMS.[22] In conclusion, VIT may be considered in patients with relapsed RMS; however, overall outcome is likely driven by disease biology and type of recurrence.

Abbreviations

CR	complete response
PD	progressive disease
PFS	progression-free survival
PR	partial response
RR	response rate
RMS	rhabdomyosarcoma
SD	stable disease
VAC/VI	vincristine, actinomycin, cyclophosphamide/vincristine, irinotecan
VIT	vincristine, irinotecan, and temozolomide

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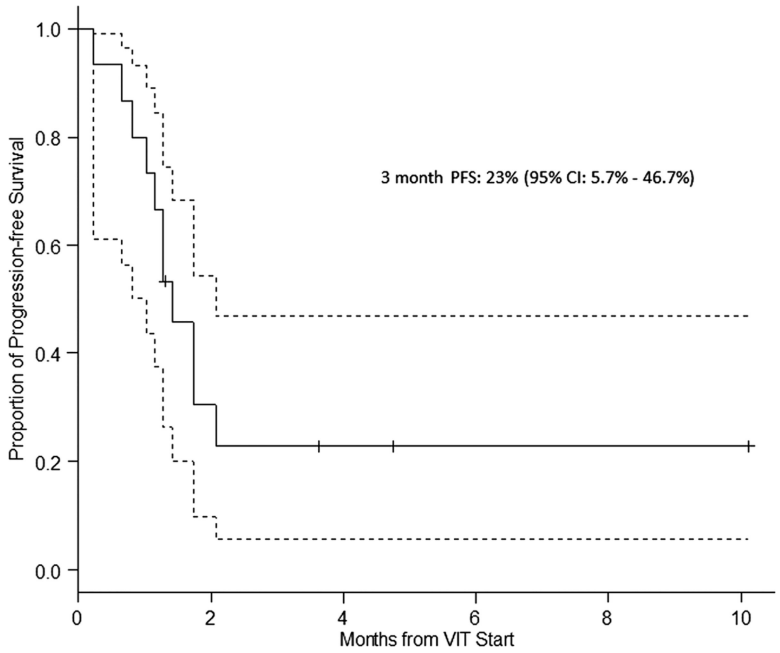

FIGURE 1.

Proportion of progression-free survival Three-month PFS 23% (95% CI: 5.7–46.7%).

TABLE 1

Demographics and treatment data

	Age at pri. dx (yrs)	Sex	Histologic subtype (fusion status) [pri. site]	Metastatic disease at pri. diagnosis	Primary chemo regimen	Time to relapse (mo)	Site of relapse	VIT line of tx	VIT regimen used[a]	Cycles of VIT[b]	Local control	Reason for stopping chemo	Best response to therapy	Length of follow-up from date of relapse/ start of VIT (mo)	Status at last follow-up
1	8	M	Emb [GU]	No	VAC	12	Local	4	1–50 mg/m^2 IV × 5 days T-150 mg/m^2 × 5 days	2	RT	PD	PD	12/2.4	DOD
2	5	F	Emb [HN non-PM]	No	VAC	9	Local	2	1–50 mg/m^2 IV × 5 days T-100 mg/m^2 × 5 days	1	None	PD	PD	3/2.7	DOD
3	14	F	Alv(+) [trunk]	No	VAC	16	Distant (bone)	2	1–50 mg/m^2 IV × 5 days T-100 mg/m^2 × 5 days	1	RT	Toxicity	PD	4/1.2	DOD
4	17	F	Emb [GU non-B/P]	No	VAC, VA	46	Distant (brainstem)	2	1–50 mg/m^2 IV × 5 days T-100 mg/m^2 × 5 days	6	RT	End of therapy	SD	17/16.6	DOD
5	10	F	Emb [GU non-B/P]	No	VAC	3	Local	3	1–100 mg/m^2 PO × 10 days T-100 mg/m^2 × 5 days	2	None	PD	PD	28/11.0	DOD
6	8	M	Emb [orbit-PM]	No	VAC	12	Local	3	1–50 mg/m^2 IV × 5 days T-100 mg/m^2 × 5 days	2	None	PD	PD	7/4.9	DOD
7	9	M	Emb [HN non-PM]	No	VAC	27	Local	2	1–50 mg/m^2 IV × 5 days T-100 mg/m^2 × 5 days	18	S + RT	End of therapy	**Not evaluable**[c]	34/33.5	Alive, on hospice care
8	9	M	Alv(unk) [extremity]	Yes	ARST0431	10	Lung	4	1–50 mg/m^2 IV × 5 days T-100 mg/m^2 × 5 days	2	None	PD	PD	11/7.4	DOD
9	4	M	Emb [cheek, PM]	Yes	ARST08P1	10	Lung	1	1–50 mg/m^2 IV × 5 days	2	RT	End of therapy	PD	2/12.6	DOD

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									T-100 mg/m^2 × 5 days						
10	14	F	Alv(unk) [trunk]	No	VAC	13	Distant (lung, bone)	2	1–50 mg/m^2 IV × 5 days T-100 mg/m^2 × 5 days	1	RT	Toxicity	**Not evaluable**[c]	2/7.1	DOD
11	7	M	Emb [GU non-B/P]	No	VAC	13	LN	1	1–50 mg/m^2 IV × 5 days T-100 mg/m^2 × 5 days	1	S + RT	PD	PD	23/23.0	DOD
12	1.75	F	Alv (+) [HN non-PM]	No	VAC	16	Local	1	1–90 mg/m^2 PO × 5 days T-100 mg/m^2 × 5 days	12	S	Physician preference	**Not evaluable**[c]	31/31.0	Alive without disease
13	7	M	Emb [pelvis]	No	VAC	23	Distant (liver)	3	1–20 mg/m^2 IV × 5 days T-100 mg/m^2 × 5 days	9	S	PD	**SD**	27/9.4	DOD
14	9	F	Alv (unk) [extremity]	No	VAC	33	Lung	3	1–50 mg/m^2 IV × 5 days T-100 mg/m^2 × 5 days	1	None	PD	PD	9/2.0	DOD
15	4	M	Emb [orbit-PM]	No	VAC	6	Local	3	1–50 mg/m^2 IV × 5 days T-100 mg/m^2 × 5 days	2	None	PD	PD	6/2.7	DOD
16	16	M	Alv (+) [cervical with LN]	Yes	ARST0431	22	Max sinus	2	1–90 mg/m^2 PO × 5 days T-150 mg/m^2 × 5 days	6	RT	PD	**SD**	17/8.6	Alive with disease
17	13	M	Emb [GU non-B/P]	No	VAC	35	Distant (lung, bone, LN, abdomen)	2	1–70 mg/m^2 PO × 5 days T-125 mg/m^2 × 5 days	2	None	PD	PD	10/2.6	DOD
18	4	M	Emb [GU non-B/P]	No	VA	18	Abdomen	1	1–50 mg/m^2 IV × 5 days T-100 mg/m^2 × 5 days	6	S	Last follow-up	**Not evaluable**[c]	4/4.0	Alive without disease

	Age at pri. dx (yrs)	Sex	Histologic subtype (fusion status) [pri. site]	Metastatic disease at pri. diagnosis	Primary chemo regimen	Time to relapse (mo)	Site of relapse	VIT line of tx	VIT regimen used[a]	Cycles of VIT[b]	Local control	Reason for stopping chemo	Best response to therapy	Length of follow-up from date of relapse/ start of VIT (mo)	Status at last follow-up
19	4	M	Alv (+) [cheek/ mandible-PM]	No	VAC	17	Local, LN	3	1–90 mg/m^2 PO × 5 days T-150 mg/m^2 × 5 days	7	None	PD	**SD**	20/14.8	Alive with disease

Yrs, years, mo, months; pri. Dx, primary diagnosis; Pri. Site, primary site; tx, treatment; M, male; F, female; Emb, embryonal; Alv, alveolar; unk, unknown; pos, positive; GU, genitourinary; HN non-PM, head and neck nonparameningeal; PM, parameningeal; LN, lymph node; VAC, vincristine, actinomycin, cyclophosphamide; VA, vincristine, actinomycin; I, irinotecan; T, temozolomide; IV, intravenous; PO, per oral; S, surgery; RT, radiotherapy; CR, complete response; SD, stable disease; PD, progressive disease; DOD, died of disease.

[a] All except patient 8 received vincristine 0.5 mg/m^2.

[b] Number.

[c] VIT used as adjuvant therapy, response not evaluable.

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