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ORIGINAL REPORT

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

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ABSTRACT

Purpose

Intermediate-risk rhabdomyosarcoma (RMS) includes patients with either nonmetastatic, unresected embryonal RMS (ERMS) with an unfavorable primary site or nonmetastatic alveolar RMS (ARMS). The primary aim of this study was to improve the outcome of patients with intermediate-risk RMS by substituting vincristine and irinotecan (VI) for half of vincristine, dactinomycin, and cyclophosphamide (VAC) courses. All patients received a lower dose of cyclophosphamide and earlier radiation therapy than in previous trials.

Patients and Methods

Patients were randomly assigned at study entry to either VAC (cumulative cyclophosphamide dose, 16.8 g/m^2) or VAC/VI (cumulative cyclophosphamide dose, 8.4 g/m^2) for 42 weeks of therapy. Radiation therapy started at week 4, with individualized local control plans permitted for patients younger than 24 months. The primary study end point was event-free survival (EFS). The study design had an 80% power (5% one-sided α-level) to detect an improved long-term EFS from 65% (with VAC) to 76% (with VAC/VI).

Results

A total of 448 eligible patients were enrolled in the study. At a median follow-up of 4.8 years, the 4-year EFS was 63% with VAC and 59% with VAC/VI ($P = .51$), and 4-year overall survival was 73% for VAC and 72% for VAC/VI ($P = .80$). Within the ARMS and ERMS subgroups, no difference in outcome by treatment arm was found. Severe hematologic toxicity was less common with VAC/VI therapy.

Conclusion

The addition of VI to VAC did not improve EFS or OS for patients with intermediate-risk RMS. VAC/VI had less hematologic toxicity and a lower cumulative cyclophosphamide dose, making VAC/VI an alternative standard therapy for intermediate-risk RMS.

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INTRODUCTION

Rhabdomyosarcoma (RMS), the most common soft tissue sarcoma in children and adolescents, comprises two major histologic subtypes: alveolar RMS (ARMS) and embryonal RMS (ERMS).[1-3] Sequential cooperative group clinical trials defined an RMS risk stratification system designed to tailor the intensity of therapy to the probability of recurrence.[4-6] The Children's Oncology Group (COG) defines intermediate-risk RMS to include ERMS that arises at an unfavorable primary site, unresected before systemic therapy, and without distant metastases or ARMS without distant metastases regardless of primary site or resection status.[4-6] The combination of vincristine, dactinomycin, and cyclophosphamide (VAC) with radiation and/or surgery for local control has been the National Cancer Institute (NCI)–funded cooperative

ASSOCIATED CONTENT

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group standard therapy for intermediate-risk RMS for > 40 years.[4,5] Intergroup Rhabdomyosarcoma Study Group and COG clinical trials have been unable to improve the outcome for patients with intermediate-risk RMS despite the addition of doxorubicin,[7] ifosfamide with or without etoposide,[8] or topotecan.[9] Similarly, escalation of the cyclophosphamide dose per course from approximately 0.9 g/m2 to 2.2 g/m2 or 3.6 g/m^2 during induction therapy[7-11] also were unable to improve outcome for patients with ARMS or intermediate-risk ERMS.

Irinotecan is a prodrug that is converted by endogenous carboxylesterases to its active metabolite SN-38, which is excreted after glucuronidation by UGT1A1. SN-38 is believed to exert its cytotoxic activity by stabilizing the topoisomerase I:DNA complex, which prevents the resealing of the topoisomerase I single-stranded DNA breaks and blocks DNA religation.[12] Preclinical studies demonstrated substantial activity in RMS models, particularly when administered over consecutive days[13-15] and in combination with vincristine.[16] A COG phase II window study of vincristine in combination with irinotecan (VI) in patients with untreated metastatic RMS showed a 70% early response rate and an 8% early progressive disease rate, which were both better than with irinotecan alone (42% and 32%, respectively).[17] The early response rate to VI was the highest ever observed in phase II window studies.[18] COG ARST0121 was a phase II study of patients with relapsed or refractory RMS that compared two schedules of irinotecan (both in combination with vincristine): daily for 5 consecutive days versus 5 consecutive days for 2 weeks. The early response rate and outcome were similar with the two schedules,[19] which supported the use of the more convenient daily for 5 consecutive days VI schedule in subsequent COG trials. On the basis of these strong preclinical and clinical data, COG conducted the current prospective, randomized phase III study, ARST0531, to test the benefit of the addition of VI to VAC chemotherapy in intermediate-risk RMS, to correlate *UGT1A1* genotype with VI toxicity, and to assess the outcome with lower-dose cyclophosphamide (ie, 1.2 g/m^2 per course) for all patients.

PATIENTS AND METHODS

Eligibility and Patient Classification

Intermediate-risk RMS was defined as ERMS (including botryoid and spindle cell variants) or ectomesenchymoma, stages II and III, clinical group 3, and any ARMS without distant metastases.[4,5] For the purpose of analysis, botryoid and spindle cell RMS and ectomesenchymoma were classified with ERMS. Tumors with mixed histologic elements were classified by the majority component. Histology confirmation by central pathology review was required before starting week 4 of protocol therapy. The central pathology review designation was used in the statistical analysis. Patients enrolled in a concurrent COG study for low-risk RMS[20,21] were eligible to transfer enrollment (with appropriate reconsent) to this study if central pathology review confirmed ARMS instead of the institutional diagnosis of ERMS. The trial was approved by the pediatric central review board and by the institutional review boards of each participating institution, as required. Informed consent was obtained from patients' parents or guardians, the patients, or both, according to NCI guidelines. Other major eligibility criteria were no prior chemotherapy or radiation therapy (RT); age less than 50 years; initiation of therapy within 42 days of diagnostic biopsy; and adequate renal, hepatic, and bone marrow function.

Clinical group and stage were determined by the enrolling institution according to criteria of the COG staging and grouping systems.[4,5] Required staging evaluations were magnetic resonance imaging (MRI) or computed tomography (CT) scan of the primary site, chest CT scan, bone scan, bilateral bone marrow aspiration and biopsy, and lumbar puncture for cytology (parameningeal primary sites only). An [^{18}F]fluorodeoxy-D-glucose (FDG) positron emission tomography (PET) scan before therapy was optional. FDG-PET evidence of regional or distant metastases required an additional confirmatory modality, such as biopsy or anatomic imaging. Regional lymph node sampling was required for selected primary sites (paratesticular and age > 10 years and extremity) and strongly recommended for clinically/radiographically enlarged regional lymph nodes before study enrollment. Stage and clinical group classifications were reviewed by study committee surgeons and used in the outcomes analysis instead of institutional classification of stage and clinical group when available.

Chemotherapy

Patients were randomly assigned to either VAC or VAC/VI. During the first 12 weeks, the two treatment arms were identical in duration and schedule, with the exception of substituting irinotecan for dactinomycin and cyclophosphamide at week 4 and for cyclophosphamide at weeks 7 and 10 in VAC/VI. During the subsequent 30 weeks of therapy, irinotecan replaced dactinomycin and cyclophosphamide at weeks 16, 19, 25, 31, and 37 in VAC/VI. The schedule of weekly vincristine differed slightly between the two treatments to allow for vincristine administration during the weeks that followed all courses of irinotecan; the total number of vincristine doses was the same in both treatments. Randomization was stratified by three categories using institutional classification: ERMS clinical group 3, stage II/III; ARMS clinical group 1 or stage I; and ARMS clinical group 2/3 and stage II/III. Patients received granulocyte colony-stimulating factor after each VAC course but not after VI courses. The treatment schedules and chemotherapy doses are shown in Figure 1 and listed in Table 1.

Primary Tumor Treatment

Patients were evaluated for response (by MRI/CT scan) at weeks 15 and 30 and at the end of therapy, with optional FDG-PET at week 4 before RT and at week 15. For patients older than 24 months, definitive RT was the planned local control modality. Delayed primary resection was allowed but not encouraged. For patients age ≤ 24 months, individualized local control approaches, including delayed primary excision and response-adapted RT, were permitted. However, adherence to the RT algorithm whenever possible for patients younger than 24 months was encouraged.

RT started at week 4, and the dose was determined by clinical group and histology at study entry: clinical group 1 or 2 without regional lymph node involvement ARMS, 36 Gy; clinical group 2 ARMS with regional lymph node involvement, 41.4 Gy; clinical group 3 ARMS with orbital primary site, 45 Gy; and clinical group 3 ERMS or ARMS at nonorbital primary sites, 50.4 Gy. RT was delivered using megavoltage photon, proton, and/or electron beams. Brachytherapy was permitted. The recommended irradiated volume was the presurgical and prechemotherapy disease extent plus 1 cm. For tumors with a rapid substantial decrease in tumor size, a volume reduction by cone down after 36 Gy was permitted, particularly for tumors with pushing rather than infiltrating margins.

Statistical Methods

Event-free survival (EFS) was defined as the time from study enrollment to disease progression, disease recurrence, second malignant neoplasm, or death as result of any cause. Overall survival (OS) was defined as the time from study enrollment to death as result of any cause. EFS and OS were censored at the patient's last contact date. The primary comparison was EFS between the two treatment arms. The long-term EFS for the study population was projected to be 65% on the basis of prior studies.[7,8] The study was designed with 80% power (one-sided $\alpha = .05$) to detect an overall increase in the long-term EFS from 65% with VAC to 76% with VAC/VI, with a sample size of 486 and a cure model where the 3-year

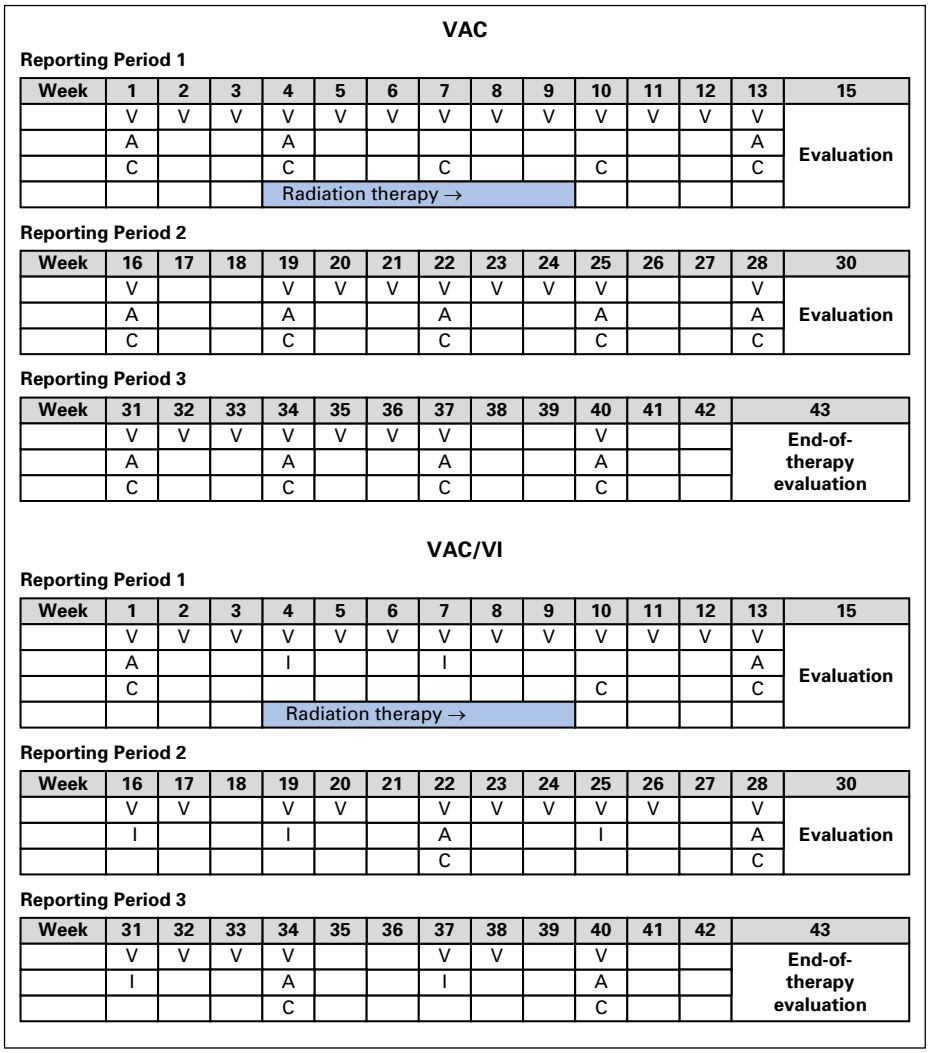

Fig 1. Treatment schema for each treatment arm and toxicity reporting period. Irinotecan administered for 5 consecutive days each course. A, dactinomycin; C, cyclophosphamide; I, irinotecan; V, vincristine.

EFS rate was 70% among VAC patients with a long-term EFS plateau at 65% and assuming a 5% loss-to-follow-up rate per year.[22] EFS and OS rates were estimated using the Kaplan-Meier method,[23] with CIs estimated by the Peto-Peto method,[24] and were compared between groups using the log-rank test.[25] The local failure rate was computed using the subdistribution estimates with an account for competing risks.[26] The study was monitored by the COG data and safety monitoring committee, and three interim analyses of EFS were conducted. Patient follow-up was current through June 30, 2016.

UGT1A1 Pharmacogenomics Studies

Blood for *UGT1A1* genotype analysis was obtained from consenting patients. Determination of *UGT1A1* genotype used a standard methodology[27-29] and are detailed in the Data Supplement. The rates of grade ≥ 3 toxicity among *UGT1A1* genotypes (6/6, 6/7, and 7/7) were compared using Fisher's exact test.

RESULTS

Patient Population

Between December 26, 2006, and December 7, 2012, 481 patients were enrolled in the study. Thirty-three (7%) were ineligible as determined by central pathology review (ERMS rather than ARMS with low-risk clinical features [n = 14], inadequate material for central pathology review [n = 5], non-RMS diagnosis [n = 2], presence of distant metastases [n = 6], inadequate staging

Table 1. Chemotherapy Doses by Patient Age for Vincristine, Dactinomycin, Cyclophosphamide, and Irinotecan

Age (year)	Vincristine	Dactinomycin (mg/kg)	Cyclophosphamide	Irinotecan (mg/m^2)
< 1	0.025 mg/kg	0.025	40 mg/kg	50
≥ 1 and < 3	0.05 mg/kg	0.045	1.2 g/m^2	50
≥ 3	1.5 mg/m^2	0.045	1.2 g/m^2	50

NOTE. Maximum single dose: vincristine, 2 mg; dactinomycin, 2.5 mg; irinotecan, 100 mg. Irinotecan administered for 5 consecutive days each course.

studies or organ function [n = 3], or other reasons [n = 3]). Of the remaining 448 eligible patients, 222 were randomly assigned to VAC and 226 to VAC/VI (Fig 2).

The clinical characteristic of the 448 eligible patients were similar and are listed in Table 2. Similar to prior intermediate-risk RMS clinical trials, most patients were male (54%), 1 to 10 years old (61%), and white (71%). ERMS was the predominant histologic type (53%). Almost all patients presented with advanced-stage disease (91% stage II or III) and clinical group (86% clinical group 3). The most common primary sites were parameningeal (46%), bladder/prostate (13%), extremity (13%), and retroperitoneal/perineal (11%).

Treatment Outcome

With a median follow-up for surviving patients of 4.8 years, the estimated 4-year EFS rates were 63% (95% CI, 55% to 70%) for VAC and 59% (95% CI, 51% to 66%) for VAC/VI ($P = .51$; Fig 3; Table 3). The estimated 4-year OS rates were 73% (95% CI, 66% to 79%) for VAC and 72% (95% CI, 65% to 79%) for VAC/VI ($P = .80$; Table 3). There was no difference in radiographic response among clinical group 3 patients as assessed by institutional report by week 15 of therapy (data not shown). No evidence was found for differential outcome by treatment arm in a histologic subgroup analysis (Table 3). Because the current study used a lower dose of cyclophosphamide in each VAC course (1.2 g/m^2 *v* 2.2 g/m^2) and earlier RT (week 4 *v* week 13) than the prior COG RMS trial (D9803), we compared current outcomes with those for patients with similar clinical features (defined by randomization stratification category) enrolled in D9803.[9] D9803 and the current study had different eligibility criteria (including the inclusion of patients with undifferentiated sarcoma and ERMS with distant metastases

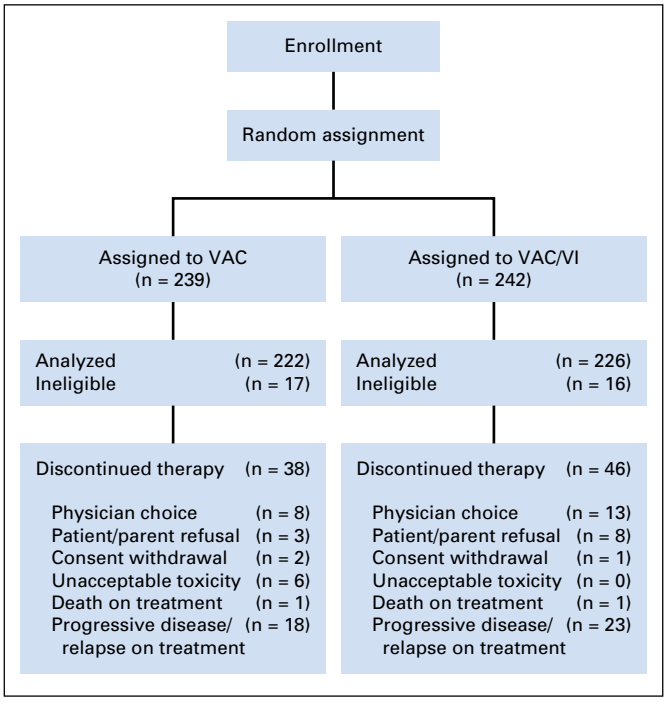

Fig 2. CONSORT diagram for Children's Oncology Group study ARST0531. VAC, vincristine, dactinomycin, and cyclophosphamide; VI, vincristine and irinotecan.

Table 2. Clinical Characteristics (n = 448)

Clinical Characteristic	VAC (n = 222) No.	VAC (n = 222) %	VAC/VI (n = 226) No.	VAC/VI (n = 226) %
Sex				
Male	121	55	120	53
Female	101	45	106	47
Age, years				
0-0.99	13	6	20	9
1-9.99	144	65	129	57
≥ 10	65	29	77	34
Race				
White	152	68	167	74
Black	34	15	28	12
Asian	6	3	7	3
Other/unknown	30	14	24	11
Ethnicity				
Hispanic or Latino	37	17	21	9
Non-Hispanic/Latino	176	79	195	86
Unknown	9	4	10	4
RMS histology				
Embryonal	114	51	123	54
Alveolar	102	46	94	42
NOS/unknown	6	3	9	4
Clinical group				
1	9	4	6	3
2	23	10	24	11
3	190	86	196	87
Stage				
I	21	9	18	8
II	74	33	64	28
III	127	57	144	64
Maximum tumor size, cm*				
< 5	96	44	101	45
5-9.99	98	45	101	45
≥ 10	26	12	23	10
T stage				
T1	99	45	99	44
T2	123	55	127	56
Regional lymph node status				
N0	175	79	171	76
N1	43	19	54	24
Nx	4	2	1	0.4
Primary site				
Orbit	3	1	4	2
Head or neck	18	8	15	7
Parameningeal	100	45	104	46
GU, bladder/prostate	31	14	29	13
GU, nonbladder/prostate	3	1	2	1
Extremity	29	13	29	13
Retroperitoneal/perineal	25	11	26	12
Trunk	11	5	12	5
Other	2	1	5	2

Abbreviations: GU, genito-urinary; N0, no clinical or radiographic evidence of regional lymph node involvement; N1, clinical and/or radiographic evidence of regional lymph node involvement; NOS, not otherwise specified; Nx, regional lymph nodes not evaluated; RMS, rhabdomyosarcoma; T1, confined to the organ of origin; T2, extends beyond organ of origin; VAC, vincristine, dactinomycin, and cyclophosphamide; VI, vincristine and irinotecan.
*Data missing for three patients.

but < 10 years of age) and histologic definition of ARMS. After adjusting for these differences, no difference was found in EFS or OS for patients with ARMS treated in the current study compared with D9803 (data not shown). Patients with ERMS had an inferior 4-year EFS rate (65%) compared with similar patients in D9803 (73%; $P = .028$), although the 4-year OS rate was similar (77% *v* 79%; $P = .21$).

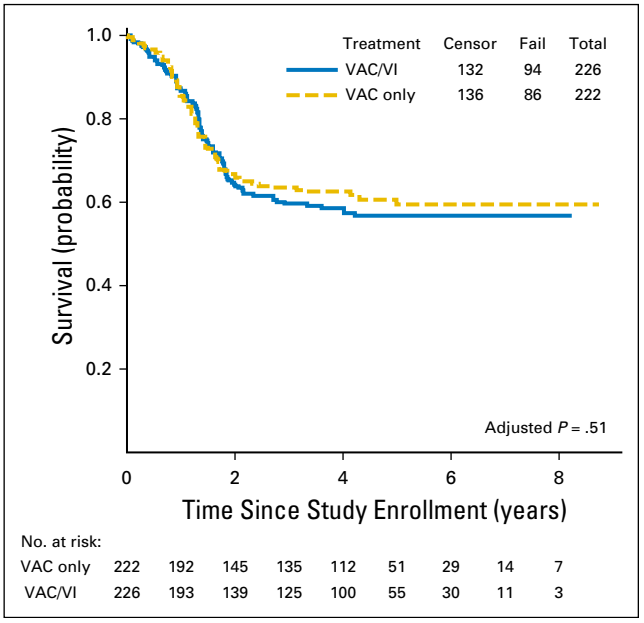

Fig 3. Event-free survival by treatment arm. VAC, vincristine, dactinomycin, and cyclophosphamide; VI, vincristine and irinotecan.

Treatment Failure

There were 180 treatment failures, including in 173 patients with tumor progression or recurrence. Three patients died before disease progression, including two (one in each treatment arm) who during therapy developed seizures with either presumed infectious meningoencephalitis or multifocal strokes with leptomeningeal enhancement on imaging, without an identified infectious cause in either case. The third patient (treated in the VAC/VI arm) had an unexplained fatal cardiopulmonary arrest after completing therapy. Four patients treated with VAC developed second cancers, including two with osteosarcoma at 4.3 and 5 years, one with acute lymphoblastic leukemia at 4.3 years, and one with undifferentiated sarcoma at 6 years. One patient in the VAC/VI arm developed three second cancers (medulloblastoma at 3.6 years and acute myelogenous leukemia and undifferentiated pleomorphic sarcoma of bone at 5.7 years) since study enrollment. The 4-year local failure rate, defined as recurrence or progression at the site of primary disease without recurrence involving regional lymph nodes or a distant site, was 22.4%. The 4-year regional lymph node failure rate, defined as recurrence or progression at regional lymph nodes without distant recurrence, was 5.7%. The 4-year distant failure rate, defined as recurrence at a distant site, was 18.0%. A more detailed analysis of the pattern of failure will be reported separately.

Toxicity

On the basis of NCI toxicity scoring criteria, the worst degree of toxicity for each of three reporting periods (weeks 1 to 15, 16 to 30, and 31 to 43) were recorded for each patient, limited to grade ≥ 3. Table 4 lists all toxicities experienced by $> 10\%$ of patients in any reporting period by treatment arm. Anemia and thrombocytopenia were both more common with VAC than VAC/VI in weeks 16 to 30 and 31 to 43. Diarrhea was more common with VAC/VI than VAC during weeks 1 to 15 and 16 to 30. Oral mucositis was more common with VAC/VI than VAC during weeks 1 to 15, and febrile neutropenia was more common with VAC than VAC/VI during weeks 16 to 30. Nine patients (seven in the VAC arm and two in the VAC/VI arm) developed hepatopathy of which two were mild, six were moderate, and only one (0.2% of all eligible patients) was severe.[30]

UGT1A1 genotype and toxicity data from weeks 4 to 9 (the first two VI courses) were available for 129 patients treated with VI (Data Supplement). Grade 3 or 4 diarrhea was significantly more common in patients with the *UGT1A1 7/7* (42%) than in those with either *6/7* (21%) or *6/6* (10%) genotypes ($P = .033$). There was no difference in the frequency of neutropenia with or without fever by *UGT1A1* genotype.

DISCUSSION

Despite strong preclinical data[13-16] and high response rates seen in patients with newly diagnosed[17] and recurrent RMS[19] that support the VI combination, its addition to VAC did not improve EFS in patients with intermediate-risk RMS in our study. Similarly, no evidence was found of a differential benefit for the addition of VI in patients with either ERMS or ARMS. The failure to improve outcome in the current study was preceded by four decades of negative randomized RMS phase III trials in North America[7-9,31,32] and Europe,[33] which have demonstrated that simply adding chemotherapeutic agents with clinical activity in recurrent disease and phase II window trials will not easily result in improved cure rates in intermediate-risk RMS. The COG Soft Tissue Sarcoma Committee proposed randomized phase II studies as an alternative strategy to identify agents worthy of a phase III study.[5] On the basis

Table 3. EFS and OS Rates by Treatment Arm

Patient Category	4-Year EFS, % (95% CI)			4-Year OS, % (95% CI)		
	VAC	VAC/VI	*P*	VAC	VAC/VI	*P*
All patients (n = 448)	63 (55 to 70)	59 (51 to 66)	.51*	73 (66 to 79)	72 (65 to 79)	.80*
ARMS only (n = 196)	58 (48 to 69)	51 (39 to 62)	.25	68 (58 to 78)	66 (55 to 77)	.59
ERMS/NOS/other (n = 252)	66 (57 to 76)	64 (54 to 73)	.85	77 (69 to 86)	76 (68 to 84)	.96

Abbreviations: ARMS, alveolar rhabdomyosarcoma; EFS, event-free survival; ERMS, embryonal rhabdomyosarcoma; NOS not otherwise specified; OS, overall survival; VAC, vincristine, dactinomycin, and cyclophosphamide; VI, vincristine and irinotecan.
*Adjusted *P* value after including randomization stratum (on the basis of central reviewed data, with 24 patients excluded for not belonging to any of the three strata) as a covariate in a Cox regression model. Eight and 16 of the 24 patients were categorized by the enrolling institution as having ARMS, stage II/III and group 2/3, and ERMS, stage II/III and group 3, respectively.

Table 4. Comparison of Toxicities (Worst Degree Within a Reporting Period) With > 10% Frequency in Any Reporting Period by Treatment Arm

	Week 1-15			Week 16-30			Week 31-43		
Grade 3 or 4 Toxicity	VAC	VAC/VI	P*	VAC	VAC/VI	P	VAC	VAC/VI	P*
Anemia	26.1	19.5	.093	27.5	8.9	< .001	28.0	8.9	< .001
Anorexia	10.4	13.7	.275	1.5	3.0	.338†	1.0	2.1	.446†
Diarrhea	5.0	15.9	< .001	2.5	10.8	< .001	0.5	2.6	.120†
Febrile neutropenia	13.5	10.6	.347	18.1	8.4	.004	8.8	6.8	.474
Infections and infestations	10.4	10.6	.929	5.9	5.9	.990	8.8	6.3	.357
Lymphopenia	17.6	15.9	.642	17.6	22.2	.253	17.6	22.1	.271
Oral mucositis	10.4	18.6	.014	2.0	2.5	.751†	0.5	1.1	.621†
Neutropenia	63.1	58.4	.313	64.7	64.5	.971	61.7	57.4	.393
Peripheral motor neuropathy	4.1	3.5	.776	7.4	10.8	.222	6.7	7.4	.809
Thrombocytopenia	12.2	5.3	.010	31.4	11.8	< .001	32.6	6.8	< .001
Leukopenia	27.5	27.9	.925	34.3	34.5	.971	32.6	31.1	.739

Abbreviations: VAC, vincristine, dactinomycin, and cyclophosphamide; VI, vincristine and irinotecan.
*Comparison by χ^2 test unless otherwise noted.
†Comparison by the Fisher's exact test.

of a positive randomized selection design phase II study conducted in patients with recurrent RMS,[34] the current COG intermediate-risk RMS study ARST1431 (ClinicalTrials.gov identifier: NCT01222715) will test this strategy by evaluating the randomized addition of temsirolimus to VAC/VI.

Although the current study failed to show an improvement in outcome for patients with intermediate-risk RMS, several observations from the study could lead to practice changes. First, the two treatment arms had similar outcomes despite a lower cumulative dose of cyclophosphamide with VAC/VI (8.4 *v* 16.8 g/m^2). Lower cumulative cyclophosphamide exposure may reduce the risk of infertility, particularly in males,[35] although this will require further confirmation. VAC/VI was associated with lower rates of hematologic toxicity compared with VAC. On the basis of the toxicity profile, the current COG intermediate-risk RMS clinical trial ARST1431 uses VAC/VI as its backbone. Second, the lower cyclophosphamide dose per course did not result in inferior EFS or OS compared with the prior COG D9803, with the exception of lower EFS for ERMS. However, outcome comparisons between D9803 and the current study may be confounded by changes in RMS histologic diagnostic criteria[36] and the timing of RT. Lower cyclophosphamide dose per course (1.2 *v* 2.2 g/m^2) likely accounts for the more modest hematologic toxicity rates compared with COG D9803, in which rates of grade 3 or 4 anemia, febrile neutropenia, and thrombocytopenia were 55% to 58%, 78% to 85%, and 51% to 53%, respectively.[9] Third, the lower cyclophosphamide dose per course can be administered in an ambulatory setting, thereby reducing medical costs compared with higher doses of cyclophosphamide that generally require inpatient supportive care.[37] A more detailed comparison of the medical costs associated with VAC and VAC/VI will be presented separately. The addition of VI had some negative implications, including the inconvenience of 5 consecutive days of ambulatory irinotecan infusion and the risk of severe diarrhea. On the basis of our *UGT1A1* genotype-toxicity analysis, prospective germline testing could identify patients at higher risk for severe diarrhea, although patients with the *UGT1A1 7/7* genotype accounted for only 21% of all patients who experienced severe diarrhea during the first two VI courses. Routine prophylaxis with oral antibiotics[38] was not included in the current study's supportive care guidelines, but oral antibiotic use in response to severe diarrhea may have contributed to the lower rate of severe diarrhea in later reporting periods.

Previous North American clinical trials have explored different radiation and surgical strategies to improve local control and EFS for intermediate-risk RMS, including radiation dose escalation with hyperfractionation[39] and delayed primary excision.[40] The current study incorporated early RT for all patients (with the exception of individualized local therapy for children younger than 24 months) at week 4. A more comprehensive analysis of local control and failure pattern, with comparison with COG D9803, is planned. Because locoregional recurrence remains the most common pattern of failure, new strategies are needed to improve local control.

We acknowledge that this study was not designed to demonstrate the noninferiority of VAC/VI compared with VAC for patients with intermediate-risk RMS. Nonetheless, the more favorable adverse effect profile of VAC/VI compared with VAC supports the use of VAC/VI as the chemotherapy backbone of the current COG phase III clinical trial (ClinicalTrials.gov identifier: NCT01222715). Outcomes remain unsatisfactory for this population, which reinforces the need to explore new trial designs, such as the randomized selection design phase II study, and treatment approaches.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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