

Activity of Vincristine and Irinotecan in Diffuse Anaplastic Wilms Tumor and Therapy Outcomes of Stage II to IV Disease: Results of the Children's Oncology Group AREN0321 Study

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PURPOSE AREN0321 evaluated the activity of vincristine and irinotecan (VI) in patients with newly diagnosed diffuse anaplastic Wilms tumor (DAWT) and whether a regimen containing carboplatin (regimen UH1) in addition to regimen I agents used in the National Wilms Tumor Study 5 (NWTS-5; vincristine, doxorubicin, cyclophosphamide, and etoposide plus radiotherapy) would improve patient outcomes.

PATIENTS AND METHODS Patients with stage II to IV DAWT without measurable disease received regimen UH1. Patients with stage IV measurable disease were eligible to receive VI (vincristine, 1.5 mg/m² per day intravenously on days 1 and 8; irinotecan, 20 mg/m² per day intravenously on days 1-5 and 8-12 of a 21-day cycle) in an upfront window; those with complete (CR) or partial response (PR) had VI incorporated into regimen UH1 (regimen UH2). The study was designed to detect improvement in outcomes of patients with stage II to IV DAWT compared with historical controls treated with regimen I.

RESULTS Sixty-six eligible patients were enrolled. Of 14 patients with stage IV measurable disease who received VI, 11 (79%) achieved CR (n = 1) or PR (n = 10) after 2 cycles. Doses of doxorubicin, cyclophosphamide, and etoposide were reduced midstudy because of nonhematologic toxicity. Four patients (6%) died as a result of toxicity. Four-year event-free survival, relapse-free survival, and overall survival rates were 67.7% (95% CI, 55.9% to 79.4%), 72.9% (95% CI, 61.5% to 84.4%), and 73.7% (95% CI, 62.7% to 84.8%), respectively, compared with 57.5% (95% CI, 47.6% to 67.4%; *P* = .26), 57.5% (95% CI, 47.6% to 67.4%; *P* = .048), and 59.2% (95% CI, 49.4% to 69.0%; *P* = .08), respectively, in NWTS-5.

CONCLUSION VI produced a high response rate in patients with metastatic DAWT. AREN0321 treatment seemed to improve outcomes for patients with stage II to IV DAWT compared with NWTS-5, but with increased toxicity. The UH2 regimen warrants further investigation with modifications to reduce toxicity.

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INTRODUCTION

Anaplasia is present in 7.5% of Wilms tumors (WTs) and carries an adverse prognosis.¹⁻⁴ In the National Wilms Tumor Study 3 (NWTS-3) and NWTS-4, patients with stage II to IV diffuse anaplastic histology WT (DAWT) were treated with vincristine, dactinomycin, and doxorubicin with or without cyclophosphamide. The 4-year relapse-free survival (RFS) estimates for those with stage II, III, or IV DAWT treated without cyclophosphamide were 40.0%, 33.3%, and 0%, respectively, compared with 71.6%, 58.7%, and 16.7%, respectively, with cyclophosphamide.¹ In NWTS-5, therapy was further increased using a regimen of vincristine, doxorubicin, and cyclophosphamide alternating with cyclophosphamide plus etoposide for

24 weeks plus radiotherapy (regimen I), resulting in additional improvement in patient outcomes.⁵

The progressive improvement in outcomes for patients with DAWT with additional chemotherapy agents suggested that additional gains may be achieved with continued augmentation of therapy. Previous phase II studies of carboplatin as a single agent and in combination with etoposide for relapsed or refractory WT showed objective response rates of 53% and 73%, respectively.^{6,7} The combination of ifosfamide, carboplatin, and etoposide has also demonstrated significant activity against WT.⁸⁻¹⁰

Preclinical and early-phase clinical data showed promising antitumor activity of topotecan in WT.^{11,12}

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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Irinotecan had similar activity to topotecan in patient-derived xenograft models and has less hematologic toxicity. The combination of camptothecins with vincristine resulted in greater-than-additive antitumor effect.¹³

On the basis of this rationale, the Children's Oncology Group (COG) AREN0321 study evaluated the antitumor activity of the vincristine and irinotecan (VI) combination in a phase II window in patients with newly diagnosed stage IV DAWT and whether an intensive regimen containing carboplatin in addition to the regimen I agents would improve event-free survival (EFS) or overall survival (OS) for patients with stage II to IV DAWT. AREN0321 also used a higher radiation dose to the flank for local stage III DAWT, because 46% of the recurrences in NWTS-5 were local.⁵ Here, we report the results of the new therapeutic strategy for stage II to IV DAWT.

PATIENTS AND METHODS

The AREN0321 study (ClinicalTrials.gov identifier: [NCT00335556](#)) was open to enrollment from June 2006 to December 2012. The study was temporarily closed to enrollment twice, for approximately 22 months, to assess toxicity and amend the treatment regimens. AREN0321 was permanently closed to accrual in November 2013 after data release by the data safety monitoring committee. The study was approved by the National Cancer Institute Pediatric Central Institutional Review Board (IRB) and local IRBs according to institutional policy. All participants or their legally authorized guardians provided consent. Central review of pathology slides, surgical summaries, and computed tomography (CT) scans was performed through mandatory prior enrollment in the COG AREN03B2 biology and classification protocol.

Patients

Eligible patients were age < 30 years with normal organ function. Patients must not have received prior systemic chemotherapy or radiotherapy unless they were enrolled in the COG AREN0532 or AREN0533 study, wherein the discovery of diffuse anaplasia at delayed nephrectomy allowed entry into this study.^{14,15}

Treatment

The COG/NWTS group standard surgical procedure was unilateral radical nephroureterectomy with lymph node sampling.^{16,17} Biopsy or nephrectomy was required before initiation of protocol therapy, which began no later than day 14 after the diagnostic procedure. Patients with unresectable tumors received chemotherapy for 6 to 12 weeks before nephrectomy. Patients with stage II to IV non-measurable DAWT received a chemotherapy regimen consisting of vincristine, doxorubicin, cyclophosphamide, carboplatin, and etoposide plus radiotherapy (regimen UH1; [Table 1](#)). Patients with stage IV measurable DAWT had the option to receive an upfront window of vincristine (1.5 mg/m² per day) intravenously on days 1 and 8 and

irinotecan (20 mg/m² per day) intravenously on days 1 to 5 and 8 to 12 of a 21-day cycle. In the absence of progressive disease (PD), a second cycle was administered. Patients with partial response (PR) to the VI window had VI incorporated into regimen UH1 (regimen UH2; [Table 1](#)). Patients with stable disease or PD after the VI window received regimen UH1 without additional VI cycles. To keep the cumulative doxorubicin dose ≤ 225 mg/m², the week 28 doxorubicin was omitted in patients who started treatment in AREN0532 or AREN0533 and received preoperative chemotherapy with doxorubicin. Dexrazoxane use was permitted but not required or recommended.

In October 2008, study enrollment was suspended because of a frequency of nonhematologic toxicities that exceeded predefined stopping rules. Regimens UH1 and UH2 were modified (called revised regimens UH1 and UH2) to reduce the cumulative doses of doxorubicin, cyclophosphamide, and etoposide to levels similar to those used in regimen I. The doxorubicin dose was reduced by 40% (to 45 mg/m², administered on day 1 only) to a total cumulative dose of 225 mg/m², and the doses of cyclophosphamide and etoposide when combined with carboplatin were reduced by 20% (by eliminating 1 of the 5 daily doses).

Radiotherapy was started with the initiation of chemotherapy, no later than 2 weeks after nephrectomy, except for patients treated in the VI window, who started radiotherapy at the beginning of regimen UH1 or UH2. At the time of study amendment for chemotherapy reduction, whole-abdomen radiotherapy doses were limited to 10.5 Gy; however, patients with stage III disease continued to receive 19.8 Gy to the flank ([Table 1](#)). Supportive care, radiotherapy guidelines, and required evaluations are provided in the Appendix (online only).

Statistical Considerations

The study was designed to detect improvement in EFS for patients with stage II to IV DAWT compared with historical controls. A baseline 4-year RFS estimate of 55% was assumed based on the superior treatment arm of NWTS-3 and NWTS-4 (regimen J) and NWTS-5 regimen I.¹ A sample size of 75 provided approximately 90% power to detect an improvement in 4-year EFS to 70%. The total accrual was set at 295 patients, including other study strata for clear cell sarcoma, focal anaplastic WT, renal cell carcinoma, and rhabdoid tumor; this report is restricted to patients with stage II to IV DAWT. A 2-stage design was used to evaluate the activity of VI in the window with the aim to accrue 10 patients in the first stage and continue accrual if ≥ 4 tumor responses were observed. The window study closed after other strata of AREN0321 reached their accrual targets.

Tumor responses to the VI window were centrally reviewed and assessed using the RECIST (version 1.1) criteria in addition to volumetric criteria for tumor size. For the

TABLE 1. Treatment Schema for COG AREN0321 Protocol

Regimen	Week																																								
	1	2	3	4	7	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	28	29	30	31	34	35	36												
UH1/revise UH1 ^a	V	V	V	Cy ^b	Cy ^b	V	V	V	V	V	V	Cy ^b			Cy ^b			V	V	V	Cy ^b		V	V	V																
	D			C	C	D			D			C			C			D			C		D																		
	Cy			E	E	Cy			Cy			E			E			Cy			E		Cy																		
	XRT ^c																																								
UH2/revise UH2 ^a	V	V	V	Cy ^b	Cy ^b	V	V			Cy ^b			V	V	V	V	V	V	Cy ^b			V	V	V	V	V	V	Cy ^b	V	V	V										
	D			C	C	I	I			C			D			D			C			I	I	D				C	D												
	Cy			E	E					E			Cy			Cy			E									Cy	E	Cy											
	XRT ^c																																								

Abbreviations: C, carboplatin (on day 1 with dose adjustment based on glomerular filtration rate [GFR] as measured by plasma clearance study using radioactive tracer or 24-hour urine collection for creatinine clearance 560 mg/m² for GFR > 150 mL/min/1.73 m², 500 mg/m² for GFR 100-150 mL/min/1.73 m², 370 mg/m² for GFR 75-99 mL/min/1.73 m², 290 mg/m² for GFR 50-74 mL/min/1.73 m², and 200 mg/m² for GFR 30-49 mL/min/1.73 m²; carboplatin was held for GFR < 30 mL/min/1.73 m²); Cy, cyclophosphamide (1,200 mg/m² per day intravenously on day 1); D, doxorubicin (37.5 mg/m² per day intravenously on days 1-2); E, etoposide (100 mg/m² per day intravenously on days 1-5); I, irinotecan (20 mg/m² per day [maximum dose, 40 mg] intravenously on days 1-5 and 8-12); V, vincristine (1.5 mg/m² per day [0.05 mg/kg per day for children age 1-2.99 years; maximum dose, 2 mg] intravenously on day 1); XRT, radiotherapy.

^aIn revised regimen UH1 and revised regimen UH2, dose of doxorubicin was reduced to 45 mg/m² administered on day 1 only, and the doses of cyclophosphamide and etoposide, when combined with carboplatin, were reduced by eliminating 1 of 5 daily doses.

^b440 mg/m² per day intravenously on days 1-5.

^cRadiation dose was 10.8 Gy to the flank for stage I to II diffuse anaplastic Wilms tumor (DAWT) and 19.8 Gy to the flank or whole abdomen for stage III DAWT. Local boost of 10.8 Gy was administered to areas of gross residual disease. Renal shielding was performed to limit dose to remaining kidney to < 14.4 Gy. After greater-than-expected toxicity was observed in 2008, study was amended to reduce chemotherapy dosing and XRT so that patients who required whole-abdomen irradiation received 10.5 Gy to whole abdomen followed by 9 Gy to the flank if age > 12 months or only 10.5 Gy to whole abdomen if age ≤ 12 months at time of radiation delivery. Additionally, for patients age < 6 months, XRT was deferred until age ≥ 6 months and tolerating therapy well. Patients with stage IV DAWT received whole-lung irradiation (12 Gy; if age ≤ 12 months, 10.5 Gy) for lung metastasis and liver irradiation (19.8 Gy) for hepatic involvement. After amending the study, liver irradiation was limited to 10.8 Gy for patients age ≤ 12 months.

volumetric criteria, the volume of up to the 3 largest lesions was calculated using the following formula: (length × width × depth)/2. Bone lesions were considered nonmeasurable.

Adverse events (AEs) were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (versions 3.0 and 4.0 [after October 1, 2011]). The study included toxicity monitoring rules for grade 4 cardiac toxicity, grade 4 sinusoidal obstruction syndrome, and treatment-related death and other grade ≥ 3 non-hematologic toxicity, with the exception of grade 3 anorexia, weight loss, nausea, fatigue, mucositis, diarrhea, fever, electrolytes/metabolic abnormalities, and infection.

The clinical characteristics of patients treated in AREN0321 and NWTS-5 were compared using the analysis of variance test for age, Fisher's exact test for race/ethnicity and treatment-related mortality rate, and χ^2 test for sex and stage. EFS, RFS, and OS were calculated from the time of diagnosis. For EFS, an event was defined as relapse/progression, development of metachronous disease, second malignant neoplasm, or death resulting from any cause, whichever occurred first. For RFS, an event was defined as relapse/progression or development of metachronous disease. Local failure was defined as relapse in

the operative bed, abdomen outside the operative bed, or pelvis; tumor spread to the liver was considered distant metastasis. The 4-year EFS, RFS, and OS rates were estimated using the Kaplan-Meier method,¹⁸ with CIs estimated by the Peto-Peto method,¹⁹ and were compared between groups using the log-rank test.²⁰ The median follow-up time was calculated based on the Kaplan-Meier estimates.²¹ Patient follow-up was current through September 30, 2017. We compared the local relapse rate between AREN0321 and NWTS-5 using the χ^2 test.

RESULTS

Eligible patients with stage II to IV DAWT were enrolled at 187 institutions over approximately 44 months. The data safety monitoring committee recommended study closure and data release when the total study accrual was 291 patients (nearing the target accrual of 295) and accrual to the stage II to IV DAWT arm was 66 of the planned 75. The clinical characteristics of the 66 patients treated in AREN0321 were similar to those of 110 historical control patients with stage II to IV DAWT treated in NWTS-5 (Table 2). Fifteen patients (stage III, n = 5; stage IV, n = 10) had delayed nephrectomy after preoperative chemotherapy.

TABLE 2. Clinical Characteristics of Patients With Stage II to IV DAWT Treated in AREN0321 or NWTS-5 According to Study

Characteristic	No. (%)		P ^a
	AREN0321 (N = 66)	NWTS-5 (N = 110)	
Age at diagnosis, years			.17
Mean	5.6	5	
Range	2.1-23.7	0.03-16.3	
Sex			.14
Male	27 (41)	33 (30)	
Female	39 (59)	77 (70)	
Race			.21
White	52 (79)	70 (64)	
Black	11 (17)	27 (25)	
Asian	0 (0)	1 (1)	
Unknown	3 (5)	12 (11)	
Ethnicity			.72
Non-Hispanic	61 (92)	66 (60)	
Hispanic	4 (6)	6 (6)	
Unknown	1 (2)	38 (35)	
Stage			.24
II	15 (23)	24 (22)	
III	27 (41)	58 (53)	
IV ^b	24 (36)	28 (25)	
Local stage III ^c	47 (71)	81 (74)	.73
Treatment			
Regimen I	0 (0)	110 (100)	
UH1	22 (33)		
Revised UH1	30 (46) ^d		
Window			
Window only	1 (2)		
Window/UH1	1 (2)		
Window/UH2	5 (8)		
Window/revised UH1	2 (3)		
Window/revised UH2	5 (8)		

Abbreviation: DAWT, diffuse anaplastic Wilms tumor.

^aUsing analysis of variance for age, Fisher's exact test for race and ethnicity (excluding unknown), and χ^2 test for sex, stage, and local stage III disease.

^bTwenty of 24 patients in AREN0321 and 23 of 28 patients in NWTS-5 had local stage III disease.

^cIncluding patients with overall stage IV/local stage III disease.

^dIncluding 5 patients with stage IV measurable disease who refused the window treatment.

Tumor Response and AEs During VI Window

Of the 24 patients with stage IV DAWT, 19 had measurable disease and 5 had lung nodules that were too small to be considered measurable. Fourteen of the 19 patients with

measurable disease participated in the VI window (Fig 1). Of these 14 patients, 1 achieved complete response (CR), 10 PR, and none stable disease, resulting in a 79% CR plus PR rate. Three patients had PD: 1 subsequently had PD on regimen UH1, 1 had CR on regimen UH1, and 1 was taken off protocol therapy and died as a result of disease 7 months later.

During the VI window, 1 patient had a grade 4 AE (hypokalemia) and 2 patients had grade 3 AEs (diarrhea and increased AST). In addition, each of the following grade 3 AEs occurred in 1 patient: anorexia, increased bilirubin, colonic hemorrhage, hyperglycemia, hypertension, hypoalbuminemia, hypoxia, thromboembolic event, and wound infection. There were no deaths during the window treatment.

Patient Outcomes

The median follow-up for survivors in AREN0321 was 6.95 years. The 4-year EFS and OS rates for the 66 patients with stage II to IV DAWT treated in AREN0321 were 67.7% (95% CI, 55.9% to 79.4%) and 73.7% (95% CI, 62.7% to 84.8%), respectively. Outcomes were similar for patients with stage II and III disease and inferior for those with stage IV disease (Table 3; Appendix Fig A1, online only). No difference in EFS was seen when comparing the original and revised regimens UH1/UH2, with a possible exception in patients with stage IV disease treated with regimen UH1 versus revised UH1, but the number of patients treated with UH1 (n = 3) was too small to draw a conclusion (Appendix Table A1, online only).

Seventeen of the 66 patients had disease relapse/progression as a first event in the lungs only (n = 11), lungs and liver (n = 1), liver only (n = 1), buttock (n = 1), abdomen only (n = 1), abdomen plus liver (n = 1), and abdomen plus lungs and distant lymph nodes (n = 1). One patient had a tumor that developed in the contralateral kidney. One patient with stage III disease had a second malignant neoplasm. For four patients, death was the first event.

Among the 15 patients with delayed nephrectomy, blastemal histology was found in 1 with stage III disease and 5 with stage IV disease. Relapse occurred in 5 of 6 patients with blastemal histology, compared with 3 of 9 patients without blastemal histology. Five patients with stage IV disease who received the window therapy had delayed nephrectomy. Four patients, including 2 of 2 patients with blastemal histology, achieved PR and 1 patient without blastemal histology had PD.

Treatment Toxicity

Table 4 summarizes all grade 3 and 4 nonhematologic AEs observed in AREN0321, excluding the window treatment. No grade 4 or 5 AEs were observed with revised UH2. Three patients age 3 to 5 years (regimen UH1, n = 1; revised regimen UH1, n = 2) died as a result

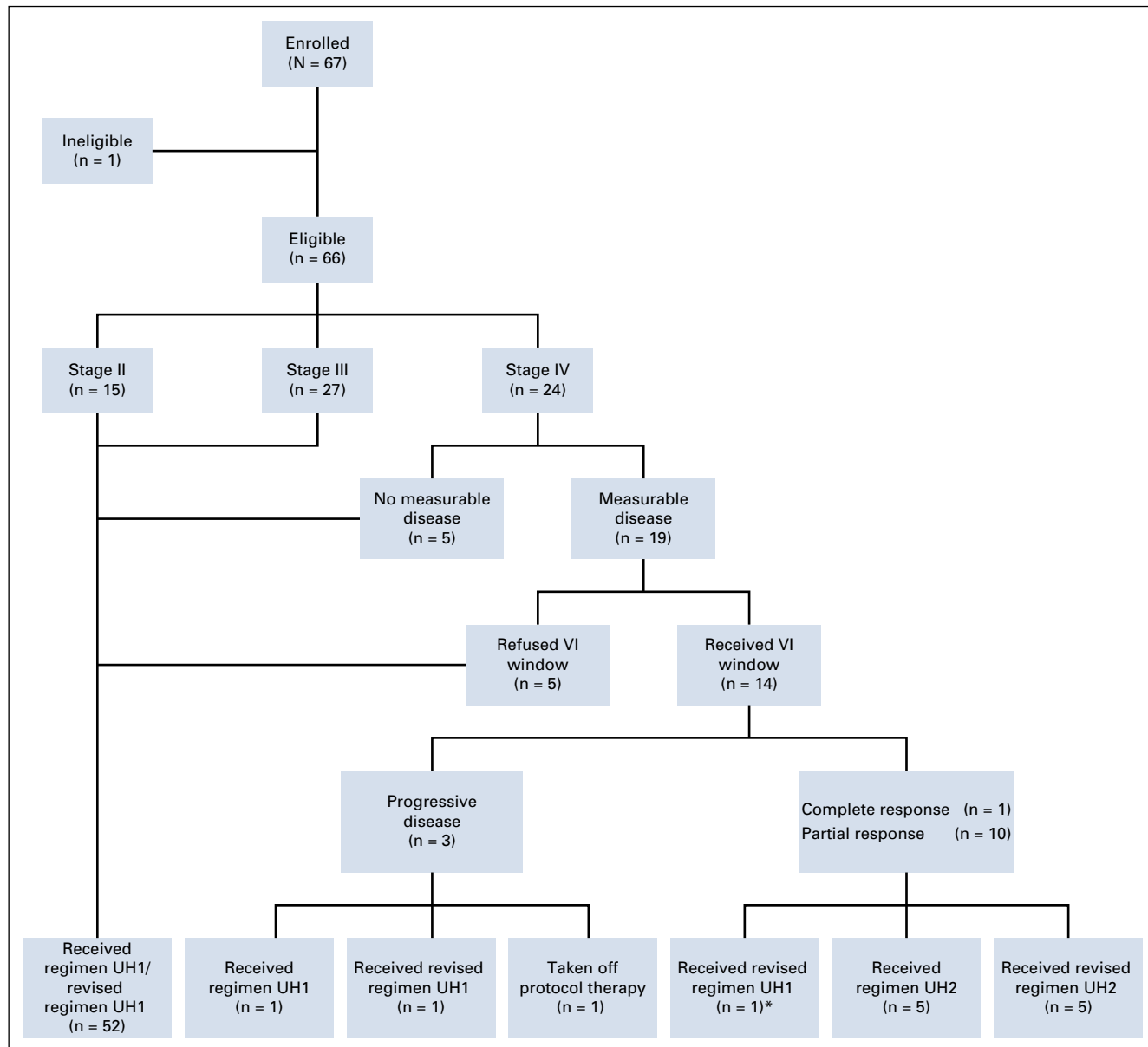


FIG 1. Study flow diagram. Patients enrolled in AREN0321 by stage and response to treatment with vincristine and irinotecan (VI) window. (*)Although a partial response was achieved, the treating physician elected to treat with revised regimen UH1.

of toxicity during therapy: cardiomyopathy ($n = 1$; cumulative doxorubicin dose, 225 mg/m^2), congestive heart failure ($n = 1$; cumulative doxorubicin dose, 45 mg/m^2), and pulmonary edema ($n = 1$). One additional patient with stage III DAWT treated with regimen UH1 died 6.5 years after the end of therapy as a result of cardiac failure in the setting of hypertension because of a new benign renal neoplasm (cumulative doxorubicin dose, 345 mg/m^2). Details regarding grade 5 toxicities are summarized in Appendix Table A2 (online only). The treatment-related mortality rate was 6%, compared with 1.3% for contemporaneous patients with clear cell sarcoma of the kidney treated with regimen I in AREN0321 ($P = .18$).

Comparison of Patient Outcomes With Those in NWTS-5

The median follow-up for survivors in NWTS-5 was 10.85 years. Four-year EFS, RFS, and OS rates in AREN0321 were 67.7% (95% CI, 55.9% to 79.4%), 72.9% (95% CI, 61.5% to 84.4%), and 73.7% (95% CI, 62.7% to 84.8%), respectively, compared with 57.5% (95% CI, 47.6% to 67.4%; $P = .26$), 57.5% (95% CI, 47.6% to 67.4%; $P = .048$), and 59.2% (95% CI, 49.4% to 69.0%; $P = .08$), respectively, for 110 patients treated in NWTS-5 (RFS was identical to EFS; Fig 2). Table 3 lists the outcomes of patients treated in AREN0321 versus NWTS-5 according to stage. Because local spill, including percutaneous needle biopsy, was considered a criterion for stage III disease in AREN0321 but was considered stage II disease in NWTS-5,

TABLE 3. Outcomes of Patients With Stage II to IV DAWT Treated in AREN0321 or NWTS-5

Stage	AREN0321			NWTS-5			<i>P</i> ^a	
	No.	4-Year EFS (%) (95% CI)	4-Year OS (%) (95% CI)	No.	4-Year EFS (%) (95% CI)	4-Year OS (%) (95% CI)	EFS	OS
II	15	86.7 (68.8 to 100)	86.2 (68.0 to 100)	24	79.2 (60.9 to 97.5)	78.4 (60.0 to 96.9)	.48	.501
				23 ^b	78.3 (59.2 to 97.4)	77.4 (58.2 to 96.7)	.44	.46
	19 ^c	84.21 (67.3 to 100)	83.88 (66.8 to 100)				.99 ^d	.99 ^d
III	27	80.9 (65.8 to 96.0)	88.6 (76.4 to 100)	58	61.3 (47.8 to 74.7)	64.7 (51.6 to 77.8)	.13	.048
				59 ^e	61.9 (48.7 to 75.2)	65.31 (52.4 to 78.2)	.14	.053
	23 ^f	81.8 (65.7 to 97.9)	90.9 (78.9 to 100)				.06 ^g	.015 ^g
IV	24	41.7 (19.6 to 63.7)	49.2 (27.5 to 71.0)	28	32.1 (14.8 to 49.4)	32.1 (14.8 to 49.4)	.62	.21
UH1 ± window ^h	13	30.8 (0 to 66.3)	34.6 (2.9 to 66.3)					
UH1, no Window	10	40.0 (0 to 82.9)	33.3 (0 to 71.1)					
UH1 + window	3	0	33.3 (0 to 86.7)					
UH2 + window	10	60.0 (29.6 to 90.4)	70.0 (41.6 to 98.4)					

Abbreviations: DAWT, diffuse anaplastic Wilms tumor; EFS, event-free survival; OS, overall survival.

^aLog-rank test.

^bExcluding 1 patient who would have been stage III according to updated staging criteria used in AREN0321.

^cIncluding 4 patients who would have been stage II according to staging criteria used in NWTS-5.

^dComparison of 19 patients in AREN0321 with stage II disease with 24 patients in NWTS-5 with stage II disease, all by NWTS-5 staging criteria.

^eIncluding 1 patient who would have been stage III according to updated staging criteria used in AREN0321.

^fExcluding 4 patients who would have been stage II according to staging criteria used in NWTS-5.

^gComparison of 23 patients in AREN0321 with stage III disease with 58 patients in NWTS-5 with stage III disease, all by NWTS-5 staging criteria.

^hIncluding 10 patients who received UH1 without window therapy because of absence of measurable disease ($n = 5$) or refusal of window therapy ($n = 5$) and 3 patients who received UH1 after receiving window therapy ($n = 3$) and excluding 1 patient who received VI window only (taken off protocol therapy and died as a result of disease 7 months later).

we repeated the analysis excluding the patients who would have had a different stage depending on the study and observed no differences.

Three of the 66 AREN0321 patients (4.5%) had local relapse, including 2 who had concurrent distant failure. All 3 patients had local stage III disease (overall stage III, $n = 1$; overall stage IV, $n = 2$). One patient received treatment before and 2 patients after the amendment to reduce chemotherapy and radiation doses. In comparison, 12 of the 110 NWTS-5 patients (10.9%) had local relapse; all 12 patients had local stage III disease (overall stage III, $n = 8$; overall stage IV, $n = 4$). The local relapse rate among those with local stage III disease (Table 2) in AREN0321 (3 [6.4%] of 47) seemed lower than that for NWTS-5 (12 [14.8%] of 81), but the difference was not statistically significant ($P = .15$).

DISCUSSION

AREN0321 identified a new combination of chemotherapy that is highly active in patients with high-risk WT. The VI combination produced a high response rate (79%) in patients with metastatic DAWT and was well tolerated. VI offers a good treatment option because of its limited potential acute and long-term toxicity and will be incorporated into future COG studies.

The outcomes of patients treated in AREN0321 were overall improved compared with those treated in NWTS-5, but only the difference in RFS achieved statistical significance. This reflects that the augmented chemotherapy regimens in AREN0321 provided better disease control, which was counterbalanced by events related to toxicity. The improvement in disease-specific outcomes continues a pattern of incremental advances with therapy augmentation

TABLE 4. No. of Patients With Grade 3 or 4 Nonhematologic AEs Observed in AREN0321 According to Treatment Regimen

AE	No. (%) of Patients						
	UH1 (n = 23) ^a		Revised UH1 (n = 32) ^a		UH2 (n = 5) ^b		Revised UH2 (n = 5) ^b
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3
Infection or infestation							
Infection or infestation other specify	17 (74)	1 (4)	9 (28)		4	1	
Sepsis		1 (4)		2 (6)			
Catheter-related infection			2 (6)				1
Pharyngitis							1
Sinusitis							1
Abdominal infection					1		
Cardiac ^a							
Cardiac arrest				1 (3)		1	
Left/right ventricular dysfunction		1 (4)	2 (6)		1		
Myocarditis				1 (3)			
GI infection or infestation							
Diarrhea	5 (22)		1 (3)		3		
Nausea	2 (9)		1 (3)				
Vomiting	3 (13)		1 (3)				1
Mucositis oral	4 (17)				1		
Gastritis					1		
Investigation							
AST/ALT increased	2 (9)	2 (9)	7 (22)				1
Blood bilirubin increased			3 (9)	1 (3)			
Creatinine increased	1 (4)		2 (6)				
Metabolism or nutrition							
Anorexia	6 (26)		8 (25)		2		
Hypokalemia	1 (4)	2 (9)	5 (16)	4 (13)			1
Dehydration	2 (9)		2 (6)				2
Hyperglycemia	1 (4)		2 (6)	1 (3)	2		
Hyponatremia	2 (9)		2 (6)		1		1
Hypophosphatemia	2 (9)	1 (4)					1
Hypoalbuminemia	1 (4)		1 (3)				1
Musculoskeletal or connective tissue disorder							
Pain in extremity					1		
Neoplasm benign or malignant ^a		1 (4)					
Psychiatric disorder							
Agitation							1
Renal or urinary ^a							
Acute kidney injury	1 (4)		1 (3)				
Proteinuria			1 (3)				
Respiratory, thoracic, or mediastinal disorder ^a							
Respiratory failure				1 (3)			
Adult respiratory distress syndrome			1 (3)	1 (3)			

(continued on following page)

TABLE 4. No. of Patients With Grade 3 or 4 Nonhematologic AEs Observed in AREN0321 According to Treatment Regimen (continued)

AE	No. (%) of Patients						
	UH1 (n = 23) ^a		Revised UH1 (n = 32) ^a		UH2 (n = 5) ^b		Revised UH2 (n = 5) ^b
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3
Pleural effusion		1 (4)	1 (3)		1	1	1
Pulmonary edema							1
Pulmonary hypertension			1 (3)				
Hypoxia	1 (4)	1 (4)	1 (3)				1
Pneumonitis		1 (4)					
Dyspnea					1		1
Pharyngolaryngeal pain					1		
Vascular disorder							
Hypotension	1 (4)	1 (4)	2 (6)	1 (3)			
Hypertension	3 (13)		3 (9)				

NOTE. Excluding window treatment.

Abbreviation: AE, adverse event.

^aExcluding AEs observed in < 3 patients treated with regimen UH1/revised regimen UH1 except for cardiac, renal, and respiratory AEs and neoplasms, which are listed even if observed in 1 patient only.

^bAll AEs observed with regimen UH2/revised regimen UH2 are listed with no percentage shown because of the small number of patients. No grade 4 AEs were observed with revised regimen UH2.

(Table 5) and may be related to the use of carboplatin, VI, a higher radiation dose for stage III patients, or a combination of these factors. Patients with stage IV DAWT who received UH2/revised UH2 seemed to fare better than patients who received UH1/revised UH1, suggesting a positive contribution of the VI combination. However, the number of patients was small, and the effectiveness of VI requires confirmation. The grade 5 toxicities were related to cardiac and pulmonary dysfunction. The upcoming COG study will incorporate VI in addition to the agents used in AREN0321 for the treatment of DAWT, with strategies to mitigate toxicity, such as using dexrazoxane as a

cardioprotectant and avoiding the administration of doxorubicin and carboplatin, potent radiosensitizers, close to the timing of radiotherapy.²²⁻²⁴

All local relapses in both studies occurred in patients with local stage III disease, suggesting that 10.8 Gy provides excellent control for local stage I or II DAWT. In addition, the local relapse rate for local stage III disease in AREN0321 (6.4%) seemed lower than that in NWTS-5 (14.8%), although not statistically significant. Although the higher dose of flank/abdomen radiation (19.8 Gy) used for local stage III DAWT in AREN0321 was perhaps more effective than the 10.8-Gy dose used in NWTS-5, it is unlikely to be

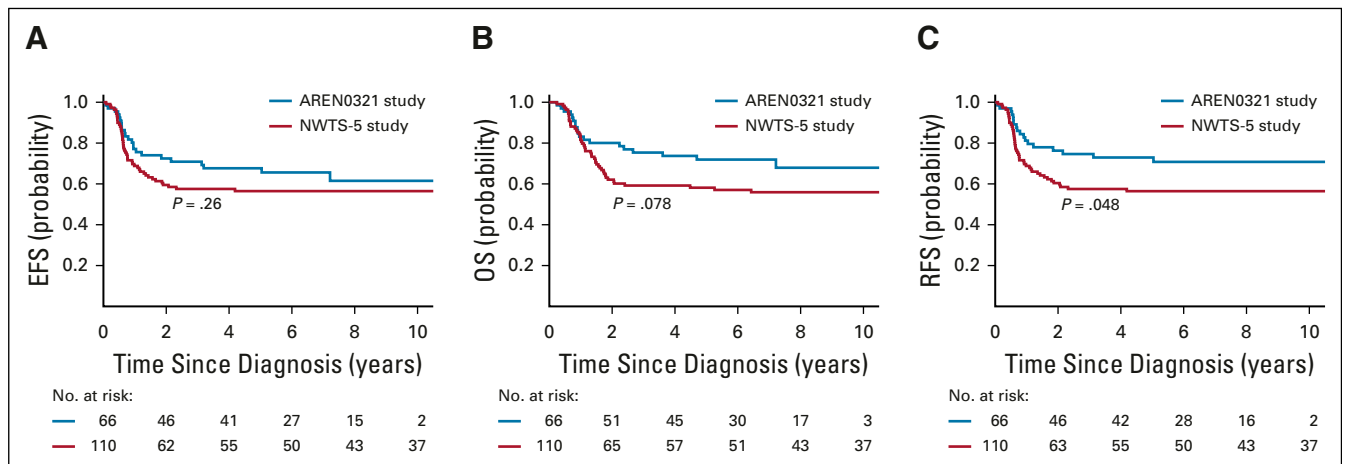


FIG 2. (A) Event-free survival (EFS), (B) overall survival (OS), and (C) relapse-free survival (RFS) of patients with stage II to IV diffuse anaplastic Wilms tumor according to study.

TABLE 5. Four-Year OS for Patients With Stage II to V DAWT Treated in NWTS-3 and NWTS-4, NWTS-5, ARENO321, or ARENO534 According to Stage

Stage	NWTS-3 and NWTS-4		NWTS-5	ARENO321
	Regimen DD-RT: VDA/XRT (%) ^{1a} (n = 29)	Regimen J: VDACy/XRT (%) ^{1a} (n = 30)	Regimen I: VDCyE/XRT (%) Unilateral (n = 110) Bilateral (n = 20) ^b	Regimen UH1/2: VDCy/CyCE/XRT (%) Unilateral (n = 66) Bilateral (n = 17) ^c
II	46.9	70.1	78.4 (60.0 to 96.9)	86.2 (68.0 to 100)
III	20.8	56.3	64.7 (51.6 to 77.8)	88.6 (76.4 to 100)
IV	0	16.7	32.1 (14.8 to 49.4)	49.2 (27.5 to 71.0) ^d
V	—	—	41.6 (19.7 to 62.2)	68.4 (24.9 to 100)

Abbreviations: A, dactinomycin; C, carboplatin; Cy, cyclophosphamide; D, doxorubicin; DAWT, diffuse anaplastic Wilms tumor; E, etoposide; OS, overall survival; V, vincristine; XRT, radiotherapy.

^aData on CI not reported in the publication.

^bData for stage II to IV disease derived from updated analysis included in this report; data for stage V disease as previously reported.⁵

^cData for stage V disease derived from ARENO534 study for bilateral WT.²⁵

^dSome patients received irinotecan as part of regimen UH2.

the only reason for the improved local control seen in ARENO321.⁵ In NWTS-3 and NWTS-4, 11 (18.6%) of 59 patients with stage II to IV DAWT had local recurrence as a first event, and a majority of patients had radiation doses > 18 Gy,¹ suggesting that a higher dose of radiation in itself is insufficient to explain the better local control rate in ARENO321. The current data support the use of 10.8 Gy to the flank for stage I to II DAWT and 19.8 Gy to the flank or 10.5 Gy to the whole abdomen followed by 9 Gy to the flank for stage III DAWT.

The ARENO321 study had several important limitations. First, the study design was a comparison with historical controls rather than a randomized controlled trial, which may have introduced biases related to changes in imaging resolution and supportive care and stage migration, all of which could have contributed to improved outcomes. With regard to stage migration, patients with local intraoperative tumor spillage or percutaneous biopsy were designated as having stage II disease in NWTS-5 and stage III disease in ARENO321. This change may have improved survival rates for both stage II and III disease, although only 4 patients in ARENO321 were so affected (Table 3). Another potential for stage migration is that the increased use and sensitivity of chest CT led to a greater number of patients with detectable subcentimeter lung nodules. It is encouraging that the stage distribution for DAWT in ARENO321 was similar to that in NWTS-5 (Table 2); however, there were 5 patients with tiny lung nodules who did not qualify for the window

therapy. The patients who received UH2/revised UH2 had outcomes at least as good as those who did not receive this therapy (Appendix Table A1), even though patients who received VI had to have measurable disease. This suggests that the apparent improvement in outcomes was not solely a result of the inclusion of patients with small lung nodules. A second limitation of the study is that the actual accrual fell short of the target because of toxicity-related interruptions in accrual (66 actual v 75 target enrollments of patients with stage II-IV DAWT). It is possible that full enrollment may have modified survival in either direction. Moreover, the therapy modifications that were made midstudy resulted in 2 differently treated groups. Comparison of those groups revealed no difference in outcomes, but it is possible that the higher-dose regimen may have benefitted patients with stage IV disease (Appendix Table A1). Finally, given the rarity of DAWT, the study was designed to detect improvement in outcomes for stage II to IV disease collectively, not for each individual stage. On the basis of these limitations and the observed toxicities, we have determined that additional study of a modified UH2 regimen is warranted.

In summary, the VI combination is highly active in DAWT. Its incorporation into future treatment regimens for WT may potentially improve patient outcomes. The ARENO321 treatment approach improved RFS compared with NWTS-5, but with increased toxicity. Strategies to alleviate toxicity will be implemented in the next COG trial.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Activity of Vincristine and Irinotecan in Diffuse Anaplastic Wilms Tumor and Therapy Outcomes of Stage II to IV Disease: Results of the Children's Oncology Group AREN0321 Study

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APPENDIX

Vincristine was held until peristalsis was established after nephrectomy. Mesna was used with cyclophosphamide for uroprotection. Absolute neutrophil count $\geq 750/\mu\text{L}$ and platelet count $\geq 75,000/\mu\text{L}$ were required to start chemotherapy cycles. Myeloid growth factor support was recommended after myelosuppressive chemotherapy but not after irinotecan. In patients who experienced grade ≥ 3 GI toxicity during the first cycle of the vincristine/irinotecan (VI) window, cefixime was used in combination with VI during the second cycle of window therapy. When used, the antibiotic was started at least 1 day (preferably 5 days) before irinotecan and continued for 1 week after the last irinotecan dose.

All treatment volumes were treated concurrently in patients who required whole-lung irradiation in addition to flank or whole-abdomen irradiation. Radiotherapy was delivered at Children's Oncology Group–approved centers, and all radiation doses, treatment plans, and fields were reviewed retrospectively at the Imaging and Radiation Oncology Core, Lincoln, Rhode Island.

Laboratory testing, computed tomography (CT) of the chest, abdomen, and pelvis, and echocardiography were performed at baseline and end of therapy, and electrocardiography was performed at baseline. An echocardiogram was repeated before the third, fourth, and fifth cycles containing doxorubicin. Glomerular filtration rate was assessed before every other carboplatin-containing cycle by a plasma clearance study using a radioactive tracer or by a 24-hour urine creatinine clearance. CT of the chest, abdomen, and pelvis was repeated after 2, 4, and 8 cycles of chemotherapy, but during the VI window, it was obtained before each cycle of VI and after completion of the second cycle.

After completion of therapy, patients had follow-up visits for disease surveillance every 3 months during the first 2 years, every 6 months during the third and fourth years, and every 12 months during the fifth year. CT of the chest, abdomen, and pelvis was obtained at every visit during the first 2 years and switched to chest radiography and abdominal ultrasonography during the subsequent years.

TABLE A1. Four-Year EFS of Patients With Stage II to IV DAWT Treated in AREN0321 According to Stage and Treatment Regimen (n = 65)

Stage	Regimen UH1		Revised Regimen UH1		Regimen UH2 ^a		Revised Regimen UH2 ^a	
	No. ^b	EFS (%) (95% CI)	No.	EFS (%) (95% CI)	No.	EFS (%) (95% CI)	No.	EFS (%) (95% CI)
II	9	88.9 (68.4 to 100)	6	83.3 (50.0 to 100)	NA		NA	
III	11	81.8 (59.0 to 100)	16	80.4 (60.2 to 100)	NA		NA	
IV	3	66.7 (0 to 100)	10	20 (0 to 55.1)	5	60 (17.1 to 100)	5	60 (17.1 to 100)

Abbreviations: DAWT, diffuse anaplastic Wilms tumor; EFS, event-free survival; NA, not applicable.

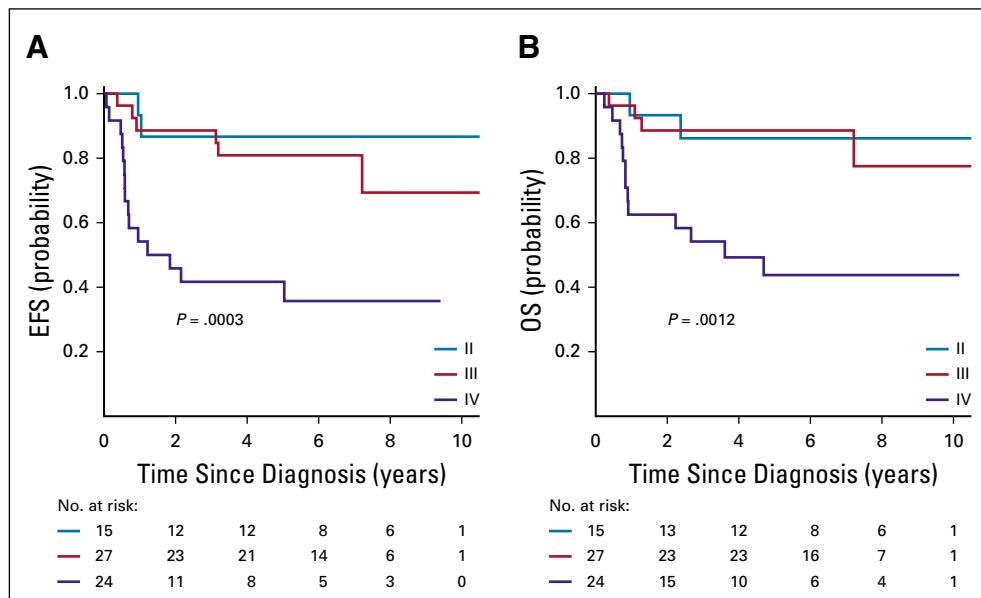
^aAll patients who received regimen UH2/revised regimen UH2 had received window therapy.

^bTotal patient number was 65 because of exclusion of 1 patient who received only window treatment (taken off protocol therapy and died as a result of disease 7 months later).

TABLE A2. Summary of Grade 5 Toxicity for Patients With DAWT Treated in AREN0321

Toxicity	Regimen	Age (years)	Stage	Cumulative Doxorubicin Dose (mg/m ²)	Radiation Dose (Gy) and Site	Onset of Toxicity	Comments
Left ventricular dysfunction	UH1	5	II	225	10.8, left flank	Week 22 VDC	Doxorubicin held because of prolonged QT interval and serially decreasing shortening fraction; patient died 3 months after completion of UH1
Congestive heart failure	Revised UH1	3	III	45	10.8, whole abdomen; 9, boost to left flank (total, 19.8)	Worsening cardiac function noted after week 7 CyCE; doxorubicin held during week 10 VDC	Institution indicated suspicion of infectious myocarditis
Pulmonary edema	Revised UH1	4	IV	110	21, whole abdomen; 12, whole lung	After week 19 CyCE	
Cardiac failure	UH1	3	III	345	20.41, left flank	6.5 years after end of therapy	Cardiac failure secondary to prior chemotherapy/chest irradiation with presumed worsening of cardiac failure in setting of hypertension secondary to new right kidney lesion (benign spindle cell neoplasm)

Abbreviations: CyCE, cyclophosphamide, carboplatin, and etoposide; DAWT, diffuse anaplastic Wilms tumor; VDC, vincristine, doxorubicin, and cyclophosphamide.

**FIG A1.** (A) Event-free survival (EFS) and (B) overall survival (OS) of 66 patients with stage II to IV diffuse anaplastic Wilms tumor treated in AREN0321 according to disease stage.