original reports

Efficacy of High-Dose Chemotherapy and Three-Dimensional Conformal Radiation for Atypical Teratoid/Rhabdoid Tumor: A Report From the Children's Oncology Group Trial ACNS0333

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abstract

PURPOSE Atypical teratoid/rhabdoid tumor (AT/RT) is an aggressive, early-childhood brain tumor without standard effective treatment. To our knowledge, we conducted the first AT/RT-specific cooperative group trial, ACNS0333, to examine the efficacy and safety of intensive postoperative chemotherapy and focal radiation to treat AT/RT.

PATIENTS AND METHODS Patients from birth to 22 years of age with AT/RT were eligible. After surgery, they received 2 courses of multiagent chemotherapy, followed by 3 courses of high-dose chemotherapy with peripheral blood stem cell rescue and involved-field radiation therapy. Timing of radiation was based on patient age and disease location and extent. Central testing of tumor and blood for *SMARCB1* status was mandated. Tumor molecular subclassification was performed retrospectively. The primary analysis was event-free survival (EFS) for patients < 36 months of age compared with a cooperative groups' historical cohort. Although accrual was based on the therapeutic question, potential prognostic factors, including age, tumor location, M stage, surgical resection, order of therapy, germline status, and molecular subtype, were explored.

RESULTS Of 65 evaluable patients, 54 were < 36 months of age. ACNS0333 therapy significantly reduced the risk of EFS events in patients < 36 months of age compared with the historical cohort ($P < .0005$; hazard rate, 0.43; 95% CI, 0.28 to 0.66). Four-year EFS and overall survival for the entire cohort were 37% (95% CI, 25% to 49%) and 43% (95% CI, 31% to 55%), respectively. Timing of radiation did not affect survival, and 91% of relapses occurred by 2 years from enrollment. Treatment-related deaths occurred in 4 patients.

CONCLUSION The ACNS0333 regimen dramatically improved survival compared with historical therapies for patients with AT/RT. Clinical characteristics and molecular subgrouping suggest prognostic differences. ACNS0333 results lay a foundation on which to build future studies and incorporate testing of new therapeutic agents.

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ASSOCIATED CONTENT

Appendix

Protocol

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

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INTRODUCTION

Atypical teratoid/rhabdoid tumor (AT/RT) is a highly malignant CNS neoplasm affecting very young children.[1-3] Prior trials, Pediatric Oncology Group (POG) 9233/4 and Children's Cancer Group (CCG) 9921, which applied dose-intensified multiagent chemotherapy to treat a spectrum of malignant brain tumors in very young children, showed AT/RT to be a highly lethal disease.[4,5] Together, these studies enrolled 63 patients with AT/RT and achieved a 24-month event-free survival (EFS) of 6.4%.

No prospective AT/RT-specific trials were reported when ACNS0333 was developed. Case series and retrospective data suggested high-dose chemotherapy (HDC) with peripheral blood stem cell (PBSC) rescue, early radiation therapy (RT), and methotrexate had activity against AT/RT.[6-11] We used these data to design the first AT/RT-specific prospective cooperative group trial, ACNS0333. Building on intensified chemotherapy regimen CCG-99703, ACNS0333 added methotrexate to multiagent induction chemotherapy.[12] It also included HDC and RT, given either postinduction or postconsolidation. To our knowledge, ACNS0333 was the first Children's Oncology Group (COG) brain tumor study to mandate submission of frozen tumor tissue and blood for central review and molecular testing as an eligibility requirement. This enabled germline and

tumor mutational analyses, as well as tumor banking for future studies.

AT/RTs exhibit characteristic low mutation genomes with biallelic alterations of the *SMARCB1* gene on chromosome 22q11.2 that lead to loss of SMARCB1 protein expression detectable by diagnostic immunohistochemistry assays.[2,13-15] Germline *SMARCB1* alterations are reported in 10%-35% of patients with AT/RT or related kidney and soft tissue tumors.[16-18] These correlate with earlier age of diagnosis and development of synchronous tumors. Despite genomic simplicity, recent transcriptional and methylation profiling studies of large retrospective cohorts indicate molecular heterogeneity of AT/RT and identify 3 subtypes.[19,20] Banked tumor tissue from ACNS0333 provided a unique opportunity to validate these retrospective findings. The COG biology study ACNS15B1-Q was approved by COG and the Cancer Therapy Evaluation Program in 2016. Primary and secondary objective results of both ACNS0333 and ACNS15B1-Q are reported here.

PATIENTS AND METHODS

Trial Oversight

ACNS0333 (ClinicalTrials.gov identifier: NCT00653068) was activated in December 2008 after approval by the Pediatric Central Institutional Review Board and/or the local institutional review board at each participating site. Written informed consent was obtained according to institutional guidelines.

Patients

Patients from birth to 22 years of age with AT/RT were included. Patients with concurrent non-CNS rhabdoid tumors or M4 disease were excluded. Complete patient criteria are provided in the treatment protocol (Data Supplement).

Trial Design

ACNS0333 was a nonrandomized phase III trial. All enrolled patients received induction therapy and were subsequently assigned to 1 of 2 treatment arms based on age, tumor location, and extent of disease (Fig 1; Table 1).

Surgery

The goal of surgery was to perform maximal safe tumor resection and to obtain tissue for diagnosis and biology studies. Second-look surgery was recommended after induction if there was resectable residual tumor. Institutions reported extent of tumor resection, defined in the protocol, as follows: gross total, near total, subtotal, partial, or biopsy (Table 2).

Chemotherapy

Two 21-day induction cycles of chemotherapy included vincristine, methotrexate, etoposide, cyclophosphamide, and cisplatin (Table 1). Collection of PBSCs took place after induction cycles. Consolidation comprised 3 cycles of carboplatin and thiotepa with PBSC support. The study was amended 2 years after opening because of an unexplained fatal pulmonary toxicity. With this, consolidation cycles were lengthened from 21 to 28 days and additional supportive care measures added (Data Supplement).

Radiation Therapy

Conformal RT was administered between induction and consolidation to patients who were at least 6 or 12 months of age with tumor localized to the infratentorial or supratentorial brain, respectively. RT was administered after completion of consolidation for younger patients or those with metastatic disease. The protocol allowed either photon or proton therapy. Total RT dose to the primary site was to be 50.4 Gy for patients $<$ 36 months of age and 54 Gy for older patients (Appendix Table A1, online only). All institutions had to complete quality assurance benchmarks and submit digital data.

Evaluation and Follow-Up

Patient assessments at regular intervals included clinical and laboratory examinations, neuroaxis imaging, and evaluations of heart function and hearing. Treating institutions assigned staging and treatment response per the protocol (Data Supplement).

Central Pathology Review and *SMARCB1* Gene Analyses

Diagnosis was centrally confirmed by study neuropathologists (P.C.B., A.R.J.). Germline and somatic *SMARCB1* gene analyses were performed in the College of American Pathologists/Clinical Laboratory Improvement Amendments–certified Cancer Cytogenetics Laboratory at Children's Hospital of Philadelphia (J.A.B.) according to published methods.[13]

Molecular Profiling of AT/RT

DNA from snap-frozen or paraffin-embedded tumor samples was processed for global methylation profiling analyses on the Illumina 850K platform (Illumina, San Diego, CA) using published methods at the University Health Network Genomics Core.[21] Processing and analyses of methylation data were performed at the Hospital for Sick Children (A.H.) as previously reported.[19,21] Methylation profiles were first analyzed relative to a reference set of 1,200 pediatric brain tumors to confirm diagnosis and then in relation to a methylation data set of 300 primary AT/RTs to establish subtype.

Statistical Methods

The primary analysis for ACNS0333 was a comparison of risk of an EFS event for patients $<$ 36 months of age at diagnosis with a historical cohort of patients from CCG-9921 and POG-9923/4 with centrally confirmed AT/RT.[4,5] EFS was defined as the time from study enrollment until detection of a relapse or second malignancy, death, or last patient contact, whichever occurred first. Overall survival (OS) was defined as the time from study enrollment to death

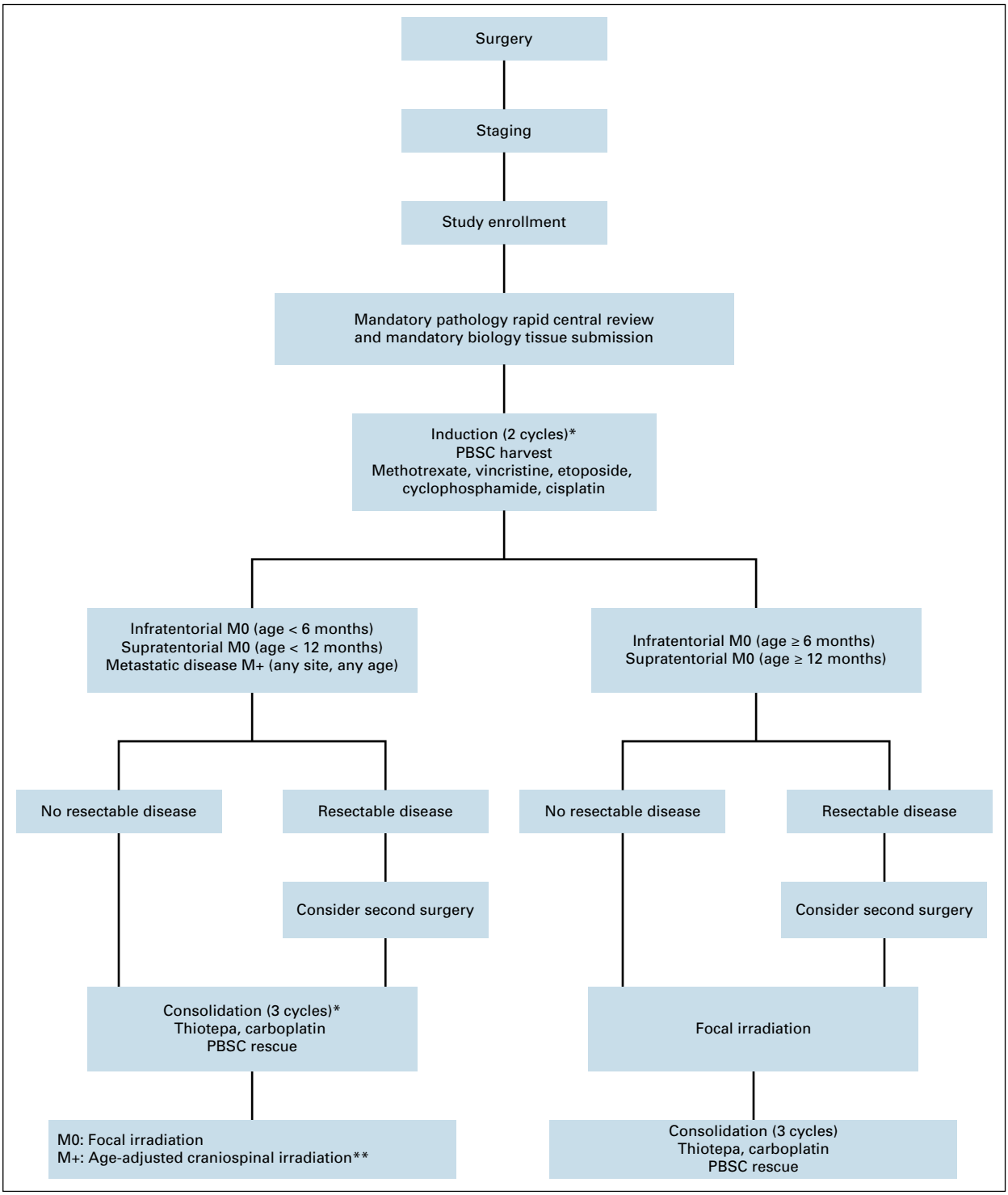

FIG 1. Experimental design schema. (*) See Chemotherapy Dosing Table (Table 1). (**) Recommended but not mandated by study. M0, no evidence of metastatic disease at the time of enrollment; M+, evidence of metastatic disease (M1-M3) at the time of enrollment. PBSC, peripheral blood stem cell.

or last patient contact, whichever occurred first. EFS and OS as a function of time since enrollment were calculated using the method of Kaplan and Meier. We used a 1-sided log-rank test to analyze risk of an EFS event across ACNS0333 and the historical cohort. A P value of $\leq .05$ was considered indicative of significant improvement associated with ACNS0333. All other statistical testing of risk for an EFS event or death was 2 sided.

TABLE 1. ACNS0333 Chemotherapy Dosing Table

Drug	Dose (maximum)	Days
Induction		
Methotrexate	8 g/m^2 (20 g)	1
Vincristine	0.05 mg/kg (1.5 mg/m^2)[a]	1, 8, and 15
Etoposide	2.5 mg/kg (75 mg/m^2)[a]	A, B, and C[b]
Cyclophosphamide	60 mg/kg (1.8 g/m^2)[a]	A and B[b]
Cisplatin	3.5 mg/kg (105 mg/m^2)[a]	C[b]
Consolidation		
Carboplatin	17 mg/kg (510 mg/m^2)[a]	1 and 2
Thiotepa	10 mg/kg (300 mg/m^2)[a]	1 and 2

[a]m^2 dosing used for patients > 36 months of age.

[b]A, B, and C refer to consecutive days after methotrexate clearance; additional details in the treatment protocol (Data Supplement).

TABLE 2. ACNS0333 Patient Characteristics at Baseline

Characteristic	Frequency (%) N = 65
Sex	
Male	30 (46)
Female	35 (54)
Age at diagnosis, months	
≤ 5	7 (11)
6-11	13 (20)
12-35	34 (52)
≥ 36	11 (17)
Race	
White	43 (66)
Black or African American	8 (12)
Other/unknown	14 (22)
Ethnicity	
Non-Hispanic	43 (66)
Hispanic	18 (28)
Unknown	4 (6)
Primary site	
Infratentorial	33 (51)
Supratentorial	26 (40)
Both infratentorial and supratentorial[a]	5 (7.5)
Spinal cord	1 (1.5)
M stage	
M0	41 (63)
M1	3 (5)
M2	10 (15)
M3	11 (17)
Extent of resection[b]	
Gross total	25 (38)
Near-gross total	11 (17)
Subtotal, partial, or biopsy	29 (45)

Abbreviations: M0, no evidence of metastasis; M1, tumor cells in CSF; M2, gross nodular seeding of brain; M3, gross nodular seeding of spine.

[a]Described as a contiguous tumor that extended through both infratentorial and supratentorial compartments.

[b]Gross total means no visible tumor mass after surgery confirmed by magnetic resonance imaging. Near-gross total means removal of > 95%, but < 100% of the tumor mass. Subtotal means removal of 50%-95% of the tumor mass; partial means removal of 10%-49% of the tumor mass; biopsy means removal of < 10% of the tumor mass.

The study design required at least 40 enrolled patients < 36 months of age (statistical stratum I). Enrollment of patients ≥ 36 months of age (statistical stratum II) continued until stratum I was complete. Historical data predicted 40 patients < 36 months could be enrolled within 3.5 years of trial initiation. With an additional 6 months of follow-up after enrollment closure, the log-rank test would have 80% power to detect a 1.8-fold decrease in risk of an EFS event in ACNS0333 compared with the historical cohort.

The study was monitored by the COG Data Safety and Monitoring Committee for the feasibility of completing induction, inferior outcome compared with the historical cohort, and excessive toxic death. Details on interim analysis are in the protocol (Data Supplement).

Type of EFS failure was further classified as (1) relapse/progression at the original site of disease (local failure); (2) relapse/progression at a site not identified as involved at enrollment (distant failure); (3) local plus distant failure; and (4) death without documented progression. The cumulative incidence of each failure type was estimated by the method of Gray. Relative hazard rates (HRs) were estimated using a proportional hazards regression model. The estimate and the 95% CI were calculated using the proportional hazards regression model with the characteristic of interest as the only variable in the model.

RESULTS

Patients and Disease Features

Seventy patients were enrolled from 41 COG institutions between February 2009 and May 2013. Data current to June 30, 2017, were used for all analyses. Table 2 lists the demographic and disease features of the 65 evaluable patients. Children < 36 months of age comprised 83% of the total cohort. Tumor location split between infratentorial (51%) and supratentorial tumors (40%), whereas 7.5% of patients had contiguous primary tumor in both locations. Metastatic disease (M1-M3) was present in 37% of patients, and 62% had residual disease after surgery.

Therapy Delivered, Feasibility of Induction, and Response

Figure 2 (Consort Diagram) demonstrates the flow of patients through this study. Median time between induction cycles 1 and 2 was 27 days. Seventeen patients did not receive postinduction therapy according to protocol. For 8 of these patients, the reason was because of physician or parent choice without meeting off-study criteria. Sixty-three patients were evaluated for treatment response after induction. Responses were as follows: 10 had a complete response, 13 had a partial response, and 17 had stable disease; 17 patients who had complete resection and were M0 pretreatment had continued complete response. Notably, only 6 patients experienced disease progression during induction.

Treatment Efficacy

Median follow-up time was 4.7 years (95% CI, 4.2 to 5.3 years).[22] At 4 years, the EFS and OS for all patients were 37% and 43%, respectively (Fig 3A). The primary analytic comparison showed ACNS0333 therapy significantly reduced the risk of EFS events in patients < 36 months of age compared with the historical cohort ($P < .0005$; estimated relative HR, 0.43; 95% CI, 0.28 to 0.66; Fig 3B). At 4 years, EFS for patients in ACNS0333 was 35% compared with 6.4% for the historical cohort. For 11 patients ≥ 36 months of age, 4-year EFS and OS were 48% and 57%, respectively.

Prognostic Variables

Table 3 shows the number of EFS events and deaths, as well as the HR for patients grouped by age at diagnosis, tumor location, M stage, surgical resection, presence of germline mutation, molecular subgroup, and order of therapy after induction. EFS at 6 months and 1, 2, and 4 years, and OS at 4 years for the same variables are shown in Table 4. We subdivided age < 36 months into infants (< 6 months), babies (6-11 months), and toddlers (12-35 months) and did not find an age group at significantly higher risk for death.

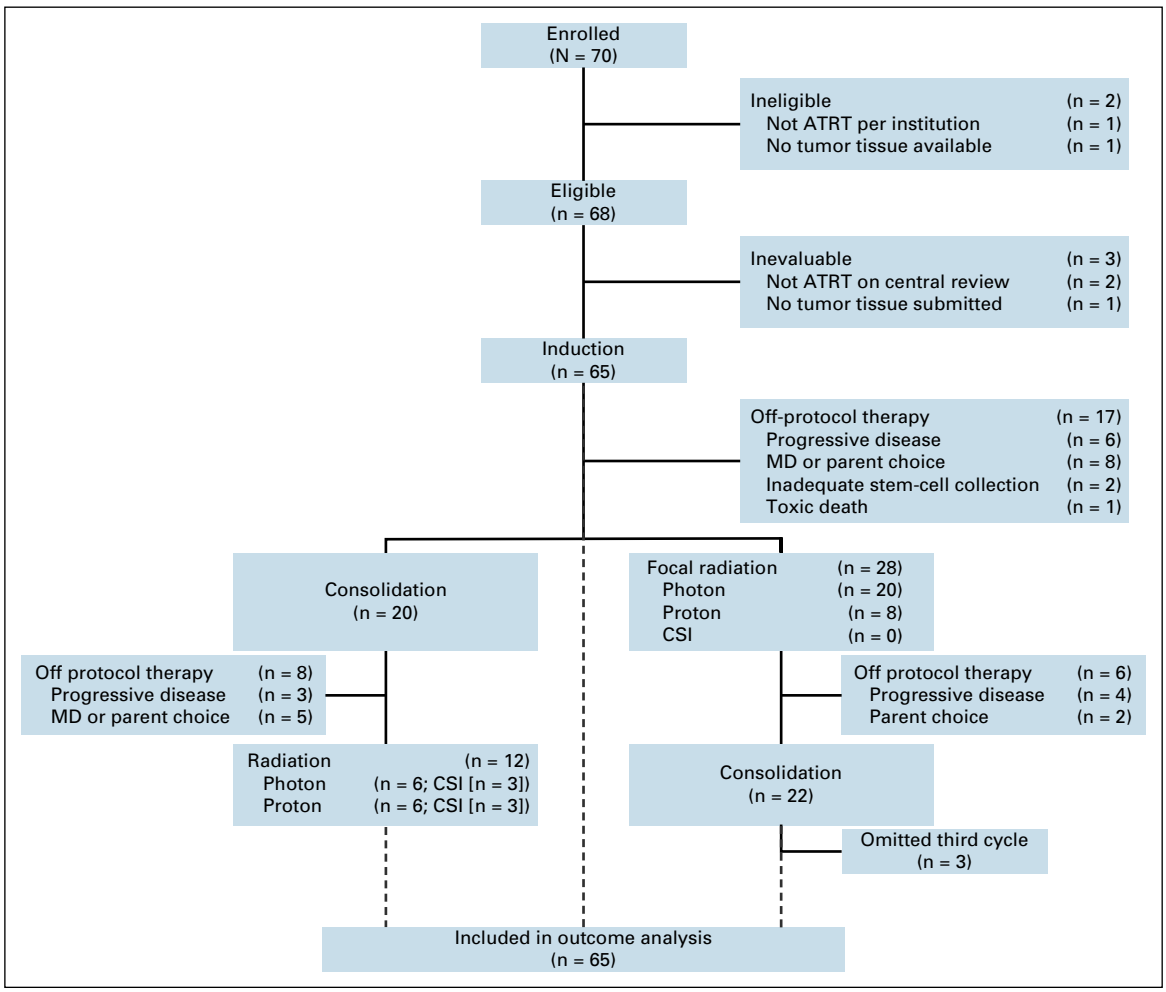

FIG 2. CONSORT diagram. Flow of patients enrolled in ACNS0333 through therapy. All patients received induction chemotherapy. The order of consolidation and radiation was based on age, tumor location, and extent of disease. All 65 evaluable patients were included in the outcome analysis, including those who came off protocol therapy without meeting off-study criteria. AT/RT, atypical teratoid/rhabdoid tumor; CSI, craniospinal irradiation; MD, physician.

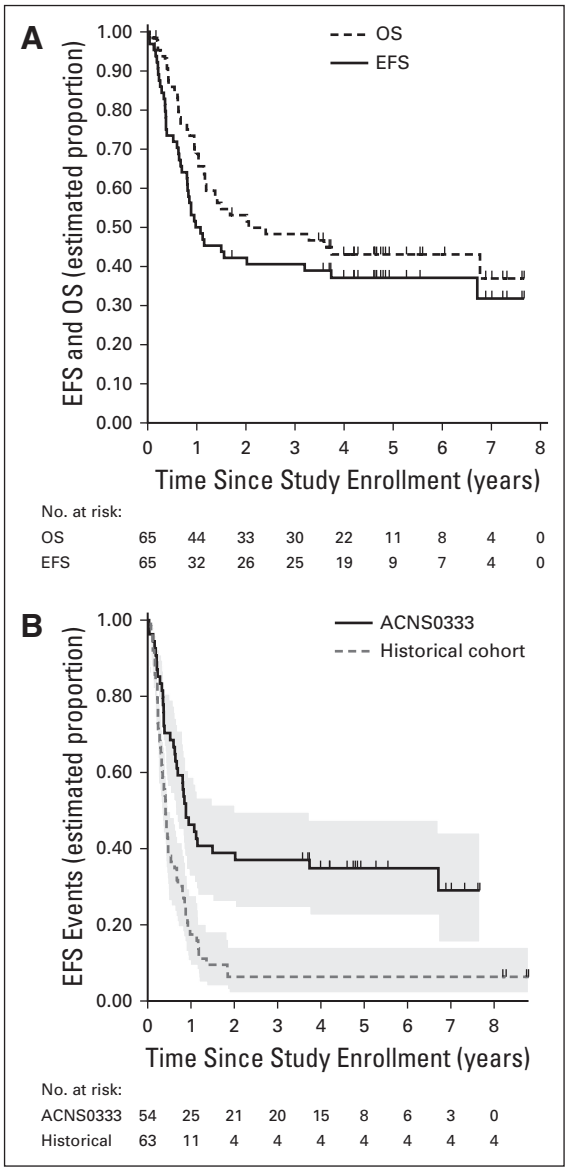

FIG 3. (A) Event-free survival (EFS) and overall survival (OS) for all 65 evaluable patients treated in ACNS0333. At 4 years, the EFS and OS (95% CI) were 37% (25% to 49%) and 43% (31% to 55%), respectively. (B) ACNS0333 therapy significantly reduced the risk for EFS events in patients < 36 months of age (n = 54) compared with the historical cohort from Pediatric Oncology Group 9233/4 and Children's Cancer Group 9921 (n = 63; $P <$ .0005; hazard rate for ACNS0333, 0.43; 95% CI, 0.28 to 0.66). Gray shaded areas represent the pointwise 95% CIs for EFS.

With 4-year OS of 54% for infratentorial tumors and 35% for supratentorial tumors, location did not have a statistically significant impact on survival. However, patients whose primary tumor contiguously involved both infratentorial and supratentorial locations or who had a spinal primary were at significantly increased risk for death (HR, 2.65; 95% CI, 1.03 to 6.85). Neither the presence of metastatic disease (M1-3) nor surgical residual disease significantly increased the risk of death (Table 3). Only 6 patients underwent second-look surgery after induction, and its impact on survival could not be evaluated. For 48 patients who continued to receive protocol therapy after induction, the sequence of radiation and consolidation did not affect EFS or OS (Table 4). The 4-year OS was 49% for RT before consolidation versus 48% for consolidation before RT. This result is notable because patients who received consolidation first were very young or had metastatic disease, both generally considered high-risk features.

SMARCB1 Analysis

A homozygous deletion, mutation, or intragenic copy number alteration of *SMARCB1* was identified in the tumor of each evaluable patient. The type of genetic alteration was not associated with significant differences in survival (analysis not shown). Ten of 64 patients tested had germline deletions or mutations of *SMARCB1*. Patients with *SMARCB1* germline alterations had a median age of 7 months (range, 4-21 months) compared with 18 months (range, 2-165 months) for those without these mutations. Seven of 10 patients with germline mutations relapsed by 2 years, and this cohort had a 4-year OS of only 20% (Table 4).

Molecular Subclassification

Fifty-six archived patient tumor samples were available for global methylation profiling. ACNS0333 AT/RTs segregated into 3 molecular classes, with a frequency of distribution similar to what has been previously reported in retrospective series.[19,20] Tumors with group 2A/TYR features were the most common. Patient with group 1/SHH-NOTCH tumors had 4-year OS of 56% compared with 41% for group 2A/TYR and 27% for group 2B/MYC (Table 4). Although patient numbers in each group were relatively small, survival patterns similar to retrospective studies emerged. Notably, patients with group 1/SHH-NOTCH tumors had a 6-month EFS of 100%, suggesting this may be a biologically less aggressive subgroup.

Treatment Failures

Thirty-three patients experienced documented treatment failure; 16 had only local failure, 7 had only distant failure, and 10 had combined local and distant failure (Fig 4). Thirty treatment failures (91%) occurred by 2 years from enrollment. The estimated cumulative incidence of isolated local failure at 2 years was 25% of all patients, more than twice as common as distant failure (11%) or combined local and distant failure (11%). Three treatment failures after 2 years were all combined local and distant. None of these patients had a germline mutation. To date, no second malignancies have been reported. Eight additional patients had death reported as a first event as a result of disease (n = 2), other causes (n = 2), or in association with treatment (n = 4).

Toxicity and Complications of Therapy

There was significant toxicity associated with the ACNS0333 regimen. Grade 4 or higher toxicities that occurred in 5% or more of patients are outlined in Appendix

TABLE 3. ACNS0333 EFS and OS Events With Associated HRs

Variable	No.	EFS No. of Events	EFS HR, % (95% CI)	*P*[a]	OS No. of Events	OS HR, % (95% CI)	*P*[b]
Entire cohort	65						
Age, months							
< 36	54	36	1	.207	33	1	.162
< 6	*7*	*4*	*1*		*4*	*1*	
6-11	*13*	*8*	*1.17 (0.35 to 3.91)*		*8*	*1.04 (0.31 to 3.47)*	
12-35	*34*	*24*	*1.33 (0.46 to 3.85)*		*21*	*1.13 (0.39 to 3.3)*	
≥ 36	11	5	0.57 (0.22 to 1.45)		4	0.51 (0.18 to 1.43)	
Location							
Infratentorial	33	18	1	.115	16	1	.113
Supratentorial	26	18	1.32 (0.68 to 2.54)		16	1.46 (0.73 to 2.94)	
Other (5 both, 1 spinal)	6	5	3.26 (1.19 to 8.93)		5	3.16 (1.15 to 8.7)	
Stage							
M0	41	26	1	.743	23	1	.581
M1+	24	15	1.11 (0.59 to 2.11)		14	1.21 (0.62 to 2.35)	
Resection							
GTR	25	14	1	.660	12	1	.392
NTR	11	7	1.11 (0.45 to 2.75)		7	1.43 (0.56 to 3.65)	
Subtotal, partial, or biopsy only	29	20	1.37 (0.69 to 2.72)		18	1.65 (0.79 to 3.44)	
SMARCB1 germline							
Yes	10	8	1	.233	8	1	.131
No	54	33	0.61 (0.28 to 1.33)		29	0.52 (0.24 to 1.15)	
Molecular subgroup							
Group 1/ SHH-NOTCH	17	8	1	.140	7	1	.266
Group 2A/TYR	24	17	1.92 (0.83 to 4.48)		15	1.51 (0.61 to 3.7)	
Group 2B/MYC	15	12	2.31 (0.94 to 5.69)		11	2.17 (0.84 to 5.63)	
Order of therapy after induction[c]							
Radiation first	28	17	1	.807	14	1	.960
Consolidation first	20	11	0.91 (0.43 to 1.94)		10	1.02 (0.45 to 2.30)	

NOTE. Estimates and confidence intervals in italics represent comparisons of risk for EFS event and risk for death relative to patients < 6 months of age at enrollment. *P*-values were not calculated for those comparisons. The *P*-values quoted for patient age are those where patients < 36 months of age at enrollment are considered the reference category and the comparison category consists of patients ≥ 36 months of age enrollment.

Abbreviations: EFS, event-free survival; GTR, gross total resection; HR, hazard ratio; M0 = no evidence of metastasis at enrollment; M1+, evidence of metastasis at enrollment; NTR, near-total resection; OS, overall survival.

[a]*P* value associated with the likelihood ratio test, the null hypothesis of no effect of the characteristic on risk of EFS event.

[b]*P* value associated with the likelihood ratio test, the null hypothesis of no effect of the characteristic on risk of OS event.

[c]EFS and OS are for patients who continued to receive protocol therapy after induction.

Table A2 (online only). The majority of reported toxicity was hematologic and infectious, occurring during both induction and consolidation. Four treatment-related patient deaths were reported. One patient died as a result of sepsis at the end of induction after prolonged myelosuppression. One patient, taken off protocol therapy after induction, died as a result of respiratory failure from pulmonary fibrosis after receiving further therapy. Two patients died as a result of CNS necrosis 49 and 494 days after completion of protocol therapy. The latter had viral encephalitis and sepsis at the time of death.

DISCUSSION

ACNS0333, to our knowledge the first cooperative group AT/RT trial, achieved significantly improved survival for children < 36 months of age compared with the historical cohort, which did not require RT for all patients or incorporate methotrexate and HDC. ACNS0333 results validate

TABLE 4. ACNS0333 EFS and OS

Variable	No.	6-Month EFS, % (95% CI)	1-Year EFS, % (95% CI)	2-Year EFS, % (95% CI)	4-Year EFS, % (95% CI)	4-Year OS, % (95% CI)
Entire cohort	65	73 (61 to 83)	50 (37 to 62)	42 (30 to 54)	37 (25 to 49)	43 (31 to 55)
Age, months						
< 36	54	70 (56 to 81)	46 (33 to 59)	39 (26 to 52)	35 (22 to 48)	40 (27 to 53)
< 6	7	71 (26 to 92)	57 (17 to 84)	43 (10 to 73)	43 (10 to 73)	43 (10 to 73)
6-11	13	69 (37 to 87)	46 (19 to 70)	38 (14 to 63)	38 (14 to 63)	38 (14 to 63)
12-35	34	71 (52 to 83)	44 (27 to 60)	38 (22 to 54)	32 (17 to 48)	40 (24 to 56)
≥ 36	11	90 (47 to 99)	70 (33 to 89)	60 (25 to 83)	48 (16 to 74)	57 (22 to 81)
Location						
Infratentorial	33	70 (51 to 82)	55 (36 to 70)	52 (34 to 67)	48 (30 to 64)	54 (36 to 69)
Supratentorial	26	88 (68 to 96)	52 (31 to 69)	36 (18 to 54)	27 (12 to 45)	35 (17 to 54)
Other (5 both, 1 spinal)	6	33 (5 to 68)	17 (1 to 52)	17 (1 to 52)		
Stage						
M0	41	76 (59 to 86)	51 (35 to 65)	41 (26 to 56)	36 (22 to 51)	43 (28 to 58)
M1+	24	70 (47 to 84)	48 (27 to 66)	44 (23 to 62)	39 (19 to 58)	43 (22 to 62)
Resection						
GTR	25	75 (53 to 88)	54 (33 to 72)	50 (29 to 68)	46 (25 to 64)	54 (32 to 71)
NTR	11	90 (51 to 99)	55 (23 to 78)	45 (23 to 78)	36 (11 to 63)	36 (11 to 63)
Subtotal, partial, or biopsy only	29	66 (45 to 80)	45 (27 to 62)	34 (18 to 51)	31 (16 to 48)	38 (21 to 55)
SMARCB1 germline						
Yes	10	70 (33 to 89)	30 (7 to 58)	20 (3 to 47)	20 (3 to 47)	20 (3 to 47)
No	54	74 (60 to 83)	53 (39 to 65)	45 (32 to 58)	39 (26 to 52)	46 (22 to 59)
Molecular subgroup						
Group 1/SHH-NOTCH	17	100	69 (40 to 86)	50 (25 to 71)	50 (25 to 71)	56 (30 to 76)
Group 2A/TYR	24	54 (33 to 71)	46 (26 to 64)	42 (22 to 60)	33 (15 to 52)	41 (22 to 60)
Group 2B/MYC	15	73 (44 to 89)	27 (8 to 50)	20 (5 to 42)	20 (5 to 42)	27 (8 to 50)
Order of therapy after induction[a]						
Radiation first	28	82 (62 to 92)	54 (34 to 70)	43 (24 to 60)	39 (21 to 56)	49 (29 to 66)
Consolidation first	20	75 (50 to 89)	50 (27 to 69)	50 (27 to 69)	44 (22 to 64)	48 (25 to 68)

NOTE. EFS at 6 months and 1, 2, and 4 years, and OS at 4 years for patients treated in ACNS0333 grouped by age at diagnosis, tumor location, M stage, surgical resection, presence of germline mutation, molecular subgroup, and order of therapy after induction.

Abbreviations: EFS, event-free survival; GTR, gross total resection; M0, no evidence of metastasis at enrollment, M1+, evidence of metastasis at enrollment; NTR, near-total resection; OS, overall survival.

[a]EFS and OS are for patients who stayed on protocol therapy after induction.

smaller, registry, and retrospective series, which suggested benefit of intensive multimodal regimens to treat AT/RT.[23-26] A multicenter phase II trial with systemic and intrathecal chemotherapy and RT reported a 2-year EFS of 53%.[23] Compared with ACNS0333, this study had a higher proportion of patients older than 36 months of age (40%) and shorter follow-up, compromising the comparability of results. In the European Rhabdoid Registry (EU-RHAB), 31 patients were treated with systemic and intrathecal chemotherapy, 23 of whom received radiation and 8 of whom received HDC.[25] The 6-year OS for patients < 36 months of age was 35%, comparable to ACNS0333. Similar to ACNS0333, most recurrences occurred in the first 2 years after diagnosis, and tumor metastases or extent of resection did not significantly affect survival. In a recent meta-analysis of 332 patients from 12 series, HDC and RT were associated with reduced risk of death, whereas complete tumor resection and the use of intrathecal chemotherapy were not.[27] These studies support our finding that a substantial portion of patients treated with HDC and RT will have durable survival regardless of staging, tumor location, or degree of resection. Smaller series report long-term survivors who did not receive either RT or HDC.[11,12,24,28] In our cohort, 7 patients who were in response after 2 phases of treatment but taken off therapy before RT (n = 5) or HCT (n = 2) because of physician or parent decision all

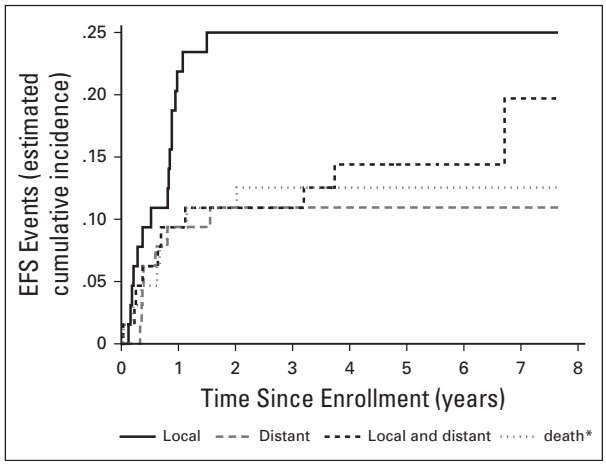

FIG 4. Event-free survival (EFS) events with patterns of failure. Thirty-three patients experienced documented treatment failure as an EFS event. Of these, 16 patients had only local failure, 7 had only distant failure, and 10 had combined local and distant failure. Thirty failures (91%) occurred before 2 years. At 2 years, the estimated cumulative incidence of isolated local failure was 25%, more than twice as common as distant failure (11%) or combined local and distant failure (11%). Failures after 2 years were all combined local and distant. (*) Eight patients had death reported as a first event due to disease (n = 2), other causes (n = 2), or in association with treatment (n = 4).

died as a result of disease. We are cautious about eliminating a phase of this regimen based on current knowledge. Although the majority of patients in ACNS0333 were < 36 months old, older patients had survival rates similar to other reports.[8] However, only 2 older ACNS0333 patients received craniospinal irradiation, suggesting that HDC and local RT alone may be adequate to achieve disease control in older patients with nonmetastatic disease.

ACNS0333 demonstrated the ability and value of mandating submission of tumor tissue and blood in prospective brain tumor trials, establishing this as a best practice for COG trials. In addition to allowing central *SMARCB1* analysis and germline characterization, tumor molecular subgrouping was performed, to our knowledge, for the first time in a uniformly treated cohort and confirmed the presence of AT/RT subgroups.[19,20]

Similar to other studies, ACNS0333 patients with germline mutations presented at a younger age; however, a lower percentage of patients (17%) had germline mutations compared with other reports.[16-18] This may be due to the ACNS0333 exclusion of patients with synchronous non-CNS tumors. Only 2 of 10 patients with germline mutations survived beyond 2 years.

ACNS0333 was designed to identify whether the therapeutic regimen improved survival. As such, the examination of prognostic variables was exploratory with no expectation of demonstrating conventional statistical significance. ACNS0333 data do suggest potential positive and negative prognostic indicators. Given the relative rarity of AT/RT, the data on tumor location, extent of disease, surgical resection, *SMARCB1* alterations, and molecular profiling should be combined with other studies to more clearly identify prognostic factors and help risk-stratify patients in future trials.

Although significant toxicity was anticipated, we acknowledge that 4 (6%) therapy-associated deaths exceeded the acceptable threshold of 4% in the protocol. This occurred because 1 death, 18 months after completing therapy, was not reported as a serious adverse event by the treating institution. The study demonstrated, however, that the protocol amendments to reduce pulmonary toxicity and placing radiation at the end of therapy might reduce treatment-related mortality. After lengthening consolidation cycles and adding respiratory supportive care measures, no further fatal pulmonary toxicity was reported. Both patients whose deaths were in part attributed to CNS necrosis received radiation (one photon, one proton) between induction and consolidation. Although this finding may be confounded by tumor location and size, deaths associated with CNS necrosis were not reported in any patient who received radiation after all chemotherapy. Additional details on radiation delivery and related changes will be reported separately. Because the timing of radiation did not affect survival for patients who continued to receive protocol therapy past induction, we strongly recommend that it follow consolidation in future trials.

With improved survival for patients with AT/RT comes the risk of long-term sequelae of both disease and treatment. The early use of RT is controversial in young patients. Some studies suggest that conformal RT alone does not significantly affect neurocognitive outcome[29,30]. Others have shown neurocognitive impairment in patients with AT/RT treated with intensive chemotherapeutic regimens without radiation.[31] The impact of combining these modalities deserves attention. ACNS0333 did not imbed neurocognitive measures with the intent to capture such data for survivors in COG Behavioral Science studies. With dramatic improvement in survival, age-appropriate measures should be included in future trials.

ACNS0333 has shown that intensive multimodal therapy significantly improves survival for patients with AT/RT. However, further intensification using cytotoxic agents is likely not feasible. There are increasing data suggesting that AT/RT may be a good candidate for pathway-specific targeted therapies. Recently, investigations of altered signaling pathways have yielded a wide array of compounds with potential therapeutic activity in AT/RT, some of which are currently in clinical trials, including AURKA, EZH2, and CDK4/6 inhibitors.[32,33] A COG study incorporating a targeted inhibitor into the ACNS0333 backbone is in development. Intense clinical and biologic investigation of AT/RT should continue to more accurately identify prognostic indicators, assist in risk stratification of patients, and inform therapy. Subsets of patients who can be cured with less therapy may exist. The goal must be to continue to improve survival and reduce toxicity with refinements in therapy based on integration of biologic and clinical risk factors.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Efficacy of High-Dose Chemotherapy and Three-Dimensional Conformal Radiation for Atypical Teratoid/Rhabdoid Tumor: A Report From the Children's Oncology Group Trial ACNS0333

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APPENDIX

TABLE A1. ACNS0333 Radiation Guidelines

Age at RT (months)	M Stage	Primary Site	Irradiation Volume	CSI Dose (Gy)	PTV Dose (Gy)	Cumulative PTV Dose (Gy)	Daily Dose (Gy)
≤ 6-≤ 36	M0	IT	Focal	0	50.4	50.4	1.8
≤ 12-≤ 36	M0	ST	Focal	0	50.4	50.4	1.8
> 36	M0	IT/ST	Focal	0	54.0	54.0	1.8
≤ 36	M+	IT/ST	Focal and craniospinal[a]	23.4	27.0	50.4	1.8
> 36	M+	IT/ST	Focal and craniospinal[a]	36.0	18.0	54.0	1.8

NOTE. The sequencing of radiation therapy and prescribed doses and volumes were based on the age of the patient at the completion of induction chemotherapy, primary tumor location (infratentorial *v* supratentorial), and the extent of disease (localized *v* metastatic) at the time of enrollment. All patients were required to receive at least 2 cycles of induction chemotherapy before irradiation. Those with infratentorial tumor location under the age of 6 months at the completion of induction chemotherapy received consolidation chemotherapy before irradiation. Those with supratentorial primary tumor location under the age of 12 months at the completion of induction chemotherapy received consolidation chemotherapy before irradiation. Patients with metastatic disease at the time of enrollment received induction and consolidation chemotherapy before irradiation. The study specified a 10-mm clinical target volume margin for treatment of the primary site and mandated the use of computed tomography–magnetic resonance imaging registration to define the primary site target volumes. The allowed primary site treatment methods were restricted to conformal or intensity-modulated radiation therapy using photons or protons; electronic data submission was required.

Abbreviations: CSI, craniospinal irradiation; IT, infratentorial; M0, no evidence of metastasis at enrollment; M+, evidence of metastasis at enrollment; PTV, planning target volume; RT, radiation therapy; ST, supratentorial.

[a]CSI was recommended and administered at the discretion of the treating institution; supplemental boost irradiation of metastatic sites (45.0-54.0 Gy) was administered at the discretion of the treating institution.

TABLE A2. Treatment-Associated Toxicity

		Reporting Period					
		Induction (n = 65)		Consolidation (n = 42)		Radiation (n = 40)	
Organ System	Toxicity Type	No.	%	No.	%	No.	%
Any organ system	Not grade 4+[a]	21	32.3	14	33.3	36	90.0
Metabolism and nutrition disorders	Hypokalemia	3	4.6	4	9.5		
Vascular disorders	Hypotension			3	7.1		
Respiratory, thoracic, and mediastinal disorders	Hypoxia	1	1.5	3	7.1	1	2.5
Infections and infestations	Infections and infestations; other, specify	4	6.2	1	2.4	1	2.5
	Sepsis	3	4.6	3	7.1		
Investigations	ALT increased	4	6.2				
	Lymphocyte count decreased	18	27.7	12	28.6	1	2.5
	Neutrophil count decreased	34	52.3	24	57.1	2	5.0
	Platelet count decreased	28	43.1	21	50.0	1	2.5
	WBC count decreased	27	41.5	22	52.4		

NOTE. Grade 4 or higher adverse events that occurred in 5% or more of patients in at least 1 phase of therapy. The majority of reported toxicity was hematologic and infectious, occurring during both induction and consolidation.

[a]Patients with "not grade 4+" had lesser adverse event grade or no adverse event reported. Grade 4 ototoxicity was reported in 1 patient only (during induction) and is not shown in the table.