ORIGINAL REPORT

Arsenic Trioxide Consolidation Allows Anthracycline Dose Reduction for Pediatric Patients With Acute Promyelocytic Leukemia: Report From the Children's Oncology Group Phase III Historically Controlled Trial AAML0631

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ABSTRACT

Purpose

The Children's Oncology Group AAML0631 trial for newly diagnosed pediatric acute promyelocytic leukemia (APL) was a phase III historically controlled trial to determine the survival of patients receiving arsenic trioxide (ATO) consolidation and reduced doses of anthracyclines.

Patients and Methods

Patients age 2 to 21 years with de novo APL confirmed by PML-RARα polymerase chain reaction were stratified as standard risk (SR) or high risk (HR) on the basis of diagnostic WBC count. All patients received all-trans retinoic acid (ATRA) during induction, each consolidation course, and maintenance. All patients received two cycles of ATO therapy during consolidation 1, an additional two (SR) or three (HR) consolidation courses that included high-dose cytarabine and anthracycline, and maintenance therapy comprising ATRA, oral methotrexate, and mercaptopurine.

Results

One hundred one patients (66 SR and 35 HR) were evaluable for outcome. The 3-year overall survival was 94%, and event-free survival (EFS) was 91%. For SR and HR patients with APL, the overall survival was 98% versus 86% ($P = .003$), and EFS was 95% versus 83% ($P = .03$), respectively. The EFS for SR patients in AAML0631 was noninferior to that of patients in the AIDA 0493 historical control, which used a significantly higher anthracycline dose and did not include ATO consolidation. Relapse risk for patients in AAML0631 from end consolidation 1 (after ATO treatment) was only 4% at 3 years and did not differ significantly between SR and HR patients.

Conclusion

ATO consolidation cycles were well tolerated in pediatric patients with APL and allowed significant reduction in cumulative anthracycline doses while maintaining excellent survival and a low relapse risk for both SR and HR patients with APL.

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INTRODUCTION

Historically, treatment of pediatric acute promyelocytic leukemia (APL) has included high doses of anthracyclines, with risk of cardiac toxicity.[1,2] This risk increases with higher cumulative doses (≥ 300 mg/m^2) and younger age at exposure.[3] Anthracycline-based chemotherapy in combination with all-trans retinoic acid (ATRA) has improved survival for pediatric APL.[4,5] In the Gruppo Italiano Malattie EMatologiche dell'Adulto–Associazione Italiana di Ematologia Oncologia Pediatrica AIDA 0493 trial, treatment with ATRA, anthracyclines, and high-dose cytarabine resulted in overall survival (OS) of approximately 90%.[5]

More recently, APL clinical trials have evaluated treatment with arsenic trioxide (ATO). The North American Intergroup study Cancer and Leukemia Group B (CALGB) 9710 demonstrated that adults with APL receiving two cycles of ATO consolidation had significantly improved OS and decreased relapse risk (RR).[6] ATO has been used with great success as a single agent and in combination with ATRA in the treatment of children with APL.[7-9] The pivotal APL0406 trial demonstrated that ATRA and ATO was not inferior to ATRA and chemotherapy in adult SR APL.[10]

Our clinical trial (AAML0631) is a phase III historically controlled Children's Oncology Group trial for pediatric APL incorporating ATO consolidation with an approximate 40% reduction in anthracycline dosing compared with the historical control trial AIDA 0493.[5] Here, we report the safety and tolerability of ATO consolidation in pediatric patients with APL treated in AAML0631 and demonstrate that ATO consolidation allowed a significant reduction in anthracycline dosing while maintaining excellent outcomes.

PATIENTS AND METHODS

Patients

AAML0631 was a nonrandomized phase III cooperative group trial in which event-free survival (EFS) from AIDA 0493 was used as the benchmark for the standard-risk (SR) group (WBC count at presentation < 10,000 cells/μL), whereas outcome for the smaller high-risk (HR) group (WBC count ≥ 10,000 cells/μL) is descriptively reported because of limitations of power. AIDA 0493 enrolled 983 patients with APL of all ages between January 1993 and June 2000, but the pediatric cohort reported by Testi et al[5] included 107 patients (69 SR, 38 HR) age < 18 years. Inclusion criteria for our trial AAML0631 were age ≥ 2 to < 22 years, clinical diagnosis of de novo APL made by examining marrow or peripheral blood, and no prior leukemia treatment except for steroids, hydroxyurea, and leukapheresis. There were no performance score or organ function exclusions in AAML0631, whereas the comparator study, AIDA 0493, did exclude patients with WHO performance status (PS) ≥ 4 or creatinine, alkaline phosphatase, and ALT or AST greater than three times upper normal limit. Patients with preexisting prolonged QT syndrome were excluded from AAML0631 because of the risk of QT interval prolongation during ATO therapy. The National Cancer Institute's central institutional review board and institutional review boards at each enrolling center approved the study; patients and their families provided informed consent or assent. The trial was conducted in accordance with the Declaration of Helsinki. The trial was registered at www.clinicaltrials.gov as NCT00866918.

Patients were stratified by diagnostic WBC count into SR (WBC count < 10,000 cells/μL) or HR (WBC ≥ 10,000 cells/μL) groups. Cytogenetic data were reviewed centrally. For patients to remain on protocol therapy and be evaluable for outcome analysis, t(15;17) needed to be confirmed by PML-RARα (promyelocytic leukemia and retinoic acid receptor alpha fusion gene) polymerase chain reaction (PCR). The centralized laboratory testing the samples used real-time quantitative reverse-transcription PCR (RQ-PCR). PML-RARα PCR was performed on patient samples at end of consolidation therapy and every 3 months thereafter until 1 year off therapy.

Treatment Protocol

ATRA was given at a dose of 25 mg/m^2/d divided twice daily on days 1 to 30 of induction and days 1 to 14 of each consolidation course and each maintenance cycle (Table 1; Data Supplement). Induction comprised ATRA and idarubicin, and consolidation comprised two cycles of ATRA and ATO. Patients received two (SR) or three (HR) additional cycles of chemotherapy consolidation. Patients received approximately 2 years (nine cycles of 12 weeks each) of maintenance therapy comprising ATRA, 6-mercaptopurine, and oral methotrexate. Patients received three (SR) or four (HR) prophylactic treatments of intrathecal cytarabine.

Statistical Analysis

Data from AAML0631 are current as of September 30, 2015. The Kaplan-Meier method was used to estimate OS (time from study entry to death) and EFS (time from study entry until failure to achieve complete remission [CR] at end of consolidation 1, relapse, or death).[12] Disease-free survival (DFS) was evaluated from the end of consolidation 1 (after completion of the ATO cycles) until relapse or death. Cumulative incidence methods were used to calculate RR, defined as time from the end of consolidation 1 for patients in CR to relapse or death, where deaths without relapse were considered competing events.[13] Appearance of promyeloblasts or abnormal promyelocytes (≥ 5%) or two consecutive positive PML-RARα RQ-PCR tests in the bone marrow was considered disease relapse. Death before achieving CR, death within 14 days of diagnosis from any cause, or refractory disease (hematologic CR not achieved by the end of consolidation 1) were defined as failures. The significance of predictor variables was tested by the log-rank statistic for OS and EFS and the Gray's statistic for RR. All estimates are reported with two times the Greenwood SEs. Patients lost to follow-up were censored at their date of last known contact.

The study was designed to have 90% power with one-sided testing at the 20% level of statistical significance to detect an 11% decrease in EFS (increase in the hazard of failure of 1.76) for SR patients treated in this trial compared with a benchmark on the basis of results from AIDA 0493. A one-sample log-rank test was used to assess whether the EFS experience for SR patients in this study was inferior to that resulting from an exponential mixture cure model that adequately modeled EFS for SR patients in AIDA 0493 (A.M. Testi, personal communication, February 2006).[5,14] To monitor insufficient EFS for SR patients, the Lan-DeMets criterion with an α-spending function αt^2 (truncated at 3 SDs) and 20% type I error was used. Interim monitoring boundaries were not crossed.

RESULTS

Patient Characteristics

This trial accrued patients between March 2009 and November 2012. Of the 108 patients enrolled, 101 (66 SR and 35 HR) were evaluable for treatment outcome. Nonevaluable patients included four whose samples were PML-RARα PCR negative and three who were excluded because of improper consent procedures at local sites (Fig 1).

Patient characteristics for HR and SR APL groups are presented in Table 2. Cytogenetic analysis revealed only the classic t(15;17) in 63% (n = 62) of patients, but an additional one, two, three, and more than three cytogenetic abnormalities were present in 31% (n = 30), 3% (n = 3), 2% (n = 2), and 1% (n = 2) of patients, respectively. Patients with SR APL in AAML0631 and the historical comparator AIDA 0493 had similar characteristics except for differences in racial/ethnic diversity and distribution of PS scores (Table 2).

Lumbar puncture was not required at initial diagnosis, but in 28 patients with diagnostic lumbar puncture, seven had blasts present in an atraumatic CSF specimen. There was no central review of CSF pathology. Six of these seven patients remain in remission, and one patient died of infectious complications during consolidation therapy.

Toxicity Data

Adverse events included grade ≥ 3 nonhematologic toxicities and grades 1 to 5 QTc interval prolongation, ventricular arrhythmia, or left ventricular systolic dysfunction. The percentage of patients with adverse events varied by treatment course and was highest during induction and high-dose cytarabine–containing courses as follows: induction (82%, n = 84), consolidation 1 cycle 1

Table 1. Treatment Regimens for the COG AAML0631 and GIMEMA-AIEOP AIDA 0493 Trials

COG AAML0631		GIMEMA-AIEOP AIDA 0493	
Induction	ATRA 25 mg/m^2/d divided twice a day on days 1-30 Idarubicin 12 mg/m^2/d on days 3, 5, and 7 for SR APL and days 1, 3, and 5 for HR APL	Induction	Idarubicin 12 mg/m^2/d on days 2, 4, 6, and 8 ATRA 25 mg/m^2/day divided twice a day on day 1 to CR
Consolidation 1 (two cycles lasting 5 weeks each)	ATRA 25 mg/m^2/d divided twice a day on days 1-14 ATO 0.15 mg/kg/d on days 1-5, 8-12, 15-19, 22-26, and 29-33	(No ATO consolidation)	
Consolidation 2	ATRA 25 mg/m^2/d divided twice a day on days 1-14 Intrathecal cytarabine* on day 1 Cytarabine 1,000 mg/m^2 every 12 hours (33.3 mg/kg if < 0.6 m^2) on days 1-3 Mitoxantrone 10 mg/m^2/d (0.33 mg/kg if < 0.6 m^2) on days 3 and 4	Consolidation 1	Idarubicin 5 mg/m^2/d on days 1-4 Cytarabine 1,000 mg/m^2/d on days 1-4
Consolidation 3	ATRA 25 mg/m^2/d divided twice a day on days 1-14 Intrathecal cytarabine* on day 1 Idarubicin 5 mg/m^2/d (0.17 mg/kg if < 0.6 m^2) on days 1, 3, and 5	Consolidation 2	Mitoxantrone 10 mg/m^2/d on days 1-5 Etoposide 100 mg/m^2/d on days 1-5
Consolidation 4 (only for HR APL†)	ATRA 25 mg/m^2/d divided twice a day on days 1-14 Intrathecal cytarabine* on day 1 Cytarabine 1,000 mg/m^2 every 12 hours (33.3 mg/kg if < 0.6 m^2) on days 1-3 Idarubicin 10 mg/m^2/d (0.33 mg/kg if < 0.6 m^2) on day 4	Consolidation 3	Idarubicin 12 mg/m^2/d on day 1 Cytarabine 150 mg/m^2 every 8 hours on days 1-5 Thioguanine 70 mg/m^2 every 8 hours on days 1-5
Maintenance (nine cycles of 12 weeks each)	ATRA 25 mg/m^2/d divided twice a day on days 1-14 Intrathecal cytarabine* on day 1 of cycle 1 only Mercaptopurine 50 mg/m^2 oral daily Methotrexate 25 mg/m^2 oral weekly	Maintenance (ATRA + chemotherapy arm); 3-month cycles repeated for 2 years	Mercaptopurine 90 mg/m^2/d oral daily Methotrexate 15 mg/m^2 IM weekly ATRA 45 mg/m^2/d for 15 days every 3 months
Cumulative anthracycline dosing	Idarubicin 51 mg/m^2 for SR APL; 61 mg/m^2 for HR APL Mitoxantrone 20 mg/m^2	Cumulative anthracycline dosing	Idarubicin 80 mg/m^2 Mitoxantrone 50 mg/m^2
Cumulative daunorubicin equivalents‡	335 mg/m^2 for SR patients; 385 mg/m^2 for HR patients	Cumulative daunorubicin equivalents‡	600 mg/m^2

Abbreviations: APL, acute promyelocytic leukemia; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; COG, Children's Oncology Group; CR, complete remission; GIMEMA-AIEOP, Gruppo Italiano Malattie EMatologiche dell'Adulto–Associazione Italiana di Ematologia Oncologia Pediatrica; HR, high risk; PML-RARα, promyelocytic leukemia and retinoic acid receptor alpha fusion gene; RQ-PCR, real-time quantitative reverse-transcription polymerase chain reaction; SR, standard risk.
*Intrathecal cytarabine dose: 25 mg if age < 3 years and 30 mg if age ≥ 3 years.
†SR patients with APL for whom PML-RARα RQ-PCR was positive after consolidation 3 were to also receive consolidation 4; however, no patients in the study met this criterion.
‡Conversion idarubicin:daunorubicin 5:1 and mitoxantrone:daunorubicin 4:1 (as per COG Late Effects Cardiac Monitoring Guidelines).[11]

(34%, n = 32), consolidation 1 cycle 2 (30%, n = 28), consolidation 2 (73%, n = 68), consolidation 3 (13%, n = 12), consolidation 4 (69%, n = 20), and maintenance cycles combined (53%, n = 48; Table 3). The most common adverse events were fever/neutropenia and infection. Differentiation syndrome (an APL-associated cardiopulmonary distress syndrome) was diagnosed in 20% (n = 20) of patients during induction, and its prevalence was 31% in HR APL and 13% in SR APL. Fifteen of these patients required temporary holding of ATRA in induction, but all were able to restart ATRA at reduced dose and advance to full dosing. The prevalence of ATRA-associated pseudotumor cerebri was ≤ 6% in each course. Targeted cardiac and liver toxicities were analyzed for the two cycles of ATO during consolidation 1. Grade 1 or 2 QTc interval prolongation occurred in 16% (n = 15) and 12% (n = 11) of patients during the ATO cycles. One patient experienced grade 3 QTc interval prolongation during ATO consolidation, and there were no grade 4 or 5 events for this toxicity. There was one event

each of grade 1 ventricular arrhythmia and grade 1 left ventricular systolic dysfunction during ATO consolidation. Starting in maintenance, yearly echocardiogram and ECG are to be obtained to 10 years from diagnosis, and the only cardiac events reported off therapy are one grade 1 QTc interval prolongation and one grade 2 ventricular arrhythmia. There have been no cardiac deaths. Liver toxicity was minimal during ATO cycles, with < 5% of patients having grade ≥ 3 increased levels of aspartate aminotransferase or alanine aminotransferase and one patient having elevated levels of bilirubin.

Response Data

Bone marrow evaluation at the end of induction relied on local assessment (without central review) of hematologic CR (hCR), which was defined as < 5% promyeloblasts/abnormal promyelocytes by morphology. The hCR rate was 81%; however, patients could remain on protocol therapy regardless of the
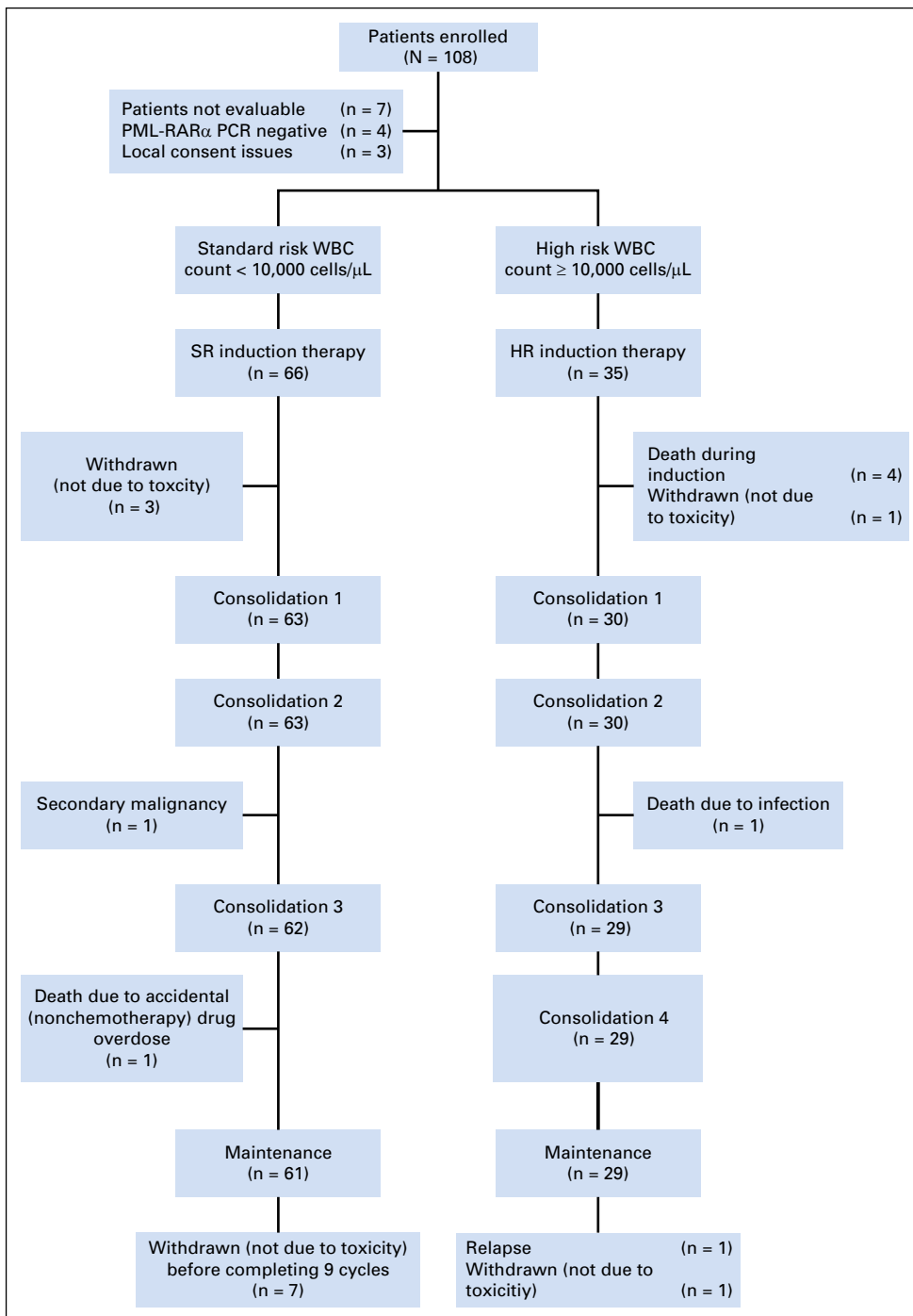
Fig 1. CONSORT diagram for the study. HR, high risk; PCR, polymerase chain reaction; PML-RARα, promyelocytic leukemia and retinoic acid receptor alpha fusion gene; SR, standard risk.

hCR response at the end of induction. PML-RARα RQ-PCR analysis at end of consolidation revealed a molecular remission rate of 100% (PCR data missing for seven patients).

The median follow-up for patients alive at last contact was 3.73 (range, 0.003 to 5.97) years. The 3-year OS was 94% ± 5%, and the 3-year EFS was 91% ± 6%. The 3-year OS for SR and HR patients with APL was 98% ± 3% and 86% ± 12%, and 3-year EFS was 95% ± 5% and 83% ± 13%, respectively (Fig 2). For patients who survived to receive ATO in consolidation 1, the 3-year DFS was 93% ± 6% for SR and 89% ± 12% for HR APL

(Fig 2). The RR for all patients was only 4% ± 4% at 3 years. The SR patients with APL in our trial had a 2-year EFS of 97% (including molecular relapse as an event) compared with that of 91% for patients in AIDA 0493 (which censored molecular relapses). This outcome met the protocol's predetermined statistical criteria to conclude that the current therapy is not inferior to that in AIDA 0493 (P = .93).

Events in this trial included three relapses, two second malignant neoplasms, and seven deaths (six HR and one SR), including one death post relapse. Four deaths (all HR) occurred

Table 2. Characteristics for Patients Enrolled in AIDA 0493 and COG AAML0631

Characteristics	AIDA 0493* SR, WBC Count < 10,000/μL (n = 69) No.	%	COG AAML0631 SR, WBC Count < 10,000/μL (n = 66) No.	%	COG AAML0631 HR, WBC Count ≥ 10,000/μL (n = 35) No.	%	COG AAML0631 All Patients (N = 101) No.	%
Sex								
Male	34	49	31	47	13	37	44	44
Female	35	51	35	53	22	63	57	56
Age, years, median (range)	11.9	(1.4-17.9)	14.83	(2.43-21.34)	15.24	(2.01-19.03)	15.04	(2.01-21.34)
Race								
White	69	100	51	81	27	77	78	80
Black	0	0	7	11	3	9	10	10
American Natives	NR	NR	2	3	0	0	2	2
Asian	NR	NR	0	0	3	9	3	3
Other	NR	NR	3	5	2	6	5	5
Unknown	0	0	3		0		3	
Ethnicity								
Non-Hispanic	NR	NR	50	78	29	85	79	81
Hispanic	NR	NR	14	22	5	15	19	19
Unknown	NR		2		1		3	
M3v (microgranular variant)	5	7	6	9	14	40	20	20
Cytogenetic complexity								
1	NR	NR	38	58	24	75	62	63
2	NR	NR	24	36	6	19	30	31
3	NR	NR	2	3	1	3	3	3
4	NR	NR	2	3	0	0	2	2
> 6	NR	NR	0	0	1	3	1	1
Missing	NR		0		3		3	
ECOG Score								
0	0	0	39	61	9	27	48	49
1	52	76	14	22	11	33	25	26
2	12	17	6	9	8	24	14	14
3	0	0	1	2	2	6	3	3
4	0	0	4	6	3	9	7	7
Not evaluated	0		2		2		4	
WBC × 1,000/μL, median (range)	2.3	(0.3-9.4)	1.8	(0.4-9.5)	25.2	(11.2-173.8)	3.8	(0.4-173.8)
Platelet count, median (range)	18	(3-48)	19	(3-198)	24	(5-107)	21.5	(3-198)

Abbreviations: COG, Children's Oncology Group; ECOG, Eastern Cooperative Oncology Group; HR, high risk; NR, not recorded; SR, standard risk.
*A.M. Testi, personal communication, April 2017.

during induction: two related to coagulopathy and two due to multiorgan dysfunction, in which differentiation syndrome likely contributed. There were two postinduction on-therapy deaths: one SR patient with APL died of accidental (nonchemotherapy) drug overdose during consolidation 3, and one HR patient with APL died of *Serratia marcescens* sepsis during consolidation 2. Of the two patients with second malignancies, one had skin cancer (carcinoma in situ) at 5 months after APL diagnosis and one had acute monoblastic/monocytic leukemia at 40 months after APL diagnosis.

The three relapses occurred in one SR and two HR patients with APL. The SR patient with APL had a combined molecular bone marrow and morphologic CNS relapse during maintenance, nearly 24 months after diagnosis. This patient achieved second remission with chemotherapy and is alive at 4 years off therapy without stem-cell transplantation. One HR APL patient had a combined hematologic bone marrow and CNS relapse during maintenance at 23 months after diagnosis. This patient received an autologous stem-cell transplantation with cyclophosphamide, total-body irradiation, and cranial radiation boost and is alive at 6 months after relapse. The other HR patient with APL had a molecular bone marrow relapse after completion of therapy at 38 months after diagnosis. This patient received allogeneic (double

umbilical cord blood) transplant with fludarabine, cyclophosphamide, and total-body irradiation but died 9 months after relapse while in remission as a result of graft-versus-host disease.

DISCUSSION

Treatment of pediatric APL with anthracyclines and ATRA has resulted in excellent outcomes, but in this young population intensive chemotherapy regimens may cause significant toxicity, including late cardiotoxicity. Our trial demonstrates that chemotherapy with ATO consolidation can result in a low relapse rate in both SR and HR APL. The use of ATO allowed an approximate 40% decrease in cumulative anthracycline dosing without compromising survival in SR APL compared with a benchmark from the AIDA 0493 trial. Furthermore, the 3-year EFS 83% and OS 86% for the HR group compares favorably to reported outcomes in other pediatric APL trials, including the 3-year EFS of 74% in AIDA 0493 and 5-year OS of 83% in Spanish Cooperative Group for Hematological Malignancies Treatment, Spanish Society of Hematology (PETHEMA) LPA96 and LPA99 trials (A.M. Testi, personal communication, April 2017).[5,15]

Table 3. Toxicities Reported in > 10% of Patients During a Course of Therapy

Toxicity	Group	Induction No.	%	Consolidation I (cycle 1) No.	%	Consolidation I (cycle 2) No.	%	Consolidation II No.	%	Consolidation III No.	%	Consolidation IV No.	%	Maintenance No.	%
Febrile neutropenia	All	32	**31.37**	0	0	1	1.08	38	**40.86**	1	1.10	10	**34.48**	8	8.89
	SR	21	**31.34**	0	0	0	0	25	**39.68**	1	1.61	—	—	5	8.20
	HR	11	**31.43**	0	0	1	3.33	13	**43.33**	0	0	10	**34.48**	3	**10.34**
Disseminated intravascular coagulation	All	8	7.84	0	0	0	0	1	1.08	0	0	0	0	0	0
	SR	4	5.97	0	0	0	0	0	0.00	0	0	0	0	0	0
	HR	4	11.43	0	0	0	0	1	3.33	0	0	0	0	0	0
Oral mucositis	All	14	**13.73**	0	0	0	0	3	3.23	0	0	1	3.45	2	2.22
	SR	10	**14.93**	0	0	0	0	1	1.59	0	0	—	—	2	3.28
	HR	4	**11.43**	0	0	0	0	2	6.67	0	0	1	3.45	0	0.00
Catheter-related infection	All	7	6.86	3	3.23	2	2.15	6	6.45	1	1.10	3	**10.34**	0	0
	SR	5	7.46	2	3.17	0	0	2	3.17	1	1.61	—	—	0	0
	HR	2	5.71	1	3.33	2	6.67	4	**13.33**	0	0	3	**10.34**	0	0
Lung infection	All	7	6.86	0	0	0	0	0	0	0	0	1	3.45	2	2.22
	SR	3	4.48	0	0	0	0	0	0	0	0	—	—	1	1.64
	HR	4	**11.43**	0	0	0	0	0	0	0	0	1	3.45	1	3.45
Other infections	All	20	**19.61**	2	2.15	4	4.30	19	**20.43**	0	0	8	**27.59**	3	3.33
	SR	11	**16.42**	1	1.59	2	3.17	12	**19.05**	0	0	—	—	1	1.64
	HR	9	**25.71**	1	3.33	2	6.67	7	**23.33**	0	0	8	**27.59**	2	6.90
ALT increased	All	2	1.96	4	4.30	1	1.08	1	1.08	1	1.10	0	0	19	**21.11**
	SR	1	1.49	4	6.35	1	1.59	0	0	1	1.61	—	—	13	**21.31**
	HR	1	2.86	0	0	0	0	1	3.33	0	0	0	0	6	**20.69**
ECG QT corrected interval prolonged	All	6	5.88	16	**17.20**	11	**11.83**	2	2.15	2	2.20	0	0	0	0
	SR	5	7.46	12	**19.05**	8	**12.70**	2	3.17	1	1.61	—	—	0	0
	HR	1	2.86	4	**13.33**	3	**10.00**	0	0	1	3.45	0	0	0	0
Pain	All	5	4.90	0	0	1	1.08	2	2.15	0	0	1	3.45	1	1.11
	SR	0	0	0	0	1	1.59	0	0.00	0	0	—	—	0	0
	HR	5	**14.29**	0	0	0	0.00	2	6.67	0	0	1	3.45	1	3.45
Hyperglycemia	All	15	**14.71**	0	0	0	0	3	3.23	1	1.10	1	3.45	0	0
	SR	12	**17.91**	0	0	0	0	2	3.17	1	1.61	—	—	0	0
	HR	3	8.57	0	0	0	0	1	3.33	0	0	1	3.45	0	0
Hypokalemia	All	17	**16.67**	3	3.23	2	2.15	5	5.38	0	0	2	6.90	0	0
	SR	12	**17.91**	2	3.17	2	3.17	3	4.76	0	0	—	—	0	0
	HR	5	**14.29**	1	3.33	0	0	2	6.67	0	0	2	6.90	0	0
Rash, maculopapular	All	1	0.98	0	0	0	0	3	3.23	1	1.10	0	0	0	0
	SR	0	0	0	0	0	0	0	0	1	1.61	—	—	0	0
	HR	1	2.86	0	0	0	0	3	**10.00**	0	0	0	0	0	0

NOTE. Boldface numbers denote the group and course in which toxicity occurred at rate of > 10%.
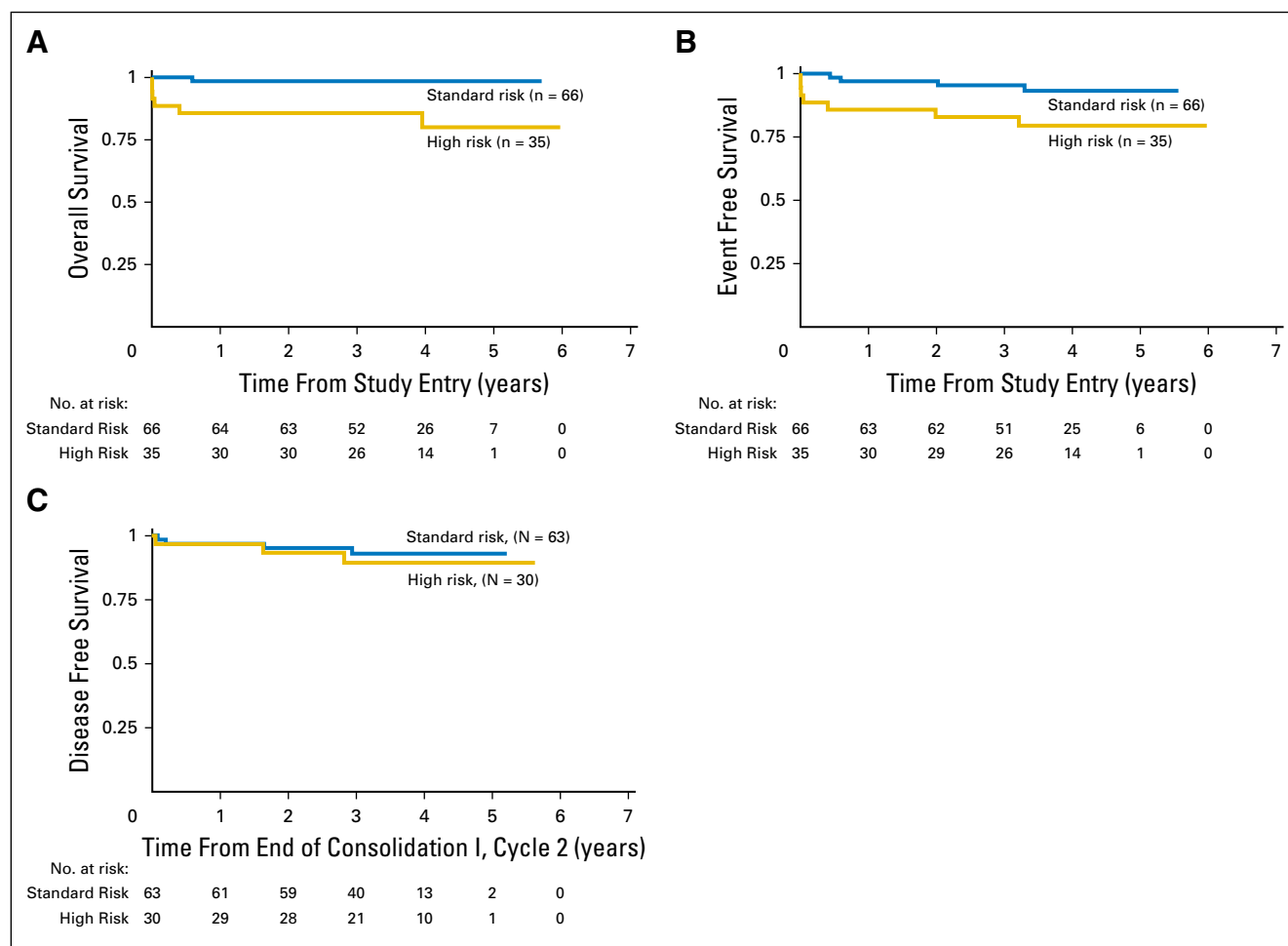Abbreviations: HR, high risk; SR, standard risk.

Fig 2. Survival by risk group including (A) overall survival, (B) event-free survival, and (C) disease-free survival.

An important goal of this trial was to study toxicities in pediatric patients treated with ATO and reduced anthracycline doses. Most deaths of patients receiving therapy occurred during induction because of disease complications of differentiation syndrome and coagulopathy. One patient died as a result of infection during consolidation 2, which includes mitoxantrone (a highly myelosuppressive anthracycline). This finding highlights the importance of recent efforts to transition to ATRA and ATO consolidation without traditional cytotoxic chemotherapy. ATO is associated with cardiac toxicity, particularly QTc prolongation.[16,17] In this trial, ATO therapy did result in prolonged QTc interval, but these were almost exclusively grades 1 and 2. There were no heart failure events or cardiac deaths. Reducing the anthracycline dose from 600 mg/m^2 daunorubicin equivalents in AIDA 0493 to 335 mg/m^2 (for SR APL) and 385 mg/m^2 (for HR APL) in the current trial represents a significant improvement in reducing the risk of acute and chronic treatment toxicity.

Two patients had second malignancies in this trial. The occurrence of squamous cell carcinoma in situ is of interest, because exposure to arsenic as an environmental toxin is linked to this disease.[18,19] A study by the MD Anderson Cancer Center found the incidence of second neoplasms in patients receiving ATO/ATRA therapy was not greater than for those receiving ATRA and

chemotherapy. Of 106 patients treated with ATO/ATRA, two patients had second neoplasms, including a case of melanoma.[20] Acute monoblastic/monocytic leukemia occurred as a second malignancy in the current trial, and the Spanish PETHEMA group found a 2.2% rate of therapy-related myeloid neoplasms in > 1,000 patients with APL (mostly adults) treated with ATRA and anthracyclines but without ATO.[21] Given the type and timing of therapy-related AML in the current study, we predict that anthracycline or etoposide exposure was the causative agent; however, the contribution of other chemotherapeutic agents or ATO remains unclear.[22]

Relapses (including molecular relapse) occurred in three patients in this trial. The 3-year relapse rate was 4% ± 4%, which compares favorably to that in AIDA 0493. In AIDA 0493, the definition of relapse during most of the accrual period included hematologic relapse only, and the protocol was later amended to include molecular relapse. Before this amendment, 85 children achieved molecular remission at the end of consolidation, 21 (25%) of whom developed hematologic relapse. The median time to relapse was 26 months (range, 6 to 72 months), which suggests that the favorable 3-year relapse rate in the current study represents a true decrease in relapse attributable to ATO. Similarly, the CALGB 9710 trial demonstrated a significant reduction in relapse

among adult patients with APL randomly assigned to ATO consolidation.[6]

Some previous reports on adult APL suggest that additional cytogenetic abnormalities (ACAs) other than t(15;17) portend a poor outcome.[23-25] In contrast, several recent and large studies including ATRA therapy have shown no effect of ACAs on outcome.[26-28] We found no significant difference in outcome on the basis of presence of ACAs.

In the current study, all patients received oral chemotherapy maintenance. In contrast, AIDA 0493 initially randomly assigned patients to four maintenance arms: mercaptopurine and methotrexate (6MP/MTX), ATRA alone, 6MP/MTX alternating with ATRA, or observation. Long-term follow-up revealed no difference in DFS among the maintenance arms.[29] Similarly, the North American Intergroup C9710 study found no difference in outcomes between a limited cohort of patients receiving observation versus ATRA maintenance or in a larger cohort of patients receiving ATRA versus ATRA plus 6MP/MTX.[30,31] It will be important to determine whether maintenance therapy can be safely removed from pediatric APL therapy that includes ATO.

This study is limited by its nonrandomized design, and the outcome of patients in the HR arm was not initially designed to have statistical power for comparison. However, because of the rarity of pediatric APL, a nonrandomized design was warranted to evaluate the safety and efficacy of ATO. The survival benchmark for this study was based on results from the pediatric cohort in AIDA 0493, which represents the largest (N = 107) and best outcomes previously published for a pediatric phase III trial in APL, although the inclusion and exclusion criteria had some variations from our current study, as noted in the methods.[5] The PS of SR patients with APL in our trial suggested less impairment (majority with PS 0) than for AIDA 0493. It is unclear whether this represents a true difference in PS or whether there is a difference in national tendencies for reporting of these scores, because all patients in AIDA 0493 had PS of 1 or 2, whereas, in AAML0631, the PS ranged from 0 to 4. The current trial was an exclusively pediatric study that included a similarly large number (N = 101) of patients. Another study limitation was the lack of central review of end induction remission status, and the reported CR rate was lower than that for historical comparisons. Without a central review, the reported CR rate might be inaccurate, but end induction remission status did not result in a change in therapy in this trial. SR patients with APL with persistent molecular disease at the end of consolidation were eligible for augmented therapy, but no patients required this intensification. The excellent molecular remission rate and the low relapse rate confirm the effectiveness of this regimen for both SR and HR APL.

The favorable results of this study incorporating ATO consolidation with reduced anthracycline dose provide a new benchmark for outcome in pediatric APL. The Italian-German APL0406 and the Australasian APML4 studies demonstrate that intensified ATO consolidation can allow further reduction or elimination of traditional chemotherapy.[10,32] The Children's Oncology Group is currently investigating similar approaches in pediatric patients with APL in an actively accruing trial. The AAML0631 trial also demonstrates that early deaths attributable to coagulopathy and differentiation syndrome remain an obstacle in the cure of APL. Further research of supportive care and treatment strategies for these complications should be an objective of APL trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Arsenic Trioxide Consolidation Allows Anthracycline Dose Reduction for Pediatric Patients With Acute Promyelocytic Leukemia: Report From the Children's Oncology Group Phase III Historically Controlled Trial AAML0631

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