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Cardiomyopathy in Children With Down Syndrome Treated for Acute Myeloid Leukemia: A Report From the Children's Oncology Group Study POG 9421

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Abstract

Purpose—To determine the outcomes, with particular attention to toxicity, of children with Down syndrome (DS) and acute myeloid leukemia (AML) treated on Pediatric Oncology Group (POG) protocol 9421.

Patients and Methods—Children with DS and newly diagnosed AML (n = 57) were prospectively enrolled onto the standard-therapy arm of POG 9421 and were administered five cycles of chemotherapy, which included daunorubicin 135 mg/m² and mitoxantrone 80 mg/m². Outcomes and toxicity were evaluated prospectively and were compared with the non-DS-AML cohort (n = 565). A retrospective chart review was performed to identify adverse cardiac events.

Results—In the DS-AML group, 54 patients (94.7%) entered remission. One experienced induction failure and two died. Of the 54 who entered remission, three relapsed and six died as a result of other causes. The remission induction rate was similar in the non-DS-French-American-British (FAB) M7 (91.7%) and non-DS-non-M7 (89.3%) groups. The 5-year overall survival was significantly better in the DS-AML group (78.6%) than in the non-DS-M7 (36.3%) or the non-DS-non-M7 (51.8%) groups (*P* < .001). No age-related difference in 5-year, event-free survival was seen between patients younger than 2 years (75.8%) and those aged 2 to 4 years (78.3%). Symptomatic cardiomyopathy developed in 10 patients (17.5%) with DS-AML during or soon after completion of treatment; three died as a result of congestive heart failure.

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Conclusion—The POG 9421 treatment regimen was highly effective in both remission induction and disease-free survival for patients with DS-AML. However, there was a high incidence of cardiomyopathy, which supports current strategies for dose reduction of anthracyclines in this patient population.

Introduction

Children with Down syndrome (DS) have a marked predisposition to leukemia with a 10- to 20-fold increased risk compared with children without DS.¹ Approximately 10% of newborns with DS develop a transient myeloproliferative disorder, which often resolves spontaneously with supportive care but can progress to myelodysplastic syndrome or to acute myeloid leukemia (AML), typically between 1 to 3 years of age.² Before 5 years of age, there is an excess risk of acute megakaryocytic leukemia; approximately 10% of children enrolled on contemporary trials for AML have DS.² After the initial report of the Pediatric Oncology Group (POG) protocol 8948, multiple cooperative-group trials confirmed that children with DS and AML (DS-AML) have superior outcomes compared with their non-DS counterparts.³⁻⁷ This difference is attributed to increased blast sensitivity to cytarabine and anthracyclines.⁸⁻¹⁰ Increased cellular sensitivity to chemotherapy also contributes to increased treatment-related morbidity and mortality for patients with DS-AML.⁴ Although infection has been reported as the major cause of morbidity in children with DS-AML, these children are also at increased risk for anthracycline-related cardiotoxicity.¹¹

In 1994, POG initiated a prospective, randomized study in children with AML to determine whether event-free survival (EFS) improved when induction included high-dose cytarabine and consolidation included cyclosporine A, an *MDR1*-modulating agent. Patients with DS-AML were enrolled onto POG 9421 and were nonrandomly assigned to the standard arm of therapy. The outcomes of children without DS who were treated on POG 9421 have been previously reported.¹²

In this article, we describe the primary results of 57 patients with DS-AML who were treated on POG 9421. Overall, the remission induction rate and disease-free survival (DFS) were excellent; however, excessive cardiac toxicity was associated with this regimen in this patient population.

Patients and Methods

Patient Eligibility

Patients were enrolled onto POG 9421 from February 15, 1995, until August 15, 1999. Eligibility criteria included age younger than 21 years and de novo AML with 30% or more nonlymphoid bone marrow blasts. Patients with more than 5% but less than 30% marrow blasts were eligible if they had typical AML karyotypic abnormalities [t(8;21) or inv(16)] or had myelofibrosis with unequivocal megakaryoblasts (French-American British [FAB] M7). Patients with therapy-related AML, prior myelodysplastic syndrome, or acute promyelocytic leukemia (FAB M3) were ineligible. The diagnosis of DS was made on the basis of the report from the treating institution. Written informed consent was obtained before enrollment. The protocol was approved by the institutional review board at each participating center. The study was evaluated at regular intervals by a data-monitoring committee.

Treatment Plan

Chemotherapy doses were modified for infants (ie, younger than 12 months of age) by using the following formula: (mass × [dose according to body-surface area]) ÷ 30 = infant dose.

Induction 1 Therapy

Patients underwent diagnostic lumbar puncture and received cytarabine (40 mg/m²) intrathecally on day 1. Thereafter, they received cytarabine (100 mg/m²/d) by continuous infusion for 7 days (total 168 hours); daunorubicin (45 mg/m²/d) intravenously, infused for 15 minutes, on days 1 through 3; and thioguanine (100 mg/m²/d) orally for 7 days.

Bone marrow evaluation was performed on day 15. For patients with hypoplastic bone marrow (< 20% cellularity by biopsy) and less than 10% blasts, induction 2 was delayed until peripheral-blood cell counts recovered (absolute neutrophil count > 0.5 × 10⁹/L; platelet count > 75 × 10⁹/L). If recovery was delayed, bone marrow aspiration was repeated on day 28 and then weekly until recovery of peripheral-blood counts or until evidence of residual leukemia was observed. Patients with residual leukemia at day 15 began induction 2 immediately.

Induction 2 Therapy

Cytarabine (1 g/m²) was administered as a 1-hour infusion every 12 hours for 5 days. Bone marrow was evaluated on day 22 of induction 2. Patients whose AML was in remission (ie, M1, < 5% blasts; M2a, 5% to 15% blasts) proceeded to consolidation therapy. Patients with residual leukemia (> 25% blasts) were removed from the study because of induction failure. Patients with hypocellular bone marrow were evaluated weekly until they attained remission or developed residual leukemia.

Consolidation Therapy

Each consolidation course began when the absolute neutrophil count was greater than 0.5 × 10⁹/L and the platelet count was greater than 75 × 10⁹/L. Consolidations 1 and 3 included etoposide (100 mg/m²) as a daily 1-hour infusion for 5 days, mitoxantrone (10 mg/m²) as a daily 30-minute infusion on days 1 through 4, and cytarabine (40 mg/m²) intrathecally on day 1. Consolidation 2 was identical to induction 2. Patients with DS-AML were not eligible for bone marrow transplantation.

Required Observations

Bone marrow aspirates were studied centrally to assess cell morphology, immunophenotype, and cytogenetics. Data pertaining to treatment toxicity were collected prospectively and were graded according to the accepted National Cancer Institute Common Toxicity Criteria (NCI-CTC) v2.0.

Cardiomyopathy

Echocardiograms were required at enrollment, before each chemotherapy cycle, and at the end of therapy. If the fractional shortening (FS) was less than 27% or if the patient had clinical evidence of congestive heart failure (CHF), anthracyclines were withheld. We performed retrospective chart reviews to identify adverse cardiac events and supplement prospectively collected toxicity data. Cardiomyopathy was defined as clinically symptomatic CHF that required medical intervention (eg, diuretics, inotropic therapy, afterload reduction) or dilated cardiomyopathy at autopsy. These correspond to grade 3 or higher left ventricular function toxicity according to the Common Terminology Criteria of Adverse Events (CTCAE) v3.0.

Statistical Analyses

EFS was defined as the time from random assignment to treatment failure (ie, relapse, second malignancy, or remission failure) or death. DFS was defined as the time from the date that remission was first observed to treatment failure or death. Overall survival (OS)

was defined as the time from random assignment to death. Actuarial curves that showed the probability of EFS, DFS, and OS were constructed according to the Kaplan-Meier method.¹³ Findings with respect to EFS, DFS, and OS probability were tested for significance with the log-rank test.¹⁴ Differences in remission rates, patient characteristics, and toxicity rates were tested with the χ^2 test. All reported *P* values are two-sided.

Results

Patient Characteristics

A total of 654 patients with AML were registered onto POG 9421; 622 were eligible, and 57 (9.2%) of these had DS-AML. Table 1 lists the characteristics of patients with DS-AML compared with those patients without DS (with and without FAB M7 morphology). Children with either DS-AML or non-DS-M7 AML were younger at diagnosis than those in the non-DS-non-M7 cohort. Two thirds of the patients in the DS-AML group were younger than 2 years (median age, 20 months). The majority (79%) of patients with DS-AML had disease that was morphologically M7, whereas only 9% of patients with non-DS-AML had that FAB subtype (*P* < .0001). Sixteen patients (28%) with DS-AML had a history of a transient myeloproliferative disorder. No patient with DS-AML had CNS involvement. Three patients (5%) had granulocytic sarcoma that involved the facial or skull bones. Cytogenetic analysis of leukemic blasts was available for 47 patients. Favorable cytogenetics, such as inv(16) and t(8;21), were not observed. Nine patients had normal karyotypes with constitutional trisomy 21 only; three had constitutional mosaicism. The remainder had complex karyotypes with aneuploidy and translocations.

Induction Response and Toxicity

All 57 patients with DS-AML were assessable for induction response (Table 2). Remission induction rates were similar for the DS-AML, non-DS-non-M7, and non-DS-M7 groups. Three patients in the DS-AML group did not enter remission. One 30-month-old girl with FAB M1 morphology experienced induction failure and died as a result of refractory leukemia. Two patients experienced early death during induction. One child with unrepaired tetralogy of Fallot (TOF) had a fatal cyanotic spell, and the other presented with fulminant meningococcemia at the time of AML diagnosis and died as a result of sepsis-related multiorgan failure 21 days after completing induction 1.

Consolidation Therapy and Outcomes

Fifty-three of the 54 patients who experienced morphologic remission proceeded to consolidation chemotherapy. One patient with underlying congenital heart disease (CHD) developed florid CHF and pulmonary hemorrhage during induction 1. Remission was demonstrated by bone marrow aspiration after induction 1, and the family chose to discontinue AML treatment. The patient underwent mitral valve replacement and remained in first remission 4 years later without additional chemotherapy.

Three patients experienced AML relapse, one on therapy and two within 9 months of therapy completion; all had the M7 morphology. Two died as a result of disease, and one died as a result of complications after an off-protocol allogeneic bone marrow transplantation, which was performed during second remission. One patient developed B-progenitor acute lymphoblastic leukemia (ALL) 8 months after completion of AML therapy. At last follow-up, both leukemias remained in first remission more than 3 years after completion of ALL therapy. The estimated 5-year DFS probability for the DS-AML cohort was $81.8\% \pm 4.5\%$.

Outcomes Stratified by Age

For the DS-AML group, the 5-year EFS and OS probabilities were 76.9% and 78.6%, respectively. These outcomes were significantly better than those of the non-DS–non-M7 group (5-year EFS, 37.9%; 5-year OS, 51.9%; $P < .001$) and of the non-DS–M7 group (5-year EFS, 34.7%; 5-year OS 36.3%; $P < .001$; Fig 1). In the POG 9421 DS-AML cohort, the oldest patient was 40 months of age at diagnosis. Outcomes were similar for children age 2 years or younger at diagnosis and those age 2 to 4 years (Table 3).

Treatment-Related Mortality

Eight deaths occurred that were not related to leukemia. Two deaths during induction (meningococcemia, TOF spell) were described above. Two patients died after becoming neutropenic after consolidation 2. One died as a result of respiratory syncytial virus pneumonia. The second developed pulmonary edema with diminished fractional shortening by echocardiogram during admission for febrile neutropenia; 10 days after admission, she suffered a cardiopulmonary arrest. No infectious agent was identified, and autopsy revealed global, severe, dilated cardiomyopathy. Four deaths occurred after the completion of therapy, two were a result of CHF. One child had a partially repaired atrioventricular canal defect with residual mitral regurgitation and was taking furosemide and enalapril at baseline with adequate prechemotherapy cardiac function (FS 39%). Three months after completion of AML therapy, the patient presented in shock after a viral upper respiratory infection. All cultures were negative, and echocardiogram revealed FS 14% before her death. The second child had a moderate ventricular septal defect (VSD) with normal function and required no cardiac medications during therapy for AML. One day after completing therapy, she developed head and neck swelling. Echocardiogram demonstrated brachiocephalic venous thrombosis and dilated cardiomyopathy. She was treated aggressively with diuretics, cardiac inotropes, and afterload reduction but ultimately died 4 years later of recalcitrant cardiomyopathy. Two other off-therapy deaths were not related definitively to cardiac factors. One child presented in cardiopulmonary arrest 2 months after completion of therapy for AML and was pronounced dead on arrival. The second child died as a result of a respiratory illness 6 months after the completion of therapy. Postmortem examinations were not performed in either case.

Prospectively gathered toxicity data revealed few differences between the DS-AML group and either the non-DS–AML group overall or the subgroup of patients without DS who were treated with identical therapy to that given to the DS-AML cohort (standard arm). Patients in the DS-AML group were twice as likely to have grade 3 or higher stomatitis. However, grade 3 or higher bacterial infections were experienced by 35% to 40% of patients in all groups. The rate of death as a result of toxicity during induction therapy was not significantly higher for patients with DS-AML (two of 57; 3.5%) compared with those without DS (14 of 560; 2.5%; $P = 1$).

Cardiomyopathy

Twenty-four patients (42%) with DS-AML had documented CHD; eight had VSDs; nine had atrial septal defects (ASDs); two had TOF; three had common atrioventricular canal defects; one had an ASD and VSD; and one had a bicuspid aortic valve. Most patients had either surgically repaired defects or asymptomatic ASD or VSD with normal function. As discussed above, there were two early cardiac events related to CHD. Two other children with CHD experienced pulmonary edema during therapy that responded to diuretics, and both survived without cardiac sequelae.

Clinically symptomatic cardiomyopathy developed in 10 patients (17.5%) with DS-AML (Table 4). All received full-dose therapy (daunorubicine 135 mg/m² and mitoxantrone 80

mg/m²) or infant dose adjustment as prescribed. Five of these 10 patients had CHD, though only one required cardiac medications at baseline. Nine presented with symptoms either while on therapy or within 6 months of therapy completion. Three children died as a result of cardiomyopathy; all of these had CHD, although one had only a functionally insignificant ASD.

Discussion

Ravindranath et al³ first reported the excellent outcome for patients with DS-AML in a group of 12 children on POG 8498 who were treated with high-dose cytarabine. Results from POG 9421 are comparable to those of other contemporary cooperative group trials (Table 5). Data from Children's Cancer Group (CCG) 2891 suggested that outcomes are worse with increasing age at diagnosis of DS-AML, particularly for children older than 4 years.²⁰ Other cooperative group studies have not found a difference in outcome among patients younger than 4 years at diagnosis.^{5,6} In CCG/Children's Oncology Group (COG) 2971, a protocol with therapy similar to CCG 2891, there was a negative impact of increasing age for those patients older than 4 years, with fewer adverse events in the 2- to 4-year-old group than was seen on CCG 2891.²¹ On POG 9421, no patient was older than 40 months, and the analysis that compared outcomes for children 2 years of age or younger with those who were 2 to 4 years old did not reveal any significant differences.

Although patients with DS-AML have significantly better DFS than those with non-DS-AML, they also have increased treatment-related toxicity with intensive regimens.^{4,6,7} On POG 9421, prospectively gathered toxicity data did not reveal excess toxicity, including infection, in the DS-AML group. However, retrospective chart review identified a substantial incidence of early-onset cardiomyopathy. Anthracycline-associated cardiomyopathy results from oxygen free-radical damage and cardiac myocyte loss through apoptosis.²² Patients who develop early-onset symptoms (within 1 year of treatment) are at the greatest risk for chronic cardiac dysfunction.²² Risk factors for anthracycline-associated cardiomyopathy include higher cumulative dose (> 300 mg/m²), female sex, age younger than 4 years, and radiotherapy.²³⁻²⁵ In addition, Krischer et al¹¹ found that trisomy 21 itself imparted a 3.4-fold relative risk for clinical cardiotoxicity. An increased risk of anthracycline-related cardiomyopathy in patients with DS may, in part, be caused by gene dosage effects of genes located on chromosome 21, including carbonyl reductase, which reduces anthracyclines to metabolites implicated in cardiotoxicity, and superoxide dismutase, which increases lipid peroxidation and hypersensitivity to oxidative stress.²⁶

CHD occurs in 45% of children with DS.²⁷ In this cohort, we did not find a significant relationship between age or presence of underlying CHD and the risk of cardiomyopathy. Although five of the 10 patients with symptomatic cardiomyopathy had CHD, 16 patients with CHD who survived long-term (ie, without AML relapse or death as a result of infection) did not develop cardiomyopathy, and five of the 10 patients with symptomatic cardiomyopathy did not have CHD. It is notable, however, that the three cardiomyopathy-related deaths occurred in children with CHD, which suggests that they had an impaired ability to tolerate a substantial decrement in cardiac function.

Cardiomyopathy has been reported infrequently in prior DS-AML studies. None was reported in the 12 patients with DS-AML treated on POG 8948 (daunorubicin 135 mg/m²), though five (15%) of 34 patients with DS-AML who were treated on POG 8821 (daunorubicin 350 mg/m²) developed cardiomyopathy (Y. Ravindranath, personal communication, June 2007).²⁸ In contrast, no difference on CCG-2891 was reported in cardiomyopathy rates between children with or without DS (1% v 2%) who received standard-timing induction therapy (daunorubicin 350 mg/m²).⁴ Among patients with DS-

AML treated on the Berlin-Frankfurt-Munster (BFM)-93 and BFM-98 protocols with anthracycline doses of 220 to 240 mg/m², 2.7% developed early-onset cardiomyopathy. Late cardiomyopathy occurred in 2 (4%) of 69 patients, which suggests that this anthracycline dose generally is tolerable in patients with DS-AML.²⁹ On POG 9421, cumulative anthracycline exposure was substantial (535 mg/m² using a 5:1 conversion for mitoxantrone).³⁰ This dose, coupled with increased host sensitivity to oxidative stress, likely accounts for the striking incidence of cardiomyopathy.

Interestingly, cardiomyopathy was only rarely reported in the POG 9421 prospectively gathered toxicity data (ie, two patient cases [1%] with grade 3 or greater cardiac function toxicity), and the true incidence became evident only on focused retrospective chart review. This reporting bias raises the question of whether the anthracycline doses on other DS-AML protocols are actually safe or if this toxicity has not been adequately captured previously. One might also expect the incidence of cardiomyopathy to be high for the POG 9421 non-DS cohort at this anthracycline dose. Prospective toxicity data identified only six (1.1%) of 560 patients with non-DS-AML who suffered cardiac function toxicity; however, this may also be an underestimate.

Given the superior DFS for patients with DS-AML, there has been a trend toward developing protocols with lower-intensity regimens to minimize toxicity without sacrificing leukemia control, including treatment strategies without anthracyclines and with low-dose cytarabine. On POG 9421, one patient received only induction 1 therapy and experienced long-term remission, which suggests that a subset of patients may require minimal therapy. In a Canadian cohort of 18 patients with DS-AML, the EFS probability was 67% for patients treated only with low-dose cytarabine, which suggests that a large proportion of patients have exquisitely sensitive disease and can be cured with lower-intensity therapy, whereas a subgroup of as yet clinically indistinguishable patients require more intensive therapy.¹⁸ The high rate of cardiomyopathy on POG 9421 and the excellent EFS of patients with AML who were administered a BFM-98 protocol that provided only a 220 mg/m² cumulative dose of anthracycline clearly support attempts to decrease anthracycline exposure for patients with DS-AML.⁵ The recently opened COG AAML0431 protocol includes daunorubicin 240 mg/m² with no mitoxantrone for children with DS-AML who are younger than 4 years at diagnosis.

Ultimately, the safe anthracycline dose for patients with DS-AML remains unknown. Given the increased sensitivity and incidence of CHD in these patients, attention to cardiac function and long-term follow-up are crucial components of DS-AML management. Patients with DS-AML may be an ideal population for prospective studies of anthracycline toxicity, including the roles of cardiac monitoring, wall stress studies, and serum troponin measurements, as well as early initiation of afterload reduction for patients with asymptomatic decrease in cardiac function. Moreover, research into the biology of DS-AML and identification of adverse features is essential to the prospective identification of those patients at risk for treatment failure and therefore in need of aggressive therapy.

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Fig 1. Overall survival probability for patients with Down syndrome (DS) and acute myeloid leukemia (AML; DS-AML), patients without DS with non-French-American-British (FAB) M7 AML (non-DS M7 AML), and patients without DS with non-M7 AML (non-DS non-M7 AML).

Table 1

Patient Characteristics

Characteristic	AML Subgroup					
	DS			Non-DS		
	No.	%	No.	%	No.	%
Total No. of patients	57		516		49	
Ethnicity						
White	36	63	338	65.5	23	47
African American	8	14	70	13.5	11	23
Hispanic	7	12	76	15	10	20
Other	6	11	32	6	5	10
Sex						
Male	29	51	269	52	29	59
Female	28	49	247	48	20	41
Age at diagnosis, years						
<2	38	67	92	18	26	53
2	19	33	424	82	23	47
Initial WBC count, $\times 10^9/L$						
<15	46	81	202	39	27	55
15-24	3	5	58	11	9	19
25-49	6	10.5	68	13	7	14
50	2	3.5	188	37	6	12
FAB subtype						
M0	4	7	25	5		
M1	3	5	102	19.5		
M2	0		148	28.5		
M4	1	2	91	18		

AML Subgroup									
Characteristic	DS				Non-DS				P (DS v non-DS)
	No.		%		No.		%		
M5	1	2	113	22					
M6	1	2	8	1.5					
M7	45	79			49	100			<.001
Other	2	3	24	4.5					
Granulocytic sarcoma	3*	5	5	1					

Abbreviations: AML, acute myeloid leukemia; DS, Down syndrome; WBC, white blood cell; FAB, French-American-British.

* Included in FAB M7 subgroup.

Table 2

Response to Induction Therapy

Measure	AML Subgroup					
	DS			Non-DS		
	No.	%	No.	%	No.	%
Total No. of patients	57		516		49	
No. of patients assessable	57	100	512	99	48	98
Induction response						
No response	1	1.8	41	8	4	8.3
Early death	2	3.5	14	2.7	0	0
Remission	54	94.7	457	89.3	44	91.7
M1*	52	96	436	95.4	39	89
M2a†	2	4	21	4.6	5	11

Abbreviations: AML, acute myeloid leukemia; DS, Down syndrome.

* M1 response indicates less than 5% bone marrow blasts.

† M2a response indicates 5% to 15% bone marrow blasts.

Table 3
Outcome Based on Age at Diagnosis Among Patients With DS-AML

Measure	DS-AML Group Stratified by Age at Diagnosis (years)									
	1		> 1-2		> 2-3		> 3-4		> 4	
	No.	%	No.	%	No.	%	No.	%	No.	%
Total No. of patients	8	14	30	53	16	28	3	5		
FAB M7 subtype	7	87.5	24	80	12	75	2	67		
Induction response										
Remission	8	100	29	97	15	94	2	67		
Treatment failure	0		0		1		0			
Death caused by toxicity	0		1		0		1			
AML relapse	0		2		1		0			
Death unrelated to AML during remission	1		4		1		0			
5-year survival probability*										
Event-free				75.8				78.3		
SE				8.1				9.8		
Overall				75.8				82.6		
SE				8.1				9.2		

Abbreviations: DS, Down syndrome; AML, acute myeloid leukemia; FAB, French-American-British.

* For calculations of survival, age subgroups were collapsed into two groups: those 2 years old at time of AML diagnosis and those age 2 to 4 years at diagnosis.

Table 4
Characteristics of 10 Patients With DS-AML and With Symptomatic Cardiomyopathy

Patient	Sex	Age at Diagnosis (months)	Type of Congenital Heart Disease	Pre-AML Cardiac Medications	Onset of Symptoms	Symptoms	Treatment	Outcome
1	M	13	ASD, normal function (FS 36%)	None	4 months off-therapy	Respiratory failure; shock	Intubation, pressors, enalapril	Alive
2	F	14	moderate VSD, mild RVH/TR, normal function	None	1 day off-therapy	Brachiocephalic venous thrombus; severe dilated cardiomyopathy	Furosemide, digoxin, enalapril, enoxaparin	Death
3	M	16	AV canal s/p repair with residual MR, normal function (FS 39%)	Furosemide, captopril	a) On-therapy; b) 3 months off-therapy	a) Pulmonary edema with transfusions; b) pulmonary edema, shock, FS 14%	a) Furosemide; b) attempted resuscitation	Death
4	M	19	ASD	None	3 months off-therapy	Pulmonary edema	Digoxin, enalapril, furosemide	Alive
5	F	26	ASD	None	On-therapy; post-consolidation II	Shock; dilated cardiomyopathy at autopsy	Attempted resuscitation	Death
6	M	13	None	None	2 years off-therapy	Not reported	Enalapril	Alive
7	F	20	None	None	5 months off-therapy	Pulmonary edema, failure to thrive; FS 15%	Acute treatment not reported, chronically on enalapril	Alive
8	M	23	None	None	a) 3 months off-therapy; b) 14 months off-therapy	a) Pulmonary edema; FS 24%; b) cardiogenic shock	Digoxin, furosemide, enalapril	Alive
9	F	26	None	None	End of therapy	FS 20%	Digoxin	Alive
10	F	31	None	None	2 months off-therapy	Shock, FS 15%	Intubation, pressors	Alive

Abbreviations: DS, Down syndrome; AML, acute myeloid leukemia; ASD, atrial septal defect; VSD, ventricular septal defect; RVH, right ventricular hypertrophy; TR, tricuspid regurgitation; AV, atrioventricular; s/p, status post; MR, mitral regurgitation; FS, fractional shortening.

Table 5
Outcomes and Cumulative Drug Doses on Contemporary DS-AML Trials

Protocol	No. of Patients	5-year EFS (%)	Relapse or Resistant Disease (%)	Death Unrelated to Leukemia (%)	Drugs Administered			
					Cytarabine (g/m ²)	Daunorubicin (mg/m ²)	Mitoxantrone (mg/m ²)	Etoposide (mg/m ²)
POG 8498 ³	12	100	0	0	40.7	135	0	3,000
POG 8821 ¹⁵	34	68	15	18	48.1	350	0	3,000
POG 9421 [*]	57	77	7	14	20.7	135	80	1,000
CCG-2891 ^{4†}	161	77	14	4	27.2	350	0	1,600
NOPHO-AML93 ¹⁶	41	83	12	5	49.6	150	30	1,600
AML-BFM98 ⁵	66	89	5	6	23-29	220	0	950
MRC AML10/12 ^{6, 17}	46	74	3	24	4.6-34.6	150-300	50-120	500-1,500
Canadian low-dose ¹⁸	18	67	33	NR	6.7	0	0	0
Japan ¹⁹	33	80	9	9	2.8-5.6	100-400	0	450-3,150

Abbreviations: DS, Down syndrome; AML, acute myeloid leukemia; EFS, event-free survival; POG, Pediatric Oncology Group; CCG, Children's Cancer Group; NOPHO, Nordic Society for Paediatric Haematology and Oncology; BFM, Berlin-Frankfurt-Munster; MRC, Medical Research Council; NR, not reported.

^{*} Current study.

[†] Standard-timing induction.