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Favorable Survival Maintained in Children Who Have Myeloid Leukemia Associated With Down Syndrome Using Reduced-Dose Chemotherapy on Children's Oncology Group Trial A2971:

A Report From the Children's Oncology Group

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Abstract

BACKGROUND—Children who are treated for myeloid leukemia associated with Down syndrome (DS) experience superior survival compared with children who have myeloid leukemia without DS. To maintain excellent outcomes while avoiding toxicity, the Children's Oncology Group (COG) conducted the phase 3 trial COG A2971, the first trial solely designed to provide uniform treatment of myeloid leukemia in North American children with DS. A2971 eliminated 2 induction drugs and 3 months of maintenance therapy from the standard-timing regimen of dexamethasone, cytarabine, 6-thioguanine, etoposide, and rubidomycin/daunomycin (DCTER) used in the previous study (Children's Cancer Group [CCG] 2891).

METHODS—COG A2971 was a multi-institutional, nonrandomized, clinical trial that enrolled 132 patients who had DS with either acute myeloid leukemia (n = 91) or myelodysplastic syndrome (n = 41).

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

A.D.S. performed research, participated in study design and data analysis, and wrote the article; A.S.G. designed the study, performed research and data analysis, and helped write the article; T.A.A. and R.B.G. participated in study design and data analysis and helped write the article; J.M.H., F.O.S., W.G.W., and R.A. contributed to study design, performed research and data analysis, and critically reviewed the article; T.W.L., L.H., D.B., J.T., and Y.R. performed research and reviewed the article.

RESULTS—The median follow-up was 4.8 years (range, 0.8–8.6 years), the median age at diagnosis was 1.7 years (range, 0.3–13.6 years), and the median white blood cell count was 6200/μL (range, 900–164,900/μL). The remission rate (92.7% ± 6%) was similar to that reported in the CCG 2891 study (91.3% ± 5%; *P* = .679). The 5-year event free survival (EFS) rate was 79% ± 7% (vs 77% ± 7% in CCG 2891; *P* = .589), the disease-free survival (DFS) rate was 89% ± 6% (vs 85% ± 6% in CCG 2891; *P* = .337), and the overall survival rate was 84% ± 6% (vs 79% ± 7% in CCG 2891; *P* = .302). Induction day-14 bone marrow response trended toward a more favorable outcome (EFS: *P* = .12). Age >4 years was an adverse risk factor (5-year EFS rate: 33% ± 38% for children aged >4 years [median, 8.5 years; n = 6] vs 81% ± 7% for children ages 0–4 years [median, 1.7 years; n = 126]; *P* = .001).

CONCLUSIONS—The COG A2971 trial reduced the chemotherapy dose and maintained survival to that achieved by the CCG 2891 trial in children who had myeloid leukemia associated with DS.

Keywords

myelodysplastic syndrome; myeloid leukemia; Down syndrome; Children's Oncology Group Trial A2971

INTRODUCTION

Children who have myeloid leukemia associated with Down syndrome (DS) exhibit unique differences in epidemiologic, clinical, and biologic patterns of disease compared with similar children who do not have DS.[1–6] Children with DS are especially vulnerable to the development of acute megakaryoblastic leukemia (AMkL), a subtype of acute myeloid leukemia (AML) that is rarely observed in the non-DS pediatric population and is typically associated with worse survival in children without DS.[7,8] Despite this increased susceptibility to AMkL, reports from sequential pediatric cooperative group trials consistently have demonstrated superior outcomes for children (aged <4 years) who have myeloid leukemia associated with DS (ML-DS) compared with other children who have AML.[4,5,9–13]

One recent study (Children's Cancer Group [CCG] 2891) conducted by the CCG highlighted the need to develop clinical trials that are specifically designed to meet the needs of North American children with ML-DS. The CCG 2891 trial demonstrated that children with ML-DS who received intensively timed cycles of combined dexa-methasone, cytarabine, 6-thioguanine, etoposide, and rubidomycin/daunomycin (DCTER) induction therapy had very high toxic death rates (32%).[14] In contrast, children with ML-DS who received standard-timing DCTER induction therapy had a toxic death rate of 11%, (*P* = .003), which was similar to that in children without DS. Overall, the study demonstrated better outcomes for children with ML-DS treated with standard-timing DCTER induction therapy, in contrast to the improved survival with the use of intensively timed DCTER induction in children without DS.

On the basis of these results, the Children's Oncology Group (COG) designed the clinical trial COG A2971 with an overall objective to reduce acute morbidity and mortality in children with ML-DS while maintaining or improving efficacy. The COG A2971 trial eliminated etoposide and dexamethasone from the CCG 2891 standard-timing DCTER induction regimen[15] and removed 3 months of systemic maintenance chemotherapy, leaving only 3 intrathecal (IT) doses of cytarabine as maintenance treatment. Because children with DS aged <2 years had better outcomes than the older cohorts of children (ages 2–4 years and aged >4 years) with ML-DS enrolled on CCG 2891, COG A2971 also sought to determine whether the prognostic impact of age was reproducible.[16]

MATERIALS AND METHODS

Study

COG A2971 was a prospective, multi-institutional, phase 3, clinical research study conducted by the COG. It was a nonrandomized trial that enrolled children with DS into 1 of 2 age-based subgroups: children with transient myeloproliferative disease (TMD)[17] and children with ML-DS. The purpose of this report is to describe the outcome for children with ML-DS.

Patients

Patients or their legal guardians provided informed consent, which was approved by local institutional review boards and complied with the Declaration of Helsinki. Eligible children included those with karyotype confirmation of a DS diagnosis and a pathologic diagnosis of either AML or myelodysplastic syndrome (MDS) that required treatment. AML and MDS were classified according to the French-American-British (FAB) criteria, which were the standard criteria used during the initiation of this study.[18–21] For this analysis, the definition of MDS was limited to ≤29% blasts in the bone marrow (BM) sample. For the purposes of this report, patients who had AML or MDS are referred to collectively to as myeloid leukemia of DS (ML-DS).[14] Pathologic and cytogenetic classifications were reported by participating institutions. This trial began before reports of an association between GATA binding protein 1 (GATA1) and ML-DS[3] and did not collect banked leukemia samples to determine mutation prevalence.

Children with a prior history of TMD, chloromas, or central nervous system (CNS) disease were included in this study. Children who had promyelocytic leukemia or who had received prior treatment for ML-DS were not eligible. Children who had MDS that did not require chemotherapeutic intervention (defined as refractory anemia, refractory anemia with ringed sideroblasts with mild cytopenias, or mild primary cytopenias without dysplasia) were enrolled on study and observed until the investigators believed therapy was indicated clinically; then, they were assigned to the treatment arm.

Eligibility for the TMD arm was defined as age <3 months with pathologic evidence of nonerythroid blasts documented in the peripheral blood or by biopsy of an affected organ. Infants with TMD were either observed with supportive care only or were provided brief intervention with exchange transfusion, leukopheresis, or low-dose cytarabine therapy. These infants were followed prospectively until TMD resolved, subsequent ML-DS developed, or the patient attained age 5 years. If patients with TMD were diagnosed subsequently with ML-DS, then they were transferred to the therapeutic arm for children with ML-DS and were included in this report. Patients with prior TMD were included whether or not they received TMD-directed chemotherapy. The diagnostic, therapeutic, and outcome data for children with TMD who did not develop ML-DS are reported separately.[17]

Treatment and Monitoring

Treatment consisted of 4 cycles of standard-timing induction therapy, 1 course of intensification therapy, and concluded with 3 additional doses of IT cytarabine injection divided over 3 weeks for maintenance therapy (Fig. 1). Chemotherapy for children aged <36 months was dosed per kilogram of body weight; children aged >36 months were dosed per meter squared of body surface area. Each cycle of oral 6-thioguanine was given with a continuous infusion of cytarabine and daunorubicin (CI-TAD). Induction therapy consisted of a 96-hour continuous infusion of cytarabine (200 mg/m^2 daily) and daunorubicin (20 mg/m^2 daily) combined with 4 once-daily doses of oral 6-thioguanine (100 mg/m^2) given on days 0 through 3. CI-TAD induction therapy did not include etoposide or dexamethasone.

Patients received standard-timing CI-TAD induction therapy, and they received each subsequent cycle when their absolute neutrophil count (ANC) was >1000/μL and their platelet count was >100,000/μL. The only exception to this rule was for patients who had >30% blasts on day 14 after the start of induction cycle 1; these patients were to proceed directly to cycle 2 before peripheral blood count recovery. An IT dose of cytarabine was administered on day 0 of each cycle of induction therapy. The IT cytarabine doses were age-dependent: 20 mg for ages 0 to 12 months, 30 mg for ages 13 to 24 months, 50 mg for ages 25 to 35 months, and 70 mg for age ≥36 months. Additional IT chemotherapy was given to children who had CNS disease.

BM response was assessed on day 14 of induction cycle 1. BM remission status was assessed after peripheral blood count recovery (approximately day 28 of each cycle) and at the end of induction cycles 1 and 4 (with the end of cycle 4 defined as the end of the induction phase of therapy). The postremission intensification phase of therapy consisted of 3-hour infusions of cytarabine 3000 mg/m^2 given every 12 hours on days 0 and 1 and on days 7 and 8 (8 total doses), and L-asparaginase 6000 U/m^2 given once intramuscularly on days 1 and 8. Afterward, patients went on to receive once-weekly IT doses of cytarabine for CNS consolidation for 3 weeks using the age-dependent dosing as described above. A final BM examination was performed with the last dose of IT chemotherapy.

Patients with ML-DS who transferred from the TMD arm may have previously received low-dose cytarabine intervention for symptomatic TMD disease (1 to 4 cycles of continuous infusion cytarabine; 1 cycle consisted of 3.33 mg/kg every 24 hours for 120 hours at 16.7 mg/kg per cycle).

Disease Response Criteria

Patients with AML were considered to be in complete remission (CR) when BM morphologic evaluation demonstrated <5% blasts (M1) with adequate peripheral blood count recovery (ANC >1000/μL and platelet count ≥75,000/μL). A partial response (PR) was defined as 5% to 29% blasts (or 5%-39% blasts in BM with severe hypo-cellularity). Patients who had AML with >5% BM blasts at the end of 4 cycles of CI-TAD therapy were considered to have refractory disease and were removed from the study.

BM response was assessed in patients with MDS at the end of the first cycle of induction therapy (approximately day 28). For study purposes, a CR was defined as <5% BM blasts with trilineage engraftment and improved peripheral blood counts (M1). A PR was defined as a reduction in the BM blast count with an improvement in cytopenias (M2). Persistent dysplasia and Auer rods were acceptable. Patients with MDS and M2 BM samples at the end of cycle 1 were allowed to proceed to cycle 2 without peripheral blood count recovery. Treatment failure (progressive disease) was defined as an increase in the BM blast count and/or persistent peripheral cytopenias (ie, no improvement or worsening). Patients with MDS were required to be in CR by the end of all 4 cycles of induction therapy.

Statistical Considerations

The primary objective of this study was to evaluate the efficacy of reduced-dose chemotherapy for DS patients diagnosed with ML-DS compared with similar DS patients enrolled on the prior CCG 2891 study. The significance of observed differences in proportions was tested using the chi-square test and the Fisher exact test when data were sparse. For continuous data, the Mann-Whitney test was used to compare the medians of skewed distributions. The Kaplan-Meier method was used to calculate estimates of overall survival (OS), event-free survival (EFS), and disease-free survival (DFS). Estimates are

reported with their Greenwood standard errors. Differences in these estimates were tested for significance using the log-rank statistic.

OS was defined as the time from entry onto the ML-DS arm to death. EFS was defined as the time from study enrollment to BM relapse, progressive disease, or death. DFS was defined as the time from the end of induction (for patients with CR or a PR) to the time of relapse or death. Relapse-free-survival (RFS) (or the cumulative incidence of relapse) was measured as the time from induction remission (at the end of induction cycle 4) to BM relapse or death from progressive disease. RFS was calculated using the competing-risk method, in which deaths from nonprogressive disease were considered competing events. The cumulative incidence of toxicity-related mortality (TRM), measured as the time from the end of induction and/or from study entry to death from nonprogressive disease, was calculated by considering relapses and deaths from progressive disease as competing events. The Gray *P* value was used for reported *P* values for cumulative incidence analyses. Children who were lost to follow-up were censored at their date of last known contact or at a cutoff of 6 months before July 7, 2008.

RESULTS

Patient Characteristics

The COG A2971 trial enrolled 132 patients with DS and AML (n = 91) or MDS (n = 41) from 98 participating COG institutions between 1999 and 2003. This included 18 children who were enrolled initially on the TMD arm, all of whom had prior resolution of their TMD before they developed ML-DS. Two patients with prior TMD required intervention with low-dose cytarabine therapy. Eighty-five percent of the children with DS were enrolled initially with de novo ML-DS. Institutions reported that 39 patients in this de novo ML-DS group had a prior history of TMD but had not been enrolled on the TMD arm. The median length of follow-up in all patients was 4.8 years (range, 0.8–8.6 years).

The demographic characteristics of the patients with ML-DS on COG A2971 are summarized in Table 1 and are comparable to those in the historic control group on the CCG 2891 trial. The median age at diagnosis was 1.7 years (range, 0.3–13.6 years), including 85 patients who were aged <2 years (birth to 2-year age group), 41 patients were between ages 2 years and 4 years (2 to 4-year age group), and 6 patients were aged >4 years (>4-year age group). In the COG A2971 study, there were statistically significant, smaller percentages of children with hepatomegaly (33.6% vs 50.9% on CCG 2891; $P = .003$) and/or splenomegaly (29% vs 49.1% on CCG 2891; $P = .001$).

Among the 18 children who were previously enrolled on the TMD arm, in which a set screening schedule was used, the median age at diagnosis of subsequent ML-DS was significantly younger than among the 39 children with a history of TMD who were not enrolled on the TMD arm (median age, 1.2 years vs 1.9 years; $P = .005$) or among the 75 children with de novo ML-DS who had no prior history of TMD (median age, 1.2 years vs 1.7 years; $P = .015$). The entire cohort of 57 children who had a reported antecedent history of TMD had clinical and disease characteristics similar to those of the children with DS of similar ages without a reported history of TMD ($P > .05$) and, thus, described together.

Table 2 summarizes the disease-related characteristics of the children in our study compared with the children enrolled on CCG 2891. Approximately 33% of the patients with AML in each group presented with a prior history of MDS (31% vs 25%, respectively; $P = .289$). Institutional FAB classification identified a lower than expected M7 prevalence and a higher than previously reported MDS prevalence, and many may have had M7 disease with low

blast percentages. Unlike the 4.3% of children with CNS disease enrolled on CCG 2891, none of the children on COG A2971 had CNS disease at diagnosis or relapse (*P* = .018).

Toxicity

Toxicities were similar to the prior study (Table 3). Children with ML-DS on A2971 received a cumulative anthracycline dose of 320 mg/m^2 with no excess cardiac toxicity detected (nonsignificant *P* value compared with CCG 2891). The relatively higher percentages of nonhematologic toxicities observed during induction and intensification on COG A2971 were not different from those observed on CCG 2891. The high proportion of patients with pulmonary toxicity on COG A2971 is consistent with the finding from the CCG 2891 study[16] and was most prevalent during the first 2 cycles of induction therapy. Only 1 postremission death was reported on the COG A2971 study (vs n = 4 on CCG 2891; nonsignificant *P* value). This child with ML-DS died on day 11 of intensification therapy (at the end of high-dose cytarabine therapy) from neutropenic fever, pseudomembranous colitis, hyponatremia, and gastrointestinal hemorrhage.

Induction Response

Remission was evaluable in 108 of the 132 study participants. Twenty-four patients were not evaluable for induction response, including 1 patient who withdrew before the third cycle of induction therapy because of toxicity, 1 patient who died of disease, 2 patients who did not have data submitted, and 20 patients who were not evaluable because of failure to obtain a BM sample at the end of the 4 cycles of induction therapy. CRs were achieved in 84% of patients, and PRs were achieved in 8% of patients. Most of the children (74%) with DS (, 82% of the patients with ML-DS who had a history of TMD but who had not birth to 4-year age group) had a good response (<5% blasts on morphologic evaluation) by day 14 of the first cycle of induction therapy (n = 77 of 104 evaluable patients) (Fig. 2). Similar to CCG 2891, only 6.4% of patients developed progressive ML-DS (*P* = .955). There were no statistically significant age-related differences between the CR rates in children aged ≤4 years (n = 89) and children aged >4 years (n = 6; *P* = .498). All 18 children who had previously enrolled on the TMD arm achieved CR by the end of induction therapy, including the 2 patients with TMD who had received prior chemotherapy. However previously enrolled on the TMD arm (n = 39) achieved CR (*P* = .163). These remission rates were not statistically different from those in the patients without antecedent TMD.

Outcome

The 5-year survival rates (OS, 84% ± 6%; EFS, 79% ± 7%) from the time of enrollment among all treated patients were similar to those reported in the CCG 2891 study (OS, 79% ± 7%; EFS, 77% ± 7%; *P* > 0.3). The DFS rates from the time of induction remission were comparable between the 2 studies, with an 89% ± 6% 5-year DFS rate in the COG A2971 study and an 85% ± 6% 5-year DFS rate in the CCG 2891 study (*P* = .337). Among the children aged <4 years (Fig. 2), there was a trend toward better EFS among those who rapidly cleared their BM blasts at the day-14 BM examination (5-year EFS rate: 86% [<5% blasts; n = 77] vs 72% [≥5% blasts; n = 27]; *P* = .12).

The children who had ML-DS with antecedent TMD (n = 57) had survival outcomes similar to those of the children who had de novo ML-DS (n = 75; *P* = .814). The 8 children who had mosaic DS had the same outcome as the rest of the children who had fully expressed, constitutional trisomy 21.

Older age remained a statistically significant adverse risk factor, with a poor 5-year EFS rate of 33% ± 38% (n = 6) in children with ML-DS who were aged >4 years (median age, 8.5 years; range, 4.2–13.6 years). This is in contrast to the favorable 81% ± 7% 5-year EFS rate

observed in children with ML-DS who were aged ≤4 years (median age, 1.7 years; range, 0.3–3.8 years; n = 126; *P* = .001). These results are consistent with the poor 33% ± 31% EFS rate observed in children aged >4 years on the CCG 2891 study. The 5-year EFS rate for children aged <2 years on the COG A2971 study was 82% ± 9% (n = 85), which was comparable to the 86% ± 7% rate (n = 94) observed on the prior CCG 2891 study (*P* = .504). The EFS rate for children ages 2 to 4 years on COG A2971 was 80% ± 13% (n = 41) compared with 68% ± 12% (n = 58) in the CCG 2891 study (*P* = .227). Unlike CCG 2891, the COG A2971 study revealed no significant difference in EFS between children aged <2 years versus the slightly older children who were in the group ages 2 to 4 years (*P* = .726) (Fig. 3). COG A2971 age-based comparisons of EFS were similar to DFS probabilities (5-year DFS in the group aged <2 years [n = 72] vs the group ages 2–4 years [n = 26]; *P* = .73; 5-year DFS in the group ages 2–4 years vs the group aged >4 years [n = 3]; *P* < .001; and 5-year DFS in the group ages birth to 4 years vs the group aged >4 years; *P* < .001). There were no overall differences observed in the TRM rate from study entry between COG 2971 (3% ± 3%) and the CCG 2891 study (4% ± 3%; *P* = .747).

DISCUSSION

COG A2971 is the first clinical trial conducted by the Children's Oncology Group that was designed prospectively to meet the unique clinical and biologic manifestations of ML in children with DS. COG A2971 achieved a 5-year EFS rate of 79% ± 7% (vs 77% ± 7% in the CCG 2891 trial; *P* = .589) while maintaining a low induction failure rate of 6.4% ± 6%, attaining a 0% CNS relapse rate, and sustaining an acceptably low 5-year postremission, induction treatment-related mortality rate of 1% ± 2%, equivalent that reported in CCG 2891 (*P* = .789). The trend toward a more favorable outcome for the children who achieved an early BM response (<5% blasts by day 14) in this study is consistent with past reports from the BFM suggesting that clearance of morphologic blasts by day 14 or 15 in the nonacute promyelocytic leukemia population may predict better outcomes and suggests a possible therapeutic stratification point for children with DS in future research trials.[22]

The poor outcome of the children with ML-DS aged >4 years (EFS rate: 33% ± 39% in COG A2971, 33% ± 31% in CCG 2891; nonsignificant *P* value) has now been confirmed in 2 consecutive CCG/COG studies. Remission failures were the primary reason for the worse EFS in the historic control group.[16] Although the cumulative numbers of older children with ML-DS on these 2 trials is small (5% of each study group), these findings are supported by recent European trials.[4,23–26] The outcome in this older ML-DS cohort is similar to that observed in the pediatric AML population without DS. Whether this worse outcome in older ML-DS children compared with their younger peers is because of a difference in leukemic cell biology (eg, GATA1 mutations[27]) remains to be determined, because such information was not collected in this trial. Consequently, older children with DS appear to require the more dose-intensive treatment used in the children without DS.

The excellent outcomes maintained by COG A2971 for the majority of children aged <4 years with ML-DS suggest that further dose reduction may be feasible for this population. The primary reason for treatment failure is disease response, and not toxic mortality. Thus, the very poor outcomes for those who fail to enter remission or relapse indicate the need to pursue a risk-based therapeutic approach combining the presence or absence of the now known GATA-1 mutation in ML-DS and response, such as the day-14 and day-15 BM examination and/or the application of minimal residual disease assays currently used by COG in the non-DS AML trial, AAML1031. This may permit dose intensification or use of more targeted therapy in the "high-risk" DS children while maintaining or allowing further therapy reduction for the majority of children with DS.

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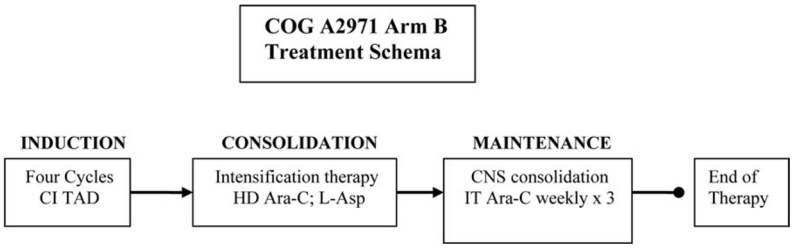
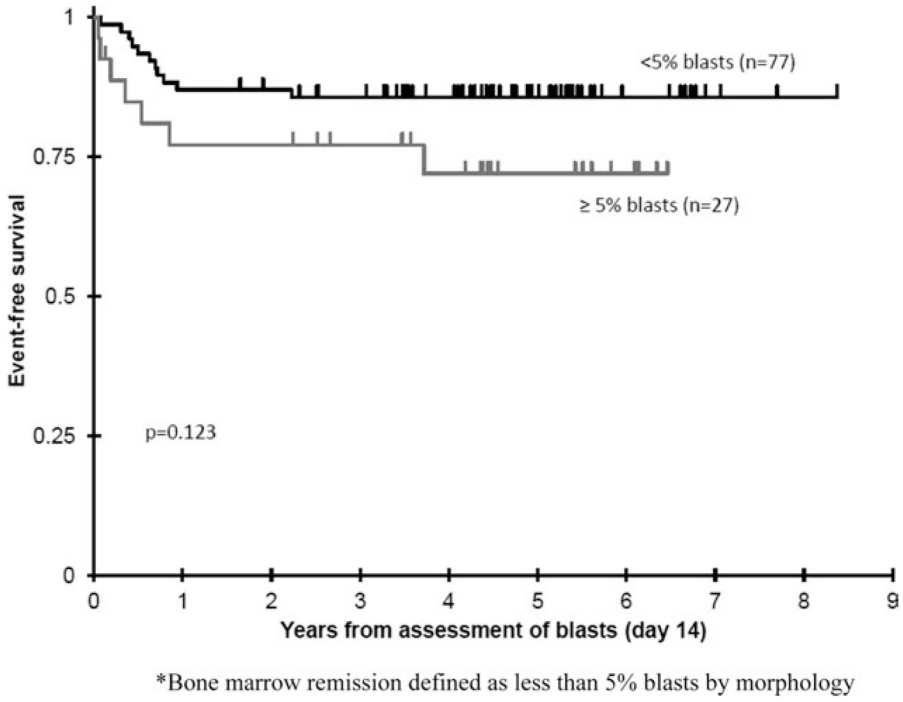


Figure 1.

Children's Oncology Group (COG) trial A2971 provided continuous-infusion cytarabine and daunorubicin plus oral 6-thioguanine (CI-TAD) therapy (according to the Regimen B treatment arm) to eligible children with Down syndrome and acute myeloid leukemia/myelodysplastic syndrome. One cycle of CI-TAD consisted of oral 6-thioguanine (T) at a dose of 50 mg/m^2 twice daily for 4 consecutive days with a 96-hour, continuous, intravenous infusion of cytarabine (A) 200 mg/m^2 for 24 hours and daunomycin (D) 20 mg/m^2 for 24 hours on days 0 through 3. Intensification therapy consisted of the Capizzi II regimen of high-dose cytarabine (HD Ara-C) 3000mg/m^2 per dose intravenously every 12 hours 4 times on days 0 and 1 and on days 7 and 8 and an intramuscular injection of L-asparaginase (L-Asp) 6000 IU/m^2 3 hours after the final dose of HD Ara-C on days 1 and 8. Central nervous system (CNS) consolidation consisted of 3 doses of intrathecal (IT) cytarabine therapy.



*Bone marrow remission defined as less than 5% blasts by morphology

Figure 2.

Early bone marrow response (induction day 14) and 5-year event-free survival are illustrated for young children (ages birth to 4 years) with Down syndrome and acute myeloid leukemia/ myelodysplastic syndrome.

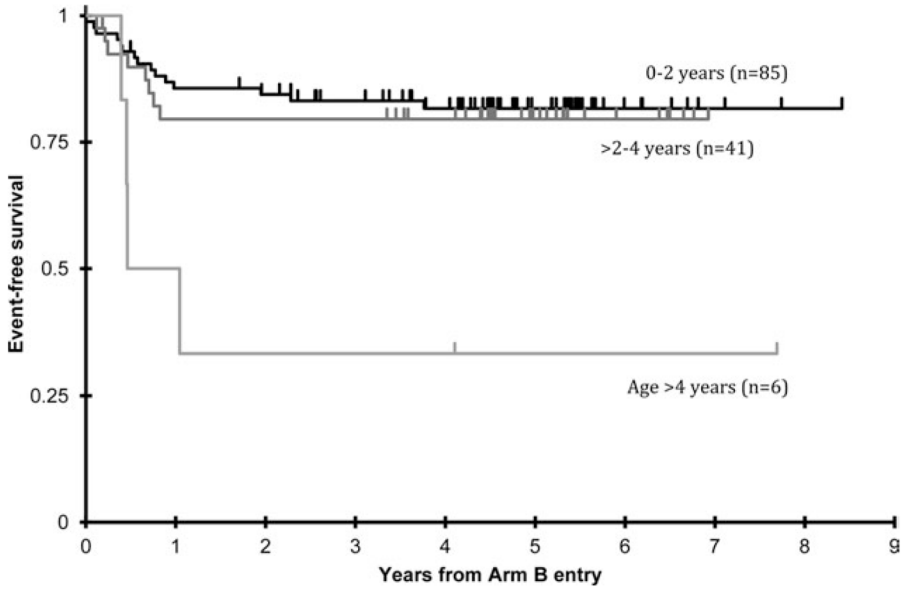


Figure 3.

Age-based event-free survival probabilities are illustrated for children with Down syndrome and acute myeloid leukemia/myelodysplastic syndrome who were treated on Children's Oncology Group Trial A2971 (COG A2971): Five-year event-free survival probability age comparisons are illustrated for children ages birth to 2 years versus children ages >2 to 4 years (P = .726), for children ages >2 to 4 years versus children aged >4 years (P = .010), and for children ages birth to 4 years versus children aged >4 years (P = .013).

Table 1

Clinical Characteristics of the Children's Oncology Group A2971 and the Children's Cancer Group 2891 Down Syndrome Cohorts

	No. of Patients (%)		
COG Study	**COG A2971**	**CCG 2891**[a]	***P***[b]
Accrual period	1999–2003	1989–1999	
Median follow-up [range], y	4.8 [0.8–8.6]	5.7 [0.2–12.6]	
No. with de novo AML/MDS enrolled on study	132	190[c]	
No. eligible and evaluable for study	132	161	
Patient characteristics[d]			
Median age at diagnosis [range], y	1.7 [0.3–13.6]	1.8 [0.1–15.5]	.093
Sex			
Male	68 (51.5)	77 (48)	.530
Female	64 (48.5)	84 (52)	
Age group, y			
Birth to 2	85 (64)	94 (58.3)	.294
>2 to 4	41 (31)	58 (36)	.371
>4	6 (4.5)	9 (5.6)	.686
Race			
White	91 (70)	93 (58)	.049
African American	17 (13.1)	26 (16)	.431
Hispanic	14 (10.8)	23 (14)	.345
Asian	6 (4.6)	8 (5)	.866
Other/unknown	4 (<1)	11 (7)	.142
Body size descriptors[e,f]			
BMI, kg/m^2			
High	13 (11.2)	27 (19.2)	.081
Normal	90 (77.6)	92 (65.3)	.030
Low	13 (11.2)	22 (15.6)	.307
BSA, m^2			
25th Percentile	0.42	0.42	
50th Percentile	0.46	0.47	.657
75th Percentile	0.52	0.53	
Total body weight, kg			.525
25th percentile	8.8	8.9	
50th percentile	10.1	10.4	
75th percentile	11.8	12.0	
Congestive heart failure	6 (4.6)	NA	
Hepatomegaly			.003
Not enlarged	87 (66.4)	79 (49.1)	
Enlarged	44 (33.6)	82 (50.9)	
Missing/unknown	1	0 (0)	

	No. of Patients (%)		
COG Study	**COG A2971**	**CCG 2891**[a]	***P***[b]
Splenomegaly			.001
Not enlarged	93 (71)	82 (50.9)	
Enlarged	38 (29)	79 (49.1)	
Missing/unknown	1	0 (0)	

Abbreviations: AML/MDS, acute myeloid leukemia/myelodysplastic syndrome; BMI, body mass index; BSA, body surface area; CCG, Children's Cancer Group; COG, Children's Oncology Group; NA, not ascertained.

[a] The CCG was incorporated into the COG in 2000.

[b] P values were obtained from chi-square tests (and Fisher exact tests for sparse data), and the Mann-Whitney test was used to determine differences between median values.

[c] Twenty-nine patients in CCG 2891 were excluded from analysis because they received treatment with intensive timing induction therapy or underwent bone marrow transplantation.

[d] Listed are characteristics at the time of enrollment.

[e] Children aged <1 year (n = 31) and those who were missing data for height and weight (n = 4) were excluded from the BMI analysis.

[f] BSA was adjusted for age, race, and sex.

Table 2

Disease Characteristics of Pediatric Patients With Down Syndrome and Acute Myeloid Leukemia/ Myelodysplastic Syndrome: Cohorts Treated on Successive Children's Oncology Group Trial A2971 and Children's Cancer Group Trial 2891[a]

	No. of Patients (%)		
Characteristic[b]	**COG A2971**	**CCG 2891**	***P***
Total evaluable no. who received chemotherapy	132 (100)	161 (100)	
History of prior MDS[a]	41 (31)	41 (25)	.289
History of prior TMD	57 (43.2)	NA[d]	
CNS disease	0 (0)	7 (4.3)	.018
WBC count: Median [range], $\times 10^3/\mu L$	6.2 [0.9–164.9]	6.8 [0.4–108.4]	.090
FAB subtype[e]			
M0	8 (6.4)	10 (6.4)	.992
M1/M2	20 (16)	12 (7.6)	.028
M4/M5	3 (2.4)	7 (4.5)	.520
M6	4 (3.2)	7 (4.5)	.760
M7	49 (39.2)	94 (59.9)	.001
MDS	41 (32.8)	27 (17.2)	.002
Unknown	7	4	
Down syndrome karyotype			
Normal/constitutional trisomy 21	118 (90.1)	NA[f]	
Trisomy 21 mosaicism	8 (6.1)		
Missing/unknown	6 (4.5)		
AML karyotype[g]			
High risk: 5q, –5, –7, 3q, t(6;9)	5 (9.1)	14 (17.7)	.210
Low risk: inv16, t(16;16), t(8;21)	3 (5.5)	0 (0)	.067
Intermediate-risk: All others	47 (85.5)	65 (82.3)	.625
Inadequate or unknown	77	82	

Abbreviations: AML, acute myeloid leukemia; CCG, Children's Cancer Group; CNS, central nervous system; COG, Children's Oncology Group; FAB, French-American-British classification system; Inv, inversion; MDS, myelodysplastic syndrome; NA, not ascertained; TMD, transient myeloproliferative disease; WBC, white blood cell.

[a] The CCG was incorporated into the COG in 2000.

[b] Listed are characteristics at the time of enrollment.

[c] P values were obtained from chi-square tests (and Fisher exact tests for sparse data), and Mann-Whitney tests were used to determine differences between median values.

[d] Previous history of TMD was not ascertained.

[e] Patients with FAB M3 disease (acute promyelocytic leukemia) were excluded from participation on A2971, and no patients with FAB M3 disease were enrolled on CCG 2891 (Bennett 1982, 1985[18,19]).

[f] Trisomy 21 karyotype data were not ascertained. Mosaicism was defined according to the International System for Human Genetic Nomenclature 1995.

[g] High-risk, low-risk, and intermediate-risk karyotype groups were defined according to the COG AML 0531 study (see Bennett 1991[20] and Vardiman 2002[21]).

Table 3

Toxicity Comparison Between the Children's Oncology Group Trial A2971 CI-TAD Regimen and the Children's Cancer Group Trial 2891 DCTER Regimen[a–c]

	No. of Patients (%)			
	Induction		Intensification[d]	
Grade ≥3 Nonhematologic Toxicity	**A2971 CI-TAD, 34 Cycles**	**CCG 2891 DCTER, 34 Cycles**	**A2971 HD Ara-C, L-Asp**	**HD Ara-C, L-Asp CCG 2891**
Total no. with available toxicity data	131 (100)	161 (100)	115 (100)	135 (100)
Any site[e–f]	79 (60)	54 (34)	61 (53)	33 (24)
Cardiac	5 (4)	3 (2)	2 (2)	1 (1)
Hepatic	13 (10)	8 (5)	2 (2)	1 (1)
Renal	0 (0)	4 (2)	0 (0)	1 (1)
Gastrointestinal	21 (16)	22 (14)	16 (14)	14 (10)
Stomatitis	9 (7)	9 (6)	11 (10)	13 (10)
Skin	4 (3)	4 (2)	5 (4)	5 (4)
CNS	0 (0)	1 (1)	0 (0)	1 (1)
Pulmonary	16 (12)	17 (11)	8 (7)	6 (4)
Toxic deaths	1 (1)	4 (2)	2 (2)	1 (1)
Median duration [range], d[e–f]	126 [33–184]	118 [10–196]	40 [7–133]	42 [16–91]

CI-TAD, 6-thioguanine plus continuous-infusion cytarabine and daunomycin; CNS, central nervous system; DCTER, oral dexamethasone and 6-thioguanine daily for 4 consecutive days combined with continuous-infusion cytarabine, daunomycin/rubidomycin, and etoposide over 96 hours; HD Ara-C, high-dose cytarabine; L-Asp, L-asparaginase.

[a] The CCG was incorporated into the COG in 2000.

[b] One cycle of CI-TAD consisted of oral 6-thioguanine (T) daily for 4 consecutive days combined with continuous infusion cytarabine (A) and daunomycin (D) over 96 hours.

[c] One cycle of DCTER consisted of oral dexamethasone (D) and 6-thioguanine (T) daily for 4 consecutive days combined with continuous-infusion cytarabine (C), daunomycin/rubidomycin (R), and etoposide (E) over 96 hours.

[d] The intensification regimen was combined HD Ara-C and L-Asp.

[e] There was a statistically significant difference (P <.05) between COG A2971 and CCG 2891 during induction.

[f] There was a statistically significant difference (P <.05) between COG A2971 and CCG 2891 during intensification.