

# Acute Myeloid Leukemia (AML) in Down's Syndrome Is Highly Responsive to Chemotherapy: Experience on Pediatric Oncology Group AML Study 8498

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The treatment of acute myeloid leukemia (AML) in children with Down's syndrome (DS) has engendered considerable controversy. Because of the concerns for toxicity and increased rate of infections, treatment approaches varied considerably in the past with mixed results. However, experience on the recently completed Pediatric Oncology Group (POG) 8498 AML study suggests that DS children with AML constitute a distinct subgroup that responds well to therapy. Twelve of 285 children on POG 8498 (protocol for newly diagnosed AML) had DS. Children with DS and AML were predominantly male (9 of 12) and were quite younger at diagnosis (<24 months in 10). The white blood cell count was less than  $50 \times 10^3/\mu\text{L}$  in all 12 and French-American-British types M6 and M7 were frequent (5 of 12). An abnormal cytogenetic marker, in addition to constitutional trisomy 21,

was present in 9 of 12 and involved chromosome 8 in 4 of 9. All cases studied ( $n = 5$ ) were positive for myeloid cell surface markers (CD33, CD13, or CD11b) and, interestingly, were also positive for the CD7 antigen. Chemotherapy included daunorubicin, cytarabine (Ara-C), and 6-thioguanine for remission induction and featured high-dose Ara-C ( $3 \text{ g/m}^2$  per dose) with or without L-asparaginase early in remission. Compared with children without DS, children with DS had a superior event-free survival (EFS at 4 years  $100\% \text{ v } 28\% \pm 6.2\%$ ;  $P = .003$ ). The EFS remained superior even when compared with non-DS children less than 2 years of age with a white blood cell count less than  $10 \times 100,000/\mu\text{L}$  ( $100\% \text{ v } 48\% \pm 17.3\%$ ;  $P = .01$ ).

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**T**HE OUTCOME of treatment for children with acute lymphoblastic leukemia (ALL) and Down's syndrome (DS) has been relatively favorable after treatment with intensive chemotherapy,<sup>1</sup> but therapy has been associated with moderate to severe toxicity. The prognosis for children with DS and acute myeloid leukemia (AML) has been thought to be poor, but this impression has been based on anecdotal experience and, perhaps, less than optimal therapy.<sup>2</sup> Psychosocial issues, the concern for increased toxicity from chemotherapy,<sup>3</sup> and the unique features of AML in children with DS (prior history of myelodysplastic syndrome [MDS], myelofibrosis, young age, and acute megakaryoblastic leukemia) may have prejudiced physicians against the use of intensive chemotherapy in these patients.<sup>2</sup> We retrospectively reviewed our recent experience of treating children with DS and AML on an intensive

Pediatric Oncology Group (POG) AML protocol to assess toxicity and outcome of treatment.<sup>4</sup>

This report describes clinical and laboratory features and outcome in 12 children with DS included in the recently completed POG 8498 AML study.<sup>5</sup>

## MATERIALS AND METHODS

Newly diagnosed, previously untreated patients less than 21 years of age with de novo or secondary AML were eligible for the POG 8498 study. Written informed consent was obtained according to institutional and Department of Health and Human Services (Bethesda, MD) guidelines before the initiation of therapy. The French-American-British (FAB) system<sup>6,7</sup> was used for morphologic classification except for a marrow blast percentage of 25% instead of 30%, as required in the FAB system. Morphologic classification and cytogenetic studies were performed at the treating institution. Cell surface marker studies were performed at the POG reference laboratory at Johns Hopkins University by methods previously described.<sup>8</sup>

The method of Kaplan-Meier was used to construct life tables<sup>9</sup> and the log rank  $\chi^2$  statistic was used to compare them.<sup>10</sup> When frequencies were sufficiently large, the classical  $\chi^2$  statistic was used to analyze contingency tables.<sup>11</sup> Otherwise, an exact test was used.<sup>12</sup>

**Treatment regimen.** This therapy has been previously reported.<sup>5</sup> Briefly, remission induction therapy consisted of 2 courses of daunorubicin, cytarabine (Ara-C), and 6-thioguanine (DAT). Post-remission therapy consisted of four sequential courses, each composed of (1) four doses of high-dose Ara-C (HdA;  $3 \text{ g/m}^2$ ) followed by L-asparaginase (L-Asp); (2) etoposide plus azacytidine; (3) POMP (6-mercaptopurine, vincristine, methylprednisolone, methotrexate [MTX]); (4) Ara-C daily 5 days by continuous infusion. Six doses of intrathecal (IT) Ara-C were administered for central nervous system (CNS) prophylaxis. In December 1986, the protocol was amended to substitute the second DAT induction course with six doses of HdA, and to give a single postinduction course of HdA (six doses) instead of the four sequential courses of HdA/L-Asp.

## RESULTS

**Patient characteristics.** The POG 8498 AML study was open from July 1984 to July 1989. There were 285 evaluable patients enrolled, of whom 12 patients (4.2%) had DS. The

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clinical and laboratory characteristics are summarized in Table 1 and compared with cases without DS in Table 2. Six of the DS children had congenital cardiac disease. Transient neonatal myeloproliferative syndrome was documented in one patient, nonimmune hydrops fetalis in one patient, and three others had a history of an MDS before the diagnosis of AML (Table 1). Most patients presented with mild organomegaly (8 of 12). White blood cell (WBC) counts ranged from 3.7 to 48.7 × 10<sup>3</sup>/μL. One patient had CNS leukemia at diagnosis compared with 47 of 273 non-DS patients with CNS involvement (26 with isolated CNS). DS children were predominantly male (3:1 v 1.2:1) and were younger at diagnosis (Table 2; 10 of 12 DS patients were <2 years of age, compared with 42 of 273 non-DS, *P* < .0001).

**Morphology, cytogenetics, and surface markers.** DS patients were more likely to have acute megakaryoblastic leukemia (M7) or acute erythroleukemia (M6) than other FAB types (50% v 3%; *P* < .00001). Three patients had less than 25% blasts in the marrow; all three had M7 leukemia and marrow was difficult to aspirate, contributing to the low estimates of percentage of blasts. In patients no. 3 and 12, diagnosis was confirmed by marrow biopsy. Patient no. 10 had nonimmune hydrops fetalis, which has been described in DS children in association with neonatal transient myeloproliferative syndrome (TMPS), and blasts with documented megakaryocytic markers.<sup>13-15</sup> Although this patient did not have TMPS as a neonate, peripheral blood karyotypes showed an abnormal clone (7% cells had +11, +21, +21); the abnormal clone disappeared by 3 months, only to reemerge 1 year later at the time of diagnosis of leukemia with additional marker chromosomes (Table 3).

Cytogenetic data are summarized in Table 3. Pretreatment marrow (leukemic blast) cytogenetic findings were not available on cases 3 and 12. Eight of the remaining 10 cases showed abnormal cytogenetic findings in the leukemic blast cells in addition to the constitutional trisomy 21

**Table 2. Comparison of DS Cases and Cases Without DS: POG 8498 AML Study**

	DS		Without DS		<i>P</i>
	N	%	N	%	
Total	12	4	273	96	—
Males	9	75	154	56	.2
Age < 2 yr	10	83	42	15	.0001
WBC < 100,000/μL	12	100	218	80	.13
EMD	2	17	67	24	.74
<b>Morphology</b>					
M1/M2	4	33	127	47	
M3	0	0	9	3	
M4/M5	1	8	115	42	
M6	2	17	1	0	< .0001
M7	5	42	6	2	
Unknown	0	0	15	6	
EFS at 3 yr	100%		33%		< .0003*

Data as of May 1991.

Abbreviation: EMD, extramedullary disease.

\*EFS remains significant when DS cases are compared with cases without DS and WBC less than 100,000/μL (*P* = .0004) and cases without DS, age less than 2 years, and WBC less than 100,000/μL (*P* = .01).

(Table 2). Three cases had trisomy 8, and three others had a fourth chromosome 21. Rare translocations [t(11q,21q), t(8;16)(q22;q24), and t(3;6) (q13;q21)] were found in three separate cases.

Immunologic cell surface marker studies were performed in 5 of 12 cases (Table 3). All expressed myeloid cell surface markers (CD33, CD13, and/or CD11b). Strikingly, all of the above cases were also positive for the CD7 antigen, more commonly associated with T-lymphoid lineage. This contrasts with an overall frequency of CD7 positivity of 19% in this study.<sup>16</sup>

**Toxicity.** The treatment regimen was relatively well tolerated. As expected from the ALL experience, most patients experienced mucositis with MTX administered during cycles of POMP, with 8 of 12 patients requiring dose

**Table 1. DS and AML: POG 8498 Study Clinical Features**

Patient No.	Sex	FAB Classification	Age (mo)	WBC (× 10 <sup>9</sup> /L)	BM Blasts (%)	CNS Leukemia	Organomegaly	MDS	CHD
1	M	M4/M5	17	4.50	43	—	—	—	+
2	M	M1/M2	22	3.70	32	—	L	*	—
3	M	M6	30	11.60	26	+	LS	—	—
4§	F	M7	11	6.20	21	—	—	—	—
5	M	M1	22	5.70	46	—	L	+	+
6	M	M2	19	11.80	32	—	K	—	—
7	M	M1	15	48.70	62	—	LS	—	—
8	M	M7	21	4.80	84	—	LSK	+	+
9	M	M6	16	22.70	60	—	—	—	+
10	F	M7†	14	13.20	21	—	LS	‡	—
11	M	M7	40	3.60	60	—	LS	—	—
12§	F	M7	16	8.90	9	—	—	+	+

Abbreviations: L, liver; S, spleen; K, kidney; CHD, congenital heart disease.

\*Neonatal myeloproliferative syndrome.

†M7 by morphology and cytochemistry, not confirmed by platelet markers or electron microscopy.

‡Nonimmune hydrops.

§Diagnosis confirmed by marrow biopsy.

**Table 3. DS and AML: POG 8498 Study Cytogenetics and Surface Markers**

Case No.	Fab Type	Mode	Cytogenetic Findings		Surface Markers
			Clonal Abnormalities		
1	M4/M5	47	t(11q;21q)*,10p+,16q-,+21		CD7,CD33,DR
2	M1/M2	47/48	+21/+8,+21		CD7,CD33,DR
3	M6	ND	—		
4	M7	47	+21		CD7,CD11b,CD4
5	M1	50	+11,+13,+21,+21,-12,+der(12),t(12;7)p12;7)		
6	M2	47	+21,t(8;16)(q22;q24)		CD7,CD33,CD34,CD56
7	M1	48/49	+8+21/+8,+14,+21		
8	M7	47/48	+21/+8,+21,+del(17)(q25),or del 5 (p11)		
9	M6	48	+21,+21/+21,+21,t(3;6)(q13;q21)		CD7,CD33,CD34,CD56
10	M7	53	XXX,+11,+13,+16,+19,+21,+21		
11	M7	47	+21		
12	M7	ND	—		

Abbreviation: ND, not determined.

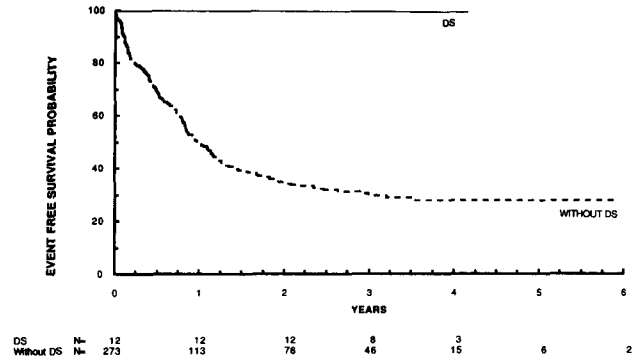
\*Exact break points of the chromosomes were not determined.

modification. There were no deaths during induction in DS children compared with a 6% (19 of 273) incidence in non-DS cases, but this difference was not significant ( $P = .47$ ). One patient was taken off study due to pancreatitis and pseudocyst after the HdA/L-Asp course, but remains in continuous remission to date with no further therapy. Preexisting congenital cardiac disease, present in 6 of 12 patients, did not appear to predispose these patients to anthracycline cardiac toxicity, but it should be pointed out that, in our treatment regimen, anthracyclines were used only during induction (total dose, 225 mg/m<sup>2</sup>) and follow-up time for late toxicity is limited. Neurotoxicity with HdA was not observed in any patient.

**Response data.** All patients with DS achieved remission after one cycle of DAT. Two children were taken off study after remission was achieved: one due to pancreatitis (see above) and another was switched to a “less intensive” postremission regimen of a prior POG study (POG 8101).<sup>8</sup> Both patients are included in this analysis. There have been no relapses to date. All patients with DS on this study are now off therapy for 27 to 60 months. The event-free survival (EFS) for these patients is 100%, compared with an EFS of 33% at 3 years for all children on this study ( $P = .0001$ ; Fig 1).

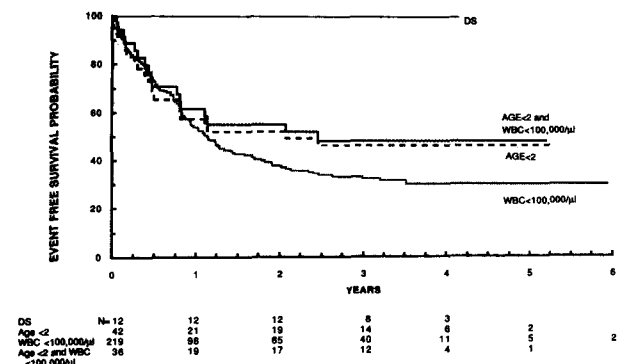
**DISCUSSION**

Children with DS are known to have an increased high risk of acute leukemia, including AML.<sup>17</sup> Retrospective reviews of AML in DS included a small number of patients and case reports. This series of 12 patients with DS and AML treated on an intensive AML protocol (POG 8498) represents the largest uniformly treated group of patients with DS and AML.



**Fig 1. POG 8498 AML study. EFS of children with DS compared with those without DS.**

The most important and unexpected finding in our study was the very good prognosis for children with DS and AML. The 3-year EFS for DS children was significantly superior to those without DS (100% v 33%;  $P = .0001$ ) (Fig 1). DS children in our study were predominantly younger, were more frequently male, had an initial WBC less than 100,000/ $\mu$ L, and had a disproportionately higher incidence of M6 and M7 subtypes of AML (Table 2). Several of these findings had been noted in prior studies.<sup>1,18</sup> Of these parameters, a low initial WBC (<100,000/ $\mu$ L) has been a favorable prognostic variable in some pediatric AML studies. Age less than 2 years at diagnosis was previously noted as a poor prognostic parameter,<sup>19,20</sup> but more recently was found to be either of no significance or, in fact, predicted for a good outcome.<sup>4,8,21</sup> In this POG 8498 study, children younger than 2 years of age (N = 52) had a 3-year EFS of 55%  $\pm$  10% compared with 27%  $\pm$  5% ( $P = .003$ ) for children older than 2 years of age (N = 233).<sup>5</sup> Excluding DS children, the 3-year EFS rates were 44%  $\pm$  12.5% and 27% for the two groups, respectively ( $P = .08$ ). The superior survival of DS children remained significant (Fig 2) even when compared with those (1) without DS and having a WBC less than 100,000/ $\mu$ L ( $P = .0004$ ); (2) without DS and less than 2 years of age ( $P = .013$ ); and (3) without DS, less than 2 years of age, and having a WBC less than 100,000/ $\mu$ L (EFS, 48%  $\pm$  17.3%;  $P = .01$ ). Thus, the differences in age and initial WBC do not fully explain the improved outcome in DS children. Likewise, the differences in the incidence of



**Fig 2. POG 8498 AML study. EFS of children with DS compared with those without DS and various prognostic subgroups.**

FAB subtypes also cannot explain the response differences because in the POG 8498 study, the FAB subtypes were not predictive of outcomes.<sup>5</sup> Prior experience with M7 AML and DS has not been favorable.<sup>22</sup> It is also interesting that a history of a prior MDS had no adverse effect on the outcome in this group of DS children.

Cytogenetic findings and surface marker studies have been reported sporadically in DS children with acute leukemia.<sup>23</sup> The cytogenetic abnormalities observed in our DS children with AML were not significantly different from AML cases without DS. Extra chromosomes 8 and/or 21 occur with a regular frequency in de novo AML.<sup>24</sup> Trisomy 8 in particular also occurs commonly in preleukemia syndromes (9.4% in the Second International Workshop survey).<sup>25</sup> The frequency of trisomy 8 in pediatric AML studies has varied from 1.7% (2 of 121) to 19.2% (5 of 26).<sup>26,27</sup> The t(8;16) translocation in case 6 involves the long arms of chromosomes 8 and 16 rather than the short arms, as in the more frequently found t(8;16) in monocytic leukemias with or without erythrophagocytosis. This case has been reported separately.<sup>28</sup>

Surface marker studies were performed in only 5 of 12 patients. The pattern of myeloid antigen positivity (CD33, CD13, and/or CD11b) was consistent with the diagnosis of AML, but the finding of CD7 positivity in all cases tested was unexpected. This high frequency of CD7 expression (5 of 5), more commonly associated with T-lymphoid lineage, in DS children contrasts with the approximate 20% incidence in a large cohort of childhood AML cases in this POG study<sup>16</sup> and is higher than the reported incidence of lymphoid marker expression in adult and pediatric AML (6% and 8%, respectively).<sup>29,30</sup>

Prior reports have indicated that induction response and survival rates in DS children with AML are the same as in those without DS.<sup>1,18</sup> The improved outcome noted by us is apparently not due to differences in clinical or laboratory characteristics alone, as DS patients included in prior reports are comparable to our series. All achieved remission with the first induction course (DAT) and all are alive and in remission (27 to 60+ months off therapy). Children without DS in this AML study had a remission induction rate of 85% and a 3-year EFS of 33%. These results are similar to those reported by several groups.<sup>8,19,20,21</sup> Recent retrospective reviews observed improved survival in DS children receiving intensive therapy compared with those receiving minimal treatment.<sup>1</sup> The postremission therapy in this study was intensive and emphasized early use of HdA.

That HdA may have contributed to the improved survival of DS children with AML is supported by the preliminary data cited by Lie.<sup>31</sup> The well-known intolerance for MTX in DS children may paradoxically confer a unique susceptibility of AML blast cells in these children to Ara-C. The increased sensitivity to MTX in DS children has been ascribed to the decreased intracellular pool of reduced folates,<sup>32</sup> a result of increased gene dosage of folate-dependent purine synthetic enzymes<sup>33</sup> and/or cystathionine synthase,<sup>34</sup> both assigned to chromosome 21.<sup>34,35</sup> Low levels of reduced folates may prime leukemic blast cells to Ara-C cytotoxic effects by allowing for a high Ara-C triphosphate (Ara-CTP) to deoxycytidine triphosphate (dCTP) ratio (and consequently greater incorporation of Ara-C into DNA), as can be induced by exposure of leukemic blast cells to MTX before Ara-C.<sup>36</sup> The POG investigators have recently shown that a higher Ara-CTP/dCTP ratio can be achieved in hematopoietic cells from children with ALL by MTX infusion before Ara-C.<sup>37</sup> This hypothesis could also explain the frequently noted superior response in AML cases with t(8;21)<sup>38-40</sup> in which the break in chromosome 21 occurs at q22 and can potentially result in increased expression of purine synthetic enzymes and cystathionine synthase now assigned to this region (21q22.3).<sup>41</sup> We were unable to do any direct comparisons of DS children treated on this study and those with t(8;21)(q22;22) as cytogenetic evaluation was not required for protocol entry and such information is not available retrospectively on all patients. It is of interest that protocols designed to modulate Ara-C metabolism in relapsed AML have shown some early success.<sup>42</sup> Regardless, the above hypothesis is speculative at this time, as no specific metabolic studies of Ara-C uptake in blast cells from DS children with AML or in AML children with t(8;21) have been performed to our knowledge.

Allogeneic bone marrow transplantation (BMT) in first remission of AML has been shown to be an effective alternative to chemotherapy in both children and young adults. Allogeneic BMT in DS children has engendered some controversy, but has been performed successfully.<sup>43,44</sup> While the number of patients in this study are small, the results are nonetheless intriguing, and question the role of allogeneic BMT for DS children with AML in first remission. Furthermore, our results suggest that less intensive Ara-C dose schedules should be explored for the treatment of AML in DS children.

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