Malignancy in Children with Trisomy 21

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Key Words. Down syndrome • Acute lymphoblastic leukemia • Acute megakaryoblastic leukemia • Myeloproliferative disorders • GATA1 transcription factor • Janus kinase 2

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Target audience: Physicians who wish to advance their current knowledge of clinical cancer medicine in pediatric oncology.

LEARNING OBJECTIVES
1. Evaluate malignancies for which children with Down syndrome are at increased and decreased risk in order to screen appropriately.
2. Analyze the clinical and biologic features of transient myeloproliferative disease and acute megakaryoblastic leukemia in children with DS.
3. Determine the clinical and biologic features of acute lymphoblastic leukemia in children with DS and outline treatment strategies.

ABSTRACT
Patients with Down syndrome (DS) display a unique spectrum of malignancies, with a 10- to 20-fold higher risk of acute leukemias, and a markedly lower incidence of solid tumors. This review discusses the current understanding of the basis for this distinctive pattern of cancer incidence and the clinical and biologic features of the malignant disorders most frequent in DS individuals: transient myeloproliferative disease, acute megakaryoblastic leukemia, and acute lymphoblastic leukemia. We also review distinctive pharmacogenetic issues, highlighting the differential chemosensitivity and toxicity profiles of DS patients compared with the general population, and epidemiologic studies of protective and adverse environmental risk factors for the development of leukemia. The Oncologist 2009;14:164–173

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INTRODUCTION
The spectrum of malignancies in patients with Down syndrome (DS) offers both insights and enigmas. Patients with DS exhibit a unique pattern of malignancies, yielding intriguing insights into cancer biology. These patients also pose distinctive challenges to the oncologist because of their particular profile of treatment-related toxicities. Patients with DS have a higher risk for leukemia, experiencing three distinct disease entities—transient myeloproliferative disorder (TMD), acute megakaryoblastic leukemia (AMKL), and acute lymphoblastic leukemia (ALL)—and have a lower risk for solid tumors. This review highlights the epidemiology of cancer in DS patients, the clinical features and biology of the leukemias that are most common in DS individuals, and the pharmacogenetic considerations specific to this population.

EPIDEMIOLOGY OF CANCER IN DS
DS results from trisomy 21 and occurs in approximately 1 in 1,000 births, a number that has decreased over the past several decades as a result of increased screening and termination of DS pregnancies [1]. Whereas the standardized incidence ratio of cancer in DS individuals does not differ significantly from that of the general population, the distribution of malignancies is strikingly different [2]. In a review of Danish registry data on 2,814 individuals with DS, leukemias constituted 60% of malignancies overall, and 97% of malignancies in patients <15 years of age. Solid tumors, in contrast, are markedly less frequent in DS individuals across all age groups, with the possible exception of retinoblastoma and germ cell tumors [2, 3].

While significant advances have occurred in the management of the diseases associated with DS, the median age at death remains considerably lower than that of the general population, reported as 49 years in a 1997 study [4]. The most frequent causes of death are nonmalignant. Nevertheless, leukemia remains a significant cause of death, particularly in DS children <10 years of age, who are more than three times more likely to have leukemia listed as a cause of death than are children without DS [4]. Death from malignancies other than leukemia is strikingly less common in patients of all ages [4].

The first report of leukemia in a DS patient occurred in 1930 [5], and the first systematic study was reported in 1957 [6]. Contemporary studies indicate that patients with DS have a 10- to 20-fold higher relative risk for leukemia, with a cumulative risk of 2% by age 5 and 2.7% by age 30 [2]. They constitute approximately 2% of all pediatric acute lymphoblastic leukemia (ALL) cases, and approximately 10% of pediatric AML cases. In addition to the higher frequency, leukemias in DS patients also differ in their clinical features, timing of occurrence, and response to therapy. Approximately 10% of DS infants exhibit an unusual myelodysplastic disorder known as TMD. TMD spontaneously regresses, but approximately 20% of these patients later develop AML. AML occurs at a considerably earlier age in DS individuals (median, 1.8 versus 7.5 years, and the majority <5 years of age) [7], whereas ALL shows a similar age distribution to that in children without DS [8]. Because of the disproportionate frequency of DS AML in children <5 years old, the overall ratio of AML to ALL is roughly equal in children with DS, whereas it is approximately 1:4 in children without DS. In DS children >5 years old, when the incidence of AML declines, the number of ALL cases and ratio of AML to ALL more closely resembles that of the general population. About 70%–85% of DS AML cases are acute megakaryocytic leukemia (AMKL), a rare subtype in patients without DS [7, 9]. The risk for AMKL in DS children is 500-fold higher [10]. Additional clinical and biological aspects of leukemias in DS patients are discussed below.

EPIDEMIOLOGIC RISK FACTORS FOR LEUKEMIA IN DS
Although much investigation in patients with DS has focused on the role of genetic factors related to trisomy 21 in the development of leukemia, another approach has been to examine the role of environmental exposures in triggering leukemogenesis in DS. There is some literature investigating environmental exposures associated with adverse or protective effects. Parental exposures investigated include alcohol intake [11], household chemical exposures [12], electromagnetic fields [13], reproductive history [14], and periconceptional vitamin supplementation [15]. Patient exposures include vitamin supplementation [16], ionizing radiation [17], and frequent early childhood infections [18]. The studies cited are retrospective case–control studies based on parental self-report, which will require confirmation using additional methodologies. Moreover, the magnitudes of the reported effect sizes are generally small, suggesting that as in leukemia in patients without DS, genetic or as yet unidentified environmental factors must also play a significant role.

PATHOGENESIS OF MALIGNANCIES IN DS
Why Are Leukemias More Common in DS?
There are an estimated 329 genes localized to the long arm of chromosome 21 [1], and several have been suggested as possible mediators of leukemogenesis through greater dosage effects. These include FPDM (the cause
of autosomal dominant familial platelet disorder), AML1, the interferon (IFN)-α/β receptor (IFNAR), cytokine family 2–4 (CRF2–4), and phosphoribosylglycinamid formyltransferase [19]. Alternatively, altered folate metabolism in patients with DS may contribute to leukemogenesis by changing methylation and rates of DNA mutation. Two lines of evidence suggest altered folate metabolism in DS individuals [20]. First, mothers of DS children have a higher incidence of polymorphisms associated with reduced activity of the methyltetrahydrofolate reductase (MTHFR) enzyme [21], and the resultant in utero folate deficiency occurring during these women’s pregnancies may be a risk factor for both DS and the development of ALL [22]. Second, a higher dosage of the cystathionine β-synthase (CBS) gene on chromosome 21 results in greater CBS expression, which also causes alterations in the folate pathway. Other possible explanations include a general increase in genetic instability caused by trisomy 21 facilitating the occurrence of leukemogenic mutations, and disomic homozygosity of a mutated tumor suppressor on chromosome 21 [20].

Why Are Solid Tumors Less Common in DS?
The basis for the lower incidence of solid tumors in DS individuals remains uncertain. In recent elegant work by Susan and colleagues, mouse models of DS were used to dissect out the protective effect of the DS genetic background against the development of intestinal tumors [23]. Ts65Dn mice, which are trisomic for mouse orthologues of about half the human chromosome 21 genes, were crossed to ApcMin mice, which are predisposed to develop intestinal tumors similar to those in familial adenomatous polyposis. The Ts65Dn–ApcMin mice developed significantly fewer intestinal tumors. Further transgenic crosses demonstrated that trisomy of just 33 orthologous genes was protective, and monosomy of those 33 genes led to more tumors. Additional studies pinpointed the ETS2 gene as largely responsible for both dosage effects, with a lower number of intestinal tumors occurring with a higher ETS2 dosage and a greater number occurring with a lower dosage. Copper-zinc superoxide dismutase (SOD) is also a candidate tumor suppressor gene because its location on chromosome 21 leads to a higher dosage.

Another protein implicated as protective against the development of solid tumors in DS individuals is endostatin, a cleavage product of collagen XVIII encoded by the COL18A1 gene on chromosome 21, which is present in the serum at higher levels in DS individuals [24]. Because endostatin has been shown to be a potent inhibitor of angiogenesis in many solid tumors, Zorick and colleagues hypothesized that the higher levels of endostatin in DS individuals may be responsible for the lower incidence of solid tumors. Finally, environmental factors may play a role, because DS individuals have a lower likelihood of tobacco and alcohol use and occupational carcinogen exposures.

**MYELOID DISORDERS IN DS**

**TMD**

**Clinical Presentation, Treatment, and Outcomes**
TMD is an intriguing disorder unique to DS, which occurs in approximately 10% of DS infants. Symptoms range from asymptomatic leukocytosis to massive organomegaly and fatal liver and/or respiratory failure. TMD is most often incidentally diagnosed in a well-appearing...
DS infant, although it can present with a clinical picture resembling leukemia, with expansion of a clonal population of blasts causing leukocytosis, hepatosplenomegaly, effusions, and liver fibrosis. It is also an occasional cause of stillbirth. TMD exhibits megakaryoblastic morphology and immunophenotype indistinguishable from those of AMKL (Fig. 1), but the natural history of TMD is one of spontaneous regression over several months. Mild cases do not require treatment, whereas symptomatic cases may require supportive care measures and occasionally chemotherapy. Although spontaneous regression occurs, about 20% of patients with TMD later develop true AMKL, generally by the age of 5 years.

In the largest prospective evaluation of TMD to date, Klusmann and colleagues reported on 146 children registered in AML-BFM group trials from 1993 to 2006 [25]. They reported a 5-year event-free survival (EFS) rate of 63% ± 4% and overall survival rate of 85% ± 3%. Early death occurred in 15% of patients and development of AMKL occurred in 23% of patients, similar to an earlier Pediatric Oncology Group (POG) study of 47 DS neonates with TMD [19]. Ascites and bleeding diathesis were associated with early death in both studies; additional risk factors in the AML-BFM study were leukocytosis, thrombocytopenia, cholestasis, or liver dysfunction. Among children at risk for early death, the 5-year EFS rate was greater in those receiving treatment than in untreated patients (52% ± 12% versus 28% ± 11%). An AML-BFM chemoprevention trial is currently under way in TMD patients, with low-dose cytarabine and minimal residual disease monitoring using GATA1s (see section on GATA1s and the pathogenesis of DS TMD and AMKL below), based on the hypothesis that eradication of the GATA1s clone may prevent the development of AMKL. Successful detection of GATA1 mutations using real-time quantitative polymerase chain reaction has been demonstrated, although it is complex because mutations are case specific [26].

### AML

#### Clinical Presentation, Treatment, and Outcomes

The clinical hallmarks of DS AML are the megakaryoblastic phenotype in the majority of cases (Fig. 1) and markedly superior outcomes compared with non-DS AML (Table 1). DS patients generally have a low initial WBC, no central nervous system (CNS) involvement, and fewer cytogenetic abnormalities than non-DS AML patients.

AMKL in DS patients is distinguished by an unusually favorable clinical prognosis, first recognized by the POG over a decade ago and confirmed by the Nordic Society for Pediatric Hematology and Oncology and the Children’s Cancer Group (CCG) [7, 27, 28]. The current EFS rate for DS AMKL patients is about 80%, whereas the EFS rate in

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**Table 1. EFS in cooperative group studies in DS AML**

<table>
<thead>
<tr>
<th>Study protocol (yrs)</th>
<th>n (DS)</th>
<th>EFS (DS)</th>
<th>EFS (non-DS)</th>
<th>Comments</th>
<th>Study</th>
</tr>
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<tbody>
<tr>
<td>AML-BFM 98 (1998–2003)</td>
<td>66</td>
<td>89% ± 4% (3-yr)</td>
<td>53% ± 2% (p = .0001)</td>
<td>Creutzig et al. [9]</td>
<td></td>
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<tr>
<td>CCG 2891 (1989–1999)</td>
<td>161</td>
<td>77% (6-yr)</td>
<td>33% (p &lt; .0001)</td>
<td>Gamis et al. [7]</td>
<td></td>
</tr>
<tr>
<td>Japan (1987–1997)</td>
<td>33</td>
<td>80% ± 7%</td>
<td>DS protocol</td>
<td>Kojima et al. [34]</td>
<td></td>
</tr>
<tr>
<td>Japan (2000–2004)</td>
<td>72</td>
<td>83.3% ± 9.1% (4-yr)</td>
<td>70/72 &lt; 4 yrs old</td>
<td>Kudo et al. [35]</td>
<td></td>
</tr>
<tr>
<td>MRC AML 10 (1987–1995)</td>
<td>23</td>
<td>70% ± 9.6% (5-yr)</td>
<td>59% ± 4.6% (p = .6)</td>
<td>OS, not EFS</td>
<td>Craze et al. [89]</td>
</tr>
<tr>
<td>NOPHO 93 (1993–2002)</td>
<td>37</td>
<td>81% ± 6% (5-yr)</td>
<td></td>
<td>Lie et al. [90]</td>
<td></td>
</tr>
<tr>
<td>POG 8498 (1984–1989)</td>
<td>12</td>
<td>100% (4-yr)</td>
<td>33% (p = .0001)</td>
<td>Ravindranath et al. [27]</td>
<td></td>
</tr>
<tr>
<td>POG 8821 (1988–1993)</td>
<td>27</td>
<td>77% ± 2.1% (3-yr)</td>
<td>34% ± 2.5%</td>
<td>Ravindranath et al. [91]</td>
<td></td>
</tr>
<tr>
<td>POG 9421 (1995–1999)</td>
<td>57</td>
<td>76.9% (5-yr)</td>
<td>51.9% (p &lt; .001)</td>
<td>O’Brien et al. [74]</td>
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<tr>
<td>Toronto (1990–2003)</td>
<td>18</td>
<td>67% ± 11% (5-yr)</td>
<td></td>
<td>Al-Ahmari et al. [36]</td>
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</table>

Abbreviations: AML, acute megakaryoblastic leukemia; BFM, Berlin-Frankfurt-Münster; CCG, Children’s Cancer Group; DS, Down syndrome; EFS, event-free survival; MRC, Medical Research Council; NOPHO, Nordic Society of Paediatric Haematology and Oncology; OS, overall survival; POG, Pediatric Oncology Group.
the rarer subgroup of non-DS AMKL patients is considerably worse than for other AML subtypes at 15%–20% [29]. Young age is an important positive prognostic factor in DS AML. The prognostic significance of age may be a result of biology, because nearly all DS AMKL occurs in children <5 years of age, and it is this AML subtype that has a favorable outcome. Virtually none of the few AML cases occurring in older DS children are AMKL, and they show no significant survival advantage [7].

Although DS AMKL patients generally fare better than other AML subgroups, they suffered greater treatment-related mortality on several intensive AML treatment regimens [30]. Intermediate-intensity therapy maximizes their chance of cure without undue toxicity [9, 31, 32]. The CCG AML Trial 2891 included randomization between standard and intensively timed chemotherapy. Children with DS had a higher toxic mortality rate with intensive timing (32%, versus 11% in the non-DS population) [33] and a lower postremission disease-free survival (DFS) rate when randomized to allogeneic bone marrow transplant (BMT) or autologous BMT, compared with chemotherapy, with DFS rates of 33%, 67%, and 89%, respectively [33]. The subsequent Children’s Oncology Group (COG) Trial A2971 therefore pursued dose reductions [30]. Recent Japanese protocols have eliminated CNS prophylaxis because of the rarity of CNS involvement in DS AML; the most recent protocol yielded a favorable 4-year EFS rate of 83% ± 9% and had no isolated CNS relapses [34, 35]. Finally, Al-Ahmari and colleagues in Toronto employed an “ultra-low” therapy in DS AMKL consisting of very-low-dose cytarabine (10 mg/m² per dose), vincristine, and retinyl palmitate, and found no significant difference in outcome compared with standard chemotherapy [36]. Although this study was small, retrospective, and nonrandomized, DS AMKL sensitivity to ultra-low-dose therapy merits further study.

Current DS AML protocols under way in Europe and the U.S. employ a similar theme of therapy reductions to decrease toxicities. The European BFM trial uses a standard BFM regimen with cytarabine and anthracycline dose reductions [37]. The U.S. trial, open only to DS children <4 years of age, features high-dose cytarabine, reduced anthracycline, and reduced intrathecal therapy. Both trials eliminate maintenance therapy, cranial irradiation, and stem cell transplantation.

GATA1s and the Pathogenesis of DS TMD and AMKL
A breakthrough in understanding TMD and AMKL occurred with the discovery that the hematopoietic transcription factor GATA1, on the X chromosome, is mutated in these disorders [38, 39]. GATA1 mutations are specific to DS TMD and AMKL [38]. The only instances of GATA1 mutations in patients without DS are in patients with acquired trisomy 21 in their hematopoietic progenitors, or in patients with constitutional mosaicism for trisomy 21.

GATA1 mutations are acquired and case specific, including insertions and deletions, and missense, nonsense, and splice site mutations. Nearly all occur in exon 2 and lead to production of a truncated protein of 40 kDa rather than 50 kDa, called GATA1short or GATA1s. Whereas complete deletion of GATA1 is embryonically lethal, GATA1s causes dysregulation of megakaryopoiesis. The GATA1 mutation present in TMD is generally the same as that associated with a given patient’s subsequent AMKL, although AMKL often exhibits additional cytogenetic abnormalities, suggesting that TMD is a preleukemic condition that originates in utero and subsequently evolves into AMKL via additional genetic events (see the section on cooperating genetic events below). Because TMD and AMKL appear to arise from the same clone, it has been proposed that they be classified as a single discrete entity, myeloid leukemia of Down syndrome, in the World Health Organization classification [40]. Additional evidence suggesting that GATA1 mutations arise in utero includes the detection of mutations in blood cells from neonatal screening cards [41] and in blasts from identical twins with acquired trisomy 21, presumably as a result of transfer of cells bearing the mutation from one twin to the other via shared circulation in utero [42].

Effects of GATA1 and GATA1s in Hematopoiesis
GATA1 regulates the maturation of megakaryocytes, erythroid cells, mast cells, and eosinophils. GATA1s promotes abnormal proliferation of megakaryocyte progenitor cells in the yolk sac and fetal liver [43]. A family carrying a germline mutation generating GATA1s provided a fortuitous demonstration that GATA1s is not leukemogenic in the absence of trisomy 21: mutation carriers had anemia, thrombocytopenia, and neutropenia but not leukemia [44]. GATA1s knock-in experiments in mouse models also indicate that the mutation alone is not sufficient to cause leukemia [43]. Some in vitro data suggest that GATA1 deficiency also contributes to leukemogenesis [45]. Thus, both the loss of wild-type GATA1 and expression of mutant GATA1s appear necessary for the development of DS AMKL. Importantly, restoration of wild-type GATA1 in a DS AMKL cell line led to erythroid differentiation [46].

Cooperating Genetic Events
Because GATA1 appears necessary but not sufficient for the development of AMKL, other as yet unidentified cooperating genetic events must contribute to leukemogenesis. In
The largest study to date of gene expression differences between DS and non-DS AMKL, Bourquin et al. [47] found that DS AMKL and non-DS AMKL formed distinct gene expression clusters. Two smaller gene expression studies identified genes with differential expression in TMD compared with DS AMKL [48, 49], but these findings were not confirmed by Bourquin et al. [47]. Unexpectedly, Bourquin et al. [47] found that RUNX1 showed lower expression in DS AMKL despite the higher dosage resulting from chromosome 21 location. Lower RUNX1 expression occurs in other leukemias and may contribute to leukemogenesis in DS AMKL as well. They did identify several chromosome 21 genes with higher expression in DS AMKL, including BACH1 (a repressor of megakaryopoiesis and possible GATA1 target) and SON (a MYC homologue). Walters et al. [50] identified activation mutations of Janus kinase 3 (JAK3) in a small subset of DS AMKL cases and provided mechanistic evidence that these mutations have the potential to effect malignant transformation. However, JAK3 mutations have been detected in only a handful of DS AMKL cases [50–53]. Other genes with important roles in non-DS AML, such as FLT3, KIT, and c-MPL, were found to be mutated in some DS cases in one recent study [54] but not in others [51, 53]. Thus, the crucial genetic events controlling the evolution of TMD into AMKL remain uncertain.

ALL

Epidemiology and Molecular Genetics of DS ALL

Although DS ALL is not a unique disease entity as are DS AMKL and TMD, it differs importantly from non-DS ALL. The incidence of DS ALL follows roughly the same age peak and range as in the general pediatric population, with the exception that almost no cases occur in infants < 1 year of age. The immunophenotype and cytogenetics of DS ALL are also distinctive [55–61]. T-cell and mature B-cell (Burkitt’s) ALL are virtually absent in DS, and recurrent chromosomal abnormalities are much less common, including hyperdiploidy, TEL-AML1, E2A-PBX1, Philadelphia chromosome, and MLL rearrangements. The frequency of TEL-AML1 and hyperdiploidy, the most common lesions in non-DS ALL, is a subject of current debate. One recent study of 215 DS ALL cases reported frequencies of approximately 10% for each [62]. However, a recent POG review of 80 cases found a comparable incidence of hyperdiploidy (7.7% with trisomy 4 and 10), but only a 2.5% incidence of TEL-AML1 [63], and a review of cases from the Italian Association of Pediatric Hematology and Oncology likewise identified only one case in 44 (2.2%) with TEL-AML1 [61]. Cytogenetic features observed with greater frequency in DS ALL include +X, t(8;14)(q11;q32), and del(9p) [62]. That DS ALL has distinctive biologic features is supported by the recent discovery of activating somatic JAK2 mutations in approximately 20% of DS ALL patients, apparently specific to this subgroup [64]. This notable discovery is the first evidence of an event occurring uniquely in DS that may play a role in the development of ALL. Nearly all the JAK2 point mutations in DS ALL patients occur at a common site, arginine 683, distinct from the V617F site commonly mutated in polycythemia vera and myeloproliferative disorders [65].

<table>
<thead>
<tr>
<th>Study protocol (yrs)</th>
<th>n</th>
<th>(DS)</th>
<th>EFS (DS)</th>
<th>EFS (non-DS)</th>
<th>Comments</th>
<th>Study</th>
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</thead>
<tbody>
<tr>
<td>BFM (1981–1995)</td>
<td>61</td>
<td>58% ± 8% (6-yr)</td>
<td>70 ± 1% (p = .14)</td>
<td>3.3% induction deaths; 6.6% “treatment deaths”</td>
<td>Dördelmann et al. [56]</td>
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<tr>
<td>CCG (1989–1995)</td>
<td>179</td>
<td>68.1% ± 3.9% (10-yr)</td>
<td>77.2 ± 0.5% (p &lt; .001)</td>
<td>3% induction deaths</td>
<td>Whitlock et al. [60]</td>
<td></td>
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<tr>
<td>CCG 1961 (1996–2002)</td>
<td>51</td>
<td>69.1% ± 8.4% (5-yr)</td>
<td>70.4% ± 1.5%</td>
<td>High-risk patients only; 8.7% induction deaths</td>
<td>Hastings et al. [66]</td>
<td></td>
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<tr>
<td>CCG 1952 (1996–2000)</td>
<td>59</td>
<td>79.6%</td>
<td>84.3% (p = .04)</td>
<td>Standard-risk patients only; more hospitalizations</td>
<td>Bassal et al. [59]</td>
<td></td>
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<tr>
<td>MRC UKALL X, XI (1985–1997)</td>
<td>55</td>
<td>53%</td>
<td>63% (p = .1)</td>
<td>11% remission deaths</td>
<td>Chessells et al. [57]</td>
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<tr>
<td>NOPHO (1984–2001)</td>
<td>64</td>
<td>51% ± 7% (10-yr)</td>
<td>70% ± 1%</td>
<td>3.1% remission deaths</td>
<td>Zeller et al. [58]</td>
<td></td>
</tr>
<tr>
<td>POG and St Jude (1979–1992)</td>
<td>37</td>
<td>65% ± 14.5% (4-yr)</td>
<td>74% ± 1.6% (p = .21)</td>
<td></td>
<td>Pui et al. [55]</td>
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</table>

Abbreviations: ALL, acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Münster; CCG, Children’s Cancer Group; DS, Down syndrome; EFS, event-free survival; MRC, Medical Research Council; NOPHO, Nordic Society of Paediatric Haematology and Oncology; POG, Pediatric Oncology Group.
Outcomes in DS ALL
The overall survival has been 10%–20% lower in DS ALL patients than in non-DS ALL patients on most protocols worldwide. However, several of the most recent reports suggest that DS and non-DS outcomes are comparable when favorable risk patients are excluded from the analysis, because favorable risk patients are underrepresented in DS ALL [59, 60, 66]. Table 2 summarizes outcomes for DS ALL in recent major series.

Although DS survival may be comparable on modern protocols, treatment-related toxicities occur with greater frequency and severity [67]. The most common toxicities in DS patients are infection, mucositis, and hyperglycemia. The current front-line COG standard-risk and high-risk ALL protocols were temporarily suspended to DS patients in 2005 as a result of excess deaths related to infection. Protocol amendments included replacement of dexamethasone with prednisone in the high-risk induction, substitution of discontinuous for continuous dexamethasone during delayed intensification, leucovorin rescue at 48 hours following intrathecal methotrexate, and greater supportive care measures including consideration of hospitalization in times of neutropenia. These modifications resulted in no further deaths among DS children on the standard-risk protocol [68], but the high-risk protocol was subsequently closed to enrollment of DS children because of continued excess deaths (personal communication, Eric Larsen). These grim events highlight the difficulty of effecting improvements in survival of children with DS ALL because improvements in disease control through intensification of therapy may come at the cost of greater treatment-related morbidity and mortality. New approaches that take into account differences in disease biology and host response to therapy are wanted for improving treatment of ALL in this group of patients.

Pharmacogenetics in DS

DS AML
The favorable prognosis of DS AMKL may in part be attributable to the greater (two- to 23-fold) sensitivity of DS AMKL blasts to antileukemic agents including ara-C, anthracyclines, and etoposide [68, 69]. Taub and colleagues have provided evidence for the mechanisms underlying this greater sensitivity [69, 70]. The greater sensitivity to ara-C has been hypothesized to be a result of a higher dosage of at least two genes localized to chromosome 21: CBS and SOD. CBS has effects on the reduced folate pathway leading to greater activation of ara-C to the active intracellular metabolite ara-CTP, and less competition with ara-C for incorporation into DNA [71]. DS AMKL cells also exhibit lower levels of cytidine deaminase (CDA), the enzyme responsible for ara-C degradation, apparently because of inhibitory effects of GATA1s on the CDA promoter, thus providing a mechanistic link between GATA1 mutations and enhanced ara-C sensitivity in DS AMKL [72]. Another factor leading to enhanced chemosensitivity in DS AMKL may be the higher dosage of the SOD gene on chromosome 21. SOD increases the generation of hydroxyl free radicals, causing greater susceptibility of DS cells to apoptosis, which may enhance chemosensitivity, particularly for anthracyclines [69].

Cardiotoxicity is an adverse effect of serious concern in DS, particularly in AML, for which anthracyclines are an integral element of most treatment protocols. Krischer and colleagues reported a 3.4-fold higher relative risk of anthracycline-related cardiotoxicity in patients with DS [73]. O’Brien and colleagues recently reported that an alarmingly high 17.5% of children with DS AML treated on POG protocol 9421 developed symptomatic cardiomyopathy, and three died from congestive heart failure [74]. Congenital heart disease was not found to be a risk factor for cardiomyopathy. The high cumulative anthracycline dosage of this protocol (535 mg/m²) likely contributed to the high incidence of cardiomyopathy, as well as greater host sensitivity to oxidative stress [75]. A recent BFM review of cardiotoxicity reported a much lower incidence of cardiomyopathy in approximately 4% of DS ALL patients, which was comparable with that observed in non-DS patients with de novo AML [76]. Potential factors contributing to the low rate of cardiotoxicity of the BFM protocols include a one-third dose reduction of anthracycline therapy in DS patients (yielding a cumulative dose of 200–300 mg/m²), the use of anthracyclines associated with a lower risk for cardiotoxicity (idarubicin and liposomal daunorubicin), and the use of continuous infusion dosing schedules yielding lower peak levels.

DS ALL
Unlike DS AMKL, DS ALL blasts do not demonstrate greater chemosensitivity with conventional ALL chemotherapy agents [68, 77]. In DS ALL, the principal areas of pharmacogenetic research to date have been ara-C (discussed above) and methotrexate, which has long been noted to cause greater toxicity in DS patients [78–81]. This is likely a result of an extra copy of the reduced folate carrier gene on chromosome 21, which is responsible for intracellular transport of methotrexate, leading to higher intracellular methotrexate levels at a given dose level than in non-DS patients, and hence both greater leukemic sensitivity and greater somatic toxicity to the host [71, 79, 82]. A recent study of vincristine pharmacokinetics indicated no
significant differences in DS children [83]. Pharmacokinetic and pharmacodynamic studies of other ALL chemotherapeutic agents in DS patients are lacking. An in vitro study of the effects of several ALL agents on DS cells did not demonstrate excessive cytotoxicity, although in vivo effects could differ [84].

The toxicity of greatest concern in DS ALL is infection, but it remains unclear which chemotherapeutic agent or agents are most responsible. Concern regarding dexamethasone, which is known for its potent immunosuppression, prompted recent COG study amendments for DS patients mandating prednisone in high-risk induction steroid randomization and discontinuous timing of dexamethasone in delayed intensification. Underlying deficits in the DS host immune system are other elements that likely make an important contribution to the higher rate of infectious complications [85–88].

CONCLUSION
Patients with DS exhibit a unique profile of malignancies, with differences in disease incidence, biology, and response to treatment. The study of cancer predisposition syndromes has yielded many important insights into cancer biology, from Li-Fraumeni syndrome and p53 to familial retinoblastoma and Rb. The recent discoveries of the roles of GATA1 in AMKL and JAK2 in ALL are important breakthroughs, but unsolved puzzles remain. In TMD and AMKL, the events subsequent to GATA1 mutation that cause malignant transformation in a subset of TMD cases remain to be determined; and our current understanding of GATA1 must be translated into further clinical advances. In ALL, the challenge remains to determine the alternative events associated with leukemogenesis in the four fifths of cases without JAK2 mutations, and to devise treatment strategies with less frequent and less severe toxicities than those in current practice. As oncologists increasingly tailor their treatment in this era of personalized medicine, patients with DS require recognition and further study because of the unique aspects of malignancies in this genetic context.

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