TRISOMY 21 IS ONE OF the most frequent of acquired numerical abnormalities in leukemia. Although some investigators have specifically attributed the development of hematologic disease to this chromosome or to its genes, others have disagreed. Trisomy 21 as a sole abnormality, aside from its presence in Down syndrome (DS), has been reported in myelodysplasias, myeloproliferative syndromes, acute myeloid leukemias (AMLs), both primary and secondary, and less frequently in acute lymphoblastic leukemias (ALLs). In addition, it is reported to be among the most common of secondary abnormalities in leukemias.

DS patients have a 20-fold increased risk of developing childhood leukemia. Although AMLs predominate, there is also an increased risk of ALL. The majority of the nonlymphocytic leukemias are of the M7 type (acute megakaryocytic leukemia). This is in apparent contrast to the types of leukemia seen in patients with acquired trisomy 21 in which granulocytic and monocytic lineages predominate. If confirmed, this would suggest that +21 is somewhat nonspecific in its contribution to the development and evolution of leukemia.

In this study, the patients with acquired and constitutional trisomy 21 identified and treated for ALL in a frontline Pediatric Oncology Group (POG) study from 1986 through 1990 are characterized. Clinical and laboratory features of their disease are compared and contrasted with particular attention to cytogenetic features.

MATERIALS AND METHODS

Between January 1986 and January 1991, a total of 1,933 eligible children, 1 to 21 years of age, with newly diagnosed non-T, non-B cell ALL were registered on the frontline POG 8602 therapeutic trial. Details of this therapy have been reported elsewhere. Before therapy, each patient had leukemia cell laboratory classification studies performed on bone marrow samples sent to POG reference laboratories. Informed consent, consistent with both institutional and Food and Drug Administration guidelines, was obtained for each participant. Cutoff for follow-up is October 29, 1992.

Cytogenetic analysis. Bone marrow samples were transported overnight in RPMI 1640 with 15% fetal calf serum. On arrival, cells were cultured for 24 hours at 37°C. Cells were exposed to colcemid (0.05 μg/mL) for 2.5 hours at 4°C and harvested routinely. Routine slide preparation and GTG banding was performed. Of the 1,933 eligible cases, 1,466 (75.8%) had successful cytogenetic studies, of which 1,036 (70.7%) were cytogenetically abnormal. There were 533 children identified with +21 as either a sole abnormality or as one of several abnormalities found. There were 33 patients with +21 as a sole abnormality.

Of the 19 non-DS (NDS) patients with +21 as a sole abnormality, 12 were evaluated for constitutional trisomy 21 mosaicism in either skin or stimulated blood cells. No evidence of mosaicism was found nor was there any clinical indication that any of these 19 patients might have DS.

Immunophenotyping. At the appropriate reference laboratory, immunophenotyping was performed using monoclonal antibodies directed against a standard battery of cell surface antigens. Ficol-Hypaque–enriched blasts were stained by immunofluorescence and analyzed by flow cytometry using either an Ortho Spectrum III or FACScan (Becton Dickinson, San Jose, CA). Surface Iggs (sIgs) and cytoplasmic Igs (cIgs) were also identified.

Statistical methods. Qualitative (yes or no) characteristics were compared by exact conditional χ² test (Fisher’s Exact Conditional Test). Quantitative characteristics were compared using the two-sided Wilcoxon test. Event-free survival (EFS) curves were com-
pared using the logrank test, and constructed using the methods of Kaplan-Meier, with standard errors of Peto et al.

**RESULTS**

Clinical and laboratory features. Trisomy 21 was found in 533 (51%) of the 1,036 cytogenetically abnormal cases (Table 1). Although usually found in association with hyperdiploidy (>50 chromosomes), there were 33 cases (3.2%) with +21 as the sole abnormality. Of these 33 cases, there were 14 DS patients and 19 NDS patients.

There also were 18 cases (14 NDS) with +21 and one additional numerical abnormality and 29 cases (20 NDS) with +21 and one additional structural abnormality only. The additional numerical abnormalities included either +X, +16, or −20 in 12 of 14 NDS cases, a seemingly nonrandom distribution. Additional structural abnormalities also were nonrandomly distributed in NDS cases, with 7 of 20 (35%) being abnormalities involving 6q and 6 of 20 (30%) being abnormalities involving 12p. Among cases primarily ascertained by +21, abnormalities of both 6q and 12p are found more frequently than +21 found among cases primarily ascertained by the presence of 6q or 12p abnormalities. Among the 1,036 cytogenetically abnormal cases were 101 cases (9.7%) with a 6q abnormality; in 23 (23%) of these patients, trisomy 21 was also present. Among 1,036 cytogenetically abnormal cases were 118 cases (11.4%) with a 12p abnormality; 9 (8%) also had +21.

The presenting features of cases with +21 as a sole abnormality (groups A [NDS] and B [DS]) are shown in Table 2. Aside from a younger age at diagnosis, the DS patients were not significantly different from the NDS patients. Both seem to have a relatively good prognosis, although sample size limits the power to detect differences. The NDS cases with +21 only (group A) have significantly later ages of diagnosis than do the DS cases with +21 as the only abnormality (group B). The NDS group A patients more frequently have a pre-B phenotype than patients with +21 and other abnormalities (group C). No significant differences were noted between the NDS +21 (sole abnormality) group and other cytogenetically abnormal cases (group D).

Therapeutic outcome. As shown in Table 2, no significant difference in the rates of treatment failure were seen between DS and NDS cases with +21 only or between NDS patients with +21 only and other cytogenetically abnormal patients.

<table>
<thead>
<tr>
<th>Table 1. Distribution of Karyotypes in Ploidy Groups Among 1,036 Chromosomally Abnormal Patients</th>
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</thead>
<tbody>
<tr>
<td>NDS</td>
</tr>
<tr>
<td>+21 (N = 506)</td>
</tr>
<tr>
<td>&lt;44 6 6 0 0</td>
</tr>
<tr>
<td>44-45 2 102 0 0</td>
</tr>
<tr>
<td>46 13 296 0 1</td>
</tr>
<tr>
<td>47-49 68 69 23 0</td>
</tr>
<tr>
<td>50 4 4 1 0</td>
</tr>
<tr>
<td>&gt;50 412 25 4 0</td>
</tr>
</tbody>
</table>
* Reported to be clinically consistent with DS phenotype.

Logrank analyses of EFS for patients with +21 as a sole abnormality yielded no significant difference for DS versus NDS cases (Fig 1 and Table 2). Although all +21 cases did somewhat better than those with other cytogenetic abnormalities, the difference was not significant (Fig 1 and Table 2).

**DISCUSSION**

Trisomy 21 is among the most common chromosome abnormalities associated with hematologic disorders. Although usually coincident with other abnormalities, it is also reported as a sole abnormality, often associated with DS. However, little information is reported on NDS patients presenting with this sole abnormality. Studies of such cases will ultimately allow for more specific prognosis within the group of hyperdiploid (47 to 50 chromosomes) patients with single abnormalities, a diverse category probably including both high- and low-risk subsets. Studies of such focused patient populations can offer insight into the role of specific chromosome abnormalities in hematologic disorders.

The actual frequency of trisomy 21 in childhood ALL has not been well resolved because most studies report it among all age groups and in association with the 47 to 50 chromosome hyperdiploid group. Our finding of trisomy 21 as a sole abnormality in 3.2% of cytogenetically abnormal cases of non-T, non-B cell ALL is only slightly higher than the 1.8% reported by Raimondi et al. However, it is important to realize that these frequencies represent estimates because the finding of trisomy 21 as the sole abnormality in the bone marrow of a DS patient may represent a failure to identify the abnormal neoplastic clone. Nevertheless, it represents a significant number of cases of childhood ALL.

As one of two abnormalities in childhood ALL, trisomy 21 occurred in another 47 cases (4.5%) among the chromosomally abnormal cases in this study. Interestingly, +X, +16, and −20 comprise 86% of the numerical second abnormalities in NDS cases, whereas abnormalities of 12p and 6q account for 65% of second abnormalities of a structural type. This unusual distribution of second abnormalities found in association with +21 in NDS cases overlaps with that reported by Pui et al in DS cases in which +X, a rare finding in cytogenetically abnormal cases of ALL, is disproportionately overrepresented. However, very few studies have investigated the cumulative impact of specific trisomies on prognosis. A recent report by Harris et al has identified a subgroup of chromosomal abnormalities for which trisomy is univariately associated with a superior EFS. Among these chromosomal abnormalities are 4, 5, 6, 10, 14, 17, 18, 21, and X. However, trisomy of chromosome 21 lost its independent prognostic significance after adjustment for presence of trisomy 4 and 10. Nevertheless, data supporting risks specific to individual chromosome aneuploidies continue to suggest that subdividing patients beyond simple ploidy classifications will allow more patient-specific prognosis.

Among structural chromosome abnormalities, those of both 12p and 6q are recurrent abnormalities in childhood ALL. The 12p abnormalities represent a major subgroup of childhood ALL, occurring in more than 11% of all cases in
Table 2. Clinical Features

<table>
<thead>
<tr>
<th></th>
<th>Group A (N = 19)</th>
<th>Group B (N = 14)</th>
<th>Group C (N = 486)</th>
<th>Group D (N = 988)</th>
<th>AvB</th>
<th>AvC</th>
<th>AvD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>10/19</td>
<td>9/14</td>
<td>283/486</td>
<td>557/987</td>
<td>.72</td>
<td>.99</td>
<td>.82</td>
</tr>
<tr>
<td>Race-Black</td>
<td>3/19</td>
<td>0/14</td>
<td>232/486</td>
<td>100/987</td>
<td>.24</td>
<td>.14</td>
<td>.43</td>
</tr>
<tr>
<td>Pre-B diagnosis</td>
<td>7/19</td>
<td>1/14</td>
<td>71/486</td>
<td>238/988</td>
<td>.098</td>
<td>.017</td>
<td>.65</td>
</tr>
<tr>
<td>Age (median)</td>
<td>5.4</td>
<td>3.9</td>
<td>4.1</td>
<td>4.7</td>
<td>.005</td>
<td>.026</td>
<td>.27</td>
</tr>
<tr>
<td>WBC (median)</td>
<td>6.0</td>
<td>7.7</td>
<td>7.0</td>
<td>9.4</td>
<td>.26</td>
<td>.61</td>
<td>.11</td>
</tr>
<tr>
<td>Fail (expected)</td>
<td>3 (4.1)</td>
<td>4 (2.9)</td>
<td>—</td>
<td>—</td>
<td>.77</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fail (expected)</td>
<td>3 (3.6)</td>
<td>—</td>
<td>79 (78.4)</td>
<td>—</td>
<td>.74</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fail (expected)</td>
<td>3 (6.0)</td>
<td>—</td>
<td>26 (263.0)</td>
<td>—</td>
<td>.22</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4-yr EFS (SE)</td>
<td>80% (12%)</td>
<td>71% (22%)</td>
<td>81% (3%)</td>
<td>69% (2%)</td>
<td></td>
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</tr>
</tbody>
</table>

Group A, +21 is only abnormality, NDS; group B, +21 is only abnormality, DS; group C, +21 and at least one other abnormality, NDS; group D, cytogenetically abnormal, not group A or B, NDS.

this study. Abnormalities of 6q are among the most common to be found in association with other abnormalities.30 Again, their effect on the relatively good prognosis afforded by trisomy 21 will require larger patient groups with these karyotypes.

The distribution of clinical/biologic features of NDS cases with trisomy 21 were similar to those of the entire group of chromosomally abnormal patients. The NDS trisomy 21 cases tended to be older than the DS cases. This is consistent with the finding that the age peak for leukemia in DS occurs earlier than it does for childhood leukemia as a group.21 The DS patients appeared to present with a pre-B diagnosis less often than did the NDS trisomy 21 cases. However, because the DS comparison group was defined by having trisomy 21 as a sole abnormality, it may include patients in whom the true leukemic clone was not found. In any case, neither the NDS +21 cases nor the DS +21 cases19 with a pre-B phenotype have the poor prognosis characteristic of patients with other cytogenetic abnormalities and pre-B ALL.

The current intensive treatment regimens for childhood leukemia have made it increasingly less likely that outcome differences will be resolved in the 47 to 50 chromosome group. However, because overall EFS for this group remains below that of some other groups, it is important to continue to subdivide this group. This will necessitate the continued accumulation of large populations receiving similar therapy to sort out those with higher risk features. Patients with

Fig 1. Kaplan-Meier analysis of EFS contrasts outcomes among patient groups. Group A, +21 is only abnormality, NDS; group B, X 21 is only abnormality, DS; group C, +21 and at least one other abnormality, NDS; group D, cytogenetically abnormal, not group A or B, NDS.
trisomy 21 as a sole abnormality do not define a high-risk subset. Although toxicity was greater, DS patients have a similar outcome to NDS cases when intensive therapy is used.22

APPENDIX

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Trisomy 21 in childhood acute lymphoblastic leukemia: a Pediatric Oncology Group study (8602)

MS Watson, AJ Carroll, JJ Shuster, CP Steuber, MJ Borowitz, FG Behm, DJ Pullen and VJ Land