Trisomy 21 in Childhood Acute Lymphoblastic Leukemia: A Pediatric Oncology Group Study (8602)

By M.S. Watson, A.J. Carroll, J.J. Shuster, C.P. Steuber, M.J. Borowitz, F.G. Behm, D.J. Pullen, and V.J. Land

Of 1,036 children with newly diagnosed non-T, non-B acute lymphoblastic leukemia (ALL) and a demonstrated cytogenetic abnormality treated on the frontline Pediatric Oncology Group (POG) therapeutic trial 8602, there were 33 patients with trisomy 21 as the sole abnormality. Of these 33, 14 had Down syndrome (DS). Although the non-DS (NDS) trisomy 21 cases tended to be older than the DS cases, there were no other significant differences in clinicobiologic features nor in treatment outcomes between the DS and NDS groups, nor between the entire trisomy 21 group and the other chromosome abnormality group.

Among NDS patients with +21 and one additional abnormality, +X, +16, −20, and structural abnormalities involving 6q or 12p were common findings. Kaplan-Meier event-free survival (EFS) curves showed a 4-year EFS of 80% (SE, 12%) in NDS trisomy 21 cases, 71% (SE, 22%) in DS cases with trisomy 21 as the sole abnormality, and 69% (SE, 2%) in cases with other chromosome abnormalities. Trisomy 21 as a sole acquired abnormality in NDS patients suggests a good prognosis.

TRISOMY 21 IS ONE OF the most frequent 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 leuke-

mias.

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 non-lymphocytic 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 some-

what 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 front-line 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 53 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. Ficolldipyque–enriched blasts were stained by immunofluorescence and analyzed by flow cytometry using either an Ortho Spectrum II or FACScan (Becton Dickinson, San Jose, CA). Surface Ig s (sIgs) and cytoplasmic Ig s (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-

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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 ascertainment by +21, abnormalities of both 6q and 12p are found more frequently than is +21 found among cases primarily ascertainment by the presence of 6q or 12p abnormalities. Among the 1,036 cytogenetically abnormal cases, there 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 DS 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 the DS and NDS cases with +21 only or between NDS patients with +21 only and other cytogenetically abnormal patients.

Table 1. Distribution of Karyotypes in Ploidy Groups Among 1,036 Chromosomally Abnormal Patients

<table>
<thead>
<tr>
<th>Groups</th>
<th>1,036 Chromosomally Abnormal Patients</th>
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<tbody>
<tr>
<td>DS</td>
<td></td>
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<tr>
<td>-21</td>
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<tr>
<td>(N = 506)</td>
<td>6</td>
</tr>
<tr>
<td>No +21</td>
<td>(N = 502)</td>
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<tr>
<td>+21</td>
<td>(N = 28)</td>
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<tr>
<td>No +21</td>
<td>(N = 1)</td>
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<tr>
<td>&lt;50</td>
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<td>44-45</td>
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<td>46</td>
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<td>47-49</td>
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<td>50</td>
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<td>&gt;50</td>
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<td>412</td>
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* Reported to be clinically consistent with DS phenotype.
Table 2. Clinical Features

<table>
<thead>
<tr>
<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>A v B</th>
<th>A v C</th>
<th>A v D</th>
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<tbody>
<tr>
<td>Male</td>
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<tr>
<td>Race-Black</td>
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<td>Pre-B diagnosis</td>
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<td>Age (median)</td>
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<td>WBC (median)</td>
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<tr>
<td>Fail (expected)</td>
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<td>Fail (expected)</td>
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<tr>
<td>4-yr EFS (SE)</td>
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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. 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. 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 cases 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
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

Principle investigators of POG participating in this study (institution, investigator, grant no.): Alberta Pediatric Oncology Consortium, Edmonton, Alberta, Canada, John Akabutu; Baylor College of Medicine, Houston, TX, Donald Fernbach, CA-03161; Bergen-Passaic Community Clinical Oncology Program, Hackensack, NJ, Michael Harris; Bowman Gray School of Medicine, Winston-Salem, NC, Richard Patterson, CA-15525; Cancer Center of Hawaii, Honolulu, HI, Robert Wilkinson, CA-28439; Charlotte Memorial Hospital, Charlotte, NC, Barry Bolome, CA-15525; Children’s Hospital Greenville System, Greenville, SC, Cary Stroud; Children’s Hospital of Michigan, Detroit, MI, Y. Ravindranath, CA-29691; Chicago Children’s Memorial Hospital, Chicago, IL, Sharon Murphy, CA-07431; Chicago Cook County Children’s Hospital, Chicago, IL, Sudha Rao; City of Hope National Medical Center, Duarte, CA, Patricia Konrad; Cook-Ft Worth Children’s Medical Center, Ft Worth, TX, Paul Bowman, CA-33625; Duke University Medical Center, Durham, NC, John Falletta, CA-15525; East Carolina University School of Medicine, Greenville, NC, Tate Holbrook, CA-15515; Emory University School of Medicine, Atlanta, GA, Abdel Ragab, CA-20549; FairFax Hospital, Falls Church, VA, Jay Greenberg; Florida Community Clinical Oncology Program, James Talbert, CA-35157; Hurley Medical Center, Flint, MI, Susumu Inoue; Johns Hopkins University, Baltimore, MD, Brijed Leventhal; Keesler Air Force Medical Center, Biloxi, MS, Thomas Absilire; Medical University of South Carolina, Charleston, SC, Biemann Othersen; McGill University, Montreal, Quebec, Canada, Michael Whitehead, CA-33587; Medical College of Virginia, Richmond, VA, Harold Maurer, CA-28530; Miami Children’s Hospital, Miami, FL, Enrique Escalon; Midwest Children’s Cancer Center, Milwaukee, WI, Bruce Camitta, CA-32053; Mount Sinai School of Medicine, New York, NY, Jeffrey Lipton, CA-38859; New England Pediatric Consortium, Providence, RI, Edwin Forman, CA-29293; Oklahoma University, Oklahoma City, OK, Kupreet Nitschke, CA-29293; Ochsner Consortium, Children’s of New Orleans, New Orleans, LA, Rafael Ducas; Roswell Park Memorial Institute, Buffalo, NY, Martin Brecher, CA-28383; Rush-Presbyterian-St. Luke’s Medical Center, Chicago, IL, Alexander Green; State University of New York, Syracuse, NY, Ronald Dubowby, CA-41721; Scott & White Memorial Hospital, Temple, TX, Lawrence Frankel; Southwestern Medical Center, Dallas, TX, George Buchanan, CA-33625; St John Hospital, Detroit, MI, Hadl Sawaf; St Jude Children’s Research Hospital, Memphis, TN, Ching-Hon Pui, CA-31566; St Christopher’s Hospital, Philadelphia, PA, Robert Wimmer, CA-45261; St Vincent Hospita, Green Bay, WI, Stuart Adair; Stanford University, Palo Alto, CA, Michael Link, CA-33603; Swiss Pediatric Oncology Group, Bern, Switzerland, Hans Wagner; UCSF: Kaiser Permenta Medical Center, Santa Clara, CA, Lily Young; Uniformized Services Oncology Consortium, Washington, DC, David Maybee, CA-28572; University of Alabama, Birmingham, AL, Robert Castlebeny, CA-25408; University of Arizona, Tucson, AZ, John Hutter; University of Arkansas, Little Rock, AR, D.H. Berry, CA-41188; Univ. California—San Diego, San Diego, CA, Faith Kung, CA-28439; University of Florida/Nemours, Gainesville, FL, Samuel Gross, CA-29281; University of Kansas, Kansas City, KS, Tribbben Wats, CA-28841; University of Miami, FL, Stuart Toledano, CA-41082; University of Mississippi, Jackson, MS, Jeanett Pullen, CA-15988; University of Missouri, Columbia, MO, Nasrollah Hakami, CA-05587; University of New Mexico, Albuquerque, NM, Marilyn Duncan, CA-11233; University of South Alabama, Mobile, AL, Yih-Ming Yang; University of South Florida, Tampa, FL, Eva Hvizdala; University of Texas-Galveston, Galveston, TX, Mary Haggard; University of Texas–M.D. Anderson, Houston, TX, Donald Pinkel, CA-03713; University of Virginia, Charlottesville, VA, Beverly R. Raney; Washington University, St Louis, MO, Vita Land, CA-05587; West Virginia University Medical Center, Charleston, WV, Kenneth Starling, CA-15525; Wichita Community Clinical Oncology Program, Wichita, KS, Henry Hynes, CA-35431; Yale University, New Haven, CT, Peter Beardsley.

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