Hyperdiploid (47-50) Acute Lymphoblastic Leukemia in Children

By Susana C. Raimondi, Paula K. Roberson, Ching-Hon Pui, Frederick G. Behm, and Gaston K. Rivera

Among ploidy groups in childhood acute lymphoblastic leukemia (ALL), hyperdiploid 47 to 50 is perhaps the least well known. From December 1979 to December 1990, we successfully studied banded karyotypes in 598 cases of newly diagnosed ALL, of which 96 (14.4%) had modal chromosome numbers of 47 to 50. In this group, the most frequently acquired numerical abnormalities were +21 (n = 34), +X (18), +8 (8), and +17 (7). The chromosomal regions most often affected by structural abnormalities were 1q (n = 13), 6q (12), 12p (18), and 19p (9). Analysis of event-free survival (EFS) for Studies X and XI among patients with hyperdiploid (47 to 50) ALL showed no significant differences in outcome according to the presence (n = 36) or absence (n = 35) of chromosomal translocations (P = .81) or the gain of specific chromosomes (P = .40). Patients with hyperdiploid (47 to 50) ALL treated in a contemporary program of multigagent chemotherapy had a significantly better outcome than did those in an earlier study using less intensive therapy (4-year EFS = 78% [95% confidence interval, 58% to 86%] vs 41% [22% to 59%]; P = .006 by the logrank test). Our findings indicate that the adverse prognosis previously attributed to hyperdiploid 47 to 50 improves significantly with more effective chemotherapy.

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MATERIALS AND METHODS

Patients. From December 1979 to December 1990, 932 consecutive children (born from 18 years of age) with newly diagnosed ALL were admitted to St Jude Children’s Research Hospital and enrolled in one of three clinical trials.24-26 The diagnosis of ALL was based on morphologic criteria of the French-American-British (FAB) Cooperative Group and on negative staining for myeloperoxidase and esterase. We successfully analyzed the leukemic cell karyotypes of 598 patients (64%), whose clinical features paralleled those of the group with unbalanced chromosomes (n = 334), except for higher leukocyte counts, higher serum lactate dehydrogenase (LDH) levels, and increased presentation with central nervous system (CNS) disease among the banded cases, both overall and within each study (data not shown). Event-free survival (EFS) for patients with or without banded karyotypes did not differ significantly between the two trials on which our prognostic analyses were based: 4-year EFS (with 95% confidence interval [CI] = 51% [42% to 60%] versus 56% [50% to 63%] in Total Therapy Study X24 and 70% [64% to 76%] versus 68% [48% to 81%] in Study XI.25 There were no significant differences in presenting features between the two groups with banded chromosomes in Studies X and XI (data not shown). All other patients were treated in Study XII26 but were not considered in the outcome assessment. Patients known to have Down syndrome or FAB-L3 B-cell ALL were excluded from analysis.

Signed informed consent was obtained from the patients or their parents, and all investigations were approved by our institutional review board.

Cytogenetic studies. Bone marrow samples were prepared by a direct method,27 with or without short-term (24-hour) culture; a modified trypsin-Wright technique was used for chromosome banding. The modal chromosome number of the stemline (ie, that with the most metaphases represented) was used when more than one abnormal line was observed within a single case. A missing chromosome in three or more cells, or an extra chromosome or structural abnormality in two or more cells, constituted a clonal abnormality. Chromosomes were described according to conventions of the International System for Human Cytogenetic Nomenclature.28

Blot cell phenotyping. Blast cell surface antigens were detected by standard indirect immunofluorescence assays with monoclonal antibodies to lymphoid-associated antigens. Blast cells were also tested for surface (slg) and cytoplasmic (clg) Ig staining and for formation of heat-stable rosettes with sheep erythrocytes. Based on their reactivity patterns, cells were classified as T (CD7+, CD5+), E-rosette+, B (slg+, pre-B (clg+), or early pre-B (clg-, slg-, T-), HLA-DR+, CD19+, CALLA+.

Statistical analysis. Presenting leukocyte counts and serum LDH values were compared between the 47 to 50 and other ploidy groups with use of the Wilcoxon rank sum test. Features of a dichotomous or categorical nature were compared by Fisher’s exact test or )), analysis. Assessment of treatment outcome was

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Table 1. Presenting Cytogenetics, Immunophenotypic Findings, and Clinical Outcome in 86 Cases of Hyperdiploid (47 to 50) ALL

<table>
<thead>
<tr>
<th>Case No.</th>
<th>No. of Metaphases Completely Analyzed</th>
<th>Cytogenetic Evaluation</th>
<th>Immunophenotype</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

(Continued on following page)
Table 1. Presenting Cytogenetics, Immunophenotypic Findings, and Clinical Outcome in 86 Cases of Hyperdiploid (47 to 50) ALL (Cont'd)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>No. of Metaphases</th>
<th>Karyotype*</th>
<th>Immunophenotype</th>
<th>Remission Duration (mo)</th>
<th>Type of Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>24</td>
<td>47,XX,i(9q),+der(?)(?);7[2]†</td>
<td>Pre-B</td>
<td>58.1+</td>
<td>—</td>
</tr>
<tr>
<td>56</td>
<td>10</td>
<td>47,XX,+12,10(13q32);7t;22t (?p13;?)[9]†</td>
<td>Pre-B</td>
<td>14.7</td>
<td>H</td>
</tr>
<tr>
<td>57</td>
<td>14</td>
<td>47,XX,+6,del(12)(p12),t(2;6)(p21;15)[12]†</td>
<td>Early pre-B</td>
<td>45.9+</td>
<td>—</td>
</tr>
<tr>
<td>58</td>
<td>20</td>
<td>47,XX,+10,t(15)[?];7(13q32)[21]†</td>
<td>Early pre-B</td>
<td>36.7+</td>
<td>—</td>
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<tr>
<td>59</td>
<td>33</td>
<td>47,XY,X,+del(13)[q14]t;7;9;p15;22[7]†</td>
<td>Pre-B</td>
<td>29.0+</td>
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</tr>
<tr>
<td>60</td>
<td>15</td>
<td>47,XY,+4,t(12;14)[q14];q32[10]†</td>
<td>T†</td>
<td>28.1+</td>
<td>—</td>
</tr>
<tr>
<td>61</td>
<td>30</td>
<td>47,XY,+X[26]/46,iderm.t(11;7)[p15;7][5]†</td>
<td>Pre-B</td>
<td>21.8</td>
<td>CNS</td>
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<tr>
<td>62</td>
<td>15</td>
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<td>2.9+</td>
<td>—</td>
</tr>
<tr>
<td></td>
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<td><strong>Modal no. 48</strong></td>
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<td></td>
</tr>
<tr>
<td>63</td>
<td>9</td>
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<td>Early pre-B</td>
<td>27.6</td>
<td>H</td>
</tr>
<tr>
<td>64</td>
<td>8</td>
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<td>B-precursor cell</td>
<td>21.1</td>
<td>H</td>
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<tr>
<td>65</td>
<td>18</td>
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<td>Pre-B</td>
<td>22.9</td>
<td>H</td>
</tr>
<tr>
<td>66</td>
<td>14</td>
<td>48,XY,+19,+21,del(6)[q13q25][10]</td>
<td>B-precursor cell</td>
<td>114.4+</td>
<td>—</td>
</tr>
<tr>
<td>67</td>
<td>6</td>
<td>48,XY,+X,+del(6)[q13q22],[t4]†</td>
<td>Early pre-B</td>
<td>21.4</td>
<td>CNS</td>
</tr>
<tr>
<td>68</td>
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<td>48,XY,+16,+7,21,del(6)[q13q21][5]t;47,XY,+16,del(6)[2]†</td>
<td>B-precursor cell†</td>
<td>92.2+</td>
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<td>12</td>
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<td>29.2</td>
<td>—</td>
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<td>70</td>
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<td>29.9</td>
<td>H + T</td>
</tr>
<tr>
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<td>48,XX,+1,1+t[19,t11;19(23p13);t3(5);q21;15][8]†</td>
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<td>5.2</td>
<td>H + CNS</td>
</tr>
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<td>Pre-B</td>
<td>19</td>
<td>AML</td>
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<tr>
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<td>13</td>
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<tr>
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<td>5.7</td>
<td>CNS</td>
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<td></td>
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<tr>
<td>76</td>
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<td>Early pre-B</td>
<td>52.4+</td>
<td>—</td>
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<tr>
<td>77</td>
<td>11</td>
<td>48,XY,+X,+6,+der(19)[1;19][q13;7][p13;7][16;12][q21][13][8]/48,iderm., del[12][p12][2]†</td>
<td>Early pre-B</td>
<td>48.8</td>
<td>AML</td>
</tr>
<tr>
<td>78</td>
<td>14</td>
<td>48,XX,t(17;7)[q25;7],+2mar[10]†</td>
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<td>87.8+</td>
<td>—</td>
</tr>
<tr>
<td>79</td>
<td>11</td>
<td>48,XY,+722,del(6)[q15q21],der(D)t[Dq7],+mar[10]†</td>
<td>Early pre-B</td>
<td>40.6+</td>
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<td>80</td>
<td>17</td>
<td>49,XY,+Y,+6,10,+21,der(12)[6;12][p21;13;19(19)[q23p13][7];49;XY,+Y,+7,21,der(15)[1;15][q11; p11;der(19)[15][3];50;XY,+Y,+17,+20,21,der(19)[1; 19][3]†</td>
<td>Pre-B</td>
<td>40.7+</td>
<td>—</td>
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<tr>
<td>81</td>
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<td>IF</td>
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<tr>
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<td>Early pre-B</td>
<td>6.4</td>
<td>H</td>
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<tr>
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<td>13.7</td>
<td>H</td>
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<td><strong>Modal no. 50</strong></td>
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<td></td>
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<td>84</td>
<td>26</td>
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<td>Early pre-B</td>
<td>—</td>
<td>IF</td>
</tr>
<tr>
<td>85</td>
<td>30</td>
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<td>Early pre-B</td>
<td>11+</td>
<td>—</td>
</tr>
<tr>
<td>86</td>
<td>16</td>
<td>50,XY,+X,XY,+10,+20,[8][21q],[+12][15]†</td>
<td>Early pre-B†</td>
<td>21+</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: c, constitutional karyotype; IF, induction failure; H, hematologic; T, testicular; AML, acute myeloid leukemia; ND, not done.

*The numbers in brackets refer to the number of metaphases analyzed.
Karyotypes previously reported.
†Myeloid associated antigens CD33, CD13, or CD15 coexpressed.

RESULTS
Of the 598 completely banded cases of ALL, 86 (14.4%) had a modal chromosome number of 47 to 50, distributed as follows: 47 (72.1%), 48 (19.8%), 49 (4.6%), and 50 (3.5%). The complete karyotypes of all 86 cases are presented in Table 1 in order of increasing complexity and number of chromosomes.
Sixty-one (71%) of the hyperdiploid (47 to 50) cases had a single hyperdiploid clone, and 25 (29%) had more than

limited to the patients in Studies X and XI; follow-up times in the current study (XII) were considered inadequate for comparison. EFS probabilities were estimated by the method of Kaplan and Meier, with differences compared by the logrank test. Time to an adverse event was measured from the date of complete remission to the date of first relapse or death from any cause. Patients who failed to enter remission were assigned a failure time in order of increasing Peti@ and number of cases. Ninety-five percent CIS for 4-year EFS probabilities were calculated with a logarithmic transformation that ensures that end-point values will lie between zero and one.
one abnormal line. In the latter category, approximately one-half the cases had the same modal number; the other one-half had lines that differed by a few chromosomes only. In all but two of the 25 cases with more than one abnormal line, the chromosomal abnormalities within each line were related. In cases 28 and 49, the abnormal lines were independent, both having a line with an extra chromosome 7. The presence of more than one abnormal line is observed in approximately 25% to 30% of ALL cases in general. A karyotype in 16 cases: a +21 in 11 cases and a +8, +9, +lo, +21, +X in one case each. Overall, the chromosomes added most often were +21 (n = 34), +X (n = 18), +8 (n = 8), and +10 (n = 7) (Table 2A). Five cases were considered hyperdiploid (47 (n = 4) or 48 (n = 1) because of added markers of unknown origin. Two other cases had 47 chromosomes due to a duplicated derivative chromosome.

The pattern of occurrence of structural abnormalities is depicted in Fig 1B. The most frequent abnormalities, in decreasing order, were: 12p (n = 12), 1q (n = 4), 6q (n = 12), 1q (n = 12), 6q (n = 12), and 19p (n = 9) (Table 2B). Overall, 41 (48%) of the 86 cases had a translocation present; eg, t(1;19)(q23; p13) (n = 7), t(9;22)(q34;q11) (n = 3), t(4;11)(q21;q23) (n = 1), and t(11;19)(q23;p13) (n = 1). The most frequently observed deletions were: del(6q) (n = 9), del(12p) (n = 6), del(13q) (n = 4), del(9p) (n = 3), del(10q) (n = 3), and del(Xq) (n = 2).

The results of immunophenotyping, available for 82 cases, were: early pre-B (n = 41), pre-B (n = 21), B-cell precursor (clg not performed) (n = 9), T-cell (n = 7), and unclassified (n = 4) (Table 1). Thirteen of the 82 cases had blasts that coexpressed one or more myeloid associated antigen (CD33, CD13, CD15). The most notable finding was that all seven T-cell cases were in the 47 chromosome group. The three cases with 50 chromosomes had an early pre-B immunophenotype.

Table 3 compares the presenting clinical and laboratory features of the 86 hyperdiploid 47 to 50 cases with those of the hyperdiploid greater than 50 group and all other cases with banded karyotypes. As might be predicted, children in the 47 to 50 group had a less favorable age distribution than did those with hyperdiploid greater than 50 karyotypes (P = .005), as well as higher leukocyte counts (P = .02), and higher serum LDH values (P < .001). In the comparison with other banded cases (hypodiploid, pseudodiploid, normal), hyperdiploid (47 to 50) ALL was associated with lower leukocyte counts (P < .001) and non-T immunophenotypes (P < .001). Small sample sizes precluded evaluation of presenting features among the four numerical subgroups (47, 48, 49, and 50); however, cursory examination of cases with 47 (n = 62) or 48 (n = 17) chromosomes indicated no substantial differences, except that all cases of T-cell ALL were restricted to the 47 chromosome subgroup, and boys were more prevalent in the 48 chromosome group (70.6% vs 51.6%).

The 4-year EFS (95% CI) for the hyperdiploid 47 to 50 group in Total Therapy Study XI was 75% (55% to 86%), as compared with 65% (57% to 72%) for patients with a normal, pseudodiploid, or hypodiploid karyotype and with 80% (69% to 88%) for the hyperdiploid greater than 50 group. This outcome, obtained with reinforced early treatment and rotational combination chemotherapy during the postremission period, stands in marked contrast to the end results of an earlier clinical trial comparing less intensive regimens. In that study, patients with 47 to 50 chromosomes had the poorest EFS among all ploidy groups: 41% (22% to 59%) at 4 years from diagnosis (Table 4). The better prognosis seen in Study XI is highly significant (Fig 2, P = .006).

We also studied the relative responses to treatment in the 47-, 48-, 49-, and 50-chromosome subgroups. Whether considered in Study X or Study XI, there was no indication that any of these additions conferred a superior outcome, although the numbers of patients with 49 or 50 chromosomes were too small to permit meaningful statistical analysis. Nor were there significant differences in outcome according to the presence (n = 36) or absence (n = 35) of chromosomal translocations (P = .81, data not shown). Likewise, the gain of specific chromosomes (eg, +21
HYPERDIPLOID (47-50) ALL

Fig 1. Numerical and structural chromosomal abnormalities associated with hyperdiploidy 47 to 50 in childhood ALL. (A) Histogram illustrating the frequency of whole chromosome gain or loss in 86 cases. (B) Histogram illustrating the frequency of structural rearrangements in 65 of the preceding 86 cases.

DISCUSSION

An association between ploidy and the clinical characteristics of ALL has been firmly established, although one subclass, hyperdiploidy 47 to 50, has received less attention than others. Recognition of the 47 to 50 ploidy group in childhood ALL was suggested by a natural division (hiatus) in the distribution of modal chromosome numbers and by differences in treatment outcome. In the present study, the incidence of hyperdiploid (47 to 50) ALL was 14.4% (86 of 598 banded cases), with single chromosome additions representing 72% of these cases; few patients had blast cells with 49 or 50 chromosomes. Twenty-four percent of the 86 cases were characterized by numerical abnormalities only, mainly +21 (39%), +X (21%), +8 (10%), and +10 (8%). Specific numerical changes were distributed in approximately equal proportions among the four incremental subdivisions (47, 48, 49, and 50 chromosomes). The pattern of structural abnormalities we identified in the 47 to 50 group was representative of ALL in general; the chromosomal regions most frequently altered were 1q, 6q, 12p, and 19p. The known recurrent (nonrandom) abnormalities included t(1;19) (n = 7), t(9;22) (n = 3), t(4;11) (n = 1), t(11;19) (n = 1), del(6q) (n = 9), del(12p) (n = 6), and del(13q) (n = 4).

In the largest subgroup in our series (47 chromosomes),
Table 3. Presenting Features of Patients With Hyperdiploid (47 to 50) ALL Compared With Other Ploidy Groups

<table>
<thead>
<tr>
<th>Age group (no. of patients) (%)</th>
<th>Modal No.</th>
<th>Modal No.</th>
<th>Other Banded</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 yr</td>
<td>(n = 154)</td>
<td>47 to 50</td>
<td>(n = 86)</td>
<td>(n = 358)</td>
</tr>
<tr>
<td>1-9 yr</td>
<td>1 (&lt;1)</td>
<td>2 (2)</td>
<td>18 (5)</td>
<td></td>
</tr>
<tr>
<td>≥10 yr</td>
<td>15 (10)</td>
<td>20 (23)</td>
<td>108 (30)</td>
<td></td>
</tr>
</tbody>
</table>

Leukocyte count (×10^9/L)
- Median: 6.8
- Range: 0.9-332
- P = .02
- P < .001

Gender (no. of boys) (%)
- Median: 79 (51)
- Range: 48 (56) to 197 (55)

Race (no. of whites) (%)
- Median: 143 (83)
- Range: 74 (86) to 298 (83)

Serum LDH (U/L)*
- Median: 329
- Range: 139-3,710
- P < .001

Immunophenotype* (no. of classified cases) (%)
- Non-T: 141 (97)
- T: 4 (3)
- P < .001

Mediastinal mass* (no. of patients) (%)
- Median: 4 (3)
- Range: 8 (9) to 60 (17)

P values not included for comparisons that did not yield a statistically significant difference.

*Data missing for some cases.

Among our 17 cases with 48 chromosomes, three (17.6%) had a numerical abnormality only. This subgroup also comprised a larger-than-average proportion of male patients (70.6%), as well as four of the seven cases with t(1;19)

Table 4. Relative Prognostic Importance of Hyperdiploid (47 to 50) ALL

<table>
<thead>
<tr>
<th>Ploidy Group</th>
<th>Study XI (n=44)</th>
<th>Study XI (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4-yr EFS (%)</td>
<td>95% CI (%)</td>
</tr>
<tr>
<td>47 to 50</td>
<td>27</td>
<td>41</td>
</tr>
<tr>
<td>&gt;50</td>
<td>37</td>
<td>62</td>
</tr>
</tbody>
</table>

seen in the 47 to 50 group overall. Nine of these 17 cases have relapsed, with two converting to AML. Only three of approximately 40 karyotypes with 48 chromosomes reported in the medical literature have been characterized solely by numerical abnormalities, two being identical with addition of chromosomes 8 and 21.

Each of our four cases with 49 chromosomes had an added structural abnormality. The prognosis in this subgroup, which included only one white patient, was poor; one child did not enter remission, while two others had hematologic relapses after 6.4 and 13.7 months. Of the estimated 20 cases of ALL with a modal chromosome number of 49 described in previous reports, all but one have had an additional structural abnormality. Among our three cases with 50 chromosomes, one had an isochromosome 8q and two copies of an isochromosome 21. Two other cases with this modal number have been reported.

The poor prognosis of hyperdiploid (47 to 50) ALL treated on the Total Therapy Study XI protocol was largely abolished by the intensified chemotherapy of Study XI.25 Fletcher et al.26 have published similar results for patients treated at the Dana-Farber Cancer Institute. In their analysis, all ploidy groups had an EFS of more than 70% at 5 years of follow-up, and none showed a significant relapse-free survival advantage over any other. It should be noted that interpretable karyotypes were available for only 45% of cases in that study.

The biologic diversity and improved prognosis seen among cases with 47 to 50 chromosomes raises the question whether it is necessary to recognize this or any ploidy group when planning therapy for childhood ALL. We submit that karyotypic classification is useful because it provides an estimate of the underlying defect(s) of the leukemic clone, which may correlate with clinical presenting features, immunophenotype, molecular genetic findings, and treatment outcome. Clearly, such information may influence therapy design. For instance, the uniformly superior outcome associated with hyperdiploid greater than 50 ALL recently prompted investigators from the Pediatric Oncology Group to begin trials with intensified but relatively nontoxic antimetabolite-based therapy for patients with a DNA index ≥1.16 in their leukemic cells.52 Regarding the
HYPERDIPLOID (47-50) ALL

47 to 50 category, we suggest that it identifies a clinically distinct subgroup (Table 3), whose prognosis is excellent with therapy as used in our Study XI (4-year EFS of 73% ± 4%) but may be substandard with less intensive regimens.

REFERENCES


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