Among 3,638 children with acute lymphoblastic leukemia (ALL) entered on Pediatric Oncology Group (POG) protocols between June 1981 and April 1989, successful cytogenetic studies were available for 2,519, 88 (2.3%) of which had the Philadelphia (Ph) chromosome detected. Features associated with the presence of the Ph chromosome were high leukocyte count (median, $33 \times 10^9/L$), older age (median, 9.6 years), a higher proportion of French-American-British L2 morphology, and a lower frequency of mediastinal mass. Immunologic marker studies at diagnosis in 56 Ph$^+$ cases identified early pre-B ALL in 42 cases (75%), pre-B-cell in 9 (16%), and T-cell in 5 (9%). This distribution is similar to that found in Ph$^-$ ALL. Intensive multiagent chemotherapy induced complete remissions in only 78% of eligible Ph$^+$ patients compared with 96% of those without an identified Ph chromosome ($P < .001$). Of 44 eligible Ph$^+$ patients treated on POG frontline protocols for children with non-T, non-B-cell ALL, 27 have failed therapy, compared with 520 of 1,892 without an identified Ph chromosome (logrank $P < .001$). Ph$^+$ ALL is an aggressive form of acute leukemia that frequently presents in older children with a high leukocyte count, FAB L2 morphology, and a pseudodiploid karyotype, and becomes multidrug-resistant early. Thus, Ph$^+$ cases require early identification to permit treatment with intensive induction regimens and experimental approaches such as bone marrow transplantation.

© 1990 by The American Society of Hematology.
one patient with Ph+ ALL who was mistakenly placed on a protocol for
patients with acute nonlymphocytic leukemia (ANLL), and
seven patients treated on pilot studies (POG 8398, n = 3; POG
8399, n = 1; POG 8698, n = 2; or POG 8699, n = 1).

One patient with Ph+ ALL was excluded from all comparisons of
clinical features and treatment outcome because that patient never
entered a POG treatment protocol. One additional case was ex-
cluded from the treatment outcome analysis but included in the
analysis of clinical features. The reason for exclusion was that the
patient was misdiagnosed initially with ANLL and treated on an
ANLL protocol. Therefore, 56 eligible patients were retained in the
analysis of treatment outcome and 57 in the analysis of clinical
features. The karyotypic features of all 58 identified patients with
Ph+ ALL are described in this report.

Informed consent was obtained from the patients, their parents, or
both, as deemed appropriate.

Cytochemistry and immunologic cell markers. Leukemic cells
were examined morphologically and classified according to FAB
criteria.13 In addition, cells were examined for cytochemical reactiv-
ity to myeloperoxidase and/or Sudan-black B,14 nonspecific esterase,
and sheep erythrocyte receptors with use of established and quality-
controlled techniques at member institutions. Surface and cyto-
plasmic immunoglobulin (sIg and cIg, respectively) and HLA-DR, T,
and “common ALL” (CALLA) antigens were identified as previ-
ously described.15-16 The ALinC 13 study used heteroantisera and
limited monoclonal antibodies; ALinC 14 used only monoclonal
reagents. Also, cytoxicity assays were used in some cases in ALinC
13 and POG 7837, whereas in ALinC 14 and POG 8704 all assays
were performed by immunofluorescence methods with flow cyto-
metry.

Cytogenetics. Cytogenetic studies were performed at member
institutions (ALinC 13) or at a central reference laboratory (Univer-
sity of Alabama at Birmingham, ALinC 14) according to standard
techniques on leukemic cells obtained at diagnosis. Repeat studies at
the time of relapse were not routinely performed. Structural and
numerical abnormalities were noted and centrally reviewed. Cases
were classified as hypodiploid (chromosome complement less than
46), hyperdiploid (47 to 51 or greater than 51 chromosome sub-
groups), pseudodiploid (modal chromosome number = 46 with
structural abnormalities or chromosome substitutions), or normal. If
a karyotype could not be determined, the case was considered
unassignable. A case was considered Ph+ if the 22q11-qter material
had been removed from the derivative chromosome 22 and had not
been replaced with any visually detectable material from another
chromosome. This resulted in the typical Ph chromosome, which
appears to be a deleted chromosome 22. A variant Ph chromosome
was defined as one in which there was no obvious chromosome 9q34
involvement in the formation of the Ph chromosome.

Immunologic classification. All newly diagnosed cases of ALL
were classified as pre-B, B, T, or early pre-B ALL according to the
following criteria: pre-B, ≥10% of marrow lymphoblasts contain cIg;
B, ≥10% of marrow lymphoblasts express sIg; and T, ≥40% of
marrow lymphoblasts lysed by pan-T (pT) heteroantisera (40%
above control lysis by cytotoxicity testing for ALinC 13). T-cell
typing after 1986 was done by flow cytometry. All cases expressing
CD5 or CD7 without HLA-DR on at least 20% of leukemic blasts
were classified as T cell. The early pre-B group included all patients
with ALL who had complete immunophenotyping and were not
classified by the above criteria, regardless of the expression of
CALLA or HLA-DR.

Study design and statistical analysis. The ALinC 13 and 14
trials for newly diagnosed patients with early pre-B or pre-B-cell
ALL and the POG studies 7837 and 8704 for T-cell ALL were
stratified and randomized studies. Because children with Ph+ ALL
had fared poorly on most therapy regimens, we attempted to identify
all such cases and to assign them by immunophenotype to the most
intensive treatment regimen on each major study.

The clinical features of patients with a detected Ph chromosome
were compared to those of Ph− patients, defined as patients with
successful cytogenetic studies, but without an identified Ph chromo-
some. Only these results are presented in this report. However, we
also analyzed the data using all eligible patients, regardless of
whether or not successful cytogenetic studies were available, and
the results were not significantly different except for the comparison
of platelet count levels for patients with or without a Ph chromosome.

In that one comparison, the P value changed from .045 to .17 when
we used only patients with successful cytogenetic studies.

Complete remission rates are reported for all eligible patients
whose Ph+ ALL was recognized at the time of diagnosis and for all
eligible Ph− patients. Event-free survival (EFS) is reported for all
eligible patients with early pre-B or pre-B ALL with successful
cytogenetic studies but lacking an identified Ph chromosome and
treated on ALinC 13 (POG 8036, 1981 to 1986, n = 942) or ALinC
14 (1986 to August 1989, n = 950), and for 14 Ph+ patients with
early pre-B or pre-B−cell ALL treated on ALinC 13 and 30 cases
treated on ALinC 14. Also, EFS is reported for all 56 eligible
patients with Ph+ ALL and for 2,453 otherwise similar patients with
successful cytogenetic studies but without an identified Ph chromo-
some who were treated on any POG study from 1981 to 1986 (Ph+,
n = 1,152 or Ph−, n = 18) and 1986 to August 1989 (Ph+, n = 1,301 or Ph−, n = 38).

Nine additional patients without a detected Ph chromosome who
were diagnosed between 1986 and 1989 have no follow-up data.

Fourteen patients with Ph+ ALL and an early pre-B or pre-B
ALL phenotype were assigned to the SARA regimen (see Appendix)
for continuation therapy, and one was treated on a pilot study (POG
8398). Three children with Ph− T-cell ALL treated during this same
time period (1981 to 1986) were treated on POG 7837 regimen 2.12

Thirty children with Ph+ ALL were treated on the ALinC 14
study, regimen C (see Appendix), and 950 without an identified Ph
chromosome were also treated on this study. An additional two
children with Ph− T-cell ALL were treated on POG 8704 during this
time period, while six other children with early pre-B or pre-B−cell
ALL were treated on POG pilot studies (POG 8398, n = 2; POG
8399, n = 1; POG 8698, n = 2; or POG 8699, n = 1).

All surviving children treated on ALinC 13 have been followed for
at least 4 years. The follow-up period for ALinC 14 and POG 8704 is
relatively short because these studies opened in 1986 and 1987,
respectively.

All reported significance levels resulted from two-sided compari-
sions; the method of Kaplan and Meier19 was used to construct life
tables and curves. Clinical and laboratory features compared by
exact methods for cases with and without the Ph chromosome
included sex, race (black v non-black), CNS leukemia, mediastinal
mass, liver or spleen below the umbilicus, moderate or marked
(visible) lymphadenopathy, CALLA expression, pre-B phenotype
(as compared with early pre-B−) leukocyte counts, age, platelet
levels, and hemoglobin levels. The distributions of quantitative
factors were compared using the Wilcoxon test.20

EFS was defined as the interval between registration and the
earliest of the following events: induction failure, relapse, death from
any cause, last contact, or bone marrow transplant. Patients who
received a bone marrow transplant (n = 7) were censored at the
time of transplant.

RESULTS

Frequency of Ph+ cases. Of 3,638 eligible cases entered
on these studies, 2,519 (69%) had successful cytogenetic
studies, of whom 57 (2.3%) had a Ph chromosome identified.
(One additional patient had a Ph chromosome identified but was not eligible; see treatment section.) Data from patients with successful cytogenetic studies were used to compare clinical characteristics of Ph+ patients with those of patients lacking an identified Ph chromosome. Information regarding treatment outcome was available on 2,509 patients, including 56 with a Ph chromosome identified at diagnosis. These patients were used in the analyses of outcome. The remaining patients were recently diagnosed and no response data were available. We acknowledge that more effort was expended to collect missing data from Ph+ patients than Ph- ones, and that more cytogenetic data were missing on the ALinC 13 than the ALinC 14 study. Approximately two thirds of patients entering the ALinC 13 study had a successful karyotype, and one third had a clonal abnormality demonstrated. These values compare to 76% of patients with a successful karyotype and 52% with a clonal abnormality detected in the ALinC 14 study. If one uses only the cytogenetically better evaluated patients from ALinC 14 to estimate the incidence of Ph+ ALL, the incidence is 2.8% if all cases with a successful karyotype are used; the incidence is 4% if only cases with a clonal abnormality are used.

**Patient characteristics.** The children with Ph+ ALL were significantly older (median = 9.6 years v 4.8 years; \( P < .001 \)). There was no significant difference in race (16% of Ph+ patients and 11% of those without an identified Ph chromosome were black; \( P = .29 \)) or sex distribution (68% v 58% were male; \( P = .11 \)) between the two groups. Characteristics at diagnosis of the 57 Ph+ patients with available clinical information are shown in Table 1, and compared to those of the children with successful cytogenetic studies without an identified Ph chromosome. The median leukocyte count was \( 33 \times 10^{9}/L \) as compared with \( 12.0 \times 10^{9}/L \) for Ph− patients (\( P = .002 \)). The median hemoglobin was 9.6 g/dL versus 7.8 g/dL for Ph− patients (\( P = .014 \)). The median platelet count was \( 68 \times 10^{9}/L \) for Ph+ patients and \( 55 \times 10^{9}/L \) for Ph− patients (\( P = .17 \)). There was no significant difference in the frequency of CNS disease at diagnosis (5% and 5%, respectively). None of the patients with Ph+ ALL had a mediastinal mass (including the five with a T-cell phenotype), as compared with 9% of children without an identified Ph chromosome. Comparisons of proportions of cases with hepatomegaly, spleenomegaly, and marked lymphadenopathy showed no significant differences between Ph+ and Ph− patients.

**FAB classification and immunophenotype.** Of the 50 successfully studied Ph+ patients, 48% had FAB L2 leukemia cells as compared with 25% in Ph− patients (\( P < .001 \)). (The comparison group is limited to ALinC 13 patients because review for ALinC 14 has been completed for Ph+ cases only.) Immunophenotyping studies indicated that 47 of 52 patients (90%) with Ph+ ALL and successful assays for CALLA expressed this antigen, compared to 80% for those with Ph− ALL (including children with T-ALL). Pre-B ALL was present in 16% of cases and T-cell ALL in 9% (five cases). Immunophenotyping studies were not available for one Ph+ patient.

**Cytogenetic features.** Cytogenetic studies (Table 2) showed the classic form of the Ph chromosome, t(9;22)(q34;q11), in 49 patients. A complex Ph translocation involving an additional chromosome was identified in five cases. Seven patients had variant Ph chromosomes, which involved a deletion of chromosome 22, del(22)(q11;qter), or a chromosome 22 translocation with no obvious (visible) involvement of 9q34 in the formation of the Ph chromosome. Among the 49 patients with the classic Ph chromosome, 24 displayed other cytogenetic abnormalities in the major clone. The most frequent of these was monosomy for part or all of chromosome 7, observed in cells from 14 patients. The ploidy distribution in the 58 patients with Ph+ ALL identified at the time of diagnosis was as follows: pseudodiploid, \( n = 34 \); hyperdiploid with 47 to 51 chromosomes, \( n = 5 \); hyperdiploid with greater than 51 chromosomes, \( n = 4 \); and hypodiploid, \( n = 15 \). Remission cytogenetic studies were performed on bone marrow cells from 20 patients. One case retained the Ph chromosome and 19 had no observed cytogenetic abnormalities.

**Treatment outcome.** Complete remission was induced in 40 of 51 children with Ph+ ALL who have completed induction (78%) and received treatment on ALinC 13 or ALinC 14 as compared with 96% of patients without an identified Ph chromosome (\( P < .001 \)). All of the 11 patients who did not enter remission had drug-resistant leukemia. One had T-cell ALL.

Of 15 Ph+ patients who entered remission on ALinC 13, a pilot study, or POG 7837, all but one has relapsed: 12 in the marrow and 2 in the CNS. Ten of the 14 relapses occurred within 2 years of diagnosis. Of the two children with T-cell ALL who entered remission after treatment on these studies, both relapsed in the bone marrow at 2 and 9 months and died at 8 and 16 months, respectively. Only 1 of 18 patients treated on AlinC 13, POG 7837, or the POG 8398 pilot study remains in continuous complete remission (at 56+ months). The one surviving child had a variant Ph chromosome without evident involvement of chromosome 9.

The Kaplan-Meier plots of EFS for the eligible patients with or without an identified Ph chromosome treated on ALinC 13 or ALinC 14 are shown in Fig 1. There is no significant difference in EFS for Ph+ patients treated on ALinC 13 versus ALinC 14 (\( P = .96 \)). Two additional children with Ph+ T-ALL were treated on POG 8704 between 1986 and May 1989. Both entered complete remission; one is disease-free at 8+ months, while the other had a bone marrow relapse at 5 months and subsequently died.

Seven patients with Ph+ ALL who entered remission on the ALinC 14 or POG 8698 (\( n = 1 \)) pilot study have
Table 2. Karyotype of Patients with Ph⁺ ALL

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Karyotype of the Major Clone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63,XX, +X, +2, +2, +3, +4, +5, +8, +9, +10, +12, +13, +15, +16, +17, +18, +21, +del(22)(q11)</td>
</tr>
<tr>
<td>2</td>
<td>51,XX, +6, +7, +8, +13, +21, +del(22)(q11), +3mar</td>
</tr>
<tr>
<td>3</td>
<td>46,XY,t(8;14)(q11;q32),t(9;22)(q34;q12)</td>
</tr>
<tr>
<td>4</td>
<td>46,XY,t(12;14)(q23;q12),t(9;22)(q34;q12)</td>
</tr>
<tr>
<td>5</td>
<td>45,XY, −7, −9, −22, +del(7)(q37)(p11), +11q34(q11), +del(22)(7)(q7)(p13)</td>
</tr>
<tr>
<td>6</td>
<td>46,XY, +9, −11, −11, −16, t(14;22)(q32;q11), +2del(11)(t11;11)(p13)</td>
</tr>
<tr>
<td>7</td>
<td>53,XXV, +X, +6, +14, +17, +18, +21, +22,t(9;22)(q34;q11)</td>
</tr>
<tr>
<td>8</td>
<td>45,XX, −1, −17, i(9q),del(22)(q11), +del(11)(t11;11)(q?)(2q22)?</td>
</tr>
<tr>
<td>9</td>
<td>45,XY, −9, −13, t(9;22)(q34;q12), +mar</td>
</tr>
<tr>
<td>10</td>
<td>46,XX,t(11;22)(p11;cq11)</td>
</tr>
<tr>
<td>11</td>
<td>47,XY, del(9)(p13), t(9;22)(q34;q11), +Ph</td>
</tr>
<tr>
<td>12</td>
<td>46,XY, del(22)(q11)</td>
</tr>
<tr>
<td>13</td>
<td>55,XY, +X, +2, +4, +6, +9, +18, +21, +22, t(9;22)(q34;q11), +Ph</td>
</tr>
<tr>
<td>14</td>
<td>45,XY, −7, −20, +del(11)(p11)t9;22(10)(q34; q11p13)</td>
</tr>
<tr>
<td>15</td>
<td>46,XY,t(12;22)(p12;q11)</td>
</tr>
<tr>
<td>16</td>
<td>45,XY, +21, +21, t(22)(q34;q11)</td>
</tr>
<tr>
<td>17</td>
<td>45,XY, −7, −11, +del(11)(t7;11)(q11;q13), t(9;22)(q34;q11)</td>
</tr>
<tr>
<td>18</td>
<td>45,XY, −7;19;22(q34;q11)</td>
</tr>
<tr>
<td>19</td>
<td>53,XX, +7, +3, +5, +17, +21, t(9;22)(q34;q11), +Ph, −mar</td>
</tr>
<tr>
<td>20</td>
<td>47,XX, +17, t(9;22)(q34;q11), t(11;14)(q13;q13)</td>
</tr>
<tr>
<td>21</td>
<td>46,XY, −9, −12, −17, −22, del(2)(p13), del(2)(p21), del(16;18)(q13;p11), +del(22)(t9;22)(q34;q11), +del(9)(t9;22)(q11?q34; q11q13;?), +del(12)(t12;p12?)</td>
</tr>
<tr>
<td>22</td>
<td>46,XY,i(9q),del(14)(q24), t(9;22)(q34;q11)</td>
</tr>
<tr>
<td>23</td>
<td>46,XY, del(9)(p13), t(9;22)(q34;q11)</td>
</tr>
<tr>
<td>24</td>
<td>45,XY, −7, −9, −22, +del(9), t(7;9)(q22)</td>
</tr>
<tr>
<td>25</td>
<td>46,XY, del(7)(q22q32), del(7)(q13), del(13)(q11q22), del(9)(q13), t(9;22)(q34;q11), +2mar</td>
</tr>
<tr>
<td>26</td>
<td>46,XX,t(6;9)(q22), t(13)p22q34; q11)</td>
</tr>
<tr>
<td>27</td>
<td>46,XY, −7, (2;9;22)(q11;11), +mar</td>
</tr>
<tr>
<td>28</td>
<td>41,XY, −3, −7, −9, −12, −14, t(9;22)(q34;q11)</td>
</tr>
<tr>
<td>29</td>
<td>45,XY, −7, −12, +del(12), t(7;12)(q11;12)(p11)t9;22(q34;q11)</td>
</tr>
<tr>
<td>30</td>
<td>45,XY, +20, t(9;22)(q34;q11)</td>
</tr>
<tr>
<td>31-34</td>
<td>45,XY, +7, t(9;22)(q34;q11)</td>
</tr>
<tr>
<td>35-49</td>
<td>46,XX,t(9;22)(q34;q11)</td>
</tr>
<tr>
<td>50-58</td>
<td>46,XX,t(9;22)(q34;q11)</td>
</tr>
</tbody>
</table>

received allogeneic bone marrow transplantation. Three survive disease-free at 10, 20, +, and 29 months posttransplantation. The other four patients treated with bone marrow transplantation died of recurrent disease (n = 3) at 8, 10, and 13 months, respectively, or of a toxic effect of bone marrow transplantation (n = 1) 8 months posttransplant.

Moreover, if EFS is compared for all children, regardless of treatment study, and grouped according to time period (1981 to 1986 or 1986 to May 1989), Ph⁺ cases fare much worse than children treated during the same time period without an identified Ph chromosome (P < .001 for both comparisons, see Fig 1).

## DISCUSSION

The frequency of the Ph chromosome (2.3%) in this relatively large series of children with ALL is slightly lower than those reported by investigators at St Jude Children's Research Hospital (Memphis, TN) and the Third International Workshop on Chromosomes in Leukemia (4.9% and 5.7%, respectively). The distribution of major immunophenotypes of childhood ALL does not differ significantly for patients with the Ph⁺ chromosome. About 73% of our cases of Ph⁺ ALL were derived from cIg⁻ B-progenitor cells, 16% were cIg⁺ (ie, pre-B cell), and 9% were derived from thymocytes. To our knowledge, all cases of Ph⁺ ALL studied at the molecular level have been of B-progenitor lineage; it remains to be demonstrated whether the genetic lesion is the same in cases of Ph⁺ ALL that involve transformation of thymocytes. The T-cell cases were of particular interest because lymphoblastic conversion of Ph⁺ CML has generally been associated with a B-progenitor phenotype, and the cytogenetic findings in Ph⁺ ALL are indistinguishable from Ph⁺ CML.

Ph⁺ CML is known to arise in a multipotent hematopoietic stem cell; the Ph chromosome is found in myeloid precursors, megakaryocytes, erythrocytes, and B-lymphoid cells. However, only recently has the Ph chromosome been found in T cells in some cases of Ph⁺ acute leukemia. In contrast to CML, childhood ALL is a clonal disorder that usually appears to involve malignant transformation of a committed lymphopoietic progenitor of either T- or B-lineage. An interesting recent report indicates that some cases of Ph⁺ ALL may involve a pluripotent hematopoietic progenitor cell.

Generally, adults or children with CML in clinical remission retain the Ph chromosome, whereas children with Ph⁺ ALL do not. Only 1 of our 20 Ph⁺ cases assessed in remission continued to demonstrate the Ph chromosome, suggesting that most of these cases probably did not represent lymphoblastic blast crises of CML. None of the patients presented here had been bone marrow findings suggesting CML at
any time, nor was a history of myeloproliferative disease obtained in any of these children.

The cytogenetic lesion in pediatric cases of Ph+ CML and ALL has been shown to differ at the molecular level. In CML, the translocation is associated with a breakpoint on chromosome 22 that generally lies within a 5.8-kilobase (kb) span of DNA known as the breakpoint cluster region (bcr). By reciprocal translocation a decapitated c-abl protooncogene from chromosome 9 is joined to the breakpoint on chromosome 22 to form a bcr-ABL fusion gene from which an 8.0-kb transcript originates. Translation results in a protein with a molecular weight of 210 Kd (p210). In contrast, most cases of Ph+ childhood ALL have breakpoints on chromosome 22 outside of the bcr, and the fusion gene created by the translocation encodes a messenger RNA of 6.5 kb, which is translated to a 185-Kd protein (p185). Both fusion genes are constitutively activated and their protein products function as tyrosine kinases, leading to speculation that they may be involved in intracellular signaling. This information indicates that different pathogenetic mechanisms may be involved in these two diseases. Molecular study of our cases might have provided additional information regarding their relationship to CML, but has not been done as of yet.

It is of interest that the only Ph+ patient who was a long-term survivor in the ALINc 13 study (1981 to 1986) had a Ph variant [del(22)(q11)] rather than a classic t(9;22)(q34; q11). This was also the case in the two survivors reported by Ribeiro et al. It is possible that patients with Ph variants have a different disease. Tachibana et al have studied one such case at the molecular level and reported the absence of the characteristic molecular defects of both Ph+ CML and Ph+ ALL. However, it should be noted that 5 of the 7 children with a Ph variant in this series failed treatment early.

Only 4 of 50 children (8%) with the classic Ph chromosome had a hyperdiploid greater than 51 karyotype, a feature found in about one fourth of children with Ph− ALL and associated with the best prognosis. The two patients treated on ALINc 13 who had a classic t(9;22) and a hyperdiploid greater than 51 karyotype failed therapy early, suggesting that this translocation confers a poor prognosis regardless of ploidy. Nine of our cases had monosomy 7, and five had a structural abnormality resulting in partial monosomy of chromosome 7. Monosomy 7 has been associated with a poor prognosis in childhood ANLL, and we have recently reported that children with both the Ph chromosome and monosomy 7 may have an even worse treatment outcome. This patient subgroup is currently being analyzed in detail, and the results will be reported separately. It is also interesting that 31 of our 58 cases had abnormalities in addition to the Ph chromosome at the time of diagnosis.

Several reports of small groups of children with Ph+ ALL have suggested that these patients tend to have other known poor risk features such as a high white blood cell (WBC) level, FAB L2 morphology, and age greater than 10 years at presentation. However, others have suggested that the Ph chromosome exerts an independent prognostic influence. Our patients generally were older and more often had higher WBC levels and FAB L2 morphology than other children with ALL. This finding agrees with those of Ribeiro et al. However, in both studies there were too few patients with adequate follow-up to permit multivariate analysis of the independent prognostic importance of this or other translocations.

Our experience, combined with that of others, provides convincing evidence of the poor prognosis of children with Ph+ ALL with the t(9;22) treated with modern multiagent chemotherapy. These patients failed induction therapy more often, and those who achieved complete remission usually relapsed early. Therefore, children with Ph+ ALL should be identified at diagnosis and given intensive multiagent induction therapy to improve their remission rate, and should then receive highly experimental therapy. The curative role of bone marrow transplantation has been established for patients with Ph+ CML. This approach to treatment is now being investigated for children with Ph+ ALL in first remission: 3 of 7 children who received allogeneic transplants in this series remain disease-free at 10+, 20+, and 29+ months. Children without detectable involvement of chromosome 9 should have molecular studies for confirmation of the diagnosis. With the availability of molecular probes that permit sensitive, rapid, and relatively simple detection of the Ph chromosome, such testing should soon become a part of the routine evaluation of all new cases of ALL.

ACKNOWLEDGMENT

The authors thank Christy Wright for editorial review and Peggy Vandiveer for typing the manuscript.

APPENDIX

SCHEMA FOR REGIMEN 3, ALINC 13 (POG 8036), STANDARD, AND ROTATING AGENTS (SARA)

Induction. Regimens 1, 2, and 3: vincristine (VCR), 2 mg/m² (max. 2 mg) intravenously (IV)/week ×4; prednisone (PRED), 60 mg/m² (max. 60 mg) orally/day ×28.

Intensification. First part = L-asparaginase (L-ASP) 6,000 U/m²/d intramuscularly (IM) ×14; cyclophosphamide (CYCLO), 1 g/m² IV on days 2 and 15 of L-ASP, followed by 2 weeks rest. Second part (regimen 3) = TIT, every 3 to 4 days x 5; 6-mercaptopurine (6-MP), 50 mg/m²/d orally.

Continuation. Backbone = 6-MP, 50 mg/m² orally/day; MTX, 20 mg/m² orally/week. Drug pulses = 2-week rotating pulses every 6 weeks: (1) VCR, 2 mg/m² (max. 2 mg) IV day 1; Adriamycin, (ADRIA) 40 mg/m² IV day 1, PRED, 60 mg/m² (max. 60 mg) orally/d ×14; (2) ARA-C, 120 mg/m²/d continuous infusion days 1 to 4; PRED as in pulse (1); (3) 6-thioguanine (6TG), 300 mg/m²/d orally days 1 to 4, CYCLO, 600 mg/m² IV day 5, PRED as in pulse (1). CNS = TIT every 6 weeks first year; then every 12 weeks.

SCHEMA FOR REGIMEN C, ALINC 14 (POG 8602), INTERMEDIATE-DOSE MTX AND ARA-C

Remission induction. PRED, 40 mg/m²/d orally (max. dose, 60 mg) x29 days; VCR, 1.5 mg/m² IV/wk ×4 weeks; L-ASP, 6,000 U/m² IM 3 times weekly × 6 doses; 6-MP, 75 mg/m² orally × 14 days (days 29 to 43). Intrathecal chemotherapy with hydrocortisone, 15 mg; MTX, 15 mg; and
ARA-C, 30 mg if 9 years or older (scaled down for younger children). Administered on days 1 and 22 of induction treatment, days 29 and 36 of CNS intensification, and thereafter on weeks 9, 12, 15, 18, 25, and every 8 weeks to week 105.

**Intensification.** Intermediate dose MTX, 1 g/m² over 24 hours with leucovorin rescue overlapping by 12 hours with ARA-C 1,000 mg/m² IV over 24 hours weeks 7, 10, 13, 16, 19, and 22.

**Continuation therapy.** MTX 20 mg/m² IM weekly and daily 6-MP (75 mg/m²/d) orally, weeks 25 to 156. Pulse: PRED and VCR at same doses as administered in induction; VCR weekly ×2 and PRED daily orally ×7 at weeks 8, 17, 25, 41, 57, 73, 89, and 105.

**REFERENCES**


23. Clark SS, McLaughlin J, Crist WM, Champlin R, Witte ON: Unique forms of the abl oncogene tyrosine kinase distinguish Ph1 positive CML from Ph positive ALL. Science 235:85, 1987


