Results of Therapy for Acute Lymphoblastic Leukemia in Black and White Children

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Context  Treatment results for acute lymphoblastic leukemia (ALL) clearly have improved over the past decade, but black children have not fared as well as white children in large national trials.

Objective  To compare the clinical outcomes of therapy for black and white children with ALL treated at a single institution.

Design, Setting, and Patients  A retrospective analysis of 412 children and adolescents (68 black, 338 white, and 6 other race) with newly diagnosed ALL who were treated consecutively at a pediatric cancer center in Memphis, Tenn. Patients were enrolled from December 1991 to July 1998 in successive Total Therapy studies regardless of race, ethnicity, or ability to pay and received risk-directed therapy according to stringent criteria.

Interventions  All patients received the same intensive, remission-induction therapy followed by 120 weeks of risk-assigned postremission therapy that included reinduction treatment, pulses of high-dose methotrexate, and early intensification of intrathecal chemotherapy.

Main Outcome Measures  Event-free and overall survival rates for black and white children were estimated by the method of Kaplan and Meier and compared with the Mantel-Haenszel test and by Cox proportional hazards regression analysis, adjusting for known prognostic factors.

Results  The 68 black children were significantly more likely than the 338 white children to have higher-risk prognostic features, including an initial leukocyte count greater than 100 × 10^9/µL, a T-cell immunophenotype, and the t(1;19) chromosomal translocation with E2A-PBX1 fusion, and were less likely to have hyperdiploid blast cells, a favorable prognostic factor in childhood ALL. However, the clinical outcomes for these 2 cohorts were not significantly different: 5-year event-free and overall survival rates were 80.7% (95% confidence interval [CI], 70.3%-91.1%) and 86.2% (95% CI, 77.2%-95.2%) for black children vs 79.4% (95% CI, 74.7%-84.1%) and 85.0% (95% CI, 80.9%-89.1%) for white children. Ten-year results also were comparable, but the CIs were wide because of the small numbers of patients who had been followed up for 10 years or more.

The lack of a racial effect on the long-term outcome of therapy was still apparent in a multivariate Cox regression analysis, adjusting for sex, age, presenting leukocyte count, leukemic cell DNA index, immunophenotype, and central nervous system status.

Conclusion  With equal access to effective antileukemic therapy, black and white children with ALL can expect the same high rate of cure.


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hood ALL can be abolished by effective treatment. Reviews of national and international data indicate a significant improvement in ALL treatment results during the 1990s. Nonetheless, 2 recent studies by the Pediatric Oncology Group (POG) and the Children’s Cancer Group (CCG) still disclosed a racial disparity in clinical outcome for patients treated within the past decade. We therefore analyzed the results of successive clinical trials during the 1990s at our cancer center to determine if the benefits of improved therapy extend equally to black and white children with ALL.

METHODS

Study Population and Setting

From December 1991 to July 1998, 412 consecutive children and adolescents with newly diagnosed ALL were enrolled in Total Therapy studies XIIIA (1991-1994) and XIIIB (1994-1998) at St Jude Children’s Research Hospital. This nonprofit tertiary care center draws most of its patients (85%) from an 8-state area (Tennessee, Mississippi, Louisiana, Illinois, Arkansas, Missouri, Kentucky, and Alabama). All patients are referred by a physician and are accepted for treatment without regard to their insurance coverage or financial status. All costs of treatment that exceed payments by third-party payers (if any) are absorbed by the hospital; families received no direct charges.

The diagnosis of ALL was based on morphological and cytochemical evaluation of bone marrow smears as well as immunophenotyping and cytogenetic analysis of lymphoid blast cells. Depending on the pattern of blast cell reactivity to a panel of monoclonal antibodies, cases were classified as T-cell or B-cell precursor, as described previously. Flow cytometric determination of the DNA content of blast cells routinely was used to classify cases according to their DNA index (ratio of DNA content of leukemic cells vs that of normal diploid G0/G1 cells). Samples of cerebrospinal fluid were examined at diagnosis, and the central nervous system (CNS) status was classified as follows: CNS1, no identifiable blast cells in an atraumatic lumbar puncture sample; CNS2, less than 5 leukocytes/µL with identifiable blast cells in an atraumatic lumbar puncture sample; CNS3, 5 leukocytes/µL or more with identifiable blast cells in an atraumatic lumbar puncture sample or the presence of cranial nerve palsy; traumatic lumbar puncture without blast cells, 10 erythrocytes/µL or more without identifiable blast cells; and traumatic lumbar puncture with blast cells, 10 erythrocytes/µL or more with identifiable blast cells.

Risk Classification and Treatment

Patients were assigned to a higher- or lower-risk group based on various combinations of presenting leukocyte count, age, genotype, immunophenotype, CNS status, presence or absence of testicular leukemia, and response to early therapy. Initial treatment for all patients in studies XIIIA and XIIIB consisted of intravenous high-dose methotrexate, mercaptopurine, or both, followed 4 days later by remission induction therapy that included prednisone, vincristine, daunorubicin, asparaginase, and etoposide plus cytarabine. On attaining complete remission, all patients received 2 weeks of consolidation therapy with high-dose methotrexate and mercaptopurine, followed by 120 weeks of risk-directed postremission therapy. Postremission therapy for lower-risk cases consisted of daily doses of mercaptopurine and weekly doses of methotrexate, reinforced by high-dose methotrexate and mercaptopurine every 8 weeks for the first year, and pulses of prednisone (study XIIIA) or dexamethasone (study XIIIB) plus vincristine every 4 weeks. Postremission therapy for higher-risk cases consisted of drug pairs administered in weekly rotation: etoposide plus cyclophosphamide; mercaptopurine plus methotrexate; methotrexate plus cytarabine; prednisone plus vincristine plus asparaginase (study XIIIA) or dexamethasone plus vincristine (study XIIIB); and mercaptopurine plus high-dose methotrexate (replaced by low-dose methotrexate after 1 year). To ensure compliance, methotrexate was given intravenously. Reinduction treatment, similar to that used during initial induction, was administered from week 32 to 37 (study XIIIA) or from week 16 to 21 (study XIIIB). The type of CNS-directed therapy was based on presenting risk factors and CNS status. All patients received triple intrathecal chemotherapy in age-appropriate doses during remission induction, consolidation, and postremission therapy (for up to 1 year). Cranial irradiation plus 5 doses of intrathecal chemotherapy (from week 56 to 59) was reserved for a subgroup of patients at high risk of CNS relapse (1800 rad) or those presenting with a CNS3 status (2400 rad).

The treatment protocols were approved by the hospital’s institutional review board and the National Cancer Institute. Written informed consent was obtained from the patients’ parents or guardians.

Statistical Analysis

The exact χ² test was used to compare presenting features between white and black patients. Event-free survival and survival rates were estimated by the method of Kaplan and Meier and were compared with the Mantel-Haenszel test. Cox proportional hazards regression analysis was used to investigate the impact of race on event-free survival and survival, adjusting for sex, age, presenting leukocyte count, leukemic cell DNA index and immunophenotype, and CNS status. The duration of event-free survival was defined as the time from diagnosis until the date of failure, including induction failure, relapse, death, or the development of a second malignancy, or until the date of last contact. Patients who did not attain a complete remission were considered failures to respond to therapy at time zero. Survival was measured from the date of initial diagnosis of leukemia to the date of death from any cause or the date of last contact. All analyses were performed on the basis of intent-to-treat.
Cumulative incidence functions of various forms of treatment failure were constructed by the method of Kalbfleish and Prentice for patients who achieved complete remission and were compared with Gray’s test. All other failures were considered competing events in the estimation of cumulative incidence functions. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for all types of time-dependent adverse events in black vs white children, using the proportional hazards regression model for cumulative incidence. The relative risk of induction failure between the 2 cohorts was calculated according to the method of Agresti. The proportional hazards assumptions were checked separately for each covariate, using a graphic method to ensure the validity of the results. All statistical analyses were performed with SAS version 8.2 (SAS Institute, Cary, NC) and StatXact5 (Cytel, Cambridge, Mass). The preset level of significance was .05.

No patients were lost to follow-up during treatment. At the time of analysis, 91% of white and 80% of black survivors had been seen within 12 months, and only 1 white and 1 black patient had not been contacted within the previous 2 years. The median follow-up for all patients was 7 years (range, 3.6-10.9 years).

RESULTS

Patient Characteristics

Of the 412 patients studied, 338 (82.0%) were white (including those of Hispanic origin) and 68 (16.5%) were black; the remaining 6 patients (1.5%) represented other races. TABLE 1 compares the presenting features of the patients by race. Black patients had a higher median leukocyte count (17.3 \times 10^3/\mu L vs 11.5 \times 10^3/\mu L), and one fourth had counts greater than 100 \times 10^3/\mu L. They also were significantly more likely to have T-cell ALL or B-cell precursor ALL with the t(1;19)/E2A-PBX1, and were less likely to have hyperdiploid leukemic cells (DNA index, \geq 1.16), which confer a favorable prognosis. A higher percentage of blacks had a traumatic lumbar puncture, which has been linked to a poorer clinical outcome. Thus, an excessive proportion of black children were characterized by higher-risk features at presentation of their disease. To obtain an indirect measure of socioeconomic status, we assessed the insurance coverage of our patients at the last follow-up analysis. Black compared with white patients were less

<table>
<thead>
<tr>
<th>Feature</th>
<th>White (n = 338)</th>
<th>Black (n = 68)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>13 (3.9)</td>
<td>2 (2.9)</td>
<td>.68</td>
</tr>
<tr>
<td>1-10</td>
<td>230 (68)</td>
<td>43 (63.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>95 (28.1)</td>
<td>23 (33.8)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>.69</td>
</tr>
<tr>
<td>Male</td>
<td>196 (57.7)</td>
<td>37 (54.4)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>143 (42.3)</td>
<td>31 (45.6)</td>
<td></td>
</tr>
<tr>
<td>Leukocyte count, \times 10^3/\mu L</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>156 (45.9)</td>
<td>24 (35.3)</td>
<td>.02</td>
</tr>
<tr>
<td>10-49</td>
<td>97 (28.7)</td>
<td>21 (30.9)</td>
<td></td>
</tr>
<tr>
<td>\geq 100</td>
<td>43 (12.7)</td>
<td>5 (7.4)</td>
<td></td>
</tr>
<tr>
<td>Cell lineage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-cell precursor</td>
<td>289 (85.5)</td>
<td>49 (74.2)</td>
<td>.03</td>
</tr>
<tr>
<td>T-cell</td>
<td>49 (14.5)</td>
<td>17 (25.8)</td>
<td></td>
</tr>
<tr>
<td>DNA index, \geq 1.16</td>
<td></td>
<td></td>
<td>.05</td>
</tr>
<tr>
<td>&lt;1.16</td>
<td>78 (23.1)</td>
<td>8 (11.8)</td>
<td></td>
</tr>
<tr>
<td>\geq 1.16</td>
<td>260 (76.9)</td>
<td>60 (88.2)</td>
<td></td>
</tr>
<tr>
<td>t(4;11)/MLL-AF4 Present</td>
<td>10 (3.0)</td>
<td>1 (1.5)</td>
<td>.70</td>
</tr>
<tr>
<td>Absent</td>
<td>328 (97.0)</td>
<td>67 (98.5)</td>
<td></td>
</tr>
<tr>
<td>TEL-AML1 Present</td>
<td>64 (18.9)</td>
<td>9 (13.2)</td>
<td>.30</td>
</tr>
<tr>
<td>Absent</td>
<td>274 (81.1)</td>
<td>59 (86.8)</td>
<td></td>
</tr>
<tr>
<td>t(9;22)/BCR-ABL Present</td>
<td>8 (2.4)</td>
<td>4 (5.9)</td>
<td>.23</td>
</tr>
<tr>
<td>Absent</td>
<td>330 (97.6)</td>
<td>64 (94.1)</td>
<td></td>
</tr>
<tr>
<td>t(1;19)/E2A-PBX1 Present</td>
<td>10 (3.0)</td>
<td>8 (11.8)</td>
<td>.005</td>
</tr>
<tr>
<td>Absent</td>
<td>328 (97.0)</td>
<td>60 (88.2)</td>
<td></td>
</tr>
<tr>
<td>CNS status</td>
<td></td>
<td></td>
<td>.045</td>
</tr>
<tr>
<td>CNS 1</td>
<td>201 (59.5)</td>
<td>30 (44.1)</td>
<td></td>
</tr>
<tr>
<td>CNS 2</td>
<td>97 (28.7)</td>
<td>21 (30.9)</td>
<td></td>
</tr>
<tr>
<td>CNS 3</td>
<td>9 (2.7)</td>
<td>3 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Traumatic lumbar puncture without blast cells</td>
<td>8 (2.4)</td>
<td>4 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Traumatic lumbar puncture with blast cells</td>
<td>23 (6.8)</td>
<td>10 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Ploidy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>46 (14.2)</td>
<td>13 (19.4)</td>
<td>.30</td>
</tr>
<tr>
<td>Hypodiploid</td>
<td>16 (4.9)</td>
<td>4 (6.0)</td>
<td></td>
</tr>
<tr>
<td>Pseudodiploid</td>
<td>120 (37.0)</td>
<td>27 (40.3)</td>
<td></td>
</tr>
<tr>
<td>Hyperdiploid 47-50</td>
<td>48 (14.8)</td>
<td>12 (17.9)</td>
<td></td>
</tr>
<tr>
<td>Hyperdiploid &gt;50‡</td>
<td>94 (29.0)</td>
<td>11 (16.4)</td>
<td></td>
</tr>
<tr>
<td>Risk group§ Higher</td>
<td>230 (68.0)</td>
<td>52 (76.5)</td>
<td>.20</td>
</tr>
<tr>
<td>Lower</td>
<td>108 (32.0)</td>
<td>16 (23.5)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system.*Percentages may not equal 100 due to rounding.†Data missing for this category.‡Comparison based on the presence or absence of hyperdiploidy \geq 50 chromosomes; P = .048.§Definition of risk classification can be found in references 19 and 20.

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likely to have private insurance (33.8%; 95% CI, 21.2%-48.1% vs 56.8%; 95% CI, 50.3%-63.3%) and more likely to have public insurance (54.4%; 95% CI, 39.3%-68.9% vs 22.5%; 95% CI, 17.3%-28.2%), suggesting that lower proportions of black patients were in the middle and upper socioeconomic classes. The uninsured rates were comparable between white and black patients (20.7%; 95% CI, 15.8%-26.3% vs 11.8%; 95% CI, 4.8%-23.5%).

**Treatment Outcome**

The overall 5-year event-free survival and survival rates were 79.4% (95% CI, 74.9%-83.9%) and 84.6% (95% CI, 80.5%-88.7%) for the entire cohort of 412 patients. The 10-year rates were 72.7% (95% CI, 52.1%-93.3%) and 79.7% (95% CI, 62.1%-97.3%), respectively.

All 68 black patients achieved complete remission compared with 330 white patients (97.6%) (relative risk, 0.29; 95% CI, 0.02-4.98; P = .20). The risks of subsequent adverse events are compared in **Table 2**. White and black patients were equally likely to relapse or to develop a second malignancy.

Event-free survival rates showed no significant differences by race (**FIGURE, A, P = .91**). Five-year Kaplan-Meier estimates were 80.7% (95% CI, 70.3%-91.1%) for black children and 79.4% (95% CI, 74.7%-84.1%) for white children, while 10-year estimates were 74.8% (95% CI, 22.9%-100%) and 73.6% (95% CI, 58.7%-88.5%), respectively. Nine black and 60 white patients have died. Comparison of overall survival rates by race revealed similar outcomes for blacks and whites (**FIGURE, B, P = .43**). Five-year survival rates were 86.2% (95% CI, 77.2%-95.2%) for black and 85.0% (95% CI, 80.9%-89.1%) for white children; 10-year rates were 86.2% (95% CI, 49.9%-100%) and 80.3% (95% CI, 67.4%-93.2%), respectively.

In a multivariate Cox analysis, black and white patients showed no significant differences in either event-free survival (HR, 0.75; 95% CI, 0.42-1.34; P = .33) or survival (HR, 0.58; 95% CI, 0.28-1.20; P = .14). Five-year event-free survival rates were similar for black patients and white patients in both the lower- and high-risk groups, as well as in a very high-risk group defined uniquely for this analysis (**TABLE 3**). Among the very high-risk group (defined by the presence of t(4;11), t(9;22), hypodiploidy, age <12 months, or leukocyte count >200 × 10^9/L in B-cell precursor ALL), the 5-year event-free survival rate was 56.1% (95% CI, 0.29-1.20; P = .14).

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**Table 2. Frequency Distribution and Risk of Adverse Events According to Race**

<table>
<thead>
<tr>
<th>Category</th>
<th>White (n = 338)</th>
<th>Black (n = 68)</th>
<th>Hazard Ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic relapse†</td>
<td>33</td>
<td>11</td>
<td>1.76 (0.90-3.46)</td>
</tr>
<tr>
<td>Isolated CNS relapse</td>
<td>6</td>
<td>0</td>
<td>. . .</td>
</tr>
<tr>
<td>Isolated testicular relapse</td>
<td>1</td>
<td>0</td>
<td>. . .</td>
</tr>
<tr>
<td>Other relapse‡</td>
<td>2</td>
<td>1</td>
<td>2.53 (0.23-27.59)</td>
</tr>
<tr>
<td>Second malignancy</td>
<td>19</td>
<td>3</td>
<td>0.87 (0.25-2.84)</td>
</tr>
<tr>
<td>Death in remission</td>
<td>9</td>
<td>0</td>
<td>. . .</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>15</td>
<td>1.08 (0.62-1.89)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CNS, central nervous system.

* Hazard ratio of specific adverse event in black vs white children. In each category, the hazard for white children is 1, so that lower or higher values indicate a decreased or increased risk for that event in black children. Confidence intervals could not be determined for isolated CNS relapse, isolated testicular relapse, and death in remission because of the lack of such events in black patients (ellipses).

† Including patients with a combined hematologic and extramedullary relapse.

‡ Ocular relapse in 2 white children and a combined CNS and mediastinal relapse in 1 black child.

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**Figure.** Kaplan-Meier Estimates of Event-Free and Overall Survival for Black and White Children With Acute Lymphoblastic Leukemia

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39.8%-72.4%) for the 44 white patients and 58.3% (95% CI, 28.1%-88.5%) for the 12 black patients.

**Prognostic Factors**

Among white patients, age of 1 to 10 years, low leukocyte count, a B-cell precursor immunophenotype, and a DNA index of 1.16 or greater were each associated with a favorable prognosis, whereas the presence of the t(4;11)/MLL-AF4 or t(9;22)/BCR-ABL conferred a poor outcome (Table 3). Similar trends were noted in black patients, but only the presence of the t(9;22)/BCR-ABL or the t(4;11)/MLL-AF4 or a CNS3 status attained statistical significance, most likely because of the relatively small sample sizes.

**COMMENT**

The results of this outcome analysis indicate that black and white children with ALL fared equally well in successive clinical trials conducted at a single pediatric cancer center during the 1990s. Five-year event-free survival rates for the 2 cohorts virtually were identical: 80.7% vs 79.4% at 5 years and 74.8% vs 73.6% at 10 years for black and white patients, respectively. With 10-year overall survival rates of 86.2% and 80.3%, it appears that approximately 80% of both black and white patients will be cured, a superior end result compared with the 75% cure rate in the 1980s.14 Although we cannot entirely exclude a clinically important difference in outcome between black and white patients given the relatively small sample of blacks, our statistical analysis had at least a 92% chance of detecting a 15% difference in 10-year event-free survival rates (96% chance for 5-year rates) at the 5% significance level.

The results presented herein contrast with those recently published by the POG and the CCG for patients treated during the 1990s.17,18 Among noninfant B-cell precursor ALL cases treated in the POG 9005 and 9006 studies between 1991 and 1994, the 5-year event-free survival rates (SE) for blacks was 69% (1.9%), compared with 78% (0.7%) for whites.18 Thus, while the clinical outcome of therapy for white children enrolled in these CCG protocols was quite good, black children continued to have a poorer result.

Because our catchment area has a higher proportion of black people than the national average, they constituted a larger fraction (16.5%) of the patients treated in studies XIIIA and XIIIB as compared with percentages in the POG (10.2%) and CCG (6.0%) studies. However, there was no indication that black

**Table 3. Prognostic Factors According to Race**

<table>
<thead>
<tr>
<th>Feature</th>
<th>White</th>
<th>P Value</th>
<th>Black</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5-Year EFS</strong></td>
<td><strong>5-Year EFS</strong></td>
<td><strong>P</strong></td>
<td><strong>5-Year EFS</strong></td>
<td><strong>P</strong></td>
</tr>
<tr>
<td><strong>% (95% CI)</strong></td>
<td><strong>% (95% CI)</strong></td>
<td></td>
<td><strong>% (95% CI)</strong></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-10</td>
<td>85.5 (80.6-90.4)</td>
<td>&lt;.001</td>
<td>86.0 (74.2-97.8)</td>
<td>.09</td>
</tr>
<tr>
<td>Others</td>
<td>66.4 (56.4-76.4)</td>
<td>.001</td>
<td>71.8 (53.8-89.8)</td>
<td>.09</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>83.2 (76.7-89.7)</td>
<td>.28</td>
<td>87.0 (74.8-99.2)</td>
<td>.50</td>
</tr>
<tr>
<td>Male</td>
<td>78.6 (70.1-83.1)</td>
<td></td>
<td>75.5 (59.0-92.0)</td>
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</tr>
<tr>
<td>Leukocyte count, ×10^9/µL</td>
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<td>.03</td>
<td></td>
<td>.21</td>
</tr>
<tr>
<td>&lt;50</td>
<td>82.0 (76.9-87.1)</td>
<td></td>
<td>86.5 (75.5-97.5)</td>
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</tr>
<tr>
<td>≥50</td>
<td>71.6 (61.2-82.0)</td>
<td></td>
<td>69.6 (49.4-89.8)</td>
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<td>Cell lineage</td>
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<tr>
<td>B-cell precursor</td>
<td>81.5 (76.6-86.4)</td>
<td>.009</td>
<td>83.6 (72.4-94.8)</td>
<td>.23</td>
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<tr>
<td>T-cell</td>
<td>66.7 (52.8-80.6)</td>
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<td>72.4 (49.9-94.9)</td>
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</tr>
<tr>
<td>DNA index</td>
<td>≥1.16</td>
<td>.01</td>
<td>100.0 (100.0-100.0)</td>
<td>.10</td>
</tr>
<tr>
<td>&lt;1.16</td>
<td>76.7 (71.0-82.4)</td>
<td></td>
<td>77.7 (65.9-89.5)</td>
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<tr>
<td>t(4;11)/MLL-AF4</td>
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<td>&lt;.001</td>
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</tr>
<tr>
<td>Absent</td>
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<td></td>
<td>81.9 (71.7-92.1)</td>
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<tr>
<td>Present</td>
<td>33.3 (2.5-64.1)</td>
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<tr>
<td>TEL-AML1</td>
<td></td>
<td>.30</td>
<td>79.5 (68.1-90.9)</td>
<td>.42</td>
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<tr>
<td>Absent</td>
<td>78.3 (73.0-83.6)</td>
<td></td>
<td>87.5 (85.2-98.9)</td>
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<tr>
<td>Present</td>
<td>84.3 (74.7-93.9)</td>
<td></td>
<td>78.7 (64.2-94.0)</td>
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<tr>
<td>t(9;22)/BCR-ABL</td>
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<td>&lt;.001</td>
<td></td>
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<tr>
<td>Absent</td>
<td>80.4 (75.7-86.1)</td>
<td></td>
<td>84.2 (74.4-94.0)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>37.5 (25.6-55.5)</td>
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<td>25.0 (0.0-55.0)</td>
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<tr>
<td>t(1;19)/E2A-PBX1</td>
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<tr>
<td>Present</td>
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<tr>
<td>CNS status*</td>
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<td>.03</td>
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<td>Traumatic lumbar puncture</td>
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<td>Others</td>
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<td>93.3 (79.6-100.0)</td>
<td>.11</td>
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<tr>
<td>Lower</td>
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<td>Higher</td>
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<td>76.8 (64.5-89.2)</td>
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Abbreviations: CI, confidence interval; CNS, central nervous system; EFS, event-free survival.

*CGN1 cases include those with traumatic lumbar puncture without blast cells; traumatic lumbar puncture status consists of those with blast cells.
†Among the very high-risk group (defined by the presence of t(4;11), t(9;22), hypodiploidy, age <12 months or leukocyte count >200×10^9/µL in B-cell precursor acute lymphoblastic leukemia), the 5-year EFS rate was 56.1% (95% CI, 89.8%-72.4%) for the 44 white patients and 56.3% (95% CI, 28.1%-88.5%) for the 12 black patients.
children with lower-risk or standard-risk ALL were preferentially referred to our center. Rather, the presenting features of black patients in this analysis were comparable with those in the CCG studies in terms of age (34% vs 31% >10 years old), leukocyte count (34% vs 30% with counts >50 × 10⁹/µL), and leukemic cell ploidy (16% vs 20% with hyperdiploidy >50 chromosomes). The median presenting leukocyte count in our black cohort (17.3 × 10⁹/µL) was considerably higher than the POG median (10.9 × 10⁹/µL) because infants and patients with T-cell ALL, who typically have high leukocyte counts and a poorer outcome, were excluded from the POG analysis. 

Although the prognostic factors identified in black and white patients were similar, they differed in frequency. Black children were significantly more likely than white children to have unfavorable prognostic features, such as a high leukocyte count, a T-cell immunophenotype, and the chromosomal translocation t(1;19), and less likely to have a favorable genotype, such as hyperdiploidy greater than 50 chromosomes, disparities that have been described in earlier studies. More recently, racial and ethnic differences have been found in the proportions of patients with genetic polymorphisms affecting drug metabolism and treatment response. Whether these host pharmacogenetic factors contribute to the generally poor prognosis of black patients with ALL is uncertain, although in one study blacks were more likely than whites to have increased levels of dihydrofolate reductase, a major target of methotrexate treatment, and increased levels of this enzyme were associated with a higher risk of relapse.

Remarkably, despite their excess of adverse risk features, black children derived as much benefit as white children from our 2 treatment protocols. This finding underscores the ability of effective therapy to abolish the prognostic impact of most clinical and biological risk factors identified to date. The XIIIA and XIIIB therapeutic protocols were based on the backbone treatment of study XI, one of the most successful clinical trials in childhood ALL in the 1980s. Several modifications in this basic regimen may have contributed to the improved results reported here. First, reinstitution treatment, as pioneered by investigators of the Berlin-Frankfurt-Münster group and later confirmed by CCG investigators, was incorporated into both protocols. Such therapy consistently has improved outcome and has become a cornerstone of contemporary treatment regimens. Second, having recognized the adverse prognostic impact of leukemic cells in the cerebrospinal fluid, even if they were introduced iatrogenically from a traumatic lumbar puncture, we introduced an early intensification phase of intrathecal treatment, a strategy that reduced the risk of CNS relapse and boosted the overall event-free survival rate. Despite a higher rate of traumatic lumbar puncture in black children in the present study, a finding we attributed to their greater lumbar lordosis, they did not develop isolated CNS relapse, nor did they have a poorer event-free survival, whether treated with protocol XIIIA or XIIIB. High-dose methotrexate, which has improved outcome in a number of clinical trials, also is an integral component of these protocols. Our stringent criteria for risk stratification, leading to the assignment of slightly more than three fourths of the black children to risk groups that received intensified therapy, could have further improved the likelihood of cure. In this regard, CCG investigators found no significant difference in event-free survival between black and white children with high-risk features who were given intensified therapy. Finally, improved supportive care also could have contributed to the increased event-free survival and survival in both race groups.

In the CCG study, black patients were overrepresented in the low parental education and low-income categories. Similarly, our analysis of insurance coverage indicated that black patients were more underprivileged than white patients. Nonetheless, all of our patients received the same risk-directed therapy, regardless of their insurance status or ability to pay, and were followed up by the same team of experienced caregivers, ensuring optimal compliance with therapy. Although the impact of this factor is difficult to quantify, it might have influenced the treatment results described here. Indeed, CCG investigators suggested that the black children in their studies may have had poor compliance with protocol-specific treatments, as rates of long-term follow-up were lower among black compared with white children. Whatever the explanation, we have demonstrated that black children with ALL can expect the same high rate of cure now being attained in white children, if they have equal access to contemporary effective antileukemic treatment delivered in a single pediatric cancer center. Additional modifications in our treatment regimens, to reduce the risk of therapy-related second malignancies, may improve clinical outcome in ALL patients still further.

Author Contributions: Study concept and design: Pui, Howard Acquisition of data: Pui, Sandlund, Rivera, Ribeiro, Rubnitz, Razzouk, Hudson, Raimondi, Behm, Downing, Relling, Evans. Analysis and interpretation of data: Pui, Pei, Cheng. Drafting of the manuscript: Pui. Critical revision of the manuscript for important intellectual content: Pui, Sandlund, Pei, Rivera, Howard, Ribeiro, Rubnitz, Razzouk, Hudson, Cheng, Raimondi, Behm, Downing, Relling, Evans. Statistical expertise: Pei, Cheng. Obtaining funding: Pui, Downing, Relling, Evans. Administrative, technical, or material support: Pui, Downing, Evans. Study supervision: Pui.

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REFERENCES