Pre-B Cell Leukemia Responds Poorly to Treatment: A Pediatric Oncology Group Study

By William Crist, Jim Boyett, Maryann Roper, Jeanette Pullen, Richard Metzgar, Jan van Eys, Abdelsalam Ragab, Kenneth Starling, Teresa Vietti, and Max Cooper

Seventy-eight of 362 children with acute lymphocytic leukemia (ALL) had leukemic cells similar in phenotype to normal pre-B cells. When the clinical and laboratory features of patients with pre-B and "null" cell phenotypes of ALL were compared, no significant differences were noted, except that the pre-B cell ALL phenotype had a higher percentage of black children. In contrast, patients with T cell ALL had a higher median age at diagnosis, frequent thymic involvement, and higher WBC counts. Patients with pre-B and "null" cell ALL were treated identically and patients with T cell ALL differently. Although no difference in remission induction rates was noted between patient groups with pre-B and "null" cell ALL, the remissions were of shorter duration for patients with pre-B cell ALL (p = 0.004). Similarly, overt leukemic involvement of both the central nervous system (CNS) and bone marrow was noted sooner in the patient group with pre-B cell ALL. Univariate and multivariate Cox life table regression analyses demonstrate the independent prognostic significance of the pre-B phenotype and illustrate that the prognostic influence of potential relapse risk factors, such as WBC, sex, and age, are specific for leukemia phenotype. These findings may have importance for the design and tailoring of therapy for children with acute leukemia.

A NEW PHENOTYPE of childhood acute lymphocytic leukemia (ALL) was recognized in 1978. This ALL phenotype was distinguished from others in that a significant proportion of the leukemic blast cells from affected individuals expressed cytoplasmic immunoglobulin (SIg) µ heavy chains, but no surface Ig (SIg). This cellular phenotype was identical to that of normal human pre-B cells. Subsequently, we reported the early results of a collaborative study of 191 children with ALL, including 35 (18%) with pre-B cell ALL. The incidence, clinical, and laboratory features and preliminary treatment response data of children with pre-B cell ALL were compared to those observed in other leukemia phenotypes; no significant differences were noted between children with pre-B and those with "null" cell ALL with respect to clinical findings at diagnosis, morphology of the leukemia cells, cytochemical features, percentage of leukemia cells bearing Fc or C3 receptors, and glucocorticoid receptor expression. Also, no significant difference in the response to treatment was noted when patients with pre-B cell ALL were compared to those with "null" cell ALL during this preliminary phase of the study. An interim analysis of the results of therapy in these patient groups, followed for a median interval of 14 mo, suggested that children with pre-B cell ALL may fare worse than those with "null" cell ALL.3

This study has continued and 279 children with non-B, non-T ALL, including 78 with pre-B cell ALL, have been evaluated, treated uniformly, and observed for a median interval of 27 mo. We present treatment response data that demonstrate a decreased response to therapy of patients with pre-B cell ALL as compared to those with "null" cell leukemia. Results of multivariate analyses also demonstrate that the pre-B cell phenotype has independent prognostic value and that the importance of clinical factors, such as WBC and age, which have traditionally been used to estimate risk of relapse, is phenotype dependent.

MATERIALS AND METHODS

After obtaining informed consent, 362 newly diagnosed children with esterase and Sudan black B negative acute leukemia were evaluated between May 1978 and May 1981. In addition to the routine history, physical examination, laboratory, and radiographic studies, the detailed classification studies (described below) were performed on leukemia cells from each patient. In each case, pretreatment bone marrow was obtained to establish the diagnosis and classification of leukemia. All patients with non-B, non-T ALL were treated in a similar manner on therapeutic protocols of the Pediatric Oncology Group (POG) (ALInC 12 [256 patients] or ALInC 13 pilot [23 patients], see Appendix I for details). The distribution of treatment assignments for patients with "null" and pre-B cell ALL were not significantly different (p > 0.8).

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**Immunologic and Cytochemical Cell Markers**

Leukemic cells were examined morphologically by a panel of five collaborating hematologists and one pathologist and classified according to FAB criteria. In addition, leukemic cells were examined for Sudan black B, periodic acid-Schiff, nonspecific esterase, chloroacetate esterase, and acid phosphatase cytochemical reactivities;**1** for SIg,**2** for receptors of sheep erythrocytes,**3** IgG,**4** and the third component of complement**12,13** by established and quality controlled techniques at member institutions. At each member institution, cells were stained for SIg, centrifuged onto glass slides, fixed in cold 95% ethanol - 5% acetic acid, washed, and mailed submerged in phosphate-buffered saline to the University of Alabama in Birmingham's Immunology Reference Laboratory by microcytotoxicity assays using heteroantisera, as described.**14** Serum immunoglobulin concentrations, determined at member institutions, were compared to local age-matched normal controls.

**Definitions**

All leukemias were classified into pre-B, B, T, or “null” cell ALL subgroups according to the following criteria: pre-B cell, if ≥10% of marrow lymphoblasts contained Clg; B cell, if ≥10% of marrow lymphoblasts had easily detected SIg without clg (i.e., μ heavy chains); T cell, if ≥40% of marrow lymphoblasts were lysed by pan-T (pT) heteroantisera (40% above control lysis by cytotoxicity testing). The “null” cell group included all patients with ALL not classified by the above criteria, irrespective of the expression of CALLA and Ia.

**Statistics**

Though some inferences are phrased in the text as if one-sided comparisons were made, all significance levels (p values) reported resulted from two-sided comparisons. The method of Kaplan and Meier was used to construct the life tables and curves.**15** Multivariate analyses were performed in a forward step-wise fashion using the Cox life table regression model in order to analyze the importance of prognostic factors in influencing the duration of continuous complete remission.**16** The Mantel-Haenszel statistic (log rank) was also used to compare life tables.**17** If expected cell frequencies permitted, contingency tables were analyzed using the classical chi-square statistic.**18** Otherwise, an exact procedure, based on the chi-square statistic, was used.**19** Distribution of quantitative factors (such as age and WBC at diagnosis) were analyzed using the Wilcoxon test**20** for two groups and the Kruskal-Wallis test**20** for more than two groups.

**RESULTS**

**Immunophenotype Distribution**

A total of 362 children with ALL were evaluated. Two hundred and seventy-nine of these patients were classified as non-B, non-T ALL, including 78 with pre-B cell ALL. Seven patients with B cell ALL and 76 with T cell ALL were also identified.

The clinical and laboratory features of the T cell ALL patients are compared to other subgroups in Table 1 for contrast. There were too few B cell ALL patients for meaningful comparisons. In no case did pre-B lymphoblasts have receptors for sheep erythrocytes or express T cell antigens. The leukemic cells from most patients with pre-B and “null” cell ALL expressed Ia antigen, and approximately 90% of both groups were “common ALL” antigen (CALLA) positive. Since the patients with T cell and B cell ALL were treated differently from the patients with non-B, non-T ALL, they were not included in the analysis of treatment outcome presented here.

Table 1. Comparative Features of ALL Subclasses

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pre-B (n = 78)</th>
<th>&quot;Null&quot; (n = 201)</th>
<th>T (n = 76)</th>
<th>p Value</th>
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<tr>
<td>Demographic</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Age (yr)*</td>
<td>4.3</td>
<td>4.4</td>
<td>7.4</td>
<td>NS†</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>1.1</td>
<td>1.3</td>
<td>2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Race (white:black)</td>
<td>3.9</td>
<td>9.1</td>
<td>4.4</td>
<td>0.03</td>
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<tr>
<td>Corporal</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediastinal mass (%)</td>
<td>1.3</td>
<td>0.5</td>
<td>38.2</td>
<td>NS</td>
</tr>
<tr>
<td>White cells (10^9/liter)*</td>
<td>13.2</td>
<td>12.1</td>
<td>61.2</td>
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<tr>
<td>Platelets (10^9/liter)*</td>
<td>55.5</td>
<td>41.0</td>
<td>65.0</td>
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<tr>
<td>Cell phenotypic</td>
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<tr>
<td>FAB L1 (%)</td>
<td>87.3</td>
<td>88.8</td>
<td>91.8</td>
<td>NS</td>
</tr>
<tr>
<td>FAB L2 (%)</td>
<td>11.3</td>
<td>9.4</td>
<td>4.9</td>
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<tr>
<td>Periodic acid-</td>
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<td>Schiff reactive (%)§</td>
<td>65.8</td>
<td>62.8</td>
<td>38.4</td>
<td>NS</td>
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<tr>
<td>Acid phosphatase reactive (%)§</td>
<td>34.7</td>
<td>27.4</td>
<td>50.8</td>
<td>NS</td>
</tr>
<tr>
<td>Ia (%)§</td>
<td>100.0</td>
<td>98.4</td>
<td>12.2</td>
<td>NS</td>
</tr>
<tr>
<td>CALLA (%)§</td>
<td>94.0</td>
<td>89.0</td>
<td>15.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Expressed as median.
†NS, no significant difference.
§Percent of patients who were positive.
||Ia (and CALLA) testing was done on 50(50) pre-B, 192(192) "null," and 74(72) T cell leukemia patients.
Other Clinical and Laboratory Characterizations

A higher proportion of children with pre-B cell ALL than with “null” cell ALL were black ($p = 0.03$). No significant differences were demonstrable between the “null” and pre-B cell ALL groups with regard to the cytological staining patterns, immunoglobulin levels, percent of cells expressing Fc or C3 receptors, FAB morphology, or other features, including age, WBC, platelet count, sex distribution, or presence of a mediastinal mass. Children with T cell ALL differed significantly from the “null” and pre-B cell groups in many respects (Table 1). All pertinent data concerning Fc, C3 receptors, and immunoglobulin levels has been previously reported and, therefore, is not presented here.

Treatment and Outcome

All of the 78 patients with pre-B cell ALL attained a complete remission, as compared to 194 of 201 (97%) of the group with “null” cell ALL; this difference is not significant ($p = 0.2$). There were 2 deaths during induction in the group with “null” cell disease. Three percent of patients with “null” cell ALL had CNS disease at diagnosis, as compared to 2% for patients with pre-B cell ALL. Sixteen patients (8%) with “null” cell ALL took longer than 35 days to enter complete remission, as compared to 6 patients (8%) with pre-B cell ALL. The median time of follow-up for patients remaining in continuous complete remission (CCR) for both pre-B and “null” cell ALL groups is greater than 27 mo. The duration of continuous complete remission for the pre-B group, as measured by the Mantel-Haenszel statistic, is significantly ($p = 0.004$) shorter than for the “null” cell group. This remains true even after adjusting for traditional risk groups as defined by the presenting WBC, age, and presence of extramedullary disease ($p = 0.009$). Plots of Kaplan-Meier life tables illustrating this difference in duration of CCR for the pre-B and “null” cell ALL patient groups are shown in Fig. 1. From the Kaplan-Meier life table shown in Fig. 1, we note that 67% (SE = 6%) of patients with “null” cell ALL and 43% (SE = 8%) of patients with pre-B cell ALL are estimated to be in CCR after 3 yr of therapy. The durations of both bone marrow (see Fig. 2) and central nervous system remissions were significantly longer for the patient group with “null” cell ALL than for the group with pre-B cell ALL ($p \leq 0.02$ for both comparisons). This remains true even after adjustment for traditional risk groups ($p \leq 0.02$ and $p < 0.04$, respectively). The 62 (39) treatment failures for children with “null”/pre-B cell ALL were of the following types: 35 (23) marrow, 13 (12) central nervous system, 8 (2) other extramedullary sites, and 6 (2) died while in remission.

Fig. 1. Duration of continuous complete remission (CCR) for patients with “null” and pre-B cell acute lymphocytic leukemia ($p = 0.004$). Failure is defined as initial relapse at any site or death while in remission. Patients who were lost to follow-up while still in CCR are considered censored observations. The number of patients who remain at risk at various points in time are noted in parentheses. The life table from which the curves were plotted is shown in abbreviated form.
**Univariate and Multivariate Analyses of Prognostic Factors in Non-B, Non-T Cell Acute Lymphocytic Leukemia**

Table 2 shows the factor-analysis and numbers of patients for whom the factor was determined and univariate \( p \) values as measured by the Cox life table regression model. Values for WBC counts, platelet counts, and hemoglobin levels were the actual counts or values, respectively. The ages used are 1–10 yr versus all other ages. Hepatosplenomegaly was a liver or spleen below the umbilicus versus smaller. Lymphadenopathy was clinically assessed as none versus moderate versus marked. While several codings in addition to those shown in Table 2 were considered for some factors (i.e., the natural log of the WBC count, and \(<\) or \(>\) an actual WBC of 10,000/cu mm, 50,000/cu mm and 100,000/cu mm; quadratic function of age and age \(<\)1, 2–7, >8; white versus nonwhite; hemoglobin of \(<\)7.5 g/dl, 7.5–10 g/dl, >10 g/dl; a platelet count of \(<\) or > 150,000/cu mm), those codings most predictive of duration of continuous complete remission were chosen for use in the multivariate analysis. The multivariate analysis utilized the methods of Cox in a forward step-wise fashion, and the results are presented in Table 3.

To emphasize the absence of evidence of treatment effects, specific treatment was included in the univariate analysis. Since the ALInC 12 and ALInC 13 pilot studies were stratified by traditional risk factors, including WBC, age, and presence of extramedullary disease, and not all treatments were assigned within each stratum, it was considered inappropriate to include treatment in the multivariate analysis. The elimination of such an important factor from this analysis was justified by the balanced distribution of treatment assignments between patient groups with pre-B and “null” cell disease and the absence of any statistically significant treatment effect in these data. Within the non-B, non-T group, the pre-B cell phenotype was an independent prognostic factor. The model adjusting for the actual WBC and age (1–10 yr versus other age groups) estimated that the instantaneous failure rate for the pre-B cell group was 1.6 times the failure rate for the “null” cell group. The same statistical procedure, when applied to the subgroup of non-B, non-T ALL patients whose cells were classified according to FAB morphology, resulted in exactly the same ordering of prognostic factors as shown in Table 3. At no step in the analysis did the FAB classification (L1 versus L2) approach statistical significance.

Table 4 shows the results of a forward step-wise Cox life table regression analysis of factors predictive of CCR within the “null” or pre-B cell ALL immune phenotypes, respectively. Sex, age, and race (black versus nonblack) were prognostically important within the pre-B cell phenotype, whereas only WBC and age were important predictive factors for patients with “null” cell disease.

**DISCUSSION**

This extended study of a large group of children with immunologically classified forms of ALL has
revealed the independent prognostic importance of the pre-B cell phenotype within the context of current chemotherapy. Although children with pre-B cell ALL entered remission as readily as those with “null” cell disease, their duration of complete remission was significantly shorter. The shorter disease-free survival of children with pre-B cell ALL was due to a significantly higher incidence of relapse affecting both the bone marrow and central nervous system. As most of the relapses occurred while the patients were on therapy, and therefore were associated with an especially poor outlook, this shorter disease-free survival will likely translate into significantly shorter ultimate survival for the group with pre-B cell ALL.

Specific reasons for the poorer prognosis for pre-B cell ALL are unclear at present. Several investigators, using univariate and/or Cox life table regression analysis, have studied large patient populations with ALL and have emphasized the independent prognostic importance of pretreatment clinical features, such as the initial WBC,21-24 Hb,21-24 sex,21-24 race,26-29 organomegaly,21,22,24,25,30 platelet count,21,27 and presence of a mediastinal mass.22,24,31,32 Additional factors that have been associated with prognosis include cell morphology,3,37 presence of Fc38 or C313 receptors, or CALLA-positive blasts.39,40 other cell surface markers,32,38 HLA groups,41-43 serum immunoglobulins,33,44,46 rapidity of achieving bone marrow remission,53-57 and the presence of leukemic cells in the central nervous system at the time of diagnosis.22,24,33 At present, there is no uniform agreement concerning the conclusions of many of these studies, and most of them do not account for the possible interactive influence of leukemic phenotype. In our patients, none of the clinical and laboratory features mentioned above differ in “null” versus pre-B cell disease categories, with the exception of race distribution (see Table 1 and reference 2). However, patients with T cell ALL differ in many respects, including higher median age, WBC count, platelet level, and incidence of thymic involvement.

The incidence of pre-B cell ALL is higher in black patients. Black patient populations with childhood ALL are known to have shorter disease-free survival than white patient populations with childhood ALL.24,27,28,30 Nevertheless, prognostic importance of the pre-B phenotype was demonstrated even after statistical adjustment for race (p < 0.02). There was no significant difference in the incidence of CNS disease at diagnosis between the pre-B and “null” cell groups. A study of HLA phenotype distribution of patients with “null” cell and pre-B cell ALL is ongoing at present. It should be noted that our group of patients with “null” cell ALL consists of patients with non-pre-B, non-B, non-T ALL, and as such, is not comparable to any patient group previously described.

The relative prognostic importance of specific risk factors was found to be dependent on the leukemic phenotype. Specifically, sex, age, and race were independently prognostically important for the pre-B cell ALL group, while only age and WBC were important predictive factors for the “null” cell ALL group. The finding of the phenotype dependency of prognostic factors has not been previously reported in childhood ALL.

Several reports of the Philadelphia (Ph) chromosome anomaly in pre-B cell ALL have appeared48,50 and two patients with the 14q+ anomaly have also been reported.51,52 The authors of these papers speculated that these cytogenetic abnormalities, which were associated with a poor prognosis, might account for the poorer prognosis of other patients with pre-B cell ALL. However, a recent large survey of the cytogenetics of childhood malignancies of B cell lineage, including 74 children with pre-B cell ALL, demonstrated the Ph anomaly in only 1 patient with pre-B ALL and the 14q+ in none of the 49 pre-B ALL patients with adequate Giemsa banding to rule out the anomaly. In contrast, all 7 children with B cell ALL had the 14q+ anomaly.53 Also, the distribution of hypo-, pseudo-, and hyperdiploidy in patients with pre-B cell ALL paralleled the “null” cell group.

Lippman54 and colleagues have reported an associa-

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**Table 3. Factors Predictive of Duration of Continuous Complete Remission in Children With Non-B, Non-T ALL Revealed by Forward Step-Wise Cox Life Table Regression Analysis**

<table>
<thead>
<tr>
<th>Variables of Independent Significance</th>
<th>df</th>
<th>( \chi^2 )</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>1</td>
<td>14.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>8.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>1</td>
<td>5.4</td>
<td>0.021</td>
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*Listed in order of entrance into model. No other variables tested were of independent significance.

†Degrees of freedom.

‡Chi-square.

**Table 4. Factors Predictive of Duration of CCR in Patients With Pre-B Cell and “Null” Cell Leukemia as Revealed by Forward Step-Wise Cox Life Table Regression Analysis**

<table>
<thead>
<tr>
<th>Variables of Independent Significance</th>
<th>df</th>
<th>( \chi^2 )</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>1</td>
<td>5.9</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>5.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Race</td>
<td>1</td>
<td>3.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Null</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>1</td>
<td>13.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>7.3</td>
<td>0.007</td>
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*Within each phenotype, variables listed in order of entrance into model. No other variables tested were of independent significance.
tion of glucocorticoid receptor levels with prognosis and noted that patients with T cell ALL have lower receptor levels than those with non-T cell disease. Furthermore, they noted a less favorable prognosis in those with lower steroid receptor levels, even within the “null” cell group, and that this trend was independent of age or WBC count. We have studied glucocorticoid receptor levels in pre-B and “null” cell ALL and noted no significant difference.

The clear difference in treatment response that we noted for pre-B cell versus “null” cell leukemias is puzzling when considered from the viewpoint of a possible biologic basis. Both leukemic phenotypes have characteristics of early B-lineage cells, and comparison of their known features (Table 5) led us to expect that pre-B cell leukemia would behave more like “null” cell than B cell leukemia. The expression of surface antibody and other receptors for growth signals potentially could influence the rapid, uncontrollable progression of B cell leukemias. Moreover, different transforming genes (for a mouse fibroblast target cell line) may be activated in pre-B and B cell malignancies. On the other hand, relatively little is presently known about comparative changes in composition, arrangement, and transcription of cellular oncogenes in the different forms of human B-lineage malignancy. In recent studies of immunoglobulin gene expression, we noted that one-third or more of the pre-B cell leukemias include subpopulations of cells that undergo heavy chain class switches and simultaneously express kappa light chains in their cytoplasm. This finding would suggest that discovery of other B-like features of pre-B cell leukemias may be anticipated in future studies. Whatever the biologic explanation, our data clearly emphasize that knowledge of leukemic phenotype is important in assessing reasons for relapse in affected patients and may have special significance for design and tailoring of therapy.

ACKNOWLEDGMENT
We gratefully acknowledge the effort of Mike Del Vecchio and Sara Taritt for technical assistance in performing the pre-B studies and Sharon Garrison for assistance in preparation of the manuscript.

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**Appendix I. Dosage and Therapy Schedule for ALinC 12 and Pilot ALinC 13 Studies**

<table>
<thead>
<tr>
<th>ALinC 12</th>
<th>Pilot ALinC 13</th>
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<tr>
<td><strong>Regimen 1 and 2</strong></td>
<td><strong>Regimen 3</strong></td>
</tr>
<tr>
<td>Number patients treated</td>
<td>40/95</td>
</tr>
<tr>
<td>Pre-B/&quot;Null&quot;</td>
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<tr>
<td><strong>Phase of treatment</strong></td>
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<tr>
<td>Induction</td>
<td>VP + A – ASE</td>
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<tr>
<td>Consolation</td>
<td>A – ASE + CP</td>
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<tr>
<td>MTX</td>
<td>MTX</td>
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<tr>
<td>Continuation</td>
<td>6MP + MTX</td>
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<td>SC treatment</td>
<td>VP</td>
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<tr>
<td>Systemic reinforcement</td>
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</tr>
<tr>
<td>Treatment of subclinical central nervous system disease</td>
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<td>+</td>
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<td>XRT</td>
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</table>

**Induction:** Regimens 1 and 2 — vincristine (V) 1.5 mg/sq m (max 2 mg)/i.v./wk × 4; prednisone (P) 40 mg/sq m (max 60 mg)/po/day × 28; L-asparaginase (A-ASE) 10,000 U/sq m/wk × 2. Regimens 3 through 6 — vincristine (V) 2 mg/sq m (max 2 mg)/i.v./wk; prednisone (P) 60 mg/sq m/po/day × 28.

**Consolidation:** Regimens 3 through 5 — L-asparaginase (A-ASE) 6,000 U/sq m/day × 14; cyclophosphamide (CP) 1 g/sq m/i.v. on days 2 and 15 of A-ASE; methotrexate (MTX) 15 mg/sq m/i.v./day × 4 for 6 courses given at 2-wk intervals. Regimen 6 — L-asparaginase (A-ASE) 6,000 U/sq m/day × 14; cyclophosphamide (CP) 1 g/sq m/i.v./day × 2 and on 15 of A-ASE.

**Continuation treatment:** Regimens 1 through 6 — 6-mercaptopurine (6MP) 50 mg/sq m/po/day; methotrexate (MTX) 20 mg/sq m/po/wk. (Total white blood cell count in regimen 1 was maintained between 1,500 and 3,000/cu mm, whereas in regimens 2 through 6 it was maintained between 3,000 and 4,500/cu mm.)

**Systemic reinforcement:** Regimens 1 through 3 — every 16 wk, vincristine (V) 1.5 mg/sq m/i.v./wk × 3 and prednisone (P) 40 mg/sq m/po/day × 21. Regimen 4 — high-dose methotrexate (HDM) 1 g/sq m/i.v. every 8 wk followed by leucovorin rescue; prednisone (P) 60 mg/sq m/po/day × 28 every 16 wk. Regimen 5 — high-dose methotrexate (HDM) 1 g/sq m/i.v. every 8 wk followed by leucovorin rescue, prednisone (P) 60 mg/sq m/po/day × 28 every 16 wk; cyclophosphamide (CP) 800 mg/sq m/i.v. 4 wk following each HDM pulse. Regimen 6 — 2-wk pulses of rotating agents interspersed between every 4 wk of 6MP and MTX. Pulse 1: prednisone 60 mg/sq m/po/day × 14 days; vincristine 2 mg/sq m/i.v./wk on days 1 and 8 of pulse; adriamycin 40 mg/sq m/i.v. on day 1 of pulse. Pulse 2: prednisone 60 mg/sq m/po/day × 14 days; cytosine arabinoside 120 mg/sq m/i.v./day on days 1–4 of pulse. Pulse 3: prednisone 60 mg/sq m/po/day × 14 days; 6-thioguanine 300 mg/sq m/po/day on days 1–4 of pulse; cyclophosphamide (CP) 600 mg/sq m/i.v. on day 5 of pulse.

**Treatment of subclinical central nervous system disease:** Regimens 1 and 2 — methotrexate 12 mg/sq m (max 15 mg) intrathecally (i.t.) twice/wk × 5 doses; cranial irradiation (XRT) 2,400 rads (≥2 yr of age), 2,000 rads (1–2 yr) or 1,500 rads (<1 yr). Regimen 3 — triple i.t. meds (MTX 15 mg/sq m [max 15 mg], hydrocortisone 15 mg/sq m [max 15 mg], cytosine arabinoside 30 mg/sq m [max 30 mg]) on day preceding each of 6 i.v. MTX courses in consolidation; triple i.t. meds every 8 wk through completion of 3 yr of treatment. Regimen 4 — triple i.t. meds on day preceding each of 6 i.v. MTX courses in consolidation; methotrexate 6 mg/sq m/i.t. every 8 wk through completion of first year of treatment. Regimen 5 — triple i.t. meds on day preceding each of 6 i.v. MTX courses in consolidation; triple i.t. meds every 8 wk through completion of first year of treatment. Regimen 6 — triple i.t. meds twice/wk × 5 doses following completion of induction; triple i.t. meds every 6 wk through first year of treatment; triple i.t. meds every 12 wk through second and third years of treatment.
Pre-B cell leukemia responds poorly to treatment: a pediatric oncology group study

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