Clinical and Biologic Features Predict A Poor Prognosis in Acute Lymphoid Leukemias in Infants: A Pediatric Oncology Group Study

By W. Crist, J. Pullen, J. Boyett, J. Falletta, J. van Eys, M. Borowitz, J. Jackson, B. Dowell, L. Frankel, F. Qudus, A. Ragab, and T. Vietti

Analysis of remission induction rates for 1,117 children 18 months to 10 years of age (group 1) and 90 infants <18 months of age (group 2) with acute lymphoid leukemia (ALL) and of duration of continuous complete remission (CCR) for 454 in group 1 and 33 in group 2 revealed that infants fared significantly worse in both measures of outcome (P = .03 and P < .0001). To examine potential reasons for the poor prognosis of affected infants, clinical and biologic features of their ALL were compared. Infants had higher WBC counts (P < .001), a higher incidence of massive splenomegaly (P < .001), massive hepatomegaly (P < .001), more central nervous system (CNS) disease at diagnosis (P < .01), and lower platelet counts (P < .001). Also, their blasts were less often PAS+ (P = .02). The incidence of non(T, B, pre-B), T and pre-B immunophenotypes of ALL did not differ significantly between the two groups. However, in patients with non(T, B, pre-B) ALL, the majority (51%) of infants had common ALL antigen (CALLA)-negative blasts, as compared with only 7% in group 1 (P < .001). Furthermore, infants with non(T, B, pre-B) cell ALL who were <12 months of age were almost always CALLA+ (18 of 21). The blasts of children from both groups usually expressed Ia-like antigens. These data illustrate that infants with ALL have extensive and bulky disease more often than do older children and are more often affected with a prognostically unfavorable phenotype of acute leukemia (AL) which expresses Ia-like antigens but is more often PAS+ and CALLA+. We believe that these clinical and biologic differences predict and explain in part the observed poor response to treatment of infants with ALL.

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The prognosis of children with acute lymphoid leukemia (ALL) has improved remarkably during the last decade. Presently, >50% of newly diagnosed children may be expected to survive. However, many children continue to fail treatment and eventually succumb to their disease. The ability to predict which children with ALL have a high probability of treatment failure has recently become possible through the definition of certain prognostic factors that may be determined at the time of diagnosis. These include such clinical or biologic factors as the level of the white blood cell (WBC) count,4-6 age,7 presence of organomegaly,8,9 gender,1,3,5,7 tumor cell ploddy and/or karyotype,1,5 platelet count,1,7 presence of a mediastinal mass,2,4,3,12 race,10,13,14 cell morphology,15-19 immunophenotype,1,3,20-24 rapidity of achieving bone marrow remission,11 the presence of central nervous system (CNS) leukemia at the time of diagnosis,12,13 glucocorticoid receptor levels in blasts, and blast PAS positivity.25 Furthermore, the relative importance of many of these prognostic factors has been shown to be dependent on the immunophenotype of ALL1 and the specific therapy given.27 This ability to predict which children have a high probability of treatment failure, made possible by prognostic factor analysis, has permitted more individualization of therapy.

One of the most powerful predictors of prognosis in most studies is the age of the affected patient. Patients >10 or 11 years of age or <1 to 2 years of age have been noted to fare much worse than children who are between 1/2 and 11 years old at the time of diagnosis.2,3,6 The reasons for treatment failure in affected patients who are younger or older than average at the time of diagnosis are presently unknown. Some investigators have reported unusually severe drug-associated or radiation-associated toxicity in infants.29,30 Often, a recommendation for a reduced drug dose is made in these young patients. Nevertheless, it is unknown whether or not such problems contribute to the high relapse rate of affected infants; a recent report suggests that drug dose reduction is not the explanation.30

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was more often PAS<sup>-</sup> and CALLA<sup>-</sup> than ALL affecting older children.

**MATERIALS AND METHODS**

After informed consent was obtained, 1,566 newly diagnosed children <11 years of age with esterase-negative and Sudan black B-negative acute leukemia were evaluated between May 1979 and May 1984. The <18-month age cutoff was used to define group 2 because previous POG analyses of its children with ALL revealed a worse prognosis for children who were below this age at the time of diagnosis. Arbitrarily, adolescents (>10 years of age) were excluded from this analysis and will be the subject of a later report. In addition to the routine history, physical examination, laboratory, and radiographic studies which were performed on all patients (N = 1566), detailed classification studies were done on lymphoblasts from most children (n = 936) at the reference laboratories of the University of Alabama at Birmingham, Duke University Medical Center and John’s Hopkins Steroid Receptor Laboratory on leukemia cells obtained at diagnosis from each patient. Only 1,207 (1,117 in group 1 and 90 in group 2) children who were evaluable failed to achieve a complete remission in four weeks with vincristine and prednisone < L-asparaginase therapy and were treated on the POG 7623 (AlinC 12) study (see Appendix for details) were used for the analyses of durations of complete remissions.

**Immunologic and cytochemical cell markers and glucocorticoid receptors.** Wright’s-Giemsa-stained leukemic cells were examined morphologically by a panel of five collaborating hematologists and one pathologist and were classified according to FAB criteria. In addition, leukemic cells were examined for Sudan black B, PAS, non-specific esterase, and chloroacetate esterase cytochemical activities by standard techniques, for surface immunoglobulin (SIg), for receptors for sheep erythrocytes (E-R),<sup>3</sup> IgG, and for the third component of complement<sup>3</sup> 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 (PBS) to the University of Alabama at Birmingham’s Immunology Reference Laboratory for cytoplasmic immunoglobulin (Clg) testing, as previously described.<sup>3</sup> Heparinized bone marrow samples were placed in tissue culture media and were shipped by express mail to Duke University’s Immunology Reference Laboratory to be examined for the expression of Ia-like (HLA-DR) and pan-T (pT) cell markers and CALLA by microcytotoxicity assays using heteroantiserum and monoclonal antibodies, as described.<sup>40,42</sup> Glucocorticoid levels in blast cells were also determined.<sup>25</sup>

**Definitions.** All leukemias were classified into T, B, pre-B or non(T, B, pre-B) 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 (ie., heavy chains); T cell, if ≥40% of marrow lymphoblasts were lysed by pan-T (pT) heteroantiserum (40% above control lysis by cytotoxicity testing). The non(T, B, pre-B) cell group included all patients with ALL not classified by the above criteria, irrespective of the expression of CALLA and Ia-like antigens. However, most of these latter cases expressed Ia-like antigens (97%); overall, most expressed CALLA (90%).

**Statistics.** Although some inferences are phrased in the text as though 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.<sup>43</sup> The Mantel-Haenszel statistic was used to compare life tables. If expected cell frequencies permitted, contingency tables were analyzed using the classical chi-square statistic. Otherwise, an exact procedure, based on the chi-square statistic, was used.<sup>44</sup> Distribution of quantitative factors (such as platelet counts and WBC counts at diagnosis) were also analyzed using the Wilcoxon test.<sup>45</sup>

**RESULTS**

**Response to treatment.** Forty-seven of 1,117 (4%) children from group 1 and 9 of 90 (10%) infants from group 2 who were evaluable failed to achieve a complete remission in four weeks with vincristine and prednisone (VP) or VP and L-asparaginase therapy (P = .03). The duration of continuous complete remission (CCR) for the 454 evaluable children from group 1 and 33 children from group 2 who entered remission and were maintained on POG 7623 (AlinC 12) treatment regimens (described in Appendix) is shown in Fig 1. The median duration of follow-up for those children who remain at risk is three years and 11 months. The duration of CCR for those who were treated according to POG 8036 are not included here since the follow-up time for this study is
short (median = 12 months). It may be seen that infants fare far poorer than do older children \( P < .0001 \). They also have significantly shorter durations of both bone marrow and CNS remissions \( (P < .03 \) and \( P < .001 \), respectively). The three-year CNS remission rate was 66% (SE = .11) for infants and 89% (SE = .02) for children in group 2 and the 3-year bone marrow remission rate for infants was 64% (SE = .11); for children in group 2, it was 74% (SE = .02).

Comparisons of possible clinical prognostic factors between age-defined subgroups of children with ALL. Data in Table 1 illustrate that the infant group is more likely to have a significantly larger proportion of affected individuals who have a high WBC count at diagnosis. Infants also have a higher incidence of massive (respective organ below the umbilicus) hepatomegaly (18% \( \times \) 6%) and splenomegaly (23% \( \times \) 8%) \( (P < .001 \) and \( P < .001 \), respectively), lower median platelet counts (36,000/\( \mu \)L \( \times \) 52,000/\( \mu \)L) \( (P < .001 \) and more CNS disease at diagnosis (11% \( \times \) 4%, \( P = .003 \)). In contrast, there was no significant difference in their sex ratio, racial distribution, incidence of a mediastinal mass, hemoglobin levels at diagnosis, percentage of marrow blasts, or incidence of bone involvement as compared with older children. There was no significant difference in the proportion of infants (29 of 46, 63%) \( \times \) older children (374 of 513, 73%) who were in complete remission on this study only.

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**Comparisons of laboratory-defined features (group 1 v group 2).** Data in Table 2 illustrate that infants with non-(T, B, pre-B) ALL are more often CALLA\(^-\) than older children (group 1), but usually express Ia-like antigens (38 of 39). Furthermore, the data show that most of the children who were CALLA\(^-\) (group 2) were in the group who were \(< 1\) year of age at diagnosis. In addition, infants (group 2) with pre-B cell ALL had blasts that were CALLA\(^-\) significantly more often than those from similar cases of pre-B cell ALL in older children (see Table 2). Table 2 also illustrates that there were no significant differences in distributions within the lineage-specific immunologic groups shown between group 1 and group 2, and between group 1 and group 2 infants \(< 1\) year of age. The small group of 12 children with B cell ALL were excluded from this analysis. Table 3 summarizes the limited cytogenetic data available for both groups 1 and 2. No significant difference in ploidy distribution or other cytogenetic features were noted. However, there was a high incidence of unsatisfactory studies and of "normal" results. It is possible that poor-quality banding studies, which were frequently noted, obscured significant differences between the patient groups regarding specific cytogenetic abnormalities such as translocations. No significant differences in the levels of corticosteroid receptors in blast cells or L1 or L2 morphology of the blasts from these patients were observed between patient groups. The blasts from infants, however, were significantly more often PAS\(-\) (\( P = .02 \)).

**DISCUSSION**

This study has demonstrated that infants have a much worse prognosis than do children who are older. They enter remission less readily (\( n = 1,207, P = .03 \) and survive in CCR for shorter periods of time than older children (\( n = 487, P = .0001 \)) (see Fig 1). Infants also have a higher incidence of CNS disease at diagnosis and experience shorter durations of both CNS and bone marrow remissions (\( P < .001 \) and \( P < .03 \)). Our data also illustrate that infants have more bulk disease (hepatosplenomegaly and higher WBC counts initially) and lower platelet counts than do children from group 1. All of these factors have been associated with a poorer prognosis in other studies.\(^{1,2,4,6,10}\)

Immunologic marker analysis of the blasts from the infants (group 2) in our study revealed that approximately two-thirds of them have ALL of well-defined cell lineage based upon detection of specific cell markers (Clg\(^-\), Slg\(^-\), CALLA\(^-\), or T cell-specific antigens). The distribution of these well-defined phenotypes of ALL is not significantly different from that seen in older affected children except for the lower incidence of CALLA expression in group 2. However, one third of these infants have AL of FAB L1 morphology, which expresses Ia-like (HLA-DR) antigens but lacks CALLA and Clg expression (see Table 2) and is more often PAS negative. Furthermore, if one considers only infants \(< 1\) year of age, more than one-half have CALLA\(^-\), Clg\(^-\), Slg\(^-\), T-antigen\(^-\), HLA-DR\(^+\) acute leukemia. The lack of CALLA expression by blast cells has been associated with a poor prognosis in some studies.\(^{2,28}\) No other similarly studied group of affected infants is available for comparison, and only occasional case reports of individual infants who were similarly studied are available.\(^{47}\) Taken together, these clinical and biologic findings supports the notion that infants often have a biologically different type of acute "undifferentiated" leukemia which appears to be more aggressive than the disease seen in older children and is less responsive to the treatments commonly used for ALL.

Nadler et al\(^{48}\) have examined B cell-associated and B cell-restricted antigens and, in some cases, the state of the immunoglobulin genes of tumor cells from 138 children and adults with non-T cell ALL. They found that leukemic cells from the patients could be assigned to one of four maturational groups based on sequential patterns of antigen expression: HLA-DR-related Ia-like antigen (Ia) alone (stage I); Ia/B4 (stage II); Ia/B4/CALLA (stage III); and Ia/B4/CALLA/B1 (stage IV). The expression of B cell-restricted antigens (B4 and B1) and rearrangements of Ig heavy chain

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**Table 1. White Blood Cell Count Distribution By Age Groups**

<table>
<thead>
<tr>
<th>WBC per ( \mu )L</th>
<th>Group 1 No of Patients (%)</th>
<th>Group 2 (Infants) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10,000</td>
<td>706 (49)</td>
<td>32 (29)</td>
</tr>
<tr>
<td>10,000–50,000</td>
<td>482 (33)</td>
<td>27 (24)</td>
</tr>
<tr>
<td>50,000–100,000</td>
<td>132 (9)</td>
<td>27 (24)</td>
</tr>
<tr>
<td>( \geq 100,000 )</td>
<td>135 (9)</td>
<td>26 (23)</td>
</tr>
<tr>
<td>( P &lt; .0001 )</td>
<td></td>
<td>POG 7865 and 8035</td>
</tr>
</tbody>
</table>
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Table 2. Incidence of Immune Phenotypes of ALL Within Age Groups of Affected Children

<table>
<thead>
<tr>
<th>Immunophenotype</th>
<th>Group 1</th>
<th></th>
<th>Group 2</th>
<th></th>
<th>Group 2 Patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5 to 10 yr</td>
<td></td>
<td>&lt;1.5 yr</td>
<td></td>
<td>&lt;1 yr</td>
<td></td>
</tr>
<tr>
<td>No. of Children (%)</td>
<td></td>
<td></td>
<td>No. of Children (%)</td>
<td></td>
<td>No. of Children (%)</td>
<td></td>
</tr>
<tr>
<td>A. Non(T, B, Pre-B)</td>
<td>59 (67)</td>
<td>39 (65)</td>
<td>21 (64)</td>
<td>B. Pre-B†</td>
<td>154 (18)</td>
<td>14 (23)</td>
</tr>
<tr>
<td>CALLA*</td>
<td>54 (93)</td>
<td>19 (49)</td>
<td>3 (14)</td>
<td>C. T</td>
<td>122 (14)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>CALLA</td>
<td>40 (7)</td>
<td>20 (51)</td>
<td>18 (86)</td>
<td>D. B</td>
<td>9 (1)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Total</td>
<td>876</td>
<td>60</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statistical analysis of data: comparison of immune phenotype distributions (A v B v C) between groups 1 and 2 (P > 0.9) and between group 1 and group 2 patients <1 year of age (P < 0.7). (C B cell patients excluded because of small numbers.) Comparison of distributions of CALLA expression for group 1 v Group 2: P < 0.001 for children with non(T, B, pre-B) cell ALL; P = .01 for children with pre-B cell ALL (see data below).

Ninety-seven percent of patients in group 1 with non(T, B, pre-B) cell ALL expressed la-like (HLA-DR) antigens as compared with 97% (38 of 39) of infants (group 2).

*Distribution of CALLA expression by 6-month increments of age in children with non(T, B, pre-B) cell ALL <6 months: 9 CALLA, 1 CALLA*: 6 to 12 months: 9 CALLA, 2 CALLA*: 12 to 18 months: 2 CALLA, 16 CALLA*.

†Ninety-three percent of pre-B cell leukemias expressed CALLA (Group 1, 96%, Group 2, 71%, group 2 infants <1 year of age, 57%).

Table 3. Results of Cytogenetic Studies Within Age Groups of Affected Children With ALL

<table>
<thead>
<tr>
<th>Ploidy</th>
<th>Group 1</th>
<th></th>
<th>Group 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5-10 yr (P)</td>
<td></td>
<td>&lt;1.5 yr (P)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>316 (63)</td>
<td>24 (59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperdiploid</td>
<td>107 (21)</td>
<td>11 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypodiploid</td>
<td>25 (5)</td>
<td>1 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudodiploid</td>
<td>40 (8)</td>
<td>5 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constitutional abnormality*</td>
<td>14 (3)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Distribution overall: P = NS; pseudodiploidy, group 1 v group 2: P = .37.

*The 14 constitutional abnormalities were: 11 Downs syndrome, 1 Klinefelter’s syndrome, 2 others.

genes provided strong evidence for the B cell lineage of stages II, III, and IV tumors. They also found normal counterparts for leukemic cells of stages II through IV among fetal and adult bone marrow cells. They concluded that the 4% of their patients who had blasts that expressed only la-like antigens (stage I) had leukemias of uncertain lineage, but they speculated that the blasts from this group represented an even earlier stage of pre-B cell differentiation than did those from the laB4* subgroup (stage II). No blasts of the stage I patients expressed CIg and results of analyses for immunoglobulin gene rearrangements were not reported for that group. The blasts from 97% of our infants with non(T, B, pre-B) ALL expressed HLA-DR (la-like) antigens, but the leukemia cells of 51% of these infants with non(T, B, pre-B) cell ALL did not express CALLA. The blasts from these cases may be analogous to Nadler’s stage I, but we cannot say how many are in each stage because testing with the monoclonal antibody B4 was not done. In addition, the blasts of several of our cases were HLA-DR*, CIg*, and CALLA*. This phenotype does not follow the maturation sequence proposed by Nadler, since the expression of CIg would be expected to occur concomitant with or after the expression of CALLA. This may represent an aberrant phenotype. Further studies are needed to define more clearly the cell lineage and maturational stage of the leukemic cells of this group of patients with AL. Blasts from one of the affected infants with AL included in this study have been examined to determine the state of the Ig genes and expression of terminal deoxynucleotidyl transferase (TdT), the blasts were also examined by electron microscopy (EM). The Ig heavy chain genes were rearranged, TdT was expressed, and EM findings compatible with common or pre-B cell ALL were observed, suggesting that this case was of early B cell lineage.49 Similar studies of the blasts from more of these infants would be of interest. Reaman et al30 have presented data regarding certain clinical features and the outcome of 115 infants (<1 year of age) treated on Children Cancer Study Group (CCSG) protocols. These infants had higher WBC counts and more CNS disease at diagnosis than did the older children in their studies. The infants with CNS disease fared poorly: 82% subsequently experienced a bone marrow relapse. Furthermore, although 96.5% of these infants achieved complete remission, only 30 of them did so by day 14 of induction, and the induction death rate was 4%. Drug dosage modification occurred in only 9% of these infants. The median duration of remission was 8.5 months. In addition, there was a similarly high CNS relapse rate in infants who received cranial irradiation (22%) or only intrathecal chemotherapy (23%) as a part of their CNS prophylaxis. The testicular relapse rate was 6%. Relapse-free survival at three years from diagnosis was only 12.5%, with only eight infants continuing in CCR >1 year following cessation of therapy. Severe neuropsychologic side effects were noted in at least 50% of these infants. The findings in our population of infants with ALL are similar to those of Reaman et al in that the WBC counts of the patients (see Table 2) were higher, as was their incidence of CNS disease (11%) and CNS relapse rate (24%). The 8.5-month median duration of remission noted in the infants reported by Reaman et al is similar to the 10-month median duration of remission noted in our infants who are <1 year of age. The CCR rate at 3 years of the infants in the CCSG study was 12.5%, which may be compared to a CCR rate of 25% at 3 years and 8% at 4 years in our infants who were <1 year of age. We do not have specific data regarding neuropsychologic side effects and drug dosage received in our patients. The clinical findings of the infants in our study
extend those reported by Reaman et al in that we noted a significantly higher incidence of massive hepatosplenomegaly and lower platelet counts.

It is clear from our studies that infants with morphological criteria, with or without immunologic criteria for the diagnosis of ALL, have a very poor prognosis when treated with chemotherapy designed for children with ALL (Fig 1). Our infant population entered remission less well and experienced more CNS and bone marrow relapses than did older children. The immunologic marker data revealed that approximately two thirds of these infants have AL of well-defined lymphoid lineage, whereas one third of them have an AL of uncertain lineage. The latter expresses Ia-like antigens without CALLA or Clg and is more often PAS− than is the ALL seen in older children. These infants appear to have a biologically different form of AL, the lineage of which remains uncertain at present. We believe that the biologic and clinical differences noted in these infants with ALL predict and explain in part their poor prognosis. Clearly, better therapy is needed for these infants since currently most succumb to their disease very quickly despite aggressive chemotherapy.

REFERENCES


APPENDIX

Dosage and Therapy Schedule for ALL in C 12 (POG 7623)

<table>
<thead>
<tr>
<th>Number of group 1 (group 2) patients treated</th>
<th>Regimen 1 and 2*</th>
<th>Regimen 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of CNS subclinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IT MTX, 12mg/M2/day</td>
<td>§Triple IT medicine q</td>
<td></td>
</tr>
<tr>
<td>M2 28/wk x 5 Shallow</td>
<td>2 wk x 6</td>
<td></td>
</tr>
<tr>
<td>Cranial RT†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuation treatment (3 yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MP, 50mg/M2/day p.o.</td>
<td>Same as in Regimen 1</td>
<td></td>
</tr>
<tr>
<td>MTX, 20mg/M2/week p.o.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic reinforcement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V, 2mg/M2/IV/wk</td>
<td>Same as in Regimen 1</td>
<td></td>
</tr>
<tr>
<td>× 3 P, 40mg/M2/IV/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS reinforcement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>§Triple IT, q 8 wk x 3 yr</td>
<td></td>
</tr>
</tbody>
</table>

*Regimen 2 was identical to regimen 1 except that the WBC count was kept between 3,000 and 4,500/μL in regimen 1 and between 1,500-3,000/μL in regimen 2. (No difference in relapse incidence has been noted between these patient groups.)
†Only patients receiving all phases of therapy are shown here and in Fig. 1.
§Cranial RT: children >2 years, 2,800 rad; children 1 to 2 years, 2,000 rad; and children <1 year, 1,500 rad.
Ara-C, arabinosyl cytosine; 6TG, 6 thioguanine; CTX, cyclophosphamide; P, prednisone; V, vincristine; L-asp, L-asparaginase; 6MP, 6 mercaptopurine; MTX, methotrexate; IT, intrathecal, q, every; CNS, central nervous system; RT, radiation therapy.
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