Complications and Outcome in Childhood Acute Lymphoblastic Leukemia With Hyperleukocytosis

By Jose M. Eguiguren, Michael J. Schell, William M. Crist, Keith Kunkel, and Gaston K. Rivera

Hyperleukocytosis (> 10^4 leukocytes/L) was identified at diagnosis of acute lymphoblastic leukemia in 64 of 358 patients enrolled on St Jude Total Therapy Study XI from February 1984 to September 1988. These children received a seven-drug induction regimen followed by high-dose methotrexate, cranial irradiation at 1 year of remission, and 120 weeks of continuation therapy with rotational administration of four drug pairs. The 27 patients with leukocyte counts ≥ 200 × 10^9/L underwent initial cytoreduction via leukapheresis or exchange transfusions. The complete remission rate for patients with hyperleukocytosis (94%) was similar to that for the overall series (96%). Stepwise regression analysis showed that hyperleukocytosis was significantly associated with age less than 1 year at diagnosis, T-cell immunophenotype, leukemic cell ploidy ≤ 50 chromosomes, organomegaly, and elevated lactic dehydrogenase. The 27 patients with extreme hyperleukocytosis (≥ 200 × 10^9/L) differed from the other 37 children only in a higher frequency of French-American-British (FAB) L2 morphology. Estimated 4-year event-free survival (EFS) was 52% ± 8% (SE) for patients with hyperleukocytosis versus 79% ± 4% for patients with leukemic counts less than 100 × 10^9/L (P = .0001). Patients with leukocyte counts of 100 to 200 × 10^9/L had a significantly better EFS than those with counts greater than 200 × 10^9/L (64% ± 10% vs 94% ± 14%; P = .04). Thus, the therapy in this trial proved satisfactory for children with leukocyte counts of 100 to 200 × 10^9/L; further study is needed to improve the outlook for children with counts greater than 200 × 10^9/L.

© 1992 by The American Society of Hematology.

Our study sample comprised the 64 patients (18%) who had hyperleukocytosis, with leukocyte counts ≥ 100 × 10^9/L at diagnosis. Twenty-seven of these 64 patients had extreme hyperleukocytosis, defined by leukocyte counts greater than 200 × 10^9/L. Four children had acute mixed leukemia at diagnosis, as defined by two positive myeloid markers in addition to the lymphoid markers.

Treatment. The 64 children with hyperleukocytosis were classified as being at high risk for treatment failure and were admitted to the intensive care unit for close clinical monitoring, placement of central venous lines, vigorous hydration, alkalization, and allopurinol therapy. Remission induction therapy was begun within 24 to 72 hours of hospitalization.

The induction regimen consisted of prednisone, vincristine, and L-asparaginase, reinforced with VM-26 and cytarabine. The 40 patients treated after June 1985 (including 17 of the 27 with extreme hyperleukocytosis), also received daunorubicin; the 24 treated before then did not.

Patients with extreme hyperleukocytosis (> 200 × 10^9/L) underwent leukapheresis or exchange transfusion before chemotherapy was started. The blood cell separator (an IBM 2997 or a Fenwal CS-3000) used for leukapheresis was set up as described previously. The units were preprimed to prevent hypovolemia in patients who weighed less than 35 kg or had hematocrit levels less than 27%. Patients who weighed less than 12 kg or had inadequate...

From the Departments of Hematology-Oncology, Biostatistics and Information Systems, and Laboratory Medicine, St Jude Children's Research Hospital; and the College of Medicine, University of Tennessee, Memphis, Memphis, TN.

Submitted June 17, 1991; accepted October 8, 1991.

Supported by grants CA-21765 from the National Cancer Institute, and by The American Lebanese Syrian Associated Charities (ALSAC). J.M.E. is recipient of the Levy Fellowship in Cancer Medicine award.

Address reprint requests to Gaston K. Rivera, MD, St Jude Children's Research Hospital, 332 N Lauderdale, PO Box 318, Memphis, TN 38101.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. section 1734 solely to indicate this fact.

© 1992 by The American Society of Hematology.


871
venous access for leukapheresis received exchange transfusions (whole blood or red blood cells reconstituted with fresh frozen plasma or normal saline solution). Initially, single-volume exchanges were performed (approximately 70 cc/kg).

BM samples were examined after completion of induction therapy (day 43). If complete remission was confirmed, patients received two courses of high-dose methotrexate (2 g/m²) with leucovorin rescue, followed by continuation therapy with the rotational administration of four drug pairs (VP-16 + cyclophosphamide, mercaptopurine + methotrexate, VM-26 + ara-C, and prednisone + vincristine) over 120 weeks. Central nervous system (CNS) preventive treatment comprised three courses of intrathecal methotrexate, hydrocortisone, and ara-C during remission induction and then one course every 8 weeks during the first year postremission, at which time all patients underwent a 10-day course of prophylactic cranial irradiation (18 Gy). The remission induction, consolidation, and continuation chemotherapy schedules are depicted in Fig 1.

Statistical considerations. Clinical features of the hyperleukocytosis group were compared with those of patients with leukocyte counts less than 100 × 10⁹/L by the Fisher exact test. Stepwise logistic regression analysis was used to determine which of these features were most strongly associated with hyperleukocytosis. Cox regression analysis was used to assess the relative influence of demographic factors on EFS.

EFS, defined as the interval from induction of complete remission to relapse or death, was estimated for various patient subgroups by the Kaplan Meier method and compared by the log-rank test. A failure time of zero was assigned to those patients who did not achieve remission.

RESULTS

Table 1 compares the initial clinical and laboratory features of the patients with hyperleukocytosis with those of patients with leukocyte counts less than 100 × 10⁹/L. Hyperleukocytosis was significantly associated with age less than 1 year at diagnosis (P = .02), T-cell immunophenotype (P < .0001), leukemic cell ploidy ≤ 50 chromosomes (P < .0001), presence of mediastinal mass (P < .0001), and CNS leukemia at diagnosis (P < .001). Other signs of large tumor burden in the 64 patients with hyperleukocytosis were hepatomegaly in 63% of the patients, splenomegaly in 73%, and highly elevated (> 1,000 U/L) serum levels of lactic dehydrogenase (LDH) in 60%. In a model that included all the significant factors identified in Table 1, stepwise regression analysis showed that all variables except CNS disease and mediastinal mass at diagnosis retained significance. Of these variables, T-cell immunophenotype
notype had the strongest association with hyperleukocytosis. Comparative analysis of patients with leukocyte counts between 100 and $200 \times 10^9/L$ showed those with counts greater than $200 \times 10^9/L$ showed only one significant difference in clinical features—a higher proportion of FAB L2 morphology in the latter group ($P = .02$).

A stepwise Cox regression model was used to determine prognostic factors for EFS using hyperleukocytosis and the demographic variables shown in Table 1. In this model, only leukocyte count attained significance as a predictor of treatment outcome. The lack of importance of the remaining factors must be interpreted cautiously because the sample size is rather small ($n = 64$).

Cytogenetic studies were performed on leukemic blast cells from 89% of the patients with hyperleukocytosis and 97% of the patients with counts less than $100 \times 10^9/L$. Chromosomal translocations were identified in 45% and 48% of these groups, respectively, with the t(9;22) (q34; q11) slightly more common among children with hyperleukocytosis (6.3% v 2.7%). Hyperdiploidy greater than 50 chromosomes—usually associated with a favorable prognosis —was present in about one-third of the patients with leukocyte counts less than $100 \times 10^9/L$, but in only 8% of those with hyperleukocytosis ($P < .0001$).

The 20 children who underwent leukopheresis had an initial median leukocyte count of $387 \times 10^9/L$ (range, 200 to 917 $\times 10^9/L$). Exchange transfusions were performed in seven patients whose median leukocyte count was $373 \times 10^9/L$ (range, 210 to 549 $\times 10^9/L$). The 37 children who received neither procedure had a median leukocyte count of $133 \times 10^9/L$. With leukopheresis, a median 62% reduction in circulating leukocytes was achieved. The median number of cells harvested was $7 \times 10^9$. The median leukocyte reduction achieved by exchange transfusions was 52%.

Early complications during remission induction therapy included fever and neutropenia in 55 patients (86%); however, bacterial septicemia (n = 2) or disseminated fungal disease (n = 4) were diagnosed in only 9% of the patients. Ten patients presented with or developed coagulopathy; three of these had cerebrovascular accidents and one had thrombophlebitis. These four patients gradually recovered without long-term neurologic or vascular sequelae. Acute renal failure requiring hemodialysis developed in one child at diagnosis and in two patients soon after chemotherapy started. Transient hyperglycemia secondary to prednisone and asparaginase therapy occurred in seven patients and was resolved by administering insulin for 1 to 8 days. There was only one early death (day 49) due to toxicity during the remission induction phase of therapy. Sixty (94%) of 64 patients attained complete remission. The complications during induction and the adverse events among the 64 patients with hyperleukocytosis are summarized in Table 2.

Estimated 4-year EFS was 52% ± 8% for patients with hyperleukocytosis versus 79% ± 4% for patients with leukocyte counts less than $100 \times 10^9/L$ (Fig 2). Kaplan Meier estimates of EFS in patients with leukocyte counts $\geq 100 \times 10^9/L$ did not differ between patients with T and non-T immunophenotypes. Patients with leukocyte counts greater than $200 \times 10^9/L$ (34% EFS) fared significantly worse than did those with leukocyte counts of 100 to $200 \times 10^9/L$ (64% EFS) ($P = .002$). In two of the patients who developed a hematologic relapse (one with acute mixed lineage leukemia at diagnosis), a lineage switch to acute myeloid leukemia was diagnosed. Five patients whose disease relapsed in the CNS are alive in second remission at 27+ to 51+ months postreinduction. There were no testicular relapses on this study.

**DISCUSSION**

This study shows the immunophenotypic and cytogenetic features of patients with ALL who present with leukocyte counts greater than $100 \times 10^9/L$ and describes a novel therapeutic strategy for their management. It is encouraging that this remission induction regimen was well tolerated and resulted in an outstanding initial remission induction rate, comparable with that for children with standard-risk ALL, and that 4-year EFS among patients with leukocyte counts of 100 to $200 \times 10^9/L$ was 64%. Of particular interest is the fact that all of the 40 patients who received daunorubicin attained a complete remission, whereas 4 of

---

**Table 2. Complications During Induction and Adverse Events in Patients With Hyperleukocytosis**

<table>
<thead>
<tr>
<th>Leukocyte Count (× 10⁹/L)</th>
<th>100–200</th>
<th>≥ 200</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 37)</td>
<td>(n = 27)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complications</th>
<th>(n = 37)</th>
<th>(n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever and neutropenia</td>
<td>34</td>
<td>21</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Hyperkalemia (≥ 6 mEq/L)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hyperphosphatemia (&gt; 10 mg/dL)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hyperuricemia (&gt; 10 mg/dL)</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>(n = 37)</th>
<th>(n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction failures</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hematologic relapse</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>CNS relapse</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Combined hematologic and CNS relapse</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other extramedullary relapse</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death in complete remission</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Patients in continuous complete remission 23 11

---

![Fig 2. Kaplan Meier estimates of EFS for patients with ALL with leukocyte counts less than 100 × 10⁹/L versus ≥ 100 × 10⁹/L. Sample sizes indicate the number of patients at risk. P < .0001.](attachment:image.png)
24 who did not receive daunorubicin failed to attain a complete remission ($P = .02$). Regardless of the choice of subsequent therapy, timely induction of durable complete remission is essential to improve the traditionally bleak outlook. A decade ago, Harousseau et al. reported that 108 pediatric patients with ALL and leukocyte counts greater than 100 $\times 10^9$/L had a remission induction rate of only 71%.

In our previous trial for patients with high-risk ALL (Total X-High Study), which was associated with more toxicity than this study, 47 (82%) of 57 children with leukocyte counts greater than 100 $\times 10^9$/L entered complete remission. Induction therapy also included VM-26 and ara-C, prednisone, vincristine, and L-asparaginase, but did not include daunorubicin.

We attribute the 4-year EFS among our patients (52% $\pm$ 8%) to intensive early therapy coupled with an effective and well-tolerated continuation regimen. In this study, drug combinations with little cross-resistance were used in an attempt to prevent drug resistance and ameliorate toxicity. Other contemporary chemotherapy approaches may produce similar results. For example, 4-year EFS estimates of 69% $\pm$ 8% were reported for the Dana Farber 81-01 protocol (n = 42), 45% $\pm$ 11% for the Children’s Cancer Study Group 192 pilot study (n = 44), and 55% $\pm$ 8% for the BFM 76-79 and 79-81 protocols (n = 45). It must be noted, however, that in some of these studies infants less than 1 year of age and black children were not included. If we exclude such patients from our series, the 4-year EFS was 53% $\pm$ 9% and the survival at 4 years was 67% $\pm$ 9%.

The independent adverse effect of T-cell immunophenotype in the overall survival of patients with ALL has been well characterized. Half of our patients with leukocyte counts greater than 100 $\times 10^9$/L had T-cell ALL. In the entire Total XI series, these patients had significantly shorter intervals of EFS than did children with B-cell progenitor ALL, but the prognostic significance of T-cell immunophenotype was abolished in patients with hyperleukocytosis. Investigators in the Pediatric Oncology Group analyzing 253 children with T-cell immunophenotype have recently reported an estimated 4-year EFS of 66% $\pm$ 7% for patients with leukocyte counts less than 50 $\times 10^9$/L, compared with 19% $\pm$ 8% to 39% $\pm$ 7% for those with leukocyte counts greater than 50 $\times 10^9$/L. Similarly, previous analysis of all 358 patients treated on Study XI showed that patients with T-cell ALL fared significantly worse than those with other immunophenotypes.

Cytogenetic studies of the present high-risk cohort showed that the proportion of patients with chromosomal translocations at diagnosis did not differ from that of patients without hyperleukocytosis. There was, however, a difference in the frequency of hyperdiploidy, a feature associated with favorable prognosis: the leukemic blast cells from only 8% of children with hyperleukocytosis were hyperdiploid (> 50 chromosomes), as compared with 32% of those with counts less than 100 $\times 10^9$/L.

The most immediate therapeutic problems in the management of patients with hyperleukocytosis are related to acute metabolic complications secondary to tumor cell lysis syndrome. The rapid destruction of leukemic blasts by chemotherapy may produce massive release of intracellular potassium, phosphates, and uric acid into the vascular compartment, with resultant acute renal dysfunction. In fact, hyperphosphatemia was the most common complication necessitating hemodialysis in our patients. Another common problem is coagulopathy induced by procoagulant substances in the cytoplasm of leukemic blast cells; this leads to thrombin activation and complicates thrombocytopenia with acute hemorrhage or thrombosis.

The use of leukapheresis to reduce tumor burden in patients with ALL and hyperleukocytosis is controversial. In our study, there were no significant differences in the occurrence or severity of complications between patients who underwent leukapheresis and those who did not (data not shown); however, in a study involving patients with ALL and leukocyte counts greater than 200 $\times 10^9$/L, Maurer et al. noted a significantly lower incidence of electrolyte abnormalities in patients who underwent leukapheresis than in those who did not. Also, it should be noted that patients in our study who underwent leukapheresis had higher leukocyte counts than those with hyperleukocytosis who were not treated with this approach. Therefore, it is possible that our patients who were treated with leukapheresis would have had more complications. A prospective, randomized trial is necessary to evaluate the efficacy of this procedure in patients with hyperleukocytosis.

A pivotal problem in patients with hyperleukocytosis is a high incidence of relapse in both the BM and the CNS. Noteworthy among our patients was the almost equal distribution of hematologic and CNS relapses. Moreover, 7 of 27 patients (26%) with leukocyte counts greater than 200 $\times 10^9$/L ended initial remission by a CNS relapse. This high proportion of isolated CNS relapses contributed to the 4-year EFS rate of 52%; however, because 5 of the 11 patients who developed CNS relapse remain in second remission at 33+ to 57+ months, the 4-year survival rate for the entire group is 66% $\pm$ 9%. Retreatment for patients with an isolated CNS relapse consisted of another course of remission induction therapy, 6 weeks of intrathecal chemotherapy administered every 7 days, and a 3- to 4-week course of craniospinal irradiation (24 Gy cranial, 15 Gy spinal). Based on the number of CNS relapses among our patients with hyperleukocytosis, we plan to modify CNS preventive therapy for this group, using more frequent intrathecal chemotherapy during induction treatment and the first weeks of continuation therapy as well as an earlier course of CNS irradiation.

Although intensive chemotherapy and supportive care can reduce the hazards of early treatment failure in patients with hyperleukocytosis, improvement of their long-term outcome continues to be a formidable challenge to pediatric oncologists.

ACKNOWLEDGMENT

We thank the St Jude Children’s Research Hospital Scientific Editing Department for critical editorial review of this manuscript.
REFERENCES

Complications and outcome in childhood acute lymphoblastic leukemia with hyperleukocytosis

JM Eguiguren, MJ Schell, WM Crist, K Kunkel and GK Rivera