Identification of Risk Groups for Development of Central Nervous System Leukemia in Adults With Acute Lymphocytic Leukemia

By Hagop M. Kantarjian, Ronald S. Walters, Terry L. Smith, Michael J. Keating, Bart Barlogie, Kenneth B. McCredie, and Emil J. Freireich

The risk of development of CNS leukemia was investigated in 153 adults with acute lymphocytic leukemia (ALL) who received systemic combination chemotherapy without CNS prophylaxis. Overall, 31 patients (20%) developed CNS leukemia after a median of 6 months of therapy; the estimated 1-year incidence of CNS leukemia was 21% (SE, 3.9%). Characteristics significantly associated with CNS involvement included the presence of elevated hemoglobin creatinine, alkaline phosphatase, fibrinogen, and lactic dehydrogenase levels; B-cell leukemia; and high leukemic cell proliferative activity. Multivariate analysis identified lactic dehydrogenase levels of ≥600 U/L and ≥14% of cells in the S + G2M compartment to have independent additive poor prognostic significance. Patients were categorized into different risk groups for CNS leukemia with 1-year incidences ranging from 4% to 55%. While related to a high occurrence of CNS leukemia at diagnosis (33%) and subsequently (100%), the low incidence of B-cell disease excluded it from the multivariate analysis. The use of systemic chemotherapy containing multiple agents with good CNS penetration and in high doses (VAD regimen) in 90 patients was associated with a trend for lower CNS leukemia at 1 year (15% ± 31%), especially in the low-risk category. We propose to develop future therapies for adults with ALL that include risk-oriented CNS prophylactic approaches.

The incidence of CNS involvement by leukemia varies widely from <5% to 60%. This heterogeneity is strongly associated with several factors, including the type of leukemia, host and leukemic cell characteristics, and therapy used. Without CNS prophylaxis, the incidence of CNS leukemia is significantly higher in patients with acute lymphocytic leukemia (ALL) compared with acute myelogenous leukemia or the chronic leukemias. CNS leukemia occurs in 35% to 60% of children with ALL and is more frequent in patients with T-cell phenotype, B-cell disease, or elevated WBC counts.

CNS prophylaxis has reduced the incidence of CNS leukemia to about 5% to 15% in children with ALL without having a major impact on overall prognosis. The natural history of CNS leukemia without CNS prophylaxis, the effect of CNS prophylaxis, and the effect of systemic high-dose chemotherapy have been extensively analyzed in comparative and randomized studies of childhood ALL. By inference, it has been accepted that adults with ALL have a similarly high incidence of CNS leukemia and would also benefit from CNS prophylaxis. Because ALL is less common in adults, few studies have addressed these issues. Recently, randomized trials have shown a decreased incidence of CNS leukemia with CNS prophylaxis in adult ALL but no effect on survival prolongation. CNS prophylaxis has been associated with several complications, including acute and chronic neurotoxicity, decreased tolerance to systemic chemotherapy, and a high incidence of infections attributed to therapy-associated immunosuppression.

The identification of prognostic factors associated with a high-risk of CNS leukemia might produce a risk-tailored approach to CNS prophylaxis in adults with ALL. Based on the lack of survival benefit from CNS prophylaxis and its associated complications, adults with ALL have not received CNS prophylaxis at our institution. Since 1983, high-dose systemic chemotherapy and multiple agents with good CNS penetration have been included into treatment regimens. The absence of CNS prophylaxis in the different programs allowed the investigation of the prognostic factors associated with CNS leukemia and the analysis of the effect of high-dose systemic therapy on reducing the incidence of CNS leukemia.

MATERIALS AND METHODS

One hundred and seventy-seven untreated adults with a documented morphologic diagnosis of ALL referred to the Leukemia Service between April 1980 and December 1987 were reviewed. Patients had an extensive work-up including history and physical examination; documentation of measurable disease; complete blood, differential, and platelet counts; SMA12 with liver and renal function studies; bone marrow aspiration and biopsy, morphology and histochemical and enzymatic stains including myeloperoxidase, chloroacetate, non-specific esterase, periodic-acid Schiff (PAS), and terminal nucleotidyl transferase (Tdt); immunophenotype, cytogenetic studies, and electron microscopic analysis as previously described. A diagnosis of ALL required confirmation by morphologic, cytotoxic, and enzymatic stain analysis (negative myeloid and monocytic stains, Tdt, and PAS block positivity), and the presence of 30% or more blasts in the bone marrow. Immunophenotyping and electronmicroscopic studies were confirmatory and helped in the diagnostic evaluation of difficult cases. Patients with B-cell ALL disease were categorized on the basis of an L2 morphology by the French-American-British (FAB) classification; the presence of a characteristic translocation between the long arms of the FAB-L2 morphology is associated with a high-risk of CNS leukemia.
chromosome 8 and 14, 2 or 22 [(t(8;14), (t(8;2), (t(8;22)); or a B-cell immunophenotype.

Flow cytometric analysis was conducted on DNA, RNA, and percentage of cells in the S + G2M compartment.38 Marrow biopsy samples were placed into RPMI 1640 culture medium containing 5,000 U/mL of heparin. Specimens were mechanically mixed and subjected to shaking and repeated syringing to obtain single-cell suspensions. Monodispersed cells were stained for DNA and RNA with the metachromatic dye acridine orange. Cytometric analysis was performed with an ICP-22 flow cytometer (Ortho Diagnostics, Westwood, MA). DNA index, RNA index, and S + G2M compartment percentage were determined as previously described.39 S + G2M compartment determination involved gating along the G1/0-S boundary from low to high RNA content values.

The therapeutic programs consisted of two major phases. Between 1980 and 1985, 73 patients were treated with induction chemotherapy including vincristine 2 mg administered intravenously (IV) on day 1, cytosine arabinoside (ara-C) 70 to 90 mg/m2 daily for seven days, prednisone 100 mg daily for five days (OAP), and doxorubicin (Adriamycin) 55 mg/m2 administered IV on day 1 (ADOAP) or amsacrine (AMSA-OAP) 70 mg/m2 administered IV daily for seven days. Maintenance chemotherapy consisted of alternating three cycles of OAP, ADOAP, and POMP (prednisone 100 mg daily for five days, vincristine 2 mg administered IV on day 1, methotrexate 7.5 mg/m2 daily for five days, and six-mercaptopurine 600 mg/m2 administered IV daily for five days) for a total duration of 18 months. Since 1985, 104 patients received therapy on the new VAD program as outlined below:

1. Induction: Vincristine 0.4 mg by continuous infusion (CI) daily for four days; Adriamycin 12 mg/m2 CI daily for four days; and dexamethasone 40 mg daily for four days on days 1 to 4, 9 to 12, and 16 to 20. A second cycle of the same chemotherapy plus cyclophosphamide 1 g/m2 administered IV on day 1 (C-VAD) was started on day 24 of cycle 1.

2. Consolidation: Methotrexate 60 mg/m2 administered IV on day 1 weekly for 4 weeks, the dose being escalated to 90, 120, and 150 mg/m2 each week if no toxicity develops; and L-asparaginase 20,000 units administered IV on day two weekly for 4 weeks.

3. Early intensification: Adriamycin 60 mg/m2 administered IV on day 1; ara-C 3 g/m2 administered IV over two hours every 12 hours for six doses; vincristine 2 mg administered IV on day 1; and prednisone 100 mg daily for five days.

4. Maintenance with M-DOMP: Three cycles at 4- to 6-week intervals given as follows: methotrexate 200 mg/m2 administered IV on day 1; daunorubicin 60 mg/m2 administered IV on day 15; vincristine 2 mg administered IV on day 15; 6-mercaptopurine 75 mg/m2 administered orally daily for five days starting on day 15; and prednisone 200 mg daily for five days starting on day 15. The dose of methotrexate was escalated to 400, 600, and 800 mg/m2 in subsequent courses according to tolerance, toxicity, and methotrexate levels at 24 and 48 hours. Hydration and alkalization with sodium bicarbonate was given with methotrexate. Citrovorum rescue was not performed unless the methotrexate levels at 24 and 48 hours were higher than 10-3 and 10-4 mol/L, respectively. An autologous bone marrow pull was performed under general anesthesia after recovery from one of the three M-DOMP cycles to be reinforced during late intensification.

5. Late intensification with CBV: Cyclophosphamide 1.5 g/m2 administered IV daily for four days; BCNU 300 mg/m2 administered IV on day 1; and etoside (VP16) 250 mg/m2 administered IV daily for three days. The autologous bone marrow was reinforced on day 6 to 7.

6. Second maintenance: three cycles of M-DOMP. The total cycle of chemotherapy was repeated one more time, but late intensification was replaced by a maintenance cycle of M-DOMP. The total duration of therapy was 24 to 30 months. The details of the VAD program will be reported separately.

Diagnosis of CNS leukemia was based on cerebrospinal fluid studies showing the presence of leukemic blasts in the cytocentrifuge preparation, or elevated and abnormal cerebrospinal fluid counts with CNS signs and symptoms.

Statistical considerations The time to development of CNS leukemia was calculated from the date of diagnosis to CNS disease documentation. Curves for time to development of CNS leukemia were estimated by the method of Kaplan and Meier,39 with patients who died without developing detectable CNS disease counted as censored observations at their date of death. Spearman correlation coefficients were computed for selected pretreatment characteristics. Differences between curves were based on a generalized Wilcoxon test for censored observations.40

Multivariate regression methods were applied to assess the relative prognostic value of patient characteristics using Cox's proportional hazards model.41 Variables were entered in the model using a forward stepwise selection procedure after initial screening (using a P value of .10 in univariate analysis as a guide to further consideration). Flow cytometry results were not available for 16 cases, and these were omitted from the multivariate analysis. The importance of the treatment administered (VAD therapy v others) on the incidence of CNS leukemia was evaluated by adding an indicator term for type of treatment to a regression model that adjusted for important patient characteristics. Gehan et al have described the use of these regression methods in detail.42

RESULTS

Of 177 patients included in the analysis, 19 underwent allogeneic bone marrow transplantation with a preparative regimen consisting of piperazinedione and total body irradiation within 2 months of achieving complete remission. Five patients presented with CNS leukemia at diagnosis; three of them had B-cell leukemia. These two groups were excluded from the analysis of the prognostic factors for risk of CNS leukemia, since the objective of the study was to identify patients at high risk of CNS involvement after undergoing systemic chemotherapy.

The characteristics of the 153 patients included in the detailed analysis are shown in Table 1. Their median age was 32 years (range, 15 to 78 years), and 82 (54%) were men.

Prognostic factors associated with development of CNS leukemia Thirty-one of the 153 patients (21%) developed CNS leukemia after a median of 6 months (range, 0.5 to 41 months) following initiation of induction chemotherapy. Only six of the 31 patients (19%; 4% of the total group) developed CNS leukemia after 12 months of therapy. The association of various host and tumor attributes with development of CNS leukemia at 1 year is detailed in Table 2. Characteristics significantly related to subsequent leukemic CNS involvement included the presence of high hemoglobin, creatinine, alkaline phosphatase, and lactate dehydrogenase levels; elevated fibrinogen levels; L3 phenotype; B-cell-associated karyotypes such as t(8;14), t(8;2), and t(8;22); and high leukemic cell proliferative activity (S + G2M compartment of 14% or more). The presence of marked leukocytosis and mediastinal involvement showed a trend for a higher occurrence of CNS leukemia, which was not statistically significant. Patient age, organomegaly (spleen, liver, lymph nodes), platelet counts, blast percentage, bilirubin
prognostic features into high- or low-risk groups for development of subsequent CNS leukemia (Table 3).

Effect of systemic therapy on the incidence of CNS leukemia. The recent VAD program has incorporated several modifications from our previous therapeutic approaches, including the use of agents with good CNS penetration or in high doses, in an attempt to reduce the frequency of CNS leukemia.

Of a total of 104 patients treated with VAD chemotherapy, 88 (85%) achieved a complete remission, 14 (13%) had resistant disease, and only two patients (2%) died during remission induction with therapy-associated myelosuppression and its complications. After a median follow-up of 16 months, 48 patients (46%) remain live and disease-free, while five patients died in remission. The median overall survival was 18 months, with a 2-year survival rate of 41%. The median remission duration was 22.5 months, with a 2-year remission rate of 45%. Twenty of the 104 patients (19%) entered on VAD therapy had Philadelphia chromosome-positive or B-cell disease, and 22 (21%) were 50 years or older. When patients with Philadelphia chromosome-positive disease or B-cell leukemia were excluded, 75 of the remaining 84 patients achieved remission (89%). Their median overall survival was 23 months, with a 2-year survival rate of 48%; the median remission duration was 23.5 months, with a 2-year remission rate of 50%.

level, and DNA and RNA indices showed no correlation with CNS involvement.

Several of these characteristics were correlated. A multivariate analysis selected lactic dehydrogenase levels ($P < .01$) and proportion of cells in the S + G2,M compartment ($P = .03$) to have independent additive prognostic importance. No other pretreatment variable added significantly to the fit of a model that included these two parameters. Patients could be categorized according to their poor

Table 2. Prognostic Factors for Development of CNS Leukemia by Host and Tumor Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Category</th>
<th>No. With CNS Leukemia/Total (%)</th>
<th>Estimated % With CNS Leukemia at 1 Year</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td>31/153 (20)</td>
<td>18</td>
<td>.09</td>
</tr>
<tr>
<td>Mediastinal involvement</td>
<td>No</td>
<td>28/140 (19)</td>
<td>18</td>
<td>.09</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>5/13 (38)</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>$&lt;10$</td>
<td>18/70 (26)</td>
<td>28</td>
<td>.06</td>
</tr>
<tr>
<td></td>
<td>$\geq10$</td>
<td>13/93 (16)</td>
<td>15</td>
<td>.04</td>
</tr>
<tr>
<td>WBC ($\times10^3$/µL)</td>
<td>$&lt;5$</td>
<td>6/60 (10)</td>
<td>13</td>
<td>.33</td>
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<td></td>
<td>$5-19$</td>
<td>11/36 (31)</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$20-49$</td>
<td>6/23 (26)</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\geq50$</td>
<td>8/34 (24)</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>L,2</td>
<td></td>
<td>26/147 (18)</td>
<td>20</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>L,3</td>
<td>6/6 (100)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg%)</td>
<td>$&lt;1.4$</td>
<td>26/136 (19)</td>
<td>18</td>
<td>.02</td>
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<tr>
<td></td>
<td>$\geq1.4$</td>
<td>5/17 (29)</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>$&lt;80$</td>
<td>6/59 (10)</td>
<td>11</td>
<td>.04</td>
</tr>
<tr>
<td></td>
<td>$\geq80$</td>
<td>24/93 (26)</td>
<td>28</td>
<td></td>
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<tr>
<td>Lactic dehydrogenase (U/L)</td>
<td>$&lt;450$</td>
<td>5/65 (8)</td>
<td>6</td>
<td></td>
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<tr>
<td></td>
<td>$450-599$</td>
<td>4/28 (14)</td>
<td>5</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>$\geq600$</td>
<td>21/58 (36)</td>
<td>44</td>
<td></td>
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<tr>
<td>Fibrinogen (mg/dL)</td>
<td>$&lt;400$</td>
<td>17/89 (19)</td>
<td>19</td>
<td>.04</td>
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<td></td>
<td>$\geq400$</td>
<td>13/50 (26)</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Karyotype</td>
<td></td>
<td>8/46 (17)</td>
<td>18</td>
<td>&lt;.01</td>
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<td>Philadelphia-positive</td>
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<td>3/19 (16)</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>B-cell karyotype</td>
<td></td>
<td>6/6 (100)</td>
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<tr>
<td>Hyperdiploid</td>
<td></td>
<td>1/13 (8)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Hypodiploid</td>
<td></td>
<td>0/6 (0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pseudodiploid</td>
<td></td>
<td>2/12 (17)</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>6q- abnormalities</td>
<td></td>
<td>2/4 (50)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Insufficient metaphases</td>
<td></td>
<td>8/45 (18)</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>S + G2,M percentage</td>
<td>$&lt;7$</td>
<td>2/34 (6)</td>
<td>9</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>$7-13$</td>
<td>8/56 (14)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\geq14$</td>
<td>17/47 (36)</td>
<td>37</td>
<td></td>
</tr>
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</table>
Fourteen of 90 patients (16%) receiving VAD therapy developed CNS leukemia, compared with 17 of 63 patients (27%) treated on previous regimens. The 1-year cumulative incidences were 15% and 31%, respectively. Further comparative analysis of the two groups showed that patients receiving VAD therapy tended to have a lower incidence of B-cell leukemia ($P = .06$), a lower proportion of cells in $S + G_2M$ compartment ($P = .05$), and lower alkaline phosphatase levels ($P = .05$). To account for the population heterogeneity, the effect of therapy was analyzed in two different ways. Therapy was added as a variable (VAD vs other regimens) to a proportional hazards regression model after accounting for the effect of lactic dehydrogenase levels, alkaline phosphatase levels, and $S + G_2M$ compartment value. Therapy entered the model at a significance level of 0.39. In Fig 1, distribution of time to diagnosis of CNS leukemia is compared for VAD and other regimens, with patients grouped according to the proportion of cells in $S + G_2M$ compartment in order to adjust for the difference in this characteristic between the treatment groups. The figure suggests that improvement associated with VAD therapy occurred in the group at lower risk of CNS disease.

B-cell leukemia and incidence of CNS leukemia. B-cell leukemia was diagnosed in nine (5%) of the 177 patients. B-cell leukemia was associated with a high incidence of CNS involvement: three of the nine patients (33%) had CNS leukemia at diagnosis, and the remaining six developed it subsequently. All nine patients (100%) had lactic dehydrogenase levels of 600 U/L or greater. An $S + G_2M$ compartment of $\geq 14\%$ was found in five of the six patients who had cytokinetic studies performed.

**DISCUSSION**

Without CNS prophylaxis, the incidence of CNS leukemia ranges from 20% to 60% in adults with ALL.\textsuperscript{13,14,23-25} This incidence has been increasing as more effective systemic chemotherapy produced longer survival and, consequently, a longer period at risk for development of CNS leukemia.\textsuperscript{10,11} The occurrence of CNS leukemia has been reduced to a range of 5% to 20% with different CNS prophylactic modalities including CNS irradiation, intrathecal or intra-Ommaya chemotherapy, and systemic high-dose chemotherapy.\textsuperscript{5,12,13,23-25}

While CNS prophylaxis is associated with a reduced incidence of CNS leukemia, it might result in significant acute and chronic neurotoxicities. There is presently no demonstrable survival advantage with CNS prophylaxis among either children\textsuperscript{4,13} or adults\textsuperscript{25} with ALL. One possible explanation is that CNS leukemia is a manifestation of a more aggressive systemic disease, rather than acting as a "reseeding" focus inducing systemic relapse. Therefore, despite prevention of CNS disease, systemic relapse would ultimately develop and determine survival.

Side effects of CNS prophylaxis include, among others, febrile reactions, arachnoiditis, leukoencephalopathy, myelopathy, and more disturbingly, a high incidence of subclinical dysfunctions including learning disabilities, subtle intellectual changes, subclinical demyelination measured by visual-evoked potentials, and computerized tomographic changes in the brain.\textsuperscript{26,32} Gross frontal lobe and cerebral abnormalities have developed in a small proportion of patients, especially in children.\textsuperscript{26-32} This indicates the need to assess carefully the benefits vs the risks of CNS prophylaxis, and to attempt implementing risk-oriented approaches in which only patients at high risk of CNS leukemia would receive CNS prophylaxis.

Our analysis had identified two major independent factors predictive for a high occurrence of CNS leukemia: elevated lactic dehydrogenase levels and a high $S + G_2M$ compartment. Patients in our same population could be classified into different risk groups, with occurrence of CNS leukemia ranging from 4% to 55% at 1 year (Table 3). High lactic dehydrogenase levels might indicate a high tumor burden. Both variables are also indicative of high disease proliferation and cell turnover, which would suggest an aggressive disease process and the potential for CNS involvement. Elevated lactic dehydrogenase levels have been previously correlated with poor prognosis in several diseases, including leukemias\textsuperscript{43-44} and lymphoma, and were also associated with CNS involvement in the latter disease.\textsuperscript{45} The association of the $S + G_2M$ compartment with CNS leukemia has not been previously reported. The correlation of high creatinine and alkaline phosphatase with CNS disease by univariate analysis might reflect a leukemic subclinical predilection to extra-medullary involvement including CNS, kidneys, or liver. Other investigators have previously found an association between

<table>
<thead>
<tr>
<th>Lactic Dehydrogenase (U/L)</th>
<th>S + G2M Percentage</th>
<th>No. With CNS Leukemia/Total (%)</th>
<th>Estimated % of CNS Leukemia at 1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;600</td>
<td>&lt;14</td>
<td>4/61 (7)</td>
<td>4</td>
</tr>
<tr>
<td>&lt;600</td>
<td>$\geq 14$</td>
<td>4/22 (18)</td>
<td>13</td>
</tr>
<tr>
<td>&gt;600</td>
<td>&lt;14</td>
<td>6/28 (21)</td>
<td>29</td>
</tr>
<tr>
<td>&gt;600</td>
<td>$\geq 14$</td>
<td>13/25 (52)</td>
<td>56</td>
</tr>
</tbody>
</table>

Fig 1. Effect of systemic chemotherapy on the incidence of CNS leukemia within risk categories.

Table 3. Incidence of CNS Leukemia by Lactic Dehydrogenase and $S + G_2M$ Percentage Values
CNS leukemia and the presence of high pretreatment WBC counts and T-cell phenotype. B-cell leukemia was also related to a strong probability of CNS leukemia. One third of the patients had CNS involvement at diagnosis, and 100% eventually developed CNS disease. The small number of patients with B-cell leukemia, and its correlation with elevated lactic dehydrogenase levels and S + G2M compartment, explains its exclusion by the multivariate analysis.

The multivariate analysis demonstrated a low risk of CNS leukemia in about half of the adults with ALL, suggesting that CNS prophylaxis might not be required in this group. Patients at low risk of CNS leukemia might thus be better observed or given milder CNS prophylaxis, while intensive CNS prophylaxis or therapy would be reserved for high-risk patients and those with documented CNS leukemia. A similar analysis in children with ALL might avoid the risks of CNS prophylaxis in a substantial proportion of patients.

The VAD program has included several agents with good penetration of the blood-brain barrier (dexamethasone, asparaginase) or in high-dose schedules (ara-C, cyclophosphamide, methotrexate, etoposide, and BCNU). VAD therapy was associated with a trend for a lower incidence of CNS leukemia overall, but especially in the low-risk group (Fig 1), although the differences did not approach statistical significance. High-dose systemic chemotherapy has been shown to reduce the risk of CNS leukemia in other studies** and should be considered in the design of future ALL therapy trials.

REFERENCES

Identification of risk groups for development of central nervous system leukemia in adults with acute lymphocytic leukemia

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