VINCRISTINE IN THE TREATMENT OF
ACUTE LEUKEMIA IN CHILDREN

Ruth M. Heyn, M.D., Chairman, Writing Committee; E. C. Beatty, Jr., M.D.,
D. Hammond, M.D., J. Louis, M.D., M. Pierce, M.D., M. L. Murphy, M.D.,
and N. Severo, Ph.D.

Department of Pediatrics and Communicable Diseases, University of Michigan Medical School,
Ann Arbor, Michigan (R.M.H.); Children's Hospital of Denver, Denver, Colorado (E.C.B., Jr.);
The Division of Hematology, Children's Hospital of Los Angeles, Los Angeles, California
(D.H.); University of Illinois, Chicago, Ill. (J.L.); Bobs Roberts Hospital, University of
Chicago, Chicago, Ill. (M.P.); Memorial Hospital, Sloan-Kettering Institute for Cancer
Research, New York, N.Y. (M.L.M.); and Department of Statistics, State University
of New York at Buffalo (N.S.)

VINCRISTINE SULFATE (hereafter referred
to as Vcr) is a dimeric alkaloidal
drug which is prepared from the plant
Vinca rosea Linn. The observation by
Cutts, Beer, and Noble in 1957,¹ that cer-
tain crude fractions of this plant induced a
peripheral granulocytopenia and depression
of bone marrow in rats led to the separation
of a purified compound, vinblastine
sulfate,² which inhibited the growth of a
number of animal tumors, and prolonged
the survival time of mice in several of the
mouse leukemias.³ In 1959, the studies of
Johnson, Wright, and Svoboda⁴ led to the
purification of other active alkaloids from
the plant, one of which was Vcr.⁵ Clinical
studies have shown that vinblastine sulfate
is effective in the lymphomas and chorioepi-
thelialomas with relatively little effect in the
acute leukemias, whereas Vcr has proved to
be effective against the acute leukemias and
certain other neoplasms as well.⁶

The biochemical pathway of action of
Vcr has not been determined although tis-
sue culture studies suggest that Vcr may in-
hibit the de novo synthesis of nucleic acids.⁶
Creasey and Markiw⁷ demonstrated an in-
hibition of the incorporation of uridine into
soluble RNA in Ehrlich ascites carcinoma in mice treated with Vcr. The inhibition of
RNA synthesis caused by Vcr was partially
prevented by pretreatment with large doses
of glutamic acid.

The present report deals with the re-
sults of a cooperative study conducted by
Leukemia Group A, designed to evaluate
the response of children with acute leukema-
to a constant weekly dose of Vcr and to
determine the effect of maintenance, versus
no maintenance therapy during remission.
The incidence, quality, and duration of
remissions, and the associated toxic effects
of the drug were measured.

MATERIAL AND METHODS

Children under 15 years of age with
acute leukemia were eligible for study
when they had become resistant to previous
anti-leukemic treatment and examination of
the bone marrow revealed that the percent-
age of leukemic cells was greater than 25%.
The status of disease at the onset of treat-
ment and at periodic intervals through-
out the study was determined by evalua-
tion in four categories—bone marrow,
blood, physical findings, and symptoms—ac-

Presented at the 12th Annual Meeting of the Society for Pediatric Research, Lake Buena

Present Address: (J.L.) Loyola University, Stritch School of Medicine, Chicago, Illinois.

Address for Reprints: (R.M.H.) Department of Pediatrics and Communicable Diseases, University
Hospital, Ann Arbor, Michigan 48104.

Received December 7, 1965; accepted for publication February 2, 1966.
quired on the fourteenth and twenty-eighth days of study and at 4-week intervals during remission.

Vcr was provided in vials of 1 mg and dissolved in five ml of distilled water. The solution was used for a period not exceeding 1 week. The dose employed was 0.075 mg/kg given intravenously on days 0, 7, 14, and 21 of study. When a patient was in complete remission as determined by the criteria for evaluation on either day 14 or 28, the maintenance regimen was determined by a constrained randomized procedure. One group received no therapy while in remission and the other continued on Vcr at the same weekly dose until relapse to disease status 3 (moderate) or 4 (advanced).

If a remission had not been attained by day 28 and signs of serious drug toxicity were not present, the dose was increased to 0.1 mg/kg for two doses. At 42 days, another marrow was done and a decision regarding subsequent therapy made. If the child entered a complete remission on day 42, or any time thereafter, he was eligible for the randomization program of maintenance vs. no maintenance therapy and was followed accordingly. Treatment was continued at 0.075 mg/kg once weekly if the patient was status quo or still showing improvement without limiting toxicity. If the patient showed deterioration in any category at 42 days, he was removed from study.

Dose adjustments were made for toxicity on a weekly basis by either halving or omitting the dose. Symptoms of muscle weakness, paralysis, severe neuritic pain, or paresthesias not due to central nervous system leukemia, or severe constipation not controlled by stool softeners were indications for lowering the dose.

A period of 28 days was arbitrarily selected as an adequate trial of therapy. The patients received no other chemotherapy or x-ray treatment while on study except that allowed to the skull for the treatment of central nervous system leukemia. When intrathecal methotrexate was used, the patient was removed from study.

Removal from study and estimation of response were based on the criteria for evaluation. Statistical analysis was done by the Department of Statistics of the State University of New York at Buffalo.

RESULTS

One hundred and sixty-three children with acute leukemia were entered on the Vcr study from 14 contributing pediatric centers (Table I). The following analysis is based on results obtained in 149 patients, 121 of whom received an adequate drug trial and 28 of whom received an inadequate trial or less than four injections of the drug. Twenty-six children expired while on study; only two of these had received adequate trials of drug.

General Characteristics of the Patients Studied

The morphological diagnosis, sex, age, and race of the patients studied is given in Table II. The morphological diagnosis was either acute lymphocytic or undifferentiated cell leukemia in 90%, acute granulocytic leukemia in 7%, and acute monocytic leukemia in 3% of the children treated. The age group of 3 to 6 years predominated, the distribution of sexes was approximately equal, and the large majority were of Caucasian extraction.

The median duration of leukemia, from onset of symptoms to treatment with Vcr, was 13.5 months (range 2 to 53 months) in this group of children. The distribution of children who were moderately, or more severely ill at onset of therapy was roughly equal; 71 patients entered the study in status 3, and 78 patients entered in status 4.

The initial leukocyte count in all children treated ranged from 300 to 343,000/cu mm with a median of 3,950/cu mm. The median percentage of blasts in the bone marrow at the onset of therapy in all patients was 84.5% with a range from 24 to 100%.

Remissions

Complete remissions (CR) were attained in 14, or 11.6% of adequate trial cases. The
TABLE I
CONTRIBUTING INSTITUTIONS AND INVESTIGATORS

<table>
<thead>
<tr>
<th>Institutions</th>
<th>Principal Investigators</th>
<th>Associate Investigators</th>
</tr>
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<tbody>
<tr>
<td>University of Michigan, Ann Arbor</td>
<td>R. Heyn</td>
<td>J. Kastelic, I. Ertel, R. Holland</td>
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<tr>
<td>Memorial Hospital Sloan-Kettering Institute, New York City</td>
<td>M. L. Murphy</td>
<td>M. Haghbin, J. Howard, R. Alberto</td>
</tr>
<tr>
<td>University of Wisconsin, Madison</td>
<td>N. Smith</td>
<td>P. Joo, L. Thatcher</td>
</tr>
<tr>
<td>University of Washington, Seattle</td>
<td>J. Hartmann</td>
<td>M. Origones</td>
</tr>
<tr>
<td>University of Chicago, Chicago</td>
<td>M. Pierce</td>
<td>S. Smith</td>
</tr>
<tr>
<td>Children's Hospital, Washington, D. C.</td>
<td>S. Leikin</td>
<td></td>
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<td>Children's Hospital, Los Angeles</td>
<td>D. Hammond, C. Brubaker</td>
<td>N. Movassaghi, N. Shore, K. Williams</td>
</tr>
<tr>
<td>Ohio State University, Columbus</td>
<td>W. Newton, Jr.</td>
<td>D. Kmetz, N. Nagi, L. Sinks</td>
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<tr>
<td>Babies Hospital, New York City</td>
<td>J. Wolff</td>
<td>A. Sitarz</td>
</tr>
<tr>
<td>University of Pittsburgh, Pittsburgh</td>
<td>V. Albo</td>
<td>W. Prin, P. Gaffney</td>
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<tr>
<td>University of Illinois, Chicago</td>
<td>J. Louis</td>
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</tr>
<tr>
<td>Children's Hospital, Denver</td>
<td>E. Beatty, Jr.</td>
<td>C. Reiquam</td>
</tr>
<tr>
<td>University of Minnesota, Minneapolis</td>
<td>W. Krivit</td>
<td></td>
</tr>
<tr>
<td>St. Christopher's Hospital, Philadelphia</td>
<td>A. McElfresh</td>
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TABLE II
SUMMARY OF PATIENT CHARACTERISTICS

<table>
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<th>Characteristics</th>
<th>No.</th>
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<tr>
<td>Morphologic diagnosis</td>
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<tr>
<td>Acute lymphocytic leukemia</td>
<td>76</td>
</tr>
<tr>
<td>Acute undifferentiated leukemia</td>
<td>57</td>
</tr>
<tr>
<td>Acute granulocytic leukemia</td>
<td>11</td>
</tr>
<tr>
<td>Acute monocytic leukemia</td>
<td>5</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>83</td>
</tr>
<tr>
<td>Female</td>
<td>66</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>0–2 years</td>
<td>16</td>
</tr>
<tr>
<td>3–6 years</td>
<td>94</td>
</tr>
<tr>
<td>7–15 years</td>
<td>39</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>139</td>
</tr>
<tr>
<td>Negro</td>
<td>9</td>
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<tr>
<td>Oriental</td>
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</table>

The median time required for induction of CR was 46.5 days. The median duration of CR in children who received maintenance drug therapy was 63.5 days, with a range from 34 to 112 days. A similar duration of remission was noted in patients who did not receive maintenance therapy, with a median duration of 59 days (range 28 to 84 days).

A larger number of patients achieved partial remissions. Forty-three, or 35.5% of adequately treated patients, had good partial remissions (GPR) which lasted a median of 35 days. Twenty-two (18.1%) achieved fair partial remissions (FPR), and 25 (20.6%), minimal remissions (MR). The actual amount of drug received by the various remission groups is given as the median of the average weekly dose of drug received prior to remission. These findings are sum-
marized in Table III, which gives data for the best response obtained by each patient.

The number of adequately treated patients achieving an A, marrow (less than 8% blasts) was 52, or 42.9%. The marrow remission rate for the acute lymphocytic and acute undifferentiated leukemias was 44%. The majority of these occurred in the CR and GPR groups. The median day for attainment of an A, marrow for all groups was 28 days. The pattern of response of cellular elements in the marrow in those patients achieving an A, rating is shown in Figure 1, which illustrates the percentage of blasts, erythroid precursors, and granulocytic elements during the first 6 weeks of therapy. An erythroid hyperplasia of 32% was present by 14 days and greater than 40% by 28 days. This hyperplasia persisted throughout remission, accompanied in a large number of patients by persistent low hemoglobin values. The percentage of granulocytic cells remained relatively low throughout remission and many of the patients had mild leukopenias in the peripheral blood.

Only two of the three patients who had CR were retreated following a maintenance period without therapy. Both had GPR following retreatment and one had a GPR after a third course of Vcr.

Eleven children with acute granulocytic leukemia achieved one CR, three GPR, and three MR. Four had inadequate trials of drug. One child with acute monocytic leukemia achieved a GPR. Two others had MR and two were failures.

The age, race, sex, duration of disease, previous drug therapy, initial peripheral leukocyte count, and disease status at onset

### Table III

<table>
<thead>
<tr>
<th>Type of remission</th>
<th>No.</th>
<th>% of adequate trial cases</th>
<th>% of trial cases</th>
<th>Median of average weekly dose to remission (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with main.</td>
<td>11</td>
<td>11.6</td>
<td>9.4</td>
<td>63.5 (34-112)</td>
</tr>
<tr>
<td>without main.</td>
<td>3</td>
<td></td>
<td></td>
<td>59 (28-84)</td>
</tr>
<tr>
<td>Good partial</td>
<td>43</td>
<td>33.5</td>
<td>28.8</td>
<td>35 (6-111)</td>
</tr>
<tr>
<td>Fail partial</td>
<td>22</td>
<td>18.2</td>
<td>14.8</td>
<td>28 (13-63)</td>
</tr>
<tr>
<td>Minimal</td>
<td>25</td>
<td>20.7</td>
<td>16.8</td>
<td>19 (2-66)</td>
</tr>
<tr>
<td>Failures</td>
<td>17</td>
<td>14.0</td>
<td>11.4</td>
<td>.067</td>
</tr>
<tr>
<td>Inadequate trials</td>
<td>28</td>
<td></td>
<td></td>
<td>.073</td>
</tr>
<tr>
<td>Total</td>
<td>149</td>
<td>100.0%</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

FIG. 1. Bone marrow response to vincristine in 52 patients achieving complete marrow remission.
of therapy did not influence the response to Vcr. The marrow picture prior to treatment, however, revealed a significantly greater ($X^2 = 23.9, p < 0.01$) number of complete and good partial remissions in those children who had less than 75% blasts in their marrow at the onset of therapy than in those with more than 75%. This is shown in Table IV.

Toxicity altered the total amount of drug given. Table V shows the mean number of drug alterations per patient for the various response groups prior to remission for the three categories of toxicity. The change in drug dose is also reflected in the median of the average weekly dose of Vcr to remission. The CR group received 0.061 mg/kg weekly, whereas all other groups received .067 mg/kg/wk or more (Table III). The opportunity of increasing the dose to 0.1 mg/kg/wk if there was no response by the twenty-eighth day was used in 40 patients, but in only two was it associated with changing the type of response to Vcr. Table VI demonstrates the changes seen in children who received 0.1 mg/kg weekly on one or more occasions. The patients were divided retrospectively into those who received the increased doses before their best status was obtained and those who received them subsequent to this. Of those who received them before, there was one GPR which became a CR and one FPR which became a GPR. One patient with a GPR and one with a FPR improved their marrow category but not their disease status, and 11 patients showed no improvement. This was also true of those patients receiving the increased doses after their best status. Four improved their marrow category rating without changing status, and 19 had no further improvement.

**Toxicity**

The symptoms and signs of toxicity were divided into four major groups—alopecia, leukopenia, gastrointestinal, and neuromuscular. The number of patients who demonstrated these signs is shown in Table VII. Alopecia developed in 72 patients (48.3%) at a median of 28 days (range 4 to 118 days). The median total dose of drug preceding alopecia was 0.27 mg/kg.

**Table VI**

<table>
<thead>
<tr>
<th>Time</th>
<th>CR</th>
<th>GPR</th>
<th>FPR</th>
<th>MR</th>
<th>Failure</th>
<th>Inadequate trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before best status</td>
<td>1 A$_2$ to A$_1$</td>
<td>1 A$_2$ to A$_1$</td>
<td>1 A$_3$ to A$_2$</td>
<td>1*</td>
<td>5*</td>
<td>2*</td>
</tr>
<tr>
<td>After best status</td>
<td>—</td>
<td>4 A$_2$ to A$_1$</td>
<td>12*</td>
<td>7*</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* No improvement.
Signs and symptoms of neuromuscular and gastrointestinal toxicity are tabulated in Table VIII. The median day of onset and the median total dose of drug to onset are given. Sixty-five children (43.6%) developed gastrointestinal toxicity including nausea and vomiting, stomatitis, abdominal pain, and constipation. Nausea and vomiting, which occurred in 17 patients, were usually transient and followed the injection of drug within 24 hours, whereas the other signs could occur at any time and be persistent. Constipation occurred in 48 patients (32.2%) and abdominal pain in 20 (13.4%). The median day of onset for all gastrointestinal symptoms was 14 days, following a total dose of 0.15 mg/kg. The most common sign of neuromuscular toxicity was diminution or absence of deep tendon reflexes which developed in 49 (32.8%) patients after a median of 31 days, following a total dose of 0.26 mg/kg Vcr. Neuritic pain developed in 17 patients (11.4%), subsequent to a total dose of 0.15 mg/kg. A distressing sign of neuritic involvement was jaw pain which was noted in six patients, occurring usually within 24 hours after the injection of drug. The jaw pain tended to be transient, but to recur when another injection was given. Mild paresthesias, which occurred in 17 children (11.4%) after a median of 21 days, followed a median total dose of 0.22 mg/kg. Muscle weakness occurred in 54 children (36.2%), preceded by a median total dose of 0.32 mg/kg. Convulsions occurred in two children who had signs and spinal fluid evidence of uncontrolled leukemic infiltration of the central nervous system.

Fever to 102 to 103°F developed in 31 children (20.8%) within 24 hours of drug injection. It usually subsided within 1 or 2 days but tended to recur after subsequent doses. Hoarseness, muscle atrophy, insomnia, and skin rash occurred in a few children. Anorexia was present in 10 children.

Seven patients were removed from study because of severe Vcr toxicity. The total dose of drug and the duration of treatment before removal were variable. In two patients, the presence of severe central nervous system leukemia made drug toxicity difficult to evaluate. A third child developed severe liver damage and generalized muscle weakness following 161 days on study and subsequently succumbed with liver failure. At autopsy this child showed diffuse parenchymal cell degeneration and necrosis of the liver, and extensive demyelination of the brain and spinal cord. Another child had marked anorexia, weight loss, depression, and constipation. The remaining three patients demonstrated a combination of moderately severe gastrointestinal and nervous system symptoms simultaneously. Only one of the seven patients did not receive an adequate trial of drug—demonstrating moderately severe constipation and neuromuscular toxicity after only two doses of drug.

### DISCUSSION

Reports of early clinical trials with Vcr in acute leukemia involved a small number of patients. Karon, Rohn, Selawry, and Tan presented a total of 35 patients, of
whom 5 achieved complete and 9 partial remissions. The doses used varied widely from 0.01 to 0.2 mg/kg/wk, with adjustments in the weekly dose based on toxicity. There was fairly general agreement that toxicity was innocuous at doses of 0.05 mg/kg/wk, or less. Karon later reported that complete remissions were obtained in 54% of 13 adequately treated children who had become refractory to 6-mercaptopurine and methotrexate. In Karon's study a complete remission began when an A, marrow was obtained, provided the other categories achieved a "one" rating before the marrow relapsed.

The largest series of adequately treated children was reported by Evans, et al., who treated 35 patients resistant to previous therapy and 17 previously untreated patients. The usual dose of Vcr was 0.1 mg/kg/wk with subsequent changes in dose for leukopenia. When Vcr was used without steroids, the marrow remission rate in stem cell leukemia was 85% for the 13 previously untreated patients, and 57% for 21 resistant patients. The mean duration of remission in the latter group was 55 days when no further treatment was given, and 60 days when maintenance therapy was given every 2 weeks. When all morphological types of acute leukemia were considered, the marrow remission rate for patients resistant to other therapy was 40%.

In the Leukemia A study involving 149 children with all types of acute leukemia in relapse to previous therapy, the CR rate for adequately treated children was 11.6%, and the GPR rate was 35.5%. The criteria for a CR were more rigid than in previously reported studies, since normality was required simultaneously in all four parameters of clinical and hematological evaluation. Using the marrow response, the 43% remission rate compares favorably with other studies.

Previous therapy did not influence the response to Vcr, suggesting a lack of cross-resistance between this agent and other effective antileukemic drugs. All patients had been previously treated with steroids and antimetabolites, and two-thirds had had cyclophosphamide. Although more patients who achieved CR entered study in disease status 3 (moderate), there were 4 of 14 who entered in disease status 4 (advanced). Among the GPR, there were 26 who entered in disease status 3, and 17 in disease status 4. This is in contrast to the findings of Leukemia Group A with cyclophosphamide, in which no patients in advanced disease status achieved a complete remission. These findings suggest that Vcr can be used in the more seriously ill patient.

Vcr gave complete or good partial remissions in 4 of the 7 adequately treated cases of acute granulocytic leukemia. Although this number is small, it compares favorably with the remission rate from steroids or antimetabolites in previously untreated patients with acute granulocytic leukemia.

One of the aims of this study was to use a constant dose of Vcr for the induction of remission. The attendant high rate of toxicity altered this to a certain extent but the decrease in dose was not detrimental since the number of dose alterations was greater in the CR group than in any other category of response.

Eleven of the patients who developed CR received maintenance therapy in contrast to 3 who did not. In this small number of patients, there was no difference in the duration of CR (63.5 vs. 59 days, respectively). These figures are similar to those reported by Evans, et al. (60 vs. 55 days).

Of the three patients who achieved a CR and had no maintenance therapy, two were retreated after relapse. Both developed good partial remissions, and had total periods on study of 159 and 218 days, respectively. The apparent lack of randomization suggested by these figures can be explained by the fact that several of the cases early in the study were put into the second phase by certain investigators when the marrow attained a one rating and before the other categories of evaluation were normal. Several of these patients were subsequently accepted as GPR since they never achieved normality in all categories, leaving the imbalance shown by these figures. There were originally 15 patients in the maintenance program of whom four became GPR; there were 11 in the non-maintenance plan of whom eight became GPR.
Since there were only five patients whose total time on study exceeded 150 days, it might suggest that intermittent therapy with Vcr deserves further trial. In order to investigate this further, Leukemia Group A is presently using Vcr as part of a cyclic therapy program to determine whether short term use will prevent early resistance to the drug.

The effect of Vcr on the marrow in those patients achieving an A1 rating was a rapid clearance of blasts concomitant with the development of an erythroid hyperplasia and a reversal of the myeloid/erythroid ratio which persisted throughout remission. A peripheral neutropenia, anemia, or both were noted in 13 (23%) of the patients who attained complete or good partial remissions. The mechanism of the anemia induced by Vcr is not clear; all stages of erythrocytic precursors are found in the marrow and a maturation arrest is not apparent. Further information regarding the effect of Vcr on the life span and metabolism of erythrocytes is needed.

Vcr has a greater degree of toxicity associated with its use than have steroids, antimetabolites, or cyclophosphamide. The histopathology induced by Vcr was studied in monkeys by Adamson, et al.,17 who noted peripheral neuropathy and demyelination in the dorsolateral columns of the sacral cord in animals who were given 0.3 mg/kg at weekly intervals. In the only patient who expired with signs of neurotoxicity and hepatic failure in this study, demyelination was noted in the lateral funiculi of the cord. Muscle weakness and loss of deep tendon reflexes were the most common signs of neurotoxicity. The muscle weakness was either generalized, localized, or both. Specific sites of involvement included ptosis, facial palsy, foot drop, thenar weakness, and hoarseness. Loss of deep tendon reflexes persisted in many patients throughout the study without attendant weakness or the development of other neurologic signs. Recovery from signs of mild neurotoxicity after the drug was discontinued progressed over several weeks. If the drug was continued after weakness, pain, or paresthesias were noted, these signs were apt to worsen.

Gastrointestinal symptoms of toxicity were common and are probably due to neuromuscular effects of the drug. Constipation developed in one third of the group treated, although prophylactic measures, such as stool softeners and lubricants, were prescribed. In spite of these precautions, many patients developed abdominal pain or obstipation which necessitated alterations in drug dose or other therapy for relief.

The alopecia which developed in a high percentage (48.3%) of the patients treated was distressing to the children, many of whom appreciated wigs. Regrowth of hair began soon after the drug was discontinued, and a few patients developed regrowth of hair while Vcr was continued without interruption over long periods of time.

Vcr did not prevent the occurrence of leukemic invasion of the central nervous system. Of the 40 patients who developed meningeal leukemia while on study, 26 were given intrathecal methotrexate either as initial treatment or subsequent to recurrence of nervous system leukemia after x-ray treatment to the skull. Twelve patients were kept on Vcr along with intrathecal methotrexate therapy. In these patients there was no accentuation of neurological symptoms or findings while receiving both drugs on the same day.

**SUMMARY**

Vcr induced complete marrow remission in 43% of children with all types of acute leukemia who were refractory to other antileukemic therapy. The median duration of disease before Vcr treatment was 13.5 months. The marrow response in those patients achieving an A1 marrow was rapid with a marked clearing of the blasts by 14 days and a complete remission by 28 days. The median duration of complete remission with and without maintenance therapy was 63.5 and 59 days, respectively.

Drug toxicity occurred in about half the patients, limiting the total dose of drug that could be given. Leukopenia, alopecia, gas-
trointestinal symptoms, and neurotoxicity were the most common problems seen. These were reversible on withdrawal of the drug.

Remissions were not improved by increasing the dose of Vcr to 0.1 mg/kg for two or more doses after 4 doses of 0.075 mg/kg. The reduction in dose necessitated by drug toxicity was not detrimental to a good response since the children attaining complete remissions experienced the greatest number of alterations in dose prior to the onset of remission.

REFERENCES

Acknowledgments
This study was supported by the following grants from the National Cancer Institute, National Institutes of Health, United States Public Health Service: CA-0315, CA-06262, and CA-05826, Memorial Hospital, New York City; CA-03526, Babies Hospital, New York City; CA-01300, Bobs Roberts Hospital, Chicago; CA-04937, University of Washington, Seattle; CYP-4985-C7, University of Illinois, Chicago; CA-05436, University of Wisconsin, Madison; CA-07439, University of Michigan, Ann Arbor; CA-03888, Children's Hospital, Washington, D.C.; CA-05436, University of Wisconsin, Madison; CA-07439, University of Pittsburgh, Pittsburgh; CA-03750, Ohio State University, Columbus; CA-01300, Bobs Roberts Hospital, Chicago; CA-04937, University of Washington, Seattle; CYP-4985-C7, University of Illinois, Chicago; CA-05436, University of Wisconsin, Madison; CA-07439, University of Pittsburgh, Pittsburgh; CA-03750, Ohio State University, Columbus; CA-04179, Children's Hospital of Denver, Denver; CA-03888, Children's Hospital, Washington, D.C.; CA-02971, University of Michigan, Ann Arbor; CA-02849, Los Angeles Children's Hospital, Los Angeles; and contract PH 43-63-1147 (Cancer Chemotherapy National Service Center), State University of New York at Buffalo.

APPENDIX
I. Criteria for rating categories.
A. Category A—bone marrow
1. A.—blasts less than 8%. Blasts, lymphocytes and pathologic cells less than 40%
under 2 years of age and less than 30% over 2 years.
3. A3—blasts and pathologic cells 25% or greater. Blasts, pathologic cells and lymphocytes 60% or greater, or percentage of lymphocytes greater than 70%.

B. Category B—blood
1. B1—following subcategory values must be met:
   a. Hemoglobin: 10 gm % or more under 2 years of age; 11 gm % or more over 2 years of age.
   b. Granulocytes: absolute count 1500-8500/cu mm.
   c. Lymphocytes: absolute count should not exceed 10,000/cu mm under 2 years of age or 7000/cu mm over 2 years of age.
   d. Platelets: within normal range for technique used.
   e. Morphology: no blasts or pathologic cells.
2. B2—abnormalities in one or two subcategories.
3. B3—abnormalities in three or more subcategories.

C. Category C—physical signs
1. Each physical finding constitutes a subcategory. The degree of abnormality for each subcategory is rated 0 (no defect), 2 (definite abnormality present), and 3 (marked abnormality present).
   a. C1—0.
   b. C2—greater than 0 but less than 4.
   c. C3—greater than 4.

D. Category D—symptoms
1. D1—asymptomatic and normally active.
2. D2—mild symptoms ascribable to leukemia; ambulatory or limited activity.
3. D3—marked symptoms and bed rest.

II. Criteria for rating disease status.
A. Disease status based on category ratings.
1. No apparent disease (1), A0, B0, C0, D0.
2. Mild disease (2), rating of 2 in one or more categories (no 3 rating).
3. Moderate disease (3), rating of 3 in one or two categories.
4. Advanced disease (4), rating of 3 in more than two categories.

III. Indications for removing patient from study.
A. Change from disease status 1 or 2 to 3 or 4.
B. Change from disease status 3 to 4.
C. Patient in disease status 3 or 4 can be removed from study when there is deterioration in category C or D with no improvement in category A or B.
D. Progressive local leukemic infiltration for which other therapy is necessary.
E. Special provision described in protocol.
F. Death.

IV. Terms describing response to therapy.
A. Complete remission—improvement to disease status 1.
B. Good partial remission—improvement to disease status 2.
C. Fair partial remission—improvement to disease status 3.
D. Minimal remission—improvement in any category without change in status.
E. Failure—deterioration after adequate trial period.
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