Treatment of Late Bone Marrow Relapse in Children With Acute Lymphoblastic Leukemia: A Pediatric Oncology Group Study

By P. David Sadowitz, Stephen D. Smith, Jonathan Shuster, Moody D. Wharam, George R. Buchanan, and Gaston K. Rivera

Children with acute lymphoblastic leukemia (ALL) who have completed 2.5 to 3 years of initial chemotherapy have an off-therapy relapse rate of approximately 20%. In an attempt to improve the survival of children with a late bone marrow (BM) relapse (ie, occurring greater than 6 months after cessation of primary therapy), the Pediatric Oncology Group designed a randomized study to compare the efficacy of doxorubicin/prednisone and cytarabine/teniposide in a multidrug retreatment chemotherapy program. Treatment consisted of remission reinduction with vincristine, prednisone, and doxorubicin, central nervous system prophylaxis with triple intrathecal chemotherapy, and continuation therapy for 12 cycles of oral 6-mercaptopurine/methotrexate and intravenous vincristine/cyclophosphamide. Patients received intermittent courses of either prednisone/doxorubicin (regimen 1) or teniposide/cytarabine (regimen 2) during continuation therapy and a late intensification phase with either vincristine, prednisone, and doxorubicin (regimen 1) or teniposide and cytarabine (regimen 2). One hundred two of 105 evaluable patients (97%) achieved a second complete remission. Twenty-eight of 50 patients on regimen 1 have failed compared with 28 of 52 patients on regimen 2 (logrank analysis, \( P = 0.68 \)), indicating that this trial was inconclusive as to which treatment regimen was superior. The overall 4-year event-free survival for children with a late BM relapse was 37% ± 6%. Age less than 10 years at initial diagnosis \( (P \leq 0.001) \), white blood cell count less than 5,000/\( \mu L \) at relapse \( (P = 0.036) \) and duration of first remission greater than 54 months \( (P = 0.039) \) were independently associated with a more favorable outcome. While the randomized trial was inconclusive, prolonged second complete remissions were secured in more than one-third of children with a late BM relapse of ALL. The prognostic factors identified may help select children with a late BM relapse who can be successfully retreated with chemotherapy alone.

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LATE MARROW RELAPSE IN CHILDREN WITH ALL

Materials and Methods

Patients. From April 1983 to November 1989, 109 patients who were less than 22 years old at diagnosis of ALL and who experienced their first BM relapse greater than 6 months after the elective cessation of initial chemotherapy were entered on to POG protocol 8304 (stratum 1). A marrow aspirate containing greater than 25% blasts (M,) and submission of BM specimens for laboratory reclassification studies, including the characterization of immune phenotype, were required for enrollment. Because patients on regimen 1 of continuation therapy were to receive 300 mg/m² of doxorubicin, patients who had already received greater than 300 mg/m² of anthracycline agents were not eligible. Signed informed consent, obtained according to the guidelines of the respective institutional review boards, was required before treatment was begun.

While the initial ALL therapy was not uniform, all patients had received multiagent systemic chemotherapy and central nervous system (CNS) prophylaxis with intrathecal methotrexate with or without whole brain irradiation or high-dose methotrexate. Most patients had been treated according to a POG frontline ALL treatment protocol (POG 7623, n = 25; POG 8036, n = 40).28,29

To determine the influence of initial chemotherapy on the outcome of the POG 8304 study, the primary chemotherapy protocols were retrospectively classified into three broad groups. Group A protocols used vincristine, prednisone, oral methotrexate, and 6-mercaptopurine with or without additional cyclophosphamide, asparaginase, and cytarabine. Group B protocols contained multiagent chemotherapy including an anthracycline, whereas group C protocols contained multiagent chemotherapy including intravenous intermediate-dose methotrexate (IDM; 1 g/m² dose). The protocols containing both an anthracycline and IDM were classified as group B; two children registered on POG 8304 received such frontline therapy. This broad classification was used to determine if BM relapse after receiving frontline therapy containing an anthracycline or IDM precluded successful treatment on the POG 8304 protocol.

One hundred seven of the 109 registered patients were eligible for treatment. Two patients were ineligible because marrow samples were not submitted for the required laboratory reclassification studies. Descriptive characteristics of the 107 eligible patients are as follows: 70 males, 37 females; 6 black, 101 nonblack; age at initial diagnosis, 0.1 to 18.1 years (median, 4.1 years); age at relapse, 4.4 to 22.4 years (median, 8.7 years). At the time of study entry, each of the patients was in first marrow relapse, had completed initial treatment, and had not received chemotherapy for at least 6 months (median time off therapy, 18 months; range, 6 to 96 months). Patients with prior marrow or extramedullary relapse were not eligible for study. The length of first remission ranged from 42 to 132 months (median, 53 months). Eighty patients had an isolated BM relapse, whereas 27 others had combined marrow and extramedullary relapse. Two patients refused all therapy, leaving 105 evaluable for further analysis.

Treatment. The POG 8304 treatment schema is shown in Table 1. BM aspiration was performed on day 29 to determine remission status. Patients were considered to be in complete remission if they had no symptoms or physical findings suggestive of leukemia and had less than 5% leukemic blast cells in BM aspirates. Patients not in remission were treated with four doses (twice weekly for 2 consecutive weeks) of teniposide (150 mg/m² as a 45-minute intravenous [IV] infusion) and cytarabine (300 mg/m² IV push), and remission status was reassessed on day 56. At registration, patients were randomized to receive one of two continuation arms; the total planned duration of therapy was 13 weeks. Patients with concomitant marrow and CNS relapse (n = 12) received additional triple intrathelial therapy (6 weekly doses) during induction, whole brain irradiation (2,400 cGy in 12 fractions) beginning on day 42, and monthly triple intrathecal chemotherapy during the continuation therapy. Patients with concomitant marrow and overt gonadal relapse (n = 16) received gonadal irradiation (2,600 cGy in 13 fractions) beginning on day 8 of induction therapy.

Chemotherapy doses were adjusted according to the absolute phagocyte count (APC), which was determined by multiplying the total leukocyte count by the percentage of neutrophils and monocytes. When the APC was 500 cells/µL or more, full doses of chemotherapy were administered; when the APC was less than 500/µL, chemotherapy was held until the APC recovered to a level greater than 500/µL.

BM aspiration was performed every 12 weeks during chemotherapy and every 4 months for 2 years after chemotherapy was completed.

Statistical Methods. Event-free survival (EFS) was measured from the date a patient achieved a complete remission until the date of relapse, death, BM transplant, or last contact. Failures included induction failures, relapses, and death from any cause; induction failures were scored as failures at time zero. Probability estimates of EFS were calculated by the method of Kaplan and Meier,20 with standard errors by the method of Petö et al.21 A stepwise Cox life-table regression analysis was used to evaluate the prognostic significance of clinical variables.22 Differences that failed to achieve a P value (determined by a two-tailed test) of .05 or less were considered nonsignificant.

<table>
<thead>
<tr>
<th>Table 1. Treatment Program for Patients With Late BM Relapse (POG 8304)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regimen 1</strong> (cycles of alternating drug pairs listed below repeated 4 times)</td>
</tr>
<tr>
<td>Vincristine, 1.5 mg/m² IV weekly × 4 (maximum dose, 2.0 mg)</td>
</tr>
<tr>
<td>Doxorubicin, 40 mg/m² IV day 1 and day 15</td>
</tr>
<tr>
<td>Prednisone, 40 mg/m² PO daily × 28 days</td>
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<tr>
<td><strong>Regimen 2</strong> (weeks 6 to 132):</td>
</tr>
<tr>
<td>Par 1 (6 weeks): 6-Mercaptopurine, 50 mg/m² PO daily</td>
</tr>
<tr>
<td>Methotrexate, 40 mg/m² PO weekly</td>
</tr>
<tr>
<td>Doxorubicin, 20 mg/m² IV day 1 (1 week)</td>
</tr>
<tr>
<td>Prednisone, 40 mg/m² PO daily × 7 days</td>
</tr>
<tr>
<td>Vincristine, 1.0 mg/m² IV weekly</td>
</tr>
<tr>
<td>Cytosine arabinoside, 300 mg/m² IV weekly</td>
</tr>
<tr>
<td><strong>Late Intensification</strong> (weeks 133 to 136):</td>
</tr>
<tr>
<td>Vincristine, 1.5 mg/m² IV weekly × 4 (maximum dose, 2.0 mg)</td>
</tr>
<tr>
<td>Doxorubicin, 40 mg/m² IV day 1 and day 15</td>
</tr>
<tr>
<td>Prednisone, 40 mg/m² PO daily × 28 days</td>
</tr>
<tr>
<td><strong>Regimen 2</strong></td>
</tr>
<tr>
<td>Teniposide, 150 mg/m² IV days 1, 4, 8, and 12</td>
</tr>
<tr>
<td>Cytosine arabinoside, 300 mg/m² IV days 1, 4, 8, and 12</td>
</tr>
<tr>
<td>Intrathecal Chemoprophylaxis (22 doses total) for Both Arms:</td>
</tr>
<tr>
<td>Methotrexate, 15 mg/m² (maximum dose, 15 mg/m²)</td>
</tr>
<tr>
<td>Hydrocortisone, 15 mg/m² (maximum dose, 15 mg/m²)</td>
</tr>
<tr>
<td>Cytosine arabinoside, 30 mg/m² (maximum dose, 30 mg/m²)</td>
</tr>
<tr>
<td>Intrathecal chemotherapy was administered on days 15, 29, 43, 57, and 71 and then every 7 weeks during continuation therapy.</td>
</tr>
</tbody>
</table>

Abbreviations: PO, orally; VM-26, teniposide; ARA-C, cytarabine; DOX, doxorubicin; PRED, prednisone.
Table 2. Results of Induction and Continuation Therapy (POG 8304)

| No. of patients entered on study | 109 |
| Ineligible patients | 2 |
| Refused all therapy | 2 |
| Reinduction therapy | 2 |

- Received vincristine, prednisone, and doxorubicin 105
- M3 marrow after induction (day 29) 6
- Early death (sepsis) 1

Complete remission 98/105
- Received teniposide/ cytarabine 6
- Complete remission after teniposide/ cytarabine (day 42) 4
- Resistant leukemia 2

Overall complete remission rate 102/105 (97%)
- BMT before continuation therapy 2

Continuation therapy
- Received continuation therapy 100
- BMT after initiation of continuation therapy (3, 3.3, 3, and 5 months) (censored) 5
- Protocol noncompliance (3 months) (censored) 1
- Hepatic toxicity (4 months) (censored) 1
- Refused further therapy (25 months) (censored) 1
- Relapses (46 BM, 3 testes, 2 CNS, 3 BM/CNS, 1 bone) 55
- Died from accidental gunshot 1
- Continued second remission 36

The univariate comparisons were made by the logrank test and all analyses were based on follow-up through May 2, 1991.

The planning parameters of this study were as follows. Annual accrual of patients was expected to be 22 reaching the divergence point between the therapies. 2-year results of the trials of others are reported for descriptive purposes with exponential distribution assumed and a logrank analysis planned. These parameters require a minimal accrual of 85 patients. In actuality, the accrual was 99 patients reaching the point of divergence. Note that lack of results, and not to "no difference."

Results of the trials of others are reported for descriptive purposes only. There is no basis for making any therapeutic conclusions on the basis of contrasting these series with that presented here.

RESULTS

Ninety-eight of the 105 evaluable children (93%) registered on POG study 8304 entered second complete remission after receiving vincristine, doxorubicin, and prednisone. One child with Down's syndrome died during induction secondary to sepsis. Six patients had an M3 marrow on day 29. Four of these six patients entered complete remission after four doses of VM-26/ARA-C and two children had an M3 marrow on day 56. The overall complete response rate was 97% (102 of 105) (Table 2).

After successful reinduction, two patients did not receive continuation therapy because BM transplantation (BMT) was performed as an alternative. Of the 100 patients beginning continuation therapy, 8 were later removed from the study for reasons other than disease recurrence: refusal to receive additional therapy (n = 1), protocol noncompliance (n = 1), hepatic toxicity (n = 1), and BM transplantation (n = 5).

Outcome. Forty-six of the 92 children who received continuation therapy subsequently relapsed in the BM, three developed isolated testicular leukemia, two had an isolated CNS relapse, three had a combined marrow and CNS recurrence, and one relapsed in the bone. Thirty-six children remain in a second complete remission (Table 2). The Kaplan-Meier projections indicate that the 4-year EFS for patients with a late BM relapse was 37% (SE = 6%) (Fig 1). Patients with a combined first marrow and extramedullary relapse did not fail therapy at a higher rate (Table 3). All seven patients removed from the study to receive a marrow transplant (6 allogeneic from HLA-identical sibling; 1 autologous) remain alive without recurrent disease (21, 24, 30, 30, 36, 36, and 78 months after transplantation).

Despite the relatively encouraging 4-year EFS data, patients continue to be at risk for relapse. Thirteen of the 55 second relapses occurred after completion of POG 8304 therapy when children were off therapy a second time. Of those 55 patients who experienced a second relapse, the actuarial 3-year survival subsequently was only 4% (SE = 4%).

Comparison of treatments for remission duration. As seen in Table 4, there was no significant difference in EFS between regimens 1 and 2 (P = .68). However, this result is inconclusive, because fairly large advantages of either treatment cannot be ruled out. A univariate Cox analysis provides a 95% confidence interval that the instantaneous risk of failure on regimen 2 ranges from 63% to 179% of that of regimen 1. While 100% (the value of equality) is contained in this interval, so are fairly substantial values, which cannot be ruled out, favoring each treatment.

The Kaplan-Meier estimates of EFS for 105 children with late BM relapse treated on POG 8304. Numbers on the curve denote patients still at risk of relapse.

![Kaplan-Meier estimates of EFS for 105 children with late BM relapse treated on POG 8304. Numbers on the curve denote patients still at risk of relapse.](image)

![Fig 1. Kaplan-Meier estimates of EFS for 105 children with late BM relapse treated on POG 8304. Numbers on the curve denote patients still at risk of relapse.](image)

Table 3. Outcome After Combined First Marrow and Extramedullary Relapse

<table>
<thead>
<tr>
<th>Sites of Relapses</th>
<th>No. of Patients</th>
<th>No. of Patients Falling Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow-testes</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Marrow-ovary</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Marrow-CNS</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Marrow-CNS-testes</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

* All relapses occurred in the marrow.
Predictors of remission duration. To identify features that might be of prognostic value in predicting DFS after a late BM relapse, the significance of age, gender, race, white blood cell count (WBC) (at initial diagnosis and at relapse), immunophenotype, the presence of extramedullary leukemia, therapy during first remission (prior therapy group A, B, or C), length of first remission, and the arm of the POG 8304 therapy received were analyzed (Table 4). Univariate analysis (logrank test) determined that age greater than 10 years at initial diagnosis and length of first remission less than 54 months had unfavorable prognostic significance. Cox forward stepwise analysis was performed using the same values as the univariate analysis except for immunophenotype (too many missing values). As seen in Table 5, age greater than 10 years, length of initial remission less than 54 months, and leukocyte count (WBC) greater than 5,000/μL at relapse were significant independent indicators of adverse prognosis. After adjustment for these features, there was no significant difference between the two treatment regimens (P = .78) (Fig 2 and Table 5).

Toxicity. Induction therapy was well tolerated. Thirty patients required hospitalization for treatment of fever and neutropenia and 12 patients developed mild to moderate mucositis. Two children (both without CNS leukemia) developed a single therapy-related seizure; one was associated with intrathecal therapy and the other with prednisone-induced hypertension.

Most patients (n = 47) on continuation therapy experienced only mild intermittent myelosuppression. Twenty-three patients were hospitalized for 34 episodes of fever and neutropenia (15 on regimen 1 and 19 on regimen 2). Eight children developed varicella or herpes zoster that resolved without significant sequelae. Five patients developed signs and symptoms of leukoencephalopathy, which was heralded by a seizure in four children. Three children (2 with CNS leukemia) had mild, stable leukoencephalopathy, while two had progressive neurologic deterioration despite discontinuation of intrathecal therapy. No patients developed congestive heart failure, but two children on continuation regimen 1 had doxorubicin discontinued because of...
creasing cardiac function. Three patients treated on continuation regimen 2 had an allergic reaction to VM-26; two children subsequently received VM-26 after pretreatment with antihistamines.

Late intensification therapy was accompanied by uncomplicated, reversible neutropenia in most patients. While one patient developed severe mucositis, there was no CNS or cardiac toxicity observed.

No deaths occurred during second remission. Late toxicity included the development of acute myelogenous leukemia (AML) (French-American-British [FAB]-M2) in a child treated on regimen 2. Karyotype analysis showed 46,XX,inv(1)(11q11q23), as noted in other patients with treatment-related AML after intensive chemotherapy programs containing VM-26.34

DISCUSSION

BM relapse remains the major obstacle to curing children with ALL. Until the last decade, marrow relapse was invariably associated with a short second remission and fatal outcome.35-37 Intensive salvage chemotherapy or BMT now provide long-term DFS for at least some children with ALL after relapse.14,15,38-49 Improvements in the prognosis for children with a late BM relapse are particularly encouraging. In 1975, Leventhal et alreported that children with ALL who relapsed more than 6 months after cessation of therapy had a better survival than children who relapsed during initial therapy or within 6 months after its completion. Recently, other studies have confirmed a more favorable prognosis for the child with ALL with a late marrow relapse, and long-term DFS rates ranging from 8% to 76% have been reported16-26 (Table 6). The drug combinations used in prior studies have varied widely; some protocols were relatively intensive, whereas others essentially repeated the initial therapy. Unfortunately, analysis of the data from these earlier reports is hampered by the incomplete description of the study populations. In addition, the small number of patients treated in these trials makes it difficult to accurately assess the prognostic factors associated with DFS. The POG 8304 study represents the largest series of children with late BM relapse of ALL treated according to a standardized protocol. The 97% complete remission rate and the 4-year EFS of 37% ± 6% offer the hope of cure for some patients.

The analysis of second hematologic remission duration showed that age less than 10 years at diagnosis, initial relapse greater than 54 months from diagnosis, and WBC less than 5,000/μL at relapse were independent favorable prognostic factors (Tables 4 and 5). We could not demonstrate a therapeutic difference between prednisone/doxorubicin and cytarabine/teniposide pulses during continuation therapy, although clinically important advantages of either drug combination cannot be ruled out. The presence of combined marrow and extramedullary leukemia was not found to be significantly prognostic because 19 of the 27 patients in this group are alive without subsequent relapse. Previous studies used craniospinal radiation therapy to treat patients with CNS leukemia,30,31 but the results of POG 8304 protocol indicate that CNS leukemia associated with a late marrow relapse can be effectively treated with cranial irradiation in conjunction with intrathecal and systemic therapy.

### Table 6. Results of Previous Studies of Chemotherapy for Patients With First BM Relapse Occurring More Than 6 Months After Completion of Initial Therapy (1968-1991)

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Reinduction therapy</th>
<th>Second complete response rate (%)</th>
<th>Continuation therapy</th>
<th>EFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivera et al17</td>
<td>24</td>
<td>PVD</td>
<td>91</td>
<td>ARA-C, MTX, PVD, 6MP, MTX, VCR, CTX</td>
<td>3 yr (33)</td>
</tr>
<tr>
<td>Chessels et al18</td>
<td>34</td>
<td>PVDA</td>
<td>90</td>
<td>DEX, 6TG, VDS, MTX (IV), DNR, IFOS, PVA, ARA-C, VM-26, MTX, 6MP, MTX (IT), HD-MTX, or IDM</td>
<td>5 yr (31)</td>
</tr>
<tr>
<td>Pui et al22</td>
<td>26</td>
<td>PVD</td>
<td>100</td>
<td>Same as above</td>
<td>5 yr (31)</td>
</tr>
<tr>
<td>Henze24</td>
<td>30</td>
<td>PVA, MTX (IV), ARA-C, VM-26, DNR, IFOS, VCR, CTX, 6TG, or DEX</td>
<td>93</td>
<td>4 yr (33)</td>
<td></td>
</tr>
<tr>
<td>Henze et al29</td>
<td>53</td>
<td>R1, MTX (IV), or DEX</td>
<td>92</td>
<td>6 yr (30)</td>
<td></td>
</tr>
<tr>
<td>Present Study</td>
<td>105</td>
<td>PVD</td>
<td>97</td>
<td>R2, 6MP, MTX (IT), HD-MTX, or IDM</td>
<td>4 yr (37)</td>
</tr>
</tbody>
</table>

Abbreviations: PVDA, prednisone, vincristine, doxorubicin, asparaginase; COAP, cytoxan, vincristine, asparaginase, prednisone; HD-MTX, methotrexate, 12 g/m² IV in 4 hours; ID3, methotrexate, 1 g/m² IV in 36 hours; MTX-IV methotrexate, 500 mg/m² IV in 24 hours; 6-MP, 6-mercaptopurine; MTX, methotrexate; ARA-C, cytarabine; VM-26, teniposide; DEX, dexamethasone; PD, prednisone; 6-TG, 6-thioguanine; VDS, vindesine; DNR, daunomycin; IFOS, ifosfamide; VCR, vincristine; CTX, cytoxan.

* Therapy consisted of alternating courses of R1 and R2 chemotherapy for the first 6 months, continuation therapy consisted of daily 6-TG and biweekly MTX for the subsequent 2 years.
LATE MARROW RELAPSE IN CHILDREN WITH ALL

BMT is the most intensive of all therapies available for the treatment of children with ALL in second remission. Most reports of BMT in ALL in second marrow remission have combined patients with early and late relapses. The only published prospective study of chemotherapy versus HLA-matched BMT for late relapsing patients showed no significant difference in EFS after either approach. Results from the International Bone Marrow Transplant Registry also indicate that BMT does not confer a survival advantage over chemotherapy alone for patients with late marrow relapse of ALL. In contrast to the relatively favorable prognosis seen in children with late marrow recurrence, children who relapse while receiving initial therapy or within 6 months after its completion (ie, early relapse) generally have a poor prognosis when treated with chemotherapy alone. For children with an early BM relapse, intensive chemotherapy followed by allogeneic BMT is preferable to chemotherapy if a suitable donor can be identified. Despite the relatively encouraging results reported here, nearly two-third of children with late initial relapse of ALL have had a second recurrence of their disease. Several issues need to be considered as new therapeutic programs are designed for these children. Patients treated on the POG 8304 protocol received primary therapy that was designed 10 to 15 years ago. In some respects, their initial therapy was less intensive than present-day primary treatment protocols; thus, future patients who experience a late BM relapse may be more resistant to retreatment than the children described here. One-third of relapses in the POG 8304 study occurred during the first year of retreatment, strongly suggesting that early rather than late intensification of therapy may produce better disease control. The acute toxicity during POG 8304 continuation chemotherapy was mild, predictable, and reversible; no toxic deaths occurred. The moderate myelosuppression encountered in all phases of the treatment indicates that the chemotherapy protocol could be intensified without increased untoward toxicity. Also, methotrexate and 6-mercaptopurine were administered orally, and many patients may not have received optimal dose intensity because of erratic absorption.55,56

Because many children with a late BM relapse of ALL will exhibit prolonged survival with the potential for cure, chronic toxicity of the retreatment program must be carefully evaluated. While doxorubicin-induced cardiomyopathy was rare and no chronic cardiac toxicity has been observed, children on regimen 1 will need close cardiac monitoring because of the possibility of late cardiac toxicity.5 Patients who were treated on regimen 2 are at risk of developing a therapy-related secondary malignancy. AML with an 11q23 breakpoint was identified in one child treated with VM-26. Children with ALL who develop a late BM relapse will need protracted follow-up to determine the late toxicity and the actual cure rate.

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APPENDIX

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