Moderate Dose Methotrexate, Vincristine, Asparaginase, and Dexamethasone for Treatment of Adult Acute Lymphocytic Leukemia

By Robert J. Esterhay, Jr., Peter H. Wiernik, William R. Grove, Susan D. Markus, and Margaret N. Wesley

Thirty-eight adults with acute lymphocytic leukemia (ALL), 24 previously untreated and 14 previously treated, were entered into a study in which sequential, moderate-dose methotrexate and asparaginase were added to vincristine and dexamethasone (MOAD) for remission induction therapy. Eighteen of 24 previously untreated patients (75%) and 11 of 14 previously treated patients (79%) achieved a complete remission (CR). Once in CR, patients were given remission continuation therapy, which included intravenous high-dose methotrexate that was used without prophylactic cranial irradiation and without intrathecal methotrexate because of its potential activity alone as prophylaxis against central nervous system (CNS) leukemia. The median duration of CR was 11.1 mo (range 0.7–55.9+) and median survival 17.0 mo (range 0.4–55.9+) for the 24 previously untreated patients. The median duration of CR was 7.5 mo (range 1.9–55.3+) and median survival 11.2 mo (range 1.1–55.3+) for the 14 previously treated patients. Only 2 of 24 previously untreated patients (8.3%) developed CNS leukemia at 3.3 and 42.7 mo from start of MOAD. None of the previously treated patients developed CNS leukemia as the initial site of relapse. MOAD is useful as induction therapy for previously untreated adults with ALL, as well as for previously treated patients, and is superior to other regimens that we have used for the treatment of adult ALL.

Although improvement in the management of adult acute lymphocytic leukemia (ALL) has not been as rapid as in the childhood form of this disease, progress has been achieved in remission induction rate, reduction in the incidence of central nervous system (CNS) leukemia and increase in survival.1–20 The most effective chemotherapeutic agents used for remission induction in both childhood and adult ALL are vincristine, prednisone, asparaginase, and daunorubicin.21,22 Combinations of these individually active agents have increased remission induction rates. Vincristine and prednisone have been employed in virtually all induction therapy programs for ALL with complete remission rates of 85%–95% in childhood ALL and 50%–60% in adult ALL.21,22 The addition of asparaginase and/or an anthracycline antibiotic, such as daunorubicin or doxorubicin, has increased the complete remission rate for adults with ALL to 70%–80% (see Table 1).6–13,17,20 Other agents, when combined with prednisone and vincristine, have also resulted in improved initial remission induction rates in both childhood and adult ALL. Such drugs include methotrexate and mercaptopurine as in the POMP regimen.14,23 In addition, thioguanine (instead of mercaptopurine) has been shown to be effective in the treatment of adult ALL, and dexamethasone has been demonstrated to have antileukemic activity equal to prednisone in both childhood and adult ALL.2,24 Sequentially administered methotrexate and asparaginase, with scheduling based on in vitro pharmacologic studies, has significant activity in refractory childhood and adult ALL.25–29 It appears that asparaginase not only increases the sensitivity of leukemic cells to methotrexate by producing a rapid regrowth phase 9–10 days after asparaginase administration, but also mutates the toxicity of methotrexate when given 24 hr after methotrexate.25–27 The primary toxicity observed in these studies was an allergic reaction to asparaginase after several months of intermittent treatment.25–29 When such reactions occurred it was possible to continue asparaginase treatment utilizing enzyme prepared from Erwinia species.30 This sequentially administered regimen has been used not only for relapse reinduction therapy, but indefinitely as remission continuation therapy with reported remission durations of greater than one year.27–29 The remission induction therapy used in this study incorporated this sequential cycling of methotrexate and asparaginase in combination with vincristine and dexamethasone.

The addition of central nervous system (CNS) prophylaxis with intrathecal methotrexate combined with cranial irradiation immediately following completion of remission induction therapy delays the onset of CNS leukemia, and thus prolongs complete remission and survival in childhood ALL.21 Although the results for adult ALL indicate that CNS prophylaxis is of value in decreasing the occurrence of CNS relapse, it has not resulted in improved remission duration or survival to date.15 It has been reported that intraventricular cerebral spinal fluid (CSF) methotrexate levels are variable after intrathecal injections and are more consistently achieved after high-dose...
intravenous infusions.\textsuperscript{31} Therapeutic (greater than $10^{-7} M$) CSF methotrexate levels can be obtained 24 hr after intravenous bolus injections of 400–600 mg/sq m of methotrexate.\textsuperscript{27} Other pharmacologic studies using higher doses of intravenous bolus and prolonged infusions of methotrexate to prevent CNS leukemia have also demonstrated that therapeutic CSF methotrexate levels can be achieved.\textsuperscript{32,33} The toxicity of very high dose methotrexate and the use of calcium leucovorin to decrease that toxicity has been well studied in a variety of malignant diseases. Prolonged infusions of hundreds of milligrams per kilogram of methotrexate can usually be given safely with calcium leucovorin.\textsuperscript{34,35} Because of these reported observations on the potential utility of high dose methotrexate with calcium leucovorin rescue for CNS prophylaxis, high dose methotrexate without intrathecal methotrexate and without cranial irradiation was incorporated in this study to simultaneously deliver both prophylactic CNS and systemic remission continuation therapy.

In childhood ALL it has been clearly shown that

### Table 1. Combination Chemotherapy for Previously Untreated Adult ALL

<table>
<thead>
<tr>
<th>Author</th>
<th>Remission Induction Regimen</th>
<th>Number of Patients</th>
<th>Percent Complete Remission</th>
<th>Prophylactic CNS Regimen</th>
<th>CNS Leukemia (%)</th>
<th>Remission Continuation Regimen</th>
<th>Median Duration CR in mo</th>
<th>Median Survival in mo</th>
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<tr>
<td>Whetstone\textsuperscript{1}</td>
<td>$V + P + ARA + C$</td>
<td>21</td>
<td>43</td>
<td>None</td>
<td>NA</td>
<td>Maintenance</td>
<td>14.5</td>
<td>5.5</td>
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<tr>
<td>Smyth\textsuperscript{2}</td>
<td>$V + D + PYR + TG$</td>
<td>17</td>
<td>53</td>
<td>PYR and CCNU</td>
<td>6/17 (35.3)</td>
<td>Maintenance</td>
<td>6.0</td>
<td>13.5</td>
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<tr>
<td>Gahro\textsuperscript{3}</td>
<td>$V + P + ARA + C + ASP$</td>
<td>12</td>
<td>58</td>
<td>None</td>
<td>NA</td>
<td>Maintenance</td>
<td>4.1</td>
<td>6.6</td>
</tr>
<tr>
<td>Armitage\textsuperscript{4}</td>
<td>$V + P + ARA$</td>
<td>13</td>
<td>67</td>
<td>IT-MTX + C</td>
<td>0/13 (0)</td>
<td>Maintenance</td>
<td>11.0</td>
<td>26.0</td>
</tr>
<tr>
<td>Gingrich\textsuperscript{5}</td>
<td>$V + P + ARA$</td>
<td>13</td>
<td>69</td>
<td>IT-MTX + C</td>
<td>NA</td>
<td>Maintenance</td>
<td>9.5</td>
<td>14.0</td>
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<tr>
<td>Lister\textsuperscript{6}</td>
<td>$V + P + DOX + ASP$</td>
<td>51</td>
<td>71</td>
<td>IT-MTX + C</td>
<td>3/51 (6.9)</td>
<td>Maintenance</td>
<td>18.5</td>
<td>21.0</td>
</tr>
<tr>
<td>Shaw\textsuperscript{7}</td>
<td>$V + P + DOX$</td>
<td>25</td>
<td>72</td>
<td>None* or IT-MTX + C</td>
<td>4/25 (16.0)</td>
<td>Maintenance</td>
<td>10.2</td>
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<td>Willen\textsuperscript{8}</td>
<td>$V + P + DNR$</td>
<td>21</td>
<td>72</td>
<td>IT-MTX + C</td>
<td>1/21 (4.8)</td>
<td>Maintenance</td>
<td>15.0</td>
<td>16.0</td>
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<tr>
<td>Henderson\textsuperscript{9}</td>
<td>$V + P + ASP + DNR$</td>
<td>149</td>
<td>72</td>
<td>IT-MTX + C</td>
<td>12/149 (8.0)</td>
<td>Maintenance</td>
<td>15.0</td>
<td>17.0</td>
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<td>Jackal\textsuperscript{10}</td>
<td>$V + P + DNR$</td>
<td>30</td>
<td>73</td>
<td>IT-MTX</td>
<td>4/30 (13.3)</td>
<td>Maintenance</td>
<td>11.0</td>
<td>15.0</td>
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<tr>
<td>Muriel\textsuperscript{11}</td>
<td>$V + P + (DNR or DOX)$</td>
<td>20</td>
<td>75</td>
<td>None* or IT-MTX + C</td>
<td>NA</td>
<td>Maintenance</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gottlieb\textsuperscript{12}</td>
<td>$V + P + DNR + ASP$</td>
<td>89</td>
<td>77</td>
<td>IT-MTX + C</td>
<td>NA</td>
<td>Maintenance</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Gee\textsuperscript{13}</td>
<td>$V + P + DNR$</td>
<td>23</td>
<td>78</td>
<td>IT-MTX* or OM-MTX</td>
<td>4/23 (17.4)</td>
<td>Consolidation</td>
<td>25.0</td>
<td>33.0</td>
</tr>
<tr>
<td>Rodriguez\textsuperscript{14}</td>
<td>$V + P + MTX + MP$</td>
<td>14</td>
<td>79</td>
<td>None</td>
<td>NA</td>
<td>Maintenance</td>
<td>8.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Omura\textsuperscript{15}</td>
<td>$V + P + MTX$</td>
<td>99</td>
<td>80</td>
<td>None or IT-MTX + C</td>
<td>14/99 (14.1)</td>
<td>Consolidation</td>
<td>16.9</td>
<td>24.2</td>
</tr>
<tr>
<td>Curtis\textsuperscript{16}</td>
<td>$V + P$</td>
<td>17</td>
<td>82</td>
<td>None* or IT-MTX + C</td>
<td>NA</td>
<td>Consolidation</td>
<td>NA</td>
<td>15.7</td>
</tr>
</tbody>
</table>

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remission continuation therapy prolongs the duration of complete remission. Various remission continuation therapy combinations of low-dose oral methotrexate and mercaptopurine or other drug combinations with vincristine and prednisone given as periodic reinduction or "reinforcement pulses" have significantly extended remission duration in some earlier childhood ALL studies. However, in comparative childhood studies that use an adequate induction regimen and effective continuation therapy, "pulses" of vincristine and prednisone during remission continuation therapy do not make a significant contribution to the overall results. The role of remission continuation therapy in adult ALL is unknown, primarily because few comparative studies have been done and many different remission continuation regimens have been reported (see Table 1). However, since neither remission duration nor survival is as good for adult ALL as it is for childhood ALL, several studies have been designed to prolong remission duration utilizing early intensification or consolidation as the first phase of remission continuation therapy. The best reported median duration of continuous complete remission (25 mo) and median survival (33 mo) in adult ALL is a study that used an intensive consolidation phase with cytarabine and thioguanine. Other studies have employed a cytoreductive therapy phase as part of the remission continuation therapy program to improve remission duration and survival. In childhood ALL, aggressive cytoreductive therapy given simultaneously with prophylactic CNS therapy did not prolong remission duration and was associated with significant morbidity. There are at least three reported studies in adult ALL, that have used the cycling of various chemotherapy agents for cytoreduction (even though it may be called maintenance) as part of remission continuation therapy. Finally, a standard maintenance phase consisting of weekly oral low-dose methotrexate and daily oral mercaptopurine given along with periodic reinforcement with vincristine and steroid has been shown to be effective remission continuation therapy for adults with ALL (see Table 1). Therefore, the remission continuation therapy in this study was designed to include consolidation, cytoreduction, and maintenance phases in an attempt to improve remission duration and survival.

This study evaluated the efficacy of the addition of sequential moderate-dose methotrexate and asparaginase to vincristine and dexamethasone for remission induction, the results of intravenous high-dose methotrexate alone without cranial irradiation and without intrathecal methotrexate for CNS prophylaxis, and the results of intravenous high-dose methotrexate and oral low-dose methotrexate plus mercaptopurine (both utilizing reinforcement pulses of vincristine and dexamethasone) for remission duration and survival.

**MATERIALS AND METHODS**

Thirty-eight adult (15 yr of age and older) patients with ALL, 24 previously untreated and 14 previously treated, were given methotrexate, vincristine, asparaginase, and dexamethasone (MOAD) induction therapy between November 1975 and November 1980.
Survival and remission duration figures were calculated as of December 1, 1980. The diagnosis of ALL was based on examination of Wright-Giemsa and cytochemically stained bone marrow aspirates. In most cases terminal deoxynucleotidyl transferase (TdT) determinations aided in diagnosis. There was no patient selection, and all patients with adult ALL seen at the Baltimore Cancer Research Center during this period were entered on study and evaluated.

Patient characteristics at the start of treatment are indicated in Table 2. The median ages for the two treatment groups (previously untreated and treated) were 31 and 30 yr with a range of 15–60 and 15–52, respectively. There were 20 males and 18 females. The median platelet count was lower and the median WBC was greater as was the median percent lymphoblasts in the peripheral blood and bone marrow of the previously untreated patients. TdT determinations were positive in 16 of 19 previously untreated and in 4 of 5 previously treated patients. The four TdT-negative patients were diagnosed as ALL on the basis of bone marrow morphology and cytochemical stains. The TdT determinations were done by 2 methods—an immunofluorescent procedure, which was verified by a radioassay method based on the enzymatic activity of TdT. There was complete agreement between the two methods. Methotrexate CSF levels were determined by an enzyme immunoassay method.

Complete remission (CR) was defined as a normal white blood count and differential, hematocrit/hemoglobin, and platelet count and a normocellular marrow with 0%–5% lymphoblasts and less than 40% lymphocytic elements in the marrow, and no signs or symptoms of ALL as defined by CALGB criteria. The duration of CR was defined as the interval from initial CR to relapse or for the previously treated (relapsed/refractory) ALL patients from reinduced CR to relapse. Relapse was defined as failure to meet the CALGB criteria for complete hematologic remission, development of CNS leukemia, or other extramedullary infiltration, or any signs or symptoms attributed to ALL. CNS leukemia was defined as the absence of a positive bacteriologic culture and the presence in the CSF of 10 or more mononuclear cells/μl mm or leukemic blasts in the stained cytocentrifuge specimen. Survival was measured from the date MOAD induction therapy began to date of death for both the previously untreated and treated patients. Remission and survival curves were plotted according to the technique of Kaplan and Meier. The curves were statistically compared using the generalized Wilcoxon test. All p values are two-sided unless otherwise stated.

**Induction (Table 3)**

Each induction course consisted of a 10-day period. Courses were continuous, with the second course beginning on day 11, the third on day 21, etc. Each course consisted of: methotrexate, 100 mg/sq m i.v. push on day 1, increasing subsequent doses by 50% each course to 225 mg/sq m, thereafter by 25% each course to minimal toxicity; vincristine, 2 mg regardless of body surface area, i.v. push on day 2; asparaginase (E. coli), 500 IU/kg by a 30-min infusion on day 2, 24 hr after methotrexate was given (if asparaginase allergy developed, Erwinia asparaginase was used); and dexamethasone, 6 mg/sq m/day, p.o. for days 1–10. Patients who did not have evidence of bone marrow improvement after 3 induction courses or who had not obtained a CR after 5 induction courses (without continuing marrow improvement after each course) were considered induction therapy failures. Patients who achieved a CR received two additional induction therapy courses. A minimum of 5 induction courses was required before beginning consolidation therapy. Those patients who developed allergy to *Erwinia* asparaginase and were in CR, regardless of the number of induction courses, bypassed consolidation therapy and immediately began cytodestruction therapy.

**Consolidation (Table 4)**

Those patients who received 2 additional induction courses after attainment of CR began consolidation therapy the day after completion of induction therapy. Consolidation therapy was a continuation of methotrexate and asparaginase as given during induction therapy, but without vincristine and dexamethasone. Patients received a total of 6 continuous consolidation courses at 10-day intervals if they
Table 5. MOAD for Adult ALL: Cytoreduction Therapy

| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 |
| VCR | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D |

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCR</td>
<td>Vincristine</td>
<td>2 mg</td>
<td>i.v. push</td>
</tr>
<tr>
<td>D</td>
<td>Dexamethasone</td>
<td>6 mg/sq m</td>
<td>p.o.</td>
</tr>
<tr>
<td>HDMTX</td>
<td>High-dose Methotrexate</td>
<td>100 mg/kg*</td>
<td>i.v. infusion†</td>
</tr>
<tr>
<td>CL</td>
<td>Calcium leucovorin</td>
<td>5% of HDMTX dose‡</td>
<td>i.v. infusion–p.o.§</td>
</tr>
</tbody>
</table>

*Increase by 25% until minimal toxicity develops.
†Over 6 hr.
‡Total dose of 5% of HDMTX dose given in 12 equally divided doses over 3 days.
§Short i.v. infusion every 6 hr for first 8 doses (days 1–2), and then last 4 doses given orally (day 3).
∥Start calcium leucovorin exactly 2 hr after the end of the methotrexate infusion.

Cytoreduction (Table 5)

Cytoreduction therapy began 1 mo after the first day of the last consolidation course and consisted of: vincristine, 2 mg regardless of body surface area, i.v. push on day 1; and high-dose methotrexate, 100 mg/kg i.v. infusion over 30 min, 24 hr after the methotrexate was given. If a patient on consolidation therapy developed allergy to both forms of asparaginase, he was started on cytoreduction therapy.

Maintenance (Table 6)

Supportive Treatment

Patients were given oral prophylactic antibiotics during periods of prolonged, severe granulocytopenia but were not placed in reverse isolation. They were empirically given intravenous broad-spectrum antibiotics for granulocytopenia and fever. Prophylactic platelet transfusions and therapeutic granulocyte transfusions were used when indicated.

RESULTS

Response to therapy is summarized in Table 7. The previously treated patients had received vincristine, glucocorticoid, anthracyclines, antimetabolites, and alkylating agents. Only one of the previously treated patients had received asparaginase, however, he responded to MOAD therapy. Eighteen of 24 (75%) of the previously untreated patients achieved a CR, as did 11 of 14 (79%) of the previously treated patients. Complete responders ranged in age from 15 to 60 yr for both groups. Median treatment days to complete remission was 9 days longer for the previously
untreated patients than for those previously treated. Almost all induction therapy for both treatment groups was given on an outpatient basis with routine supportive care. However, there were more severe infections during induction (41.7% versus 21.4%) for the previously untreated patients. The median duration of complete remission was 11.1 mo (range 0.7–55.9+) for the previously untreated patients and 7.5 mo (range 1.9–55.3+) for the previously treated patients (Fig. 1). There was a low incidence of CNS leukemia (8.3% and 0%) for both treatment groups. The median survival for previously untreated CR patients has not been reached and for the previously treated CR patients was 17.2 mo (range 2.6–55.3+) (Fig. 2). The median survival for all previously untreated patients was 17.0 mo (range 0.4–55.9+) and for all previously treated patients was 11.2 mo (1.1–55.3+) (Fig. 3).

Hematologic toxicity during induction and consolidation for the previously untreated patients is shown in Table 8. The myelosuppressive effect of MOAD decreased with bone marrow improvement, even with escalation of the methotrexate dose from 100 to 550 mg/sq m. Hematologic toxicity of this degree was not observed for the previously treated patients because they were treated earlier and had fewer blasts in the peripheral blood and bone marrow at the time of treatment.

There were a total of 16 infections in the previously untreated patients, 10 of which were severe; 4 microbiologically documented pneumonias (Escherichia coli, Staphylococcus aureus, Aspergillus fumigatus, and Aspergillus flavus plus Serratia marcescens), 1 gastrointestinal mucositis (Candida albicans), 4 bacteremias (Enterobacter cloacae, Pseudomonas aeruginosa, Staphylococcus aureus, and Clostridium butyricum) and 1 clinically documented pharyngitis. Four patients died of infection, 2 while in CR. One of the 2 previously untreated patients in CR died during induction and the other during consolidation. Both patients developed severe granulocytopenia fever, and then sepsis following chemotherapy. It was also noted that neither patient had been taking their oral prophylactic antibiotics. The other 2 previously untreated patients who died of infection presented with pneumonias and died during their initial remission induction therapy despite appropriate antibiotic therapy. There were a total of 7 infections in the previously treated patients, 3 of which were severe; 2 microbiologically documented pneumonias (Aspergillus fumigatus), 1
with a bacteremia (*Staphylococcus epidermidis*), and 1 clinically documented esophagitis.

The major nonhematologic toxicities that were observed also occurred during induction and consolidation. An acute allergic reaction (severe enough to require treatment) to the *E. coli* strain of asparaginase necessitated switching to *Erwinia* asparaginase in 27 of 38 patients (71%). A subsequent allergic reaction to *Erwinia* asparaginase occurred in 14 of those 27 patients (52%). Seven of these 14 patients did not complete a total of 6 continuous consolidation courses of therapy. However, there was no difference in CR duration for these 7 patients. Stomatitis, defined as multiple mucosal ulcerations severe enough to limit food intake, was observed in 26 of 38 patients (68%) during induction and consolidation, with a median methotrexate dose of 150 mg/sq m (range, 100–350 mg/sq m). In contrast, only 3 of 18 patients (17%) developed stomatitis during cytoreduction with a median methotrexate dose of 125 mg/kg (range 100–300 mg/kg). Stomatitis was worse during induction and consolidation with asparaginase as “rescue” than during cytoreduction with calcium leucovorin rescue. The median methotrexate dose was greater for those patients who did not develop stomatitis either during induction and consolidation (225 versus 150 mg/sq m) or during cytoreduction (150 versus 125 mg/kg). Stomatitis was worse during induction and consolidation with asparaginase as “rescue” than during cytoreduction with calcium leucovorin rescue. The median methotrexate dose was greater for those patients who did not develop stomatitis either during induction and consolidation (225 versus 150 mg/sq m) or during cytoreduction (150 versus 125 mg/kg). Stomatitis was worse during induction and consolidation with asparaginase as “rescue” than during cytoreduction with calcium leucovorin rescue. The median methotrexate dose was greater for those patients who did not develop stomatitis either during induction and consolidation (225 versus 150 mg/sq m) or during cytoreduction (150 versus 125 mg/kg).

Peripheral neuropathy and Cushingoid features associated with vincristine and dexamethasone were observed in 22 of 38 patients (58%) and in 24 of 38 patients (63%), respectively. In no case was the peripheral neuropathy or hyperglycemia severe or life-threatening. Dose adjustment of vincristine was required in 5 of 38 patients (13%). Hyperglycemia requiring temporary insulin administration occurred in 6 of 38 (16%) previously nondiabetic patients.

Remission continuation therapy with consolidation, cytoreduction, and maintenance was given to 25 patients achieving CR. Hematologic toxicity from consolidation, cytoreduction, and maintenance was minimal, and only one significant infection (the previously mentioned infectious death during consolidation) developed during remission continuation therapy.

Only 2 of 24 previously untreated patients (8.3%) developed CNS leukemia. One patient relapsed simultaneously in the CNS and bone marrow during consolidation therapy at 3.3 mo from the start of MOAD induction therapy. The other patient relapsed in the CNS alone during maintenance therapy at 42.7 mo from the start of MOAD. The bone marrow has been the only initial site of relapse for the 14 previously treated patients. However, it should be noted that 4 of
the 14 previously treated patients had received either prophylactic CNS therapy or therapy for CNS leukemia prior to receiving MOAD. Figure 4 shows that therapeutic (greater than $10^{-7}$ M) CSF methotrexate levels were achieved during cyto-reduction with high-dose methotrexate starting at 100 mg/kg. It appears that increasing the dose of methotrexate did not increase the CSF methotrexate molar concentration. In contrast, therapeutic CSF methotrexate levels were not achieved during induction and consolidation.

Relapses have occurred for both the previously untreated and treated patients (see Table 9). The initial site of relapse has been the bone marrow for 5 of 8 of the previously untreated patients and for all of the previously treated patients. Three previously untreated patients died in CR, 2 of infection and 1 as a result of severe stomatitis secondary to methotrexate. One previously treated patient died in CR of a pulmonary embolus. Total relapse rates have been similar for the two patient groups. Seven previously untreated patients remain in CR from 0.7 to 55.9+ mo and 4 previously treated patients remain in CR from 2.6 to 55.3+ mo. Once failing primary remission induction therapy with MOAD or relapsing, 7 patients have subsequently received doxorubicin, cytosine arabinoside, and thioguanine with 3 achieving second complete remissions of short duration.

**DISCUSSION**

The MOAD combination for remission induction therapy produced a complete remission in 75% of previously untreated and in 79% of previously treated adults with ALL. The median duration of complete remission with remission continuation therapy, consolidation (sequential, moderate-dose methotrexate and asparaginase), cyto-reduction (high-dose methotrexate with calcium leucovorin, vincristine, and dexamethasone), and maintenance (oral, low-dose methotrexate and mercaptopurine with vincristine and dexamethasone) was 11.1 mo for the previously untreated and 7.5 mo for the previously treated patients. The median survival of previously untreated CR patients has not been reached. However, the median cannot be less than 17.8 mo. The median survival of previously treated CR patients was 17.2 mo. The median survival of all previously untreated patients was 17.0 mo and of all previously treated patients 11.2 mo. There were no statistically significant differences in remission duration or survival between previously untreated and previously treated patients.

The MOAD combination is an effective regimen for inducing complete remission in adults with ALL. It is also highly effective as a relapse reinduction regimen for patients who have not previously received asparaginase. The CR rate of 75% (95% confidence limits, 58%–92%) obtained for the previously untreated patients in this study is comparable with the results of other recent studies (see Table 1). The CR rate of 79% (95% confidence limits, 58%–100%) obtained for the previously treated patients compares well to that achieved with other recently reported regimens for

**Table 9. MOAD for Adult ALL: Relapses**

<table>
<thead>
<tr>
<th>Initial Site of Relapse</th>
<th>Previously Untreated</th>
<th>Previously Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Patients</td>
<td>Months of Remission</td>
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<tr>
<td>Marrow</td>
<td>5</td>
<td>4.4, 8.3, 8.4, 11.2, 11.4</td>
</tr>
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<td>CNS</td>
<td>1</td>
<td>28.1</td>
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<tr>
<td>CNS and marrow</td>
<td>1</td>
<td>5.0</td>
</tr>
<tr>
<td>Breast</td>
<td>1</td>
<td>13.5</td>
</tr>
<tr>
<td>Died in remission</td>
<td>3</td>
<td>1.9+, 2.1+, 5.9+</td>
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<tr>
<td>Total relapses</td>
<td>8/18 (44.4%)</td>
<td>0.7+, 2.0+, 26.1+</td>
</tr>
<tr>
<td>Complete remissions</td>
<td>7</td>
<td>28.1, 49.0, 51.4+, 55.9+</td>
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</tbody>
</table>
refractory adult ALL.\textsuperscript{14,29,45-49} The median duration of complete remission of 11.1 mo for the previously untreated patients is also comparable to many reported studies (see Table 1). The median duration of complete remission of 7.5 mo for the previously treated patients compares well to other recently reported studies for refractory adult ALL.\textsuperscript{14,29,45-49} Remission continuation therapy resulted in an increase in the median survival for previously untreated patients at our institution (see Table 10). The median survival (11.2 mo) for the previously treated patients is higher than that in most reported studies for refractory adult ALL.\textsuperscript{14,29,45-49}

MOAD induction therapy was generally well tolerated and could be given on an outpatient basis with routine supportive care. Although myelosuppression was tolerable, there were 10 severe infections in 24 (41.7\%) of the previously untreated patients. This was double, 3 of 14 (21.4\%), that seen for the previously treated patients. This difference is not statistically significant. Most of the severe infections for the previously untreated patients occurred early in induction when myelosuppression was maximal (see Table 8). Because the previously treated patients were treated earlier (fewer blasts at time of treatment), myelosuppression may have been less and there were fewer severe infections. The incidence of severe infections for the previously untreated patients is less than that reported in our previous study in which 10 of 17 patients (59\%) had severe infections during induction.\textsuperscript{42} Again, the difference is not statistically significant. In that study, patients were not given oral prophylactic antibiotics. In addition, the number of severe infections in previously untreated patients is comparable (95\% confidence limits, 22\%–61\%) to that reported for adults with acute nonlymphocytic leukemia undergoing initial induction with the protection of oral prophylactic antibiotics without reverse isolation.\textsuperscript{45,46} Most of the infections for the previously untreated and treated ALL patients during induction were due to hospital-acquired pathogens. The organisms causing the bacteremias had been shown by surveillance cultures to be colonizing the alimentary canal, the mucosa of which may have been damaged by methotrexate during remission induction therapy.

Although the majority of adult ALL patients do not have severe or life-threatening infections during remission induction therapy, the number of severe infections increases as more myelosuppressive therapy is attempted. In CALGB study no. 7113, life-threatening infections occurred in 13 of 27 patients (48\%) who were given asparaginase simultaneously with vincristine and prednisone.\textsuperscript{9} When doxorubicin was added to vincristine and prednisone in a Southwest Oncology Group study, 14 of 25 patients (56\%) developed a severe infection during remission induction therapy.\textsuperscript{7} When cytoarabine was added to vincristine and prednisone, 6 of 13 patients (46\%) developed bacteremias and despite appropriate antibiotic therapy, 3 of these patients (23\%) died.\textsuperscript{4} Even with vincristine and prednisone alone, 8 of 14 patients (57\%) had infections or fever without proven infection during remission induction therapy.\textsuperscript{19} Therefore, more intensively treated adult ALL patients are at an increased risk of infection and require infection prevention measures, especially during remission induction therapy.

An acute allergic reaction to \textit{E. coli} asparaginase necessitated switching to \textit{Erwinia} asparaginase in 27 of 38 patients (71\%). A subsequent acute allergic reaction to \textit{Erwinia} asparaginase then occurred in 14 of those 27 patients (52\%). This incidence is higher than those reported elsewhere; 6 of 15 patients (40\%) receiving \textit{E. coli} asparaginase intravenously versus 0 of 9 patients treated intramuscularly with \textit{E. coli} asparaginase.\textsuperscript{28} Systemic anaphylaxis was a potentially dangerous aspect of MOAD induction therapy, however, all episodes were reversible with epinephrine and supportive care. When less acute allergic reactions occurred, such as transient hives or facial flush, reactions were not subsequently prevented or diminished with the use of an antihistamine and/or epinephrine given prior to or at the time of the asparaginase infusion. It may be that an intramuscular injection of asparaginase provides for a slower release of drug and less hypersensitivity than a 30-min intravenous infusion. Rescue with asparaginase did not appear to be as effective as calcium leucovorin, since the incidence of stomatitis was greater (68\%) with asparaginase than with calcium leucovorin (17\%). The use of asparaginase as a rescue rather than calcium leucovorin was not preferable, as previously reported.\textsuperscript{29} Cytoreduction with high-dose methotrexate and calcium leucovorin rescue was essentially nontoxic. The excellent therapeutic results of MOAD induction therapy, which suggest a possible therapeutic synergy between methotrexate and asparaginase, dictate that this treatment be further explored in larger studies.

\begin{table}[h]
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\hline
 & VCR + PRED or POMP & TODD & MOAD \\
\hline
Patients & 40 & 18 & 24 \\
Median age (yr) & 24 & 26 & 31 \\
Complete remission (CR) & 42\% & 56\% & 75\% \\
Partial remission & 7\% & 30\% & — \\
Median duration CR & 7.0 mo & 6.0 mo & 11.1 mo \\
CNS leukemia & 42.5\% & 33.3\% & 8.3\% \\
Median survival, all treated & 7.0 mo & 13.5 mo & 17.0 mo \\
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\end{tabular}
\caption{Baltimore Cancer Research Program: Therapy of Previously Untreated Adult ALL 1965–1980}
\end{table}
The potential for intravenous, high-dose methotrexate without cranial irradiation and without intrathecal methotrexate to prevent CNS leukemia was of major interest in the present study. CNS leukemia developed in only 2 of 24 previously untreated patients (8.3%). One patient, while on consolidation therapy, relapsed simultaneously in the CNS and bone marrow before cytoreduction (high-dose methotrexate) therapy was started. The other patient had a CNS relapse alone, which occurred after cytoreduction during the maintenance phase of remission continuation therapy. The CSF fluid was repeatedly negative for lymphoblasts, but the patient had clinical findings of CNS leukemia and a positive CAT scan. The patient was treated with cranial irradiation and intrathecal chemotherapy, was then restarted on the maintenance phase of remission continuation therapy, and is still in bone marrow remission at 4+ yr from initial MOAD induction therapy. Only 3 of the 14 previously treated patients received therapy for CNS leukemia prior to starting MOAD induction. This alone cannot account for the low incidence of CNS leukemia in this group of patients. During remission induction and consolidation, (with moderate-dose methotrexate), therapeutic CSF methotrexate levels were not achieved (see Fig. 1). However, therapeutic levels were achieved during cytoreduction with high-dose methotrexate. It appears that high-dose methotrexate delays the onset or reduces the incidence of CNS leukemia compared to our historical experience with either no CNS prophylaxis (42.5%) or with oral pyrimethamine CNS prophylaxis (33.3%). The reported incidence of CNS leukemia in adult ALL has ranged from 7% to 75%. At least one study establishes that CNS prophylaxis is of value in decreasing the occurrence of CNS relapse in adult ALL. However, CNS prophylaxis did not improve remission duration or survival in that study. Since the effect of CNS prophylaxis on remission duration in childhood ALL is not observed during the first 24 mo of remission, it is reasonable to expect that the effect of CNS prophylaxis on adult ALL will not become evident until improved remission duration and survival is achieved. Therefore, the final evaluation of high-dose methotrexate alone for CNS prophylaxis must be its effectiveness in preventing relapse during remission continuation therapy and after therapy has been stopped and the late consequences of that therapy with respect to the CNS. Full evaluation of this method must await a longer period of follow-up.

There has been only one extramedullary relapse other than CNS. That was a relapse that presented as a breast mass that was TdT positive and was treated with whole breast and axillary irradiation. The patient continued on the maintenance phase of remission continuation therapy and remains in remission now for greater than 3 yr since relapse.

The question of when remission continuation therapy should be stopped has not yet clearly been resolved for adult ALL. Our 7 long-term survivors continue on the maintenance phase of therapy from 2 to 4.5 yr. The usual practice for childhood ALL is to discontinue treatment after 2.5–5 yr of continuous complete remission following institution of effective treatment regimens. However, even if a continuous complete remission has been maintained for 2.5–3 yr in childhood ALL, the overall frequency of relapse following cessation of treatment is about 25%.

In this study, age and sex were not prognostic indicators of initial response to therapy, remission duration, or survival. Patients less than 20 yr or less than 40 yr did not show any significant difference with respect to CR rate, remission duration, and survival when compared to patients older than 40. Five of the 7 long-term survivors (greater than 2 yr) are females, 4 previously untreated and 1 previously treated. The median age for the 5 females is 31 yr (range 25–55). There was no difference with respect to patient characteristics at the start of treatment (see Table 2) for these long-term survivors compared to the other patients on this study. None of the long-term survivors was infected on admission.

MOAD is superior to TODD (thioguanine, vincristine, dexamethasone), POMP (prednisone, vincristine, methotrexate, and mercaptopurine), and vincristine with prednisone which we have used for previously untreated adult ALL (see Table 10 and Fig. 5). There has been improvement in the complete remission rate as well as the median duration of complete remission. Likewise, there has been a
decrease in CNS leukemia, and the median survival has improved. Other factors may have contributed to these improved results over the 15-yr period that these studies were done. Such factors as patient selection, more accurate diagnosis utilizing cytotoxic, immunologic, and biochemical methods that were not available for the POMP and TODD studies, possible presence of more poor risk patients for the earlier studies, and improved supportive care for the MOAD study may have all contributed to the improvement in the therapy of adult ALL at the Baltimore Cancer Research Program. Nevertheless, we conclude that MOAD is an effective antileukemic regimen. It is useful as remission induction therapy for both previously untreated and treated adults with ALL and is superior to the other regimens that we have used for the treatment of adult ALL. To what extent MOAD contributes to remission duration and survival is unknown because of the utilization of high-dose methotrexate, low-dose methotrexate and mercaptopurine, and vincristine and dexamethasone reinforcement for remission continuation therapy.

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