Acute Monoblastic Leukemia in Infancy and Early Childhood: Successful Treatment With an Epipodophyllotoxin

By Lorrie F. Odom and Erlinda M. Gordon

Four of five infants and young children with acute monoblastic leukemia, a disease that heretofore has been highly refractory to therapy, were successfully treated with sequential infusions of a podophyllin derivative employed as a single agent over a protracted period of time. In three of the five children, monocytic leukemia cutis was present at birth. Treatment was begun in two of them when the disease had progressed to systemic involvement at a few months of age, and in the third when disease was still localized. The other two children were 11 and 18 months of age at initial presentation with widespread disease. Four children are off therapy 11 months, 26 months, 5 years, and 6 years, respectively.

Acute Monoblastic Leukemia (AMOL) in infancy and early childhood is a rare and usually rapidly fatal disease. AMOL in infancy may present solely with bluish cutaneous nodules (monocytic leukemia cutis), but the disease usually progresses rapidly to involve the bone marrow within six months. Although initially responsive to therapy, this type of leukemia invariably becomes refractory to agents such as vincristine (VCR), prednisone (PDN), L-asparaginase (L-ASP), 6-mercaptopurine (6MP), methotrexate (MTX), daunorubicin (DNR), and cytosine arabinoside (Ara-C). Using a highly intensive chemotherapy regimen for 61 untreated children with acute myelogenous leukemia, Weinstein et al reported that the monocytic subtype was associated with a significantly shorter duration of remission and higher incidence of central nervous system disease. Seven children in his study had the histologic subtype of AMOL, six of whom were under 2 years of age at diagnosis. Of these six children, five have subsequently relapsed and only one child is surviving.

In 1974 and 1975, it was reported by Mathé et al and McKenna and coworkers that the epipodophyllotoxin, VP-16-213 (VP-16), could induce a second remission in patients with relapsed AMOL. Based on that information, we began our study using VP-16 in a 22-month-old, previously treated child with AMOL in first relapse. After encouraging results with this child, we expanded the study to include previously untreated infants. Because VP-16 is taken up only sparingly by the rat brain and has no significant activity against intracerebral L-1210 leukemia, we later substituted VM-26 for VP-16. VM-26 has demonstrable activity in L-1210 CNS leukemia and antitumor effect in human intracranial neoplasms, despite CSF levels less than 1% of serum levels of the drug.

VM-26 (teniposide; 4'-demethyl-epipodophyllotoxin-β-D-thienylidine glucoside; NSC-122819) and VP-16-213 (etoposide; 4'-demethyl-epipodophyllotoxin-9,4,6-O-ethylidene-β-D-glycopyranoside; NSC-141540) are semisynthetic glucoside compounds. They are derivatives of podophyllin, the crude resinous extract of the root of the May apple plant, Podophyllum peltatum. Stahelin discovered that the mechanism of action of both VP-16 and VM-26 is based on preventing cells from entering the mitotic phase or destroying cells preparing for mitosis, as opposed to the action of a typical spindle poison. Among the biochemical effects of VP-16 and VM-26 are inhibition of nucleoside transport into cells and also a concentration-dependent inhibitory effect on DNA and RNA synthesis. The full spectrum of biochemical activity in tumor cells by these cytostatic agents remains to be elucidated.

The schedule of epipodophyllotoxin administration in our patients was intensive, commencing with a once or twice weekly interval, which was gradually increased to a three-week interval over the total treatment period of 2 to 2½ years. The agents were tolerated exceptionally well. In spite of the fact that each surviving child received 50 or more infusions of the podophyllin derivative, side effects during the course of treatment were minimal, and follow-up has so far shown no adverse sequelae. All four surviving children are presently leading normal lives.


<table>
<thead>
<tr>
<th>Patient 1</th>
<th>18 mo (5/75)</th>
<th>Acute Monoblastic leukemia</th>
<th>Clinical</th>
<th>Peripheral Blood</th>
<th>Pathology</th>
<th>Therapy</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>White male; bluish skin nodules on face and back; generalized lymphadenopathy; hepatomegaly</td>
<td>Hb: 11.3 gm% WBC: 15,300/µL (26% blasts) PIt: 200,000/µL</td>
<td>BM: 95% large mononuclear cells, NSE +, NaF sensitive</td>
<td>VCR, PDN, CPM, IT MTX</td>
<td>Remission after 4 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(6/75)</td>
<td>Normal</td>
<td>BM: remission</td>
<td>2,400 rad cr XRT, IT MTX, 6MP, MTX, VCR-PDN-CPM pulses</td>
<td>BM relapse after 3 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 mo (9/75)</td>
<td>Lethargy; pallor</td>
<td>Hb: 8.9 gm% WBC: 1,000/µL PIt: 16,000/µL</td>
<td>BM: 60% monoblasts</td>
<td>VP-16 200 mg/m²/wk x 3</td>
<td>BM remission in 3 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10/75)</td>
<td>Normal</td>
<td>BM: remission</td>
<td>VP-16 200 mg/m²/wk x 20, DNR 20 mg/m² q 3 wk x 7, Ara-C 50 mg/m² q 3 wk x 7, IT MTX alt w/ IT Ara-C q 3 mo</td>
<td>BM relapse after 5 mo (peripheral blasts and nuc RBC, anemia)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 mo (3/76)</td>
<td>Pale, lethargic</td>
<td>Hb: 9.2 gm% WBC: 2,500/µL (2% blasts, 7% nuc RBC) PIt: 307,000/µL</td>
<td>BM not done</td>
<td>VM-26 100 mg/m²/wk x 3</td>
<td>Disappearance of peripheral blasts and nuc RBC; ↑ in Hb w/o transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4/76)</td>
<td>Normal</td>
<td>BM and CSF: remission</td>
<td>VM-26 100–140 mg/m²/wk x 69</td>
<td>Clinical remission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46 mo (9/77)</td>
<td>Normal</td>
<td>BM and CSF: remission</td>
<td>VM-26 140 mg/m² q 2 wk x 7, q 3 wk x 6</td>
<td>Continued remission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 yr, 5 mo (4/78)</td>
<td>Normal</td>
<td>BM and CSF: remission</td>
<td>Discontinue therapy</td>
<td>Continued remission</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient 2</th>
<th>Newborn (8/76)</th>
<th>Acute Monoblastic leukemia</th>
<th>Clinical</th>
<th>Peripheral Blood</th>
<th>Pathology</th>
<th>Therapy</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spanish-American male; bluish skin nodules on head, back, and legs (disappeared spontaneously by 3 wk of age); mild hepatomegaly</td>
<td>Hb: 15.3 gm% WBC: 6,600/µL PIt: 140,000/µL</td>
<td>BM: normal Skin: dense infiltration of deep dermis and subcutaneous fat with monoblasts</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 mo (12/76)</td>
<td>Irritability; epistaxis; recurrence of massive skin infiltration on head, back, thighs; proptosis; hepatosplenomegaly; enlarged and firm testicles</td>
<td>Hb: 9.7 gm% WBC: 6,900/µL PIt: 30,000/µL</td>
<td>BM: 20% monoblasts Skin: dense monoblast infiltrate of dermis and subcutaneous fat, NSE +, NaF sensitive</td>
<td>VP-16 100 mg/m² 2x/wk x 4</td>
<td>Dramatic clinical improvement after one dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(12/76)</td>
<td>Resolving skin infiltrates</td>
<td>BM and CSF: remission</td>
<td>VP-16 100 mg/m² approx q wk x 4 and q 2 wk x 44</td>
<td>Remission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29 mo (1/79)</td>
<td>Normal</td>
<td>BM and CSF: remission</td>
<td>VP-16 100 mg/m² q 3 wk x 7, 2,400 rad cr XRT, IT Ara-C wkly x 4 (5–6/79)</td>
<td>Continued remission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35 mo (7/79)</td>
<td>Normal</td>
<td>BM and CSF: remission</td>
<td>Discontinue therapy</td>
<td>Continued remission</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Acute Monoblastic Leukemia in Three Infants and Two Young Children: Clinical Presentation and Response to Therapy
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Patient 3</th>
<th>Newborn (5/80)</th>
<th>White female; bluish skin nodules on face and torso</th>
<th>Hb: 18.1 gm%</th>
<th>BM: normal</th>
<th>Skin: dense mononuclear infiltrate of dermis, NSE+, NaF sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 d (6/80)</td>
<td>Partial regression of skin nodules</td>
<td>Normal</td>
<td>WBC: 5,900/μL</td>
<td>BM-26 150 mg/m²</td>
<td>2 x/wk x 3</td>
</tr>
<tr>
<td>2 mo (7/80)</td>
<td>Normal</td>
<td>Normal</td>
<td>Pt: 242,000/μL</td>
<td>VM-26 75-100 mg/m²</td>
<td>2 x/wk x 13</td>
</tr>
<tr>
<td>19 mo (12/81)</td>
<td>Normal</td>
<td>Normal</td>
<td>BM and CSF: remission</td>
<td>VM-26 90 mg/m² q 3 wk x 8</td>
<td>Continued remission</td>
</tr>
<tr>
<td>26 mo (7/82)</td>
<td>Normal</td>
<td>Normal</td>
<td>BM and CSF: remission</td>
<td>Discontinue therapy</td>
<td>Continued remission</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient 4</th>
<th>Newborn (8/81)</th>
<th>White female; bluish skin nodules (partial regression by 2 wk of age)</th>
<th>Hb: 16 gm%</th>
<th>BM: normal</th>
<th>Skin: dense mononuclear infiltrate of dermis and subcutaneous fat, NSE+, NaF sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mo (10/81)</td>
<td>New skin nodules; lymphadenopathy, hepatosplenomegaly; pallor</td>
<td>Hb: 7.2 gm%</td>
<td>WBC: 6,100/μL</td>
<td>BM-26 100 mg/m²</td>
<td>2 x/wk x 4</td>
</tr>
<tr>
<td>3 mo (11/81)</td>
<td>Normal</td>
<td>Normal</td>
<td>Pt: 315,000/μL</td>
<td>VM-26 100 mg/m²/ wk x 21, q 9-11 d x 10, q 2 wk x 7</td>
<td>Continued remission</td>
</tr>
<tr>
<td>20 mo (4/83)</td>
<td>Normal</td>
<td>Normal</td>
<td>BM and CSF: remission</td>
<td>VM-26 100 mg/m² q 3-4 wk x 8; IT Ara-C wkly x 4</td>
<td>Continued remission</td>
</tr>
<tr>
<td>26 mo (10/83)</td>
<td>Normal</td>
<td>Normal</td>
<td>BM and CSF: remission</td>
<td>Discontinue therapy</td>
<td>Continued remission</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient 5</th>
<th>11 mo (1/83)</th>
<th>Vietnamese male; diffuse bluish nodules 0.5-1 cm in diameter on face, eyelid, scalp, thorax, and abdomen; tumor nodules and masses, 1-3 cm in diameter on arms and legs; hepatosplenomegaly; inguinal adenopathy; bilaterally enlarged and firm testicles</th>
<th>Hb: 13.2 gm%</th>
<th>BM: 20% large mononuclear cells, NSE+, NaF sensitive</th>
<th>Skin: dense mononuclear infiltrate of dermis, subcutaneous fat, NSE+, NaF sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 mo (2/83)</td>
<td>Normal</td>
<td>Normal</td>
<td>WBC: 6,800/μL</td>
<td>Testicle biopsies: dense mononuclear infiltrate</td>
<td>VM-26 100 mg/m²/ wk x 3</td>
</tr>
<tr>
<td>(2/83)</td>
<td>Scattered bluish nodules</td>
<td>Normal</td>
<td>Pt: 200,000/μL</td>
<td>IT Ara-C x 1</td>
<td>Recurrence of skin nodules after three doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DNR 30 mg/m²/ wk x 1; IT Ara-C x 1</td>
<td>Marked growth of skin nodules after 1 wk</td>
</tr>
</tbody>
</table>

AMOL: TREATMENT WITH EPIPODOPHYLLOTOXIN
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Peripheral Blood Pathology</th>
<th>Therapy</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 mo (2/83)</td>
<td>Increased nodules</td>
<td>Normal</td>
<td>(After 5 doses VP-16)</td>
</tr>
<tr>
<td>13 mo (3/83)</td>
<td>One palpable nodule on face</td>
<td>Normal</td>
<td>VP-16 and ASP 2x/wk × 3 then wkly × 3</td>
</tr>
<tr>
<td>14 mo (4/83)</td>
<td>Scattered nodules</td>
<td>Neutropenia</td>
<td>VP-16 and low-dose TBI wkly × 6</td>
</tr>
<tr>
<td>16 mo (6/83)</td>
<td>Scattered tumor masses and nodules, feeling well</td>
<td>Normal</td>
<td>Palliative XRT to local disease</td>
</tr>
<tr>
<td>18 mo (8/83)</td>
<td>Increased masses and nodules; fever, lethargy</td>
<td>Hb: 11.2 gm% WBC: 19,000/μL (32% blasts) PIt: 29,000/μL</td>
<td>Discontinue XRT</td>
</tr>
</tbody>
</table>

MATERIALS AND METHODS

Since 1976, four consequently diagnosed children with AMOL under two years of age at The Children’s Hospital, Denver, and one infant at Rainbow Babies and Children’s Hospital were entered into this treatment program. Table 1 summarizes the presenting signs and symptoms, the peripheral blood counts, and the bone marrow aspirate and skin biopsy results. All children presented with scattered firm bluish cutaneous nodules, ranging in size from 0.5 to 1 cm in diameter in four of the children, most prominent on the scalp, face, chest, and abdomen. In the fifth child, diagnosed at 11 months of age, these nodules were confluent in areas of the scalp and face, with a prominent nodule on the right eyelid, infiltration of both testicles, and massive infiltration of skin and subcutaneous tissue of all extremities with tumors up to 3 cm in diameter. This child, as well as two others, had hepatosplenomegaly at the time treatment was begun, and two children had generalized lymphadenopathy. Four of the five children had bone marrow infiltration at the onset of treatment.

The diagnosis of AMOL was made from skin nodule biopsy and/or bone marrow aspirate, based on morphological and cytochemical features according to the FAB classification.14 The infiltrating cells were moderately large and homogeneous, possessing oval or reniform and frequently indented nuclei with usually prominent nucleoli, and abundant bluish-gray cytoplasm with indistinct cytoplasmic borders, and occasional pseudopod extensions (type M5) (Fig 1A). These cells showed strongly positive nonspecific esterase (NSE) activity (α-naphthyl acetate substrate) (Fig 1B), which was inhibited by sodium fluoride (NaF).15,16 They did not take up the myeloperoxidase, Sudan black, or periodic acid-Schiff (PAS) stains.

Diagnostic karyotype analysis of bone marrow leukemic blasts from patient 5 showed at least four cells to have a deletion of the long arm of chromosome 16. Diagnostic cytogenetic studies of leukemic cells from the other patients were not obtained.

The potential risks of VP-16 or VM-26 were fully explained to the parents, and appropriate consent, approved by the committee on the Use of Human Subjects in Research of the Children’s Hospital of Denver and the University Hospitals of Cleveland, was obtained.

Treatment

The therapeutic modalities used for each patient are summarized in Table 1. Patient 1, whose initial treatment was in May 1975, was induced into remission with a combination of VCR, PDN, cyclophosphamide (CPM), and intrathecal (IT) MTX. He then received 2,400 rad cranial irradiation (XRT), four weekly doses of IT MTX, and continuation therapy with 6MP, MTX, and pulses of VCR.
PDN, and CPM. His first remission terminated in a bone marrow relapse after three months. A trial of VP-16 alone in a dose of 200 mg/m²/wk resulted in normalization of peripheral blood counts and achievement of remission marrow status after three doses. To intensify this remission, DNR and Ara-C were administered every three weeks, along with IT MTX alternating with IT Ara-C every three months. The child remained stable on this regimen for over three months, but shortly thereafter, the hemoglobin dropped and peripheral blasts and nucleated red cells appeared. The previous chemotherapy was then discontinued, and in March 1976, he was placed on VM-26, 100 mg/m²/wk. A bone marrow exam was not performed at this time, as the intent of the therapy was palliative. Peripheral counts normalized within two weeks, and VM-26 was continued in a dose ranging from 100 to 145 mg/m² in an interval gradually increasing to every three weeks by November 1977. Clinical, bone marrow, and CNS remission continued and VM-26 was cautiously discontinued in April 1978.

Patient 2 was started on chemotherapy at 4 months of age. He received VP-16, 100 mg/m² twice weekly for four doses, then approximately weekly for four doses, followed by administration approximately every other week for 24 months and every three weeks for six more months. Because proptosis had been present at the time VP-16 was instituted, CNS treatment, consisting of 2,400 rad cranial XRT and four weekly injections of IT Ara-C, was administered shortly before chemotherapy was discontinued.

The chemotherapeutic regimen for patients 3 and 4 consisted of VM-26 100 to 150 mg/m² twice a week for three to four doses, 90 to 100 mg/m² weekly for two to three months, and then gradually decreasing frequency of administration to an every three-week interval for several months, before it was discontinued (Table 1). VM-26 was begun at 17 days of age in patient 3 and at 2 months of age in patient 4. Neither infant had CNS XRT, but surveillance CSF examinations were obtained frequently during the last six months of therapy in both children. Patient 4 received four weekly injections of IT Ara-C prior to discontinuation of chemotherapy.

Patient 5 received four doses of VM-26 100 mg/m² twice weekly. The interval between doses was then increased to weekly because of apparent viral gastroenteritis. Shortly thereafter, the patient developed recurrent disease, which was refractory to DNR but showed dramatic response to VP-16 administered twice weekly in a dose of 100 mg/m². After nine doses of VP-16, one remaining facial skin nodule was biopsied and still positive for disease, although the bone marrow, bilateral testicular biopsies, and CSF were all free of tumor at that time. Treatment with intermittent L-ASP was then added, but shortly thereafter generalized extramedullary disease appeared, which was stabilized for almost four months by low-dose total body irradiation (TBI) followed by local XRT to sites of bulky disease.

Evaluation of Toxicity

Complete blood counts were obtained at each patient visit. Liver and renal function studies were examined a minimum of every three months. Symptoms were carefully monitored during and after administration of each dose of chemotherapy.

Evaluation of Growth and Development

The patient’s height, weight, and head circumference were plotted on percentile charts adapted from the National Center for Health Statistics. Patient 4 received the Denver Developmental Screening Test monthly.

RESULTS

Therapeutic Efficacy

Four of five patients are alive and well with no evidence of disease, three to 8½ years (mean, six years) from the time single-agent podophyllin derivative therapy was begun. None of these patients have developed evidence of CNS disease, although presymptomatic cranial XRT was employed in two patients, one of whom had proptosis at the time VP-16 was instituted. Chemotherapy was discontinued in four patients after two to 2½ years, and they are off therapy 11 months, 26 months, five years, and almost six years, respectively.

Patient 5, who presented with massive skin and subcutaneous tumors infiltrating his extremities, in addition to other extensive disease (Table 1), had an initially dramatic response to VM-26. After two doses of VM-26, virtually all evidence of disease had disappeared. Shortly after a delayed fourth dose of VM-26, a few suspicious skin nodules developed, a biopsy of which showed recurrent monocytic leukemia cutis. Recurrent disease proved refractory to treatment with DNR, but dramatic temporary clinical response occurred with VP-16 employed as a single agent. After a protracted period of asymptomatic palliation using low-dose TBI and local XRT to bulky lesions, the patient died of disease seven months after diagnosis. Autopsy showed massive generalized nodular monoblastic infiltration in the dermis and subcutaneous tissues, liver, spleen, pancreas, gastrointestinal tract, lymph nodes, and bone marrow. A more delicate insinuation of the leukemic cells was noted in the meninges, the interstitium of the myocardium and lungs, and the testicles.

Toxicity of Treatment

No life-threatening reactions secondary to VP-16 or VM-26 were observed in any of these children. Mild side effects, such as myelosuppression, gastrointestinal toxicity, and alopecia, were apparent when the agent was administered on a twice or once weekly basis, but these disappeared when the interval of administration was extended to two or more weeks. Allergic manifestations were easily preventable with prior administration of diphenhydramine.

Hematologic side effects. Neutropenia during the course of twice weekly VM-26 necessitated the hospital admission of two infants (patients 3 and 4) with fever. Supportive transfusions of packed red cells were administered to both infants for anemia during this period. One infant subsequently developed thrombocytopenia and a presumed viral illness associated with rash and marked nasal congestion. Significant myelo-
suppression disappeared in each of these infants when the interval between podophyllin infusions increased from twice weekly to weekly. No subsequent hospital admissions due to myelosuppression were necessary.

**Gastrointestinal symptoms.** Infrequent vomiting and diarrhea lasting up to three days after the administration of VM-26 was observed in one child, and one or two episodes of vomiting within four hours of the infusion occurred in another child. Occasional diarrhea and/or constipation occurred in two children, which may or may not have been related to administration of the podophyllin derivatives. Patient 5 developed presumed viral gastroenteritis during induction, but again, the relationship to VM-26 is unknown. None of these side effects were incapacitating.

**Allergic manifestations.** One child (patient 1) developed hives and wheezing during his 21st infusion of VM-26. Subsequently, oral diphenhydramine was given prior to each infusion, enabling the administration of 63 more doses of VM-26 without allergic problems. None of the other four children developed allergic symptoms, although patient 5 received prophylactic diphenhydramine prior to each dose of VM-26 on an empiric basis.

**Alopecia.** Mild alopecia appeared to be present when the interval of podophyllin administration was twice or once weekly, and became less apparent as the interval increased to two or more weeks.

All five patients tolerated the epipodophyllotoxin infusions remarkably well. Patient 5 presented with evidence of a mild coagulopathy similar to disseminated intravascular coagulation, which became more pronounced after treatment was instituted, necessitating support with continuous infusion low-dose heparin and twice daily transfusions of fresh frozen plasma for the first four days of therapy. Other known toxicities of these derivatives, such as phlebitis, hepatic and renal dysfunction, hypotension, neuropathy, mucositis, cardiac arrhythmias, and immune hemolytic anemia, were not observed in any patient. The agent was administered through a semipermanent central line (Broviac catheter) in patients 4 and 5.

**Effect on Growth and Development**

Administration of the podophyllotoxins on a twice or once weekly basis, over the initial three to four months of therapy, was associated with a fall of two percentile ranks for length in three patients and from two to four percentile ranks for weight in the four evaluable children. These drops were followed by stabilization of growth when the agent was administered less frequently and resumption of a normal growth pattern when it was administered every three weeks in the four children who reached that phase of treatment.

The Denver Developmental Screening Test, performed serially in patient 4 during the course of VM-26 administration, showed normal developmental milestones during the entire course of therapy. The mental and physical development of patients 1 and 2 has been commensurate with that of their peers. The mental development of patient 3, now 4 years of age, is presently evaluated as precocious when compared with that of her peers.

**DISCUSSION**

AMOL, initially described by Reschad and Schilling in 1913, is an uncommon and highly aggressive form of leukemia. It occurs most frequently in children under 10 years of age and in adults over 40 years of age. AMOL frequently presents with characteristic clinical features, such as skin nodules, extramedullary masses, gingival hypertrophy, and hypercoagulability with features of disseminated intravascular coagulation. The leukemic monocytes have distinct cyt morphological, cytochemical, electron microscopic, and immunologic characteristics. These cells usually appear to be initially sensitive to various cytotoxic agents, but invariably rapidly acquire resistance to these agents, even when used in combination. Weinstein et al. reported that patients with the AMOL subtype had the shortest duration of remission of the major AML variants, even when treated with a highly intensive therapeutic regimen. The majority of the patients with AMOL in this series were under 2 years of age at diagnosis. Of six children in this group, five died of recurrent disease, two of whom developed CNS disease as the first site of relapse. It should be noted that this regimen did not incorporate specific CNS treatment other than moderate dose systemic Ara-C.

The present study describes the clinical features of AMOL in three infants and two young children, demonstrating the successful treatment of four of these patients with an epipodophyllotoxin used as a single agent. Diffuse skin infiltration by a characteristic population of malignant monocytic cells or undifferentiated blasts possessing monocytic activity may be the only presenting feature of AMOL in this age group. The skin nodules may be associated with lymphadenopathy, hepatosplenomegaly, other extramedullary disease, and/or bone marrow involvement. It is of interest that a deletion of the long arm of chromosome 16, found in the leukemic blasts of patient 5, has recently been reported to show an association with acute nonlymphocytic leukemia along with other abnormalities of chromosome 16.

Our patients confirm the observation that if neonatal monocytic leukemia cutis is not treated initially, the disease may undergo a spontaneous temporary
AMOL: TREATMENT WITH EPIPODOPHYLLOTOXIN

regression but usually recurs in a more generalized form within a few months.\textsuperscript{1} Prior to our experience, AMOL was known to be a rapidly fatal form of leukemia in infants.\textsuperscript{1}

Since 1975 reports have appeared in the literature\textsuperscript{1,28,29} demonstrating that the epipodophyllotoxins can induce transient partial or complete remission in refractory childhood lymphoblastic and nonlymphoblastic leukemia. Refractory AMOL in adults has also been responsive to short-term trials of VM-26 or VP-16 used either as single agents or in combination with other antileukemic agents.\textsuperscript{3,10} Remission was achieved in all five young children in this trial using VM-26 or VP-16 as the single antileukemic agent. Four of these patients are in sustained complete remission for as long as eight years from the time of initiation of treatment and six years since chemotherapy was discontinued. No patient has relapsed in the central nervous system, which is a common site of disease progression in patients who are not successfully treated.\textsuperscript{7} No life-threatening or significant toxicity developed in these patients using the dose schedule outlined. Myelosuppression was the dose-limiting factor in two patients during twice weekly administration of VM-26. Frequent administration of the podophyllin derivative also produced transient inhibition of growth, and stabilization or catch-up growth was observed when the agents were administered at less frequent intervals. Intellectual and emotional development has been normal in the four surviving patients and commensurate with that of their peers.

The fact that disease recurred in patient 5 shortly after a complete response was observed is not surprising in view of the massive disease present at diagnosis and the high likelihood that a few cells could have inherent partial or complete resistance to the action of VM-26. It is of interest that disease resistant to VM-26 was temporarily controlled by VP-16 in this patient. In patient 1, on the other hand, disease that appeared clinically resistant to VP-16 was permanently controlled by VM-26. Thus, there is presumptive clinical evidence of a lack of complete cross-resistance between these closely related agents, a phenomenon that may be of clinical significance. Additional clinical observations to substantiate these findings appear to be warranted. Differences in the mechanism of action between the two agents that could lead to a lack of cross-resistance remain to be elucidated.

The optimum time to initiate chemotherapy in an infant with monocytic leukemia cutis is unknown. Of the three newborns described in this article, one baby (patient 2) was initially lost to follow-up until generalized disease recurred at 4 months of age; the parents of patient 4 initially refused treatment until the disease recurred, again in a generalized fashion, at 2 months of age. With the availability of a potentially successful therapeutic regimen relatively devoid of severe toxicities, we elected to begin VM-26 at 17 days of age in patient 3. The early initiation of chemotherapy, at a time when disease was localized to the skin and subcutaneous tissue, influenced our subsequent decision to omit central nervous system treatment of this infant. Routine diagnostic cytocentrifuge examinations of the spinal fluid performed sequentially during and off therapy have shown no evidence of central nervous system involvement.

The upper age limit for which to use a single-drug schedule also remains to be determined. In our series, three of the four long-term survivors were 4 months of age or younger at the time therapy was instituted, and one long-term survivor, who is now nearly six years off therapy, was 28 months of age when single-agent VM-26 was begun. It has been demonstrated that aggressive chemotherapy excluding podophyllin derivatives is generally not curative for AMOL under 2 years of age.\textsuperscript{7} Thus, if other agents are to be used in this age group, we suggest that they be employed in a dose schedule designed to least compromise the frequent administration of podophyllin derivatives. One might speculate, based on our observations, that alternating courses of VM-26 and VP-16 might prove to be a therapeutically stronger regimen and should be considered as an alternative for a child who is older than a few months of age or who has massive disease at diagnosis.

Another dilemma is when to consider the incorporation of cranial XRT and/or IT chemotherapy. If the diagnostic CSF cytospin preparation shows the presence of leukemic monocytes and/or there are signs or symptoms of meningeal or parameningeal infiltration, the incorporation of cranial XRT into the total treatment regimen should be considered. In the young child, it would be optimum to delay this XRT as long as possible, ideally until a few months prior to discontinuing chemotherapy. When disease is localized to the skin and subcutaneous tissues at the time therapy is instituted, it may be safe to omit both cranial XRT and IT treatment, as long as intermittent diagnostic CSF cytospins remain normal, as in patient 3 in this report.

It is our hope that future clinical investigations based on these observations will provide information regarding the optimum time to initiate chemotherapy, when to incorporate CNS therapy, whether utilizing alternating courses of VM-26 and VP-16 offers better therapeutic efficacy than treatment with a single epipodophyllotoxin, what diagnostic parameters are an indication for the addition of other chemotherapeutic agents, and the optimum duration of chemotherapy.
Additional long-term follow-up of infants with AMOL who have been treated with epipodophyllotoxins in this fashion is needed to determine their ultimate effect on growth and development, as well as their oncogenic potential.

The successful use of single-agent treatment defies conventional methods of antileukemia therapy. Possibly such frequent administration of an epipodophyllotoxin recruited arrested cells into cycle and/or prevented the development of alternate metabolic pathways, delaying the development of drug resistance.

In conclusion, our observations indicate that VM-26 or VP-16 used intensively as a single antileukemic agent is effective and safe in the treatment of AMOL in infancy and early childhood.

ACKNOWLEDGMENT

The authors are grateful to Blaise Favara, MD, Loren E. Golitz, MD, Gary Gross, MD, Ray Rademacher, MD, David G. Tubergen, MD, Jan Davis, BSN, Peter F. Coccia, MD, Sarah Strandjord, MD, Leonard Rome, MD, Michael Michael, MD, and Anne Chapman, BSN, for their support in the performance of this study and to Shelley Magee for typing the manuscript.

REFERENCES

Acute monoblastic leukemia in infancy and early childhood: successful treatment with an epipodophyllotoxin

LF Odom and EM Gordon