Treatment of Large Granular Lymphocyte Leukemia With Oral Low-Dose Methotrexate

By Thomas P. Loughran, Jr, Pamela G. Kidd, and Gordon Starkebaum

Morbidity and mortality in patients with T large granular lymphocyte (T-LGL) leukemia result from infections acquired during severe neutropenia. Optimum treatment for severe neutropenia remains undefined. We conducted an uncontrolled but prospective study of low-dose oral methotrexate, up to 10 mg/m² weekly, in 10 patients with this disease. Therapeutic response was assessed by serial clinical evaluations and laboratory determinations including complete blood counts, lymphocyte phenotyping, and T-cell receptor gene rearrangement studies. A partial response was defined as a sustained increase in neutrophil count greater than 500/μL. A complete clinical remission was defined as achievement of a normal complete blood count and CD3+ LGL count. Previous prednisone treatment in eight of these patients had produced one clinical remission and four partial responses; tapering of prednisone in each of these patients resulted in recurrence of severe neutropenia. Five patients in this study received both methotrexate and tapering doses of prednisone. Complete clinical remissions on methotrexate were observed in five patients; an additional patient had a partial response. Molecular analyses of T-cell receptor gene rearrangement could not detect the abnormal clone in three of five patients achieving a complete clinical remission. Two weeks to 4 months of therapy were needed before attaining a neutrophil count greater than 500/μL. Complete and partial responses have been maintained on therapy, with a follow-up period ranging from 1.3 to 9.6 years. Low-dose oral methotrexate therapy is an effective treatment for some patients with LGL leukemia.

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MATERIALS AND METHODS

Treatment Plan

This was an uncontrolled prospective study. Samples from patients with suspected LGL leukemia were sent to us from clinicians throughout the United States. Once the diagnosis of LGL leukemia was established in our laboratory, the patient was considered for the treatment protocol if the additional following eligibility criteria were met: (1) persistent increase in neutrophil counts above 600/μL (normal LGL counts in our lab = 232 ± 994). LGL were defined morphologically on Wright-Giemsa stained blood smears and/or by reactivity with monoclonal antibody (MoAb) anti-CDS7; (2) evidence for lymphocyte clonality by TCR gene rearrangement studies; (3) normal renal function as determined by serum creatinine; and (4) no evidence for ascites and/or pleural effusions. In consultation with one of the authors (TPL or GS), treatment options including the use of methotrexate were discussed. The decision to treat the patient was made by the referring physician, who was responsible for the clinical management of the patient. The primary indication for treatment in patients 2 through 10 was severe neutropenia (≤ 500/μL). Increasing activity of rheumatoid arthritis was the primary indication for methotrexate treatment in patient 1 and also a contributing indication in patient 2. Methotrexate was administered orally as low-dose pulse therapy in split-doses in AM and PM, once weekly. Weekly doses were started at from 5.0 mg to 7.5 mg, with escalation up to 15 to 20 mg/wk (10 mg/m²) over 1 to 3 months.

Response to therapy was determined by periodic evaluations as well as by laboratory assessments of complete blood counts (CBC) and differential counts, lymphocyte phenotype, TCR gene rearrangement studies, and anti-neutrophil antibody studies. The primary response criteria were prospectively defined based on results of CBC and lymphocyte phenotyping. A complete clinical response
was defined as normalization of CBC and CD3+ LGL counts (CD3+, CD57+ cells). A partial response was defined as a sustained increase in neutrophil count greater than 500/μL. The secondary endpoint of this study was reduction in severe infections requiring hospitalization. Drug safety was monitored monthly by laboratory blood chemistries including serum-creatinine and liver function tests. Patients could not receive any other treatment modality while on methotrexate, with the exception of prednisone. Prednisone therapy was allowed if the dose of prednisone was tapered during methotrexate treatment, as occurred in patients 1 through 3, 6, and 9.

Lymphocyte Phenotyping

Peripheral blood mononuclear cells were first isolated from whole blood using Ficoll-Hypaque density gradient centrifugation. These cells were subsequently analyzed for the presence of cell surface antigens using an EPIC flow cytometer (Coulter, Hialeah, FL) with direct one-color and two-color analysis using a panel of fluorescein-conjugated or R-phycoerythrin-conjugated mouse MAb, as described. These MoAbs were purchased from Becton Dickinson (Mountain View, CA) and included: Leu-4 (anti-CD3), Leu-3 (anti-CD4), Leu-2 (anti-CD8), Leu-11 (anti-CD16), and Leu-7 (anti-CD57). Leukemic LGL of T-cell lineage were identified by coexpression of CD3 and CD57.

TCR Gene Rearrangement Studies

Genomic DNA was extracted from peripheral blood mononuclear cells and digested with BamHI, EcoRI, or HindIII. Digested DNA was separated on 1% agarose gels and transferred onto nitrocellulose membranes by method of Southern. Filters were then hybridized to DNA probes 32P-labeled by random priming and visualized by autoradiography. The Jurkat cDNA clone, containing the constant and joining regions of TCRβ gene,16 was kindly provided by Dr Tak Mak (Ontario Cancer Institute, Toronto, Canada). The Jy1 probe, containing a 700-bp HindIII-EcoRI fragment of the TCRγ gene,11 was kindly provided by Drs M.P. LeFranc and T.H. Rabbitts (Medical Research Council, Cambridge, UK). This methodology can detect an abnormal clone constituting at a minimum 1% to 5% of the entire population of T cells.

Neutrophil-Reactive IgG

Serum from each patient was diluted 1:100 in 500 μL phosphate-buffered saline containing 1% bovine serum albumin and was incubated with 1 × 106 fresh normal neutrophils at room temperature for 30 minutes. After two washes, surface-bound IgG was detected with FITC-conjugated F(ab')2 goat anti-human IgG (Tago, Burlingame, CA). Immunofluorescence was measured by flow cytometry using a Becton-Dickinson FACScan (San Jose, CA) operating with Consort 30 software. Ten thousand cells were acquired and analyzed using gates based on forward and side angle light scatter. The mean channel fluorescence of the gated population was determined for each sample. The results are expressed as an index calculated as follows: Index = Patient's Serum/Mean +2 SD of Normal Sera. Thus, any value over 1.0 was considered elevated. Sera from 11 normal individuals (9 men, 2 women, ranging in age from 22 to 48) were used as controls. Mean ± 1 SD fluorescence values for normal sera was 43 ± 6.

Statistics

The level of significance in the difference of hospitalization rates for infections pre- and post-methotrexate was calculated by χ² analysis.

RESULTS

Clinical features are shown in Table 1. The patients, three men and seven women, ranged in age from 25 to 87 years. All but one had a history of recurrent, serious bacterial infections, such as cellulitis, pharyngitis, sinusitis, peri-rectal abscesses, pneumonia, and bacteremia; patients 1, 3 through 6, 9 and 10 had each been hospitalized one or more times for infectious episodes. Five patients (1 through 3, 6, 10) had rheumatoid arthritis; patients 1 and 2 had been receiving prednisone for active arthritis. Splenomegaly was detected in seven patients and hepatomegaly in four.

At diagnosis, all patients had neutrophil counts under 400/μL, with several patients having no circulating granulocytes (Table 2). Patient 8 also had a Coomb’s positive hemolytic anemia, with hemocrits ranging between 24% and 26%. Of note, two patients were leukopenic and did not have an absolute lymphocytosis. All patients had markedly increased numbers of CD3+, CD57+ cells; in nine patients the majority of the peripheral blood lymphocytes had characteristic morphologic features of LGL. Clonal rearrangement of TCRγ gene was found in mononuclear cell DNA from all patients except patient 6; in that patient, TCRγ gene was clonally rearranged.

Most patients had previously received other treatment for neutropenia including prednisone (see below). Patient 1 had also undergone splenectomy, with an increase in neutrophil count above 1,000/μL postsplenectomy, which was sustained on prednisone therapy. Immunoperoxidase staining of spleen sections from patient 1 showed the typical findings of LGL leukemia with CD3+, CD8+ cells infiltrating the red pulp cords19; such studies were not performed in patient 4 who also underwent splenectomy. Intravenous infusion of gamma globulin (20 g) as well as splenectomy had no effect on the neutropenia in patient 4.

Results of laboratory studies during methotrexate treatment are summarized in Table 2 and Fig 1. Complete clinical responses with normalization of neutrophil and LGL counts

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**Table 1. Clinical Features of Patients With LGL Leukemia**

<table>
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<tr>
<th>Patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<td>F</td>
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<td>M</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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Table 2. Laboratory Evaluation of Therapeutic Response to Methotrexate in Patients With LGL Leukemia

<table>
<thead>
<tr>
<th>Patient</th>
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<th>ANC</th>
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<tbody>
<tr>
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<td>13,500</td>
<td>200</td>
<td>405</td>
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<td>250</td>
<td>98</td>
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<tr>
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<td>800</td>
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Normals: 4,400-11,300 WBC and 1,800-7,700 ANC. The mean and standard deviation for CD3+, CD57+ cells was determined for 10 normals in our laboratory. All cell counts are per μL.

Abbreviations: WBC, white blood cell counts; ANC, absolute neutrophil count; Dx, values at initial diagnosis; Rx, latest follow-up values on therapy; anti-PMN Ab, antineutrophil antibody; TCR, T-cell receptor; ND, not done.

were seen in five patients (1 through 5). Repeat T-cell receptor gene rearrangement studies showed no detectable abnormal clone in three of these patients (Fig 2). Patient 6 achieved a normal neutrophil count on treatment; however, increased numbers of CD3+ LGL and the abnormal T-cell clone have persisted. Patients 7 and 8 had no response after 3 and 6 months of methotrexate, at doses of up to 15 mg/wk and 17.5 mg/wk, respectively. Before starting methotrexate, six patients had moderately elevated levels of neutrophil-reactive IgG, which decreased slightly in five while taking methotrexate (Table 2).

Patients 9 and 10 both died of infectious causes early after starting methotrexate. LGL leukemia was diagnosed 3 years previously in patient 9 and her clinical course was marked by increasing frequency of severe infections 6 months before her death. Treatment with 60 mg/d of prednisone was initiated and her neutrophil count increased to 800 μL. Methotrexate was then added and prednisone tapered. Her neutrophil count was maintained at greater than 1,000/μL for 2 weeks on 30 mg prednisone daily and 10 mg (6.7 mg/m2) of methotrexate weekly. Three weeks before her death methotrexate was increased to 15 mg (10 mg/m2) weekly and prednisone decreased to 20 mg daily. However, her neutrophil count decreased to 116/μL and she died of pneumonia. Patient 10 had had LGL leukemia for 20 years; previous treatment with prednisone did not correct neutropenia. Six
months before his death he developed systemic symptoms of fever, night sweats, and weight loss and was hospitalized for infections on five occasions. Methotrexate was started 1 week before his death when his neutrophil count was 21/μL; he received only one 5-mg dose. He died of septic shock after presenting with abdominal pain and diarrhea. Both deaths were attributed to infections related to severe neutropenia rather than to methotrexate toxicity.

Before receiving methotrexate, eight patients (1 through 3, 5, 6, 8 through 10) had been treated with prednisone in doses ranging from 20 to 60 mg daily (Table 3). Three patients (1, 8, and 10) did not respond to prednisone alone. Four patients (2, 3, 6, and 9) had partial responses with increased granulocyte counts ranging from 800/μL to 1,700/μL. Although patient 5 achieved a normal granulocyte count on prednisone, T-cell receptor gene rearrangement studies documented persistence of the abnormal clone. Similar findings were noted in each of three other patients studied (2, 3, and 6) who had partial responses to prednisone, as well as in patient 1 who achieved a partial response to splenectomy plus prednisone therapy. Prednisone was discontinued in patient 5 after achieving clinical remission, resulting in recurrence of severe neutropenia. Severe neutropenia also recurred in patients 2, 3, and 6 when prednisone was tapered. Attempts to taper prednisone in patient 1, whose neutrophil count remained at 1,500/μL post-splenectomy, resulted in low-grade fevers and arthralgias. Methotrexate was then added to the treatment regimens of these four patients. Addition of methotrexate allowed reduction of daily prednisone dose from 10 mg to none in patient 1, from 10 mg to 5 mg in patient 2, from 20 mg to 5 mg in patient 3, and from 30 mg to 10 mg in patient 6.

The duration of methotrexate therapy needed to achieve a sustained neutrophil count greater than 500/μL (partial response) is shown in Table 4. The neutrophil response of patient 1 was not evaluable since his neutrophil count was 1,500/μL on prednisone therapy when methotrexate was started. Improvement in severe neutropenia was observed within 2 to 4 weeks of adding methotrexate in patients 2, 3, and 6 who were already receiving prednisone. Patients 4 and 5 had increases in neutrophil count >500/μL within 3 to 4 months after starting methotrexate alone.

Complete clinical responses were seen in patients 1, 3, and 4 after 8 to 9 months of methotrexate therapy. Patient 2 received methotrexate for 4 years before attaining complete clinical remission. Of note, patient 2 received only 5 mg/m² of methotrexate weekly because of gastric intolerance to higher doses. In patient 5 a partial response was maintained for almost 2 years on 7.5 mg/m² of methotrexate weekly; a complete response was observed 9 months after increasing the dose to 10 mg/m² weekly.

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**Table 3. Summary of Therapeutic Responses in LGL Leukemia**

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<th>Patient</th>
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<th>Pred and MTX</th>
<th>MTX</th>
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<td>CR†</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>PR</td>
<td>CR</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>PR</td>
<td>CR†</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>ND</td>
<td>ND</td>
<td>CR</td>
</tr>
<tr>
<td>5</td>
<td>CR</td>
<td>ND</td>
<td>CR†</td>
</tr>
<tr>
<td>6</td>
<td>PR</td>
<td>PR</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>ND</td>
<td>ND</td>
<td>NR</td>
</tr>
<tr>
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<td>NR</td>
<td>ND</td>
</tr>
<tr>
<td>10</td>
<td>NR</td>
<td>ND</td>
<td>NE</td>
</tr>
</tbody>
</table>

Abbreviations: Pred, prednisone; MTX, methotrexate; NR, no response; PR, partial response; CR, complete response; NE, not evaluable; ND, not done.

*Patient 1 had a partial response following splenectomy while being maintained on prednisone therapy.

†These patients had a molecular remission, with abnormal LGL clone no longer detectable.
The effect of methotrexate therapy on hospitalizations for life-threatening infections in the six patients who responded to treatment is shown in Table 5. Before beginning methotrexate, five of these patients had each been hospitalized one to four times. In contrast, after starting methotrexate only one patient has been hospitalized for an infectious episode over an observation period of 276 months (P < .01, Table 4).

DISCUSSION

The results of our uncontrolled but prospective study strongly suggest that low-dose methotrexate is an effective treatment for some patients with LGL leukemia. In this study six patients responded to methotrexate as shown by normalization of neutrophil counts, tapering of prednisone, and the marked decrease in infections. However, two other patients failed to respond to methotrexate and two patients died shortly after starting methotrexate. Although the deaths in these severely neutropenic patients were attributed to infections, a toxic effect of methotrexate contributing to the fatal outcome cannot be excluded. Given the potential marrow suppressive effect of methotrexate, its use should be monitored closely and avoided in patients with impaired renal or hepatic function.

The primary indication for treatment in these patients was severe neutropenia with recurrent bacterial infections. Chronic neutropenia is a common feature of LGL leukemia, resulting in significant morbidity and mortality. In our series of 28 patients with documented clonal disease followed for 1 to 13 years, 25 have eventually needed treatment and 13 have died, mainly of infectious causes (T.P. Loughran, Jr., and G. Starkebaum, unpublished observations, April 1994). There have been few reports of satisfactory treatment for neutropenia in this disease. Only one case report has documented sustained improvement in neutrophil counts and elimination of the abnormal LGL clone with therapy. Splenectomy usually results in only transient increases in numbers of circulating neutrophils and does not affect the underlying disorder. Indeed, increased numbers of leukemic cells are observed post-splenectomy as was seen in our two splenectomized patients. Experience with hematopoietic growth factors in this disease is limited. Some investigators did not find GM-CSF to be effective; whereas others did not find GM-CSF to be effective. A few patients with LGL leukemia have responded to G-CSF, whereas others have not. Furthermore, neither G-CSF nor GM-CSF affected the abnormal LGL clone even in patients responding with increased neutrophil counts.

Prednisone treatment may fail to ameliorate the severe neutropenia in LGL leukemia patients. Although five of our patients responded to prednisone alone, only one patient achieved a normal neutrophil count. Furthermore, the abnormal LGL clone persists in patients whose neutrophil counts improve on prednisone treatment, a finding which was also observed in this study. In contrast, when methotrexate was added to the regimen, several patients then achieved clinical remission and the abnormal LGL clone could not be detected by molecular analyses in two of three patients. Methotrexate treatment may also have acted as a steroid-sparing agent, allowing the prednisone dose to be tapered while maintaining the neutrophil count in an adequate range. It is conceivable that pretreatment with prednisone may have augmented the effect of methotrexate. Therefore, it is important to note that methotrexate was also effective in producing a clinical remission in two patients not receiving prednisone, including one patient who had never received prednisone previously. A complete molecular response was observed in one of these patients. Documentation of "molecular" remissions in the three patients in this study was shown by Southern blot analyses. However, such a technique is not the most sensitive method for defining molecular remission, as it can detect clonal rearrangements only at the level of 1% to 5%. It is now feasible to monitor minimal residual disease in T cell malignancies using polymerase chain reaction amplification with clonotype specific primers. Such studies would be of

<table>
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<th>Patient</th>
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<th>Date Methotrexate Started</th>
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<td>6/91</td>
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<td>10/91</td>
<td>Bronchitis/COPD 11/91</td>
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<td>11/89</td>
<td>Neutropenic fever, pharyngitis 8/99</td>
<td>7/91</td>
<td>None</td>
</tr>
</tbody>
</table>

| 6       | 11/91            | Neutropenic fever, acute cholecystitis 5/91| 4/92                      | None                             |
interest in further assessing the therapeutic response at the molecular level in this disease.

Methotrexate has been reported to reverse the neutropenia associated with Felty’s syndrome, a complication of rheumatoid arthritis. Rheumatoid arthritis is a common feature of LGL leukemia. Small series have identified clonal LGL disease in 11% to 35% of patients labeled as having Felty’s syndrome; it is now apparent that there is considerable overlap between LGL leukemia and Felty’s syndrome. Methotrexate is a reported treatment for Felty’s syndrome.

Recent studies suggest that the true prevalence of LGL proliferation in patients with rheumatoid arthritis may be greatly underestimated. Each of our four evaluable patients with rheumatoid arthritis had complete normalization of their neutrophil counts on methotrexate therapy and two patients had complete response by both clinical and molecular criteria. Complete clinical remissions were also documented in two LGL leukemia patients without rheumatoid arthritis, showing the efficacy of methotrexate in this setting. The mechanism whereby methotrexate raised the neutrophil count in these patients is unclear. Although levels of neutrophil-reactive IgG were slightly elevated in most LGL leukemia patients, the levels fell minimally during treatment with methotrexate.

It is encouraging that methotrexate therapy resulted in durable partial and complete remissions. Failure to detect the abnormal LGL clone might suggest that the dose of methotrexate could eventually be reduced or perhaps eliminated in these patients. Not all patients responded to methotrexate, however, and a relatively long time was needed to achieve a partial response in some. The need to hasten neutrophil recovery is highlighted by the occurrence of two infectious deaths in LGL leukemia patients who received methotrexate for only 1 week to 2 months before death. Further studies are required to optimize treatment for this disease.

ACKNOWLEDGMENT

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REFERENCES

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