Results of a phase 1 clinical trial of thalidomide in combination with fludarabine as initial therapy for patients with treatment-requiring chronic lymphocytic leukemia (CLL)

Asher Chanan-Khan, Kena C. Miller, Kenichi Takeshita, Alexandra Koryzna, Kathleen Donohue, Zale P. Bernstein, Alice Mohr, Donald Kippenstein, Paul Wallace, Jerome B. Zeldis, Christine Berger, and Myron S. Czuczman

Tumor necrosis factor α (TNF-α) and vascular endothelial growth factor (VEGF) play an important role in the biology of chronic lymphocytic leukemia (CLL) cells. Thalidomide is a first-generation immunomodulating agent that down-regulates TNF-α and VEGF. We initiated a phase 1/2 clinical trial to determine the safety and efficacy of combining thalidomide with fludarabine in patients with treatment-naïve CLL. Patients received 6 months of continuous daily thalidomide with standard monthly doses of fludarabine. Three dose levels of thalidomide (100, 200, and 300 mg) were studied. Results from the phase 1 part of this study are reported here. Thirteen patients were enrolled in the phase 1 component of the study. Dose-limiting toxicity was not reached. The most common toxicities noted were fatigue, constipation, and peripheral sensory neuropathy. Overall response rate was 100% with 55% of patients achieving complete remissions. At a median follow-up of 15+ months none of the patients have had a relapse and the median time to disease progression has not yet been reached. Responses were noted at all dose levels. Thalidomide given up to 300 mg/day concurrently with fludarabine in patients with previously untreated CLL shows encouraging clinical efficacy and acceptable toxicity. An ongoing phase 2 part of this study will help validate the clinical efficacy of this regimen. (Blood. 2005;106:3348-3352)

© 2005 by The American Society of Hematology

Introduction

Chronic lymphocytic leukemia (CLL) is an incurable malignant lymphoproliferative disorder. Patients with relapsed or refractory disease have limited therapeutic options. All patients with intermediate- or high-risk disease eventually progress and die of disease-associated complications. Standard initial treatment options usually incorporate either chlorambucil or fludarabine with an associated complete remission (CR) rate of 4% and 20% and an overall response rate (ORR) of 37% and 63%, respectively.1-4 Clearly, most patients treated with these standard therapies have residual measurable disease with median progression-free survival of 20 and 25 months, respectively, without any survival benefit.1 Durable CRs that may improve progression-free and overall survival rates remain an important clinical challenge in the management of this disease. New therapeutic agents with different antitumor mechanisms and novel combination therapies are warranted to improve on the results from current standard treatment options.

Tumor necrosis factor α (TNF-α) is a pleiotropic cytokine that is constitutively produced by the malignant leukemic B cells in patients with CLL.5 Various studies have shown that TNF-α is an important cytokine for the survival of CLL cells in vivo.6,7 CLL cells express TNF receptor and evidence indicates that TNF-α may serve as an autocrine growth factor for malignant CLL cells.8 Targeting TNF-α thus seems an attractive therapeutic approach to treat patients with CLL.

Although the role of angiogenesis in CLL is not clearly delineated, growing evidence implicates abnormal angiogenesis in leukemic disease progression as well as the potential role of vascular growth factors in directly modulating the biology of the CLL leukemic cell.9 Kay et al have reported on the potential role of vascular endothelium growth factor (VEGF) in CLL cell survival through an autocrine mechanism of stimulation, thus suggesting a possible role in the pathogenesis of CLL.10,11 Thalidomide is an immunomodulating agent that has been noted to have antitumor activity.12 The exact mechanism of action of thalidomide remains unknown although antiangiogenic as well as immunomodulatory effects through cytokine modulation in tumor microenvironment have been reported.13,15 We therefore hypothesized that targeting the CLL tumor microenvironment with

From the Departments of Medicine, Health Behavior, Radiology, and Pathology, Roswell Park Cancer Institute, Buffalo, NY; Division of Hematology, New York University, New York, NY; and Celgene Corporation, Summit, NJ.


Supported by a clinical research grant from Berlex Corporation. This protocol is in part supported by a grant from the Alliance Foundation at Roswell Park Cancer Institute (A.C.-K.).

J.B.Z. and C.B. are employed by Celgene Corporation (Summit, NJ), whose product (Thalomid) was studied in the present work.

A.C.-K. designed and conducted research, analyzed data, and wrote the paper; K.C.M. designed and conducted research; K.T. designed research and assisted in manuscript preparation. A.K. conducted research and collected data; K.D. analyzed data and assisted in manuscript preparation; Z.P.B. conducted research; A.M. conducted research and cared for patients; D.K. analyzed radiologic data; P.W. conducted flow cytometry and analyzed resulting data; J.B.Z. designed and supported research, and assisted in manuscript preparation; C.B. designed and conducted research; and M.S.C. designed and conducted research, and assisted in manuscript preparation.

Reprints: Asher Chanan-Khan, Department of Medicine, Roswell Park Cancer Institute, Elm & Carlton Sts, Buffalo, NY 14051; e-mail: asher.chanan-khan@roswellpark.org.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 U.S.C. section 1734.

© 2005 by The American Society of Hematology

3348 BLOOD, 15 NOVEMBER 2005 • VOLUME 106, NUMBER 10
thalidomide may result in enhanced antitumor activity of fludara- 
bine against neoplastic CLL cells.

We have initiated a phase 1/2 clinical trial exploring the 
tolerability as well as clinical benefit of thalidomide in combination 
with fludarabine in patients with previously untreated CLL. In this 
clinical study, patients with untreated CLL who required therapy as 
per the revised National Cancer Institute Working Group (NCI-WG) 
guidelines16 were treated with thalidomide in combination with 
fludarabine. Because the optimal dose of thalidomide in patients 
with CLL is unknown, the phase 1 component of this clinical trial 
explored 3 doses of thalidomide (100, 200, and 300 mg) in 3 
separate cohorts. Extensive experience with thalidomide in patients 
with multiple myeloma have shown that optimal clinically active 
dose of thalidomide is in the range of 100 to 400 mg, with most 
patients tolerating a daily dose of 200 mg.17 Because the premise 
of this clinical trial is to chronically alter the CLL cell microen-
vironment with continuous modulation of its cytokine milieu, we 
sought an optimal dose that was not only well tolerated but also 
clinically active that can be given continuously over an extended 
period of time (6 months). In this study, the maximum 300-mg dose 
of thalidomide was thus proposed. Patients were given thalidomide 
daily at a specified dose level while fixed-dose (25 mg/m²) 
period of time (6 months). In this study, the maximum 300-mg dose 
sought an optimal dose that was not only well tolerated but also

**Patients, materials, and methods**

All patients were enrolled and treated at Roswell Park Cancer Institute in a 
clinical study approved by the Institutional Review Board. All patients gave 
written informed consent. Only patients with a histologically confirmed 
diagnosis of CLL requiring therapy as defined by the NCI-WG criteria were 
eligible.16 Eligible patients may not have received any prior therapy for 
CLL. Patients were evaluated at baseline with parameters of high-risk 
disease including Rai stage, β2-microglobulin, interphase cytogenetic 
analysis, rapid lymphocyte doubling time, and pattern of bone marrow 
involveant. Treatment was offered based on the recommendations out-
lined by Cheson et al in the NCI-WG 1996 guidelines16; no patient 
segregation was done on baseline risk factors. Patients who completed a full 
6 months of thalidomide therapy were considered evaluable for response; 
toxicity is reported on all patients who were enrolled and received any 
amount of therapy.

**Pretreatment evaluation**

Prior to initiating treatment in this study all patients underwent complete 
staging evaluation including physical evaluation; complete blood counts; 
differential; chemistry profiles; computed tomography of the chest, 
abdomen, and pelvis; bone marrow aspirates; and biopsy and peripheral 
blood flow cytometry.

**Study design and treatment regimen**

This is a phase 1, single-institution study with thalidomide given daily at a 
preassigned dose level. Three dose levels of thalidomide (100, 200, and 300 
mg every day) were studied. Patients were accrued to each dose level in 
cohorts of 3 starting from dose level 1 (100 mg). No dose escalation was 
planned after achieving the 300-mg dose. Thalidomide was started on day 1 
of cycle 1 at the assigned dose and continued for 6 months; fludarabine (25 
mg/m²/d) was given for 5 days starting on the seventh day after initiating 
thalidomide. Patients received fludarabine every 28 days for 4 or 6 cycles. 
Patients with poor tolerance to fludarabine (repeated neutropenic infections 
despite appropriate growth factor support, development of hemolytic 
anemia, or an overall worsening performance status) were given only 4 
cycles with 6 months of thalidomide therapy. Allopurinol 300 mg daily was 
initiated 2 to 3 days prior to treatment for prevention of tumor lysis 
syndrome. Prior to starting thalidomide treatment, all patients were started 
on low-dose warfarin (1 or 2 mg) based on body weight (≥ 70 or ≥ 70 kg, 
respectively) for prevention of thalidomide-related venous thromboembo-
lism (VTE).

**Statistical analysis**

Treatment response was defined as complete or partial response. Time to 
response was measured as the time from the date of initial treatment until 
the first objective documentation of response. Duration of response was 
defined as the time from first objective response to the first documentation 
of progressive disease. Descriptive statistics (means, medians, and ranges) 
and the construction of frequency tables were used to analyze patient 
baseline clinical characteristics and treatment outcomes.

**Patient characteristics**

Patients were accrued between August 2003 and March 2004. Thirteen 
patients have been enrolled in the phase 1 part of this study and data are 
reported for response and toxicity. Characteristics of these patients are listed in 
Table 1.

**Assessment of safety**

Toxicity was graded according to NCI Common Toxicity Criteria (version 
2.0). Dose-limiting toxicity (DLT) was defined as any grade 3 or 4 
nonhematologic toxicity of the combination therapy that occurred in the 
first cycle of the treatment. If no DLT was noted during the first cycle, 
patients were allowed to continue therapy for a maximum of 6 cycles. All 
toxicities thereafter were recorded but did not constitute DLT. Patients were 
accrued in cohorts of 3; if a DLT was noted then 3 more patients were to be 
accrued to the same cohort; if no DLT was noted, patients were accrued in 
the subsequent dose level. If 2 or more DLTs were noted in a cohort, further 
dose escalations were to stop and the maximum tolerated dose (MTD) 
would be one dose level below this dose. There was no reduction or

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>69</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6</td>
<td>46</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td><strong>WBCs, × 10⁹/L</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 or fewer</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>20–50</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>50 or more</td>
<td>6</td>
<td>46</td>
</tr>
<tr>
<td><strong>Indication for treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic/unacceptable adenopathy</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>Rapid lymphocyte doubling time</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Symptomatic splenomegaly</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B symptoms: fatigue, weight loss, and night sweats</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>Progressive autoimmune</td>
<td></td>
<td></td>
</tr>
<tr>
<td>thrombocytopenia/anemia</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Advanced-stage disease</td>
<td>6</td>
<td>46</td>
</tr>
<tr>
<td><strong>Interphase cytogenetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>p53 deletion</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Deletion 13q</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

Median age of patients was 65 years (range, 38–74 years).

*Available on 7 patients only.
All patients were available for toxicity assessment. The MTD was assessed during the first 30 days of combination therapy. The toxicities observed on this phase 1 study are summarized in Table 2. Nine patients completed 6 months of therapy and were available for follow-up of 15+ months (range, 3+ to 18+ months) none of the patients have had a relapse. Median duration of response has not yet been reached.

The design of the study, in which thalidomide alone was given for the first 7 days of cycle 1 prior to fludarabine, allowed assessment of single-agent activity of thalidomide in CLL by comparing day 0 absolute lymphocyte count (ALC) with that on day 7 prior to the first dose of fludarabine (Table 4). Eleven of the 13 patients (85%) showed a decrease in ALC at day 7. The median decrease was 25% or more decrease in ALC at day 7. The median duration of response has not yet been reached.

### Table 2. Treatment-related toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. of patients (%)</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>grades 1 and 2</td>
<td>grades 3 and 4</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (46)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Constipation</td>
<td>8 (61)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8 (61)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pulmonary thromboembolism</td>
<td>0 (0)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (31)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Flare reaction*</td>
<td>6 (46)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pedal edema</td>
<td>0 (0)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (38)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0 (0)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 (23)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7 (54)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Tenderness and increased swelling of the involved lymph nodes

### Results

Thirteen patients were enrolled in the phase 1 component of this study: 6 patients in cohort 1 (100 mg thalidomide), 3 in cohort 2 (200 mg thalidomide), and 4 in the third cohort (300 mg thalidomide). Because one patient in cohort 1 developed a pulmonary embolism, five more patients were enrolled in this cohort as per study design. Pretreatment features of all patients are summarized in Table 1. The median age was 65 years (range, 38-74 years). According to the Rai staging criteria, 6 patients had intermediate-risk (stage I or II) and 7 had high-risk (stage III or IV) CLL. The median β2-microglobulin level was 2.7 (range, 1.6-4.1).

### Toxicity

Fatigue, constipation, and peripheral sensory neuropathy were the most common side effects noted in 10 (76.9%), 8 (61.5%), and 8 (61.5%) patients, respectively. Peripheral sensory neuropathy observed was grade 1 only, which completely resolved after cessation of therapy. None of the patients developed any nonhematologic grade 3 or 4 toxicities during the first cycle. None of the patients required a reduction in fludarabine dose. The most common hematologic toxicities were thrombocytopenia (54%), anemia (38%), and neutropenia (31%). Overall, the combination of fludarabine with thalidomide was well tolerated in this patient population.

A “flare reaction” characterized by tenderness and an increase in the size of involved lymph nodes along with associated erythema was noted in 6 patients (46%). This was treated with oral ibuprofen and subsided completely with the institution of fludarabine on day 7. All patients who developed a flare reaction were able to continue thalidomide without interruption of thalidomide and were able to receive fludarabine at the planned day 7 of treatment. Fine-needle aspiration of the lymph node obtained (on day 7) on the initial 2 patients with accessible lymph nodes did not show transformation of CLL cells to aggressive lymphoma.

### Response

Nine patients completed 6 months of therapy and were available for response. Four patients were considered ineligible for response evaluation because they were not able to complete intended duration of therapy (3 patients for toxicity reasons as mentioned and 1 patient who neglected to take the assigned thalidomide dose on schedule was removed from the study). Of 9 evaluable patients, 5 achieved CRs (Table 3) by completion of therapy and 4 were assessed to be in nodular partial remission (nPR). At a median follow-up of 15+ months (range, 3+ to 18+ months) none of the patients have had a relapse. Median duration of response has not yet been reached.

### Table 3. Response to treatment

<table>
<thead>
<tr>
<th>Response category</th>
<th>Response at completion of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>5</td>
</tr>
<tr>
<td>nPR</td>
<td>4</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
</tr>
</tbody>
</table>

CR indicates complete remission; nPR, nodular partial remission; PR, partial remission; SD, stable disease; PD, progressive disease.
Table 4. Change in peripheral blood malignant lymphocyte count after 7 days of thalidomide treatment

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>ALC at baseline, $\times 10^9$ cells/L</th>
<th>ALC on day 7, $\times 10^9$ cells/L</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>106.85</td>
<td>114.30</td>
<td>+7</td>
</tr>
<tr>
<td>2</td>
<td>201.30</td>
<td>210.74</td>
<td>+5</td>
</tr>
<tr>
<td>3</td>
<td>73.50</td>
<td>69.70</td>
<td>-5</td>
</tr>
<tr>
<td>4</td>
<td>1.94</td>
<td>1.70</td>
<td>-12</td>
</tr>
<tr>
<td>5</td>
<td>11.00</td>
<td>8.31</td>
<td>-24</td>
</tr>
<tr>
<td>6</td>
<td>39.19</td>
<td>28.78</td>
<td>-27</td>
</tr>
<tr>
<td>7</td>
<td>110.90</td>
<td>67.70</td>
<td>-39</td>
</tr>
<tr>
<td>8</td>
<td>44.34</td>
<td>20.10</td>
<td>-55</td>
</tr>
<tr>
<td>9</td>
<td>123.30</td>
<td>55.80</td>
<td>-55</td>
</tr>
<tr>
<td>10</td>
<td>41.20</td>
<td>18.64</td>
<td>-55</td>
</tr>
<tr>
<td>11</td>
<td>115.20</td>
<td>49.60</td>
<td>-57</td>
</tr>
<tr>
<td>12</td>
<td>33.08</td>
<td>12.69</td>
<td>-62</td>
</tr>
<tr>
<td>13</td>
<td>6.71</td>
<td>1.07</td>
<td>-84</td>
</tr>
</tbody>
</table>

Discussion

CLL remains an incurable disease with limited therapeutic options. Standard therapies involve chlorambucil or fludarabine with suboptimal clinical responses. Recently, the use of a chemoimmunotherapy approach with fludarabine in combination with rituximab with or without cyclophosphamide has shown improved clinical responses.\(^{19,20}\) These novel combinations have resulted in an increased incidence of CRs with a durable progression-free survival. Byrd et al recently reported a trend toward an improved survival when fludarabine is combined with rituximab,\(^{19}\) thus suggesting that a chemoimmunotherapeutic approach in treating patients with CLL can potentially improve clinical outcome.\(^{21}\) Despite these encouraging results, all patients eventually have a relapse and develop refractory disease. Development of novel agents with alternate mechanisms of action or novel combinations that can potentially yield higher complete and overall response rates is an ongoing need in this patient population.

This is the first report of the use of thalidomide in patients with treatment-naive CLL. Although thalidomide is currently only approved for the treatment of erythema nodosum leprosum (ENL), it is known to have antitumor activity in various malignant disorders including multiple myeloma and renal cell cancer.\(^{22-25}\)

In this study we have used thalidomide in combination with fludarabine in an effort to improve on the response rates of fludarabine alone. We hypothesized that targeting the microenvironment using thalidomide concurrently with targeting the tumor cell with standard chemotherapy (fludarabine) in patients with CLL may improve the antitumor efficacy of the chemotherapy and result in an improvement in disease control.

The design of this trial allowed some assessment of the efficacy of thalidomide alone during the first 7 days of treatment. Anti-CLL effects were noted by day 7. The clinical significance of this observation is unclear, although our data strongly suggest that thalidomide itself has anti-CLL efficacy. Further studies are needed to assess the efficacy of thalidomide in CLL.

This phase 1 study demonstrated that thalidomide up to 300 mg daily can be instituted safely in combination with fludarabine in patients with CLL. VTE is a known toxicity associated with thalidomide therapy; 2 (15%) patients in this study developed VTE, but only 1 patient had received the combination treatment. Thus, our phase 1 experience did not show any significant increase in the incidence of VTE when thalidomide is combined with fludarabine. The true incidence of VTE in this treatment regimen remains to be determined. In evaluable patients, the ORR of this combination in this small study of previously untreated CLL patients was 100%, with all patients achieving a major response based on NCI-WG 1996 criteria, as evaluated at completion of 6 months of therapy. The response rates noted in this study are higher than the standard therapy with fludarabine alone, which has an ORR of 40% to 60% and a CR rate of about 20%.\(^{1,26}\) It is to be noted that this is a phase 1 clinical trial designed to study the feasibility of concurrent administration of thalidomide with fludarabine. Although the results of this study are encouraging, the ongoing phase 2 component of this clinical trial will provide further data to determine whether these preliminary clinical findings hold true in a larger cohort of patients with CLL. Based on our phase 1 experience and the lack of DLT, we have selected a dose of 200 mg thalidomide to be investigated in the phase 2 setting. The rationale for this dose selection is based on extensive experience in safety and efficacy of long-term use of 200 mg thalidomide in other disease models and the fact that we did not see any dose-response effect in our phase 1 experience. Additional studies are needed to determine whether the addition of thalidomide to fludarabine is beneficial in the management of patients with CLL.

Acknowledgment

Deborah Donaldson is acknowledged for help in preparation of the manuscript.

References


17. Wechalekar AD, Chen CI, Sutton D, Reece D, Voralia M, Stewart AK. Intermediate dose thalidomide (200 mg daily) has comparable efficacy and less toxicity than higher doses in relapsed multiple myeloma. Leuk Lymphoma. 2003;44:1147-1149.


Results of a phase 1 clinical trial of thalidomide in combination with fludarabine as initial therapy for patients with treatment-requiring chronic lymphocytic leukemia (CLL)

Asher Chanan-Khan, Kena C. Miller, Kenichi Takeshita, Alexandra Koryzna, Kathleen Donohue, Zale P. Bernstein, Alice Mohr, Donald Klippenstein, Paul Wallace, Jerome B. Zeldis, Christine Berger and Myron S. Czuczman

Updated information and services can be found at:
http://www.bloodjournal.org/content/106/10/3348.full.html

Articles on similar topics can be found in the following Blood collections
Clinical Trials and Observations (4514 articles)
Neoplasia (4182 articles)

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml