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)

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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)

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 anticancer 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

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thalidomide may result in enhanced antitumor activity of fludarabine 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) guidelines[16] 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 microenvironment 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/m^2) fludarabine was given for 5 days every 4 weeks for 4 to 6 cycles. We now report the results of the completed phase 1 component of this study with associated toxicity profile, response rates, and preliminary follow-up.

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, β_2-microglobulin, interphase cytogenetic analysis, rapid lymphocyte doubling time, and pattern of bone marrow involvement. Treatment was offered based on the recommendations outlined by Cheson et al in the NCI-WG 1996 guidelines[16]; 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; differentials; 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/m^2/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 ($\leq$ 70 or $\geq$ 70 kg, respectively) for prevention of thalidomide-related venous thromboembolism (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 1. Baseline clinical characteristics in 13 patients

Characteristic	No. of patients	Percentage
Sex		
Female	4	31
Male	9	69
Stage		
I	6	46
II	0	0
III	3	23
IV	4	31
WBCs, × 10^9/L		
20 or fewer	3	23
20–50	4	31
50 or more	6	46
Indication for treatment		
Symptomatic/unacceptable adenopathy	3	23
Rapid lymphocyte doubling time	2	15
Symptomatic splenomegaly	0	0
B symptoms: fatigue, weight loss, and night sweats	4	31
Progressive autoimmune thrombocytopenia/anemia	1	8
Advanced-stage disease	6	46
Interphase cytogenetics*		
Normal	2	15
Trisomy 12	3	23
p53 deletion	1	8
Deletion 13q	1	8

Median age of patients was 65 years (range, 38–74 years).
*Available on 7 patients only.

Table 2. Treatment-related toxicities

	No. of patients (%), grades 1 and 2	No. of patients (%), grades 3 and 4
Nonhematologic		
Fatigue	6 (46)	4 (31)
Somnolence	4 (31)	0 (0)
Constipation	8 (61)	0 (0)
Neuropathy	8 (61)	0 (0)
Pulmonary thromboembolism	0 (0)	2 (15)
Rash	4 (31)	0 (0)
Flare reaction*	6 (46)	0 (0)
Pedal edema	0 (0)	1 (8)
Diarrhea	0 (0)	1 (8)
Hematologic		
Anemia	5 (38)	0 (0)
Leukopenia	0 (0)	1 (8)
Neutropenia	3 (23)	1 (8)
Thrombocytopenia	7 (54)	0 (0)

*Tenderness and increased swelling of the involved lymph nodes

escalation in the dose of thalidomide among patients within each cohort. Patients developing a "flare reaction" from thalidomide were treated with 400 to 800 mg ibuprofen orally every 6 to 8 hours.

Assessment of efficacy

Peripheral blood counts were assessed weekly. Interim evaluation for response was done after completing 3 cycles of fludarabine therapy, which included physical examination, complete blood counts with differential, and chemistry profiles. Computed tomography of the chest, abdomen, and pelvis was done only if clinically indicated. Each patient with an objective response or stable disease remained on the treatment protocol to complete a maximum of 6 cycles of fludarabine and 6 months of thalidomide therapy. A complete restaging (including a bone marrow biopsy and peripheral blood flow cytometry) for response assessment was done within 1 month of completing thalidomide treatment. After completion of treatment, patients were re-evaluated at 3-month intervals with complete restaging as mentioned. Patients with progressive disease were taken off the treatment protocol but are included for response and toxicity analysis.

Each patient was assigned a response category at 3- and 6-month assessment, and thereafter, at each follow-up visit. Responses were categorized using the revised 1996 NCI-WG guidelines.[16]

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,[18] 6 patients had intermediate-risk (stage I or II) and 7 had high-risk (stage III or IV) CLL.[18] The median β_2-microglobulin level was 2.7 (range, 1.6-4.1).

Toxicity

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. Three patients were removed from the study because of toxicity concerns. Two patients (1 patient each in cohort 1 and 2) developed pulmonary embolism, 1 during the first week of thalidomide therapy alone prior to starting fludarabine and thus never received combination therapy. Another patient developed it after the fourth cycle of therapy and had thalidomide discontinued at that time. Both patients were receiving low-dose warfarin for VTE prophylaxis. One patient developed asymptomatic reactivation of hepatitis C after completing 3 cycles with persistent elevation of liver function tests (LFTs).

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.

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 55% (range, 5%-84%) and 8 (61%) patients showed a 25% or more decrease in ALC at day 7.

Table 3. Response to treatment

Response category	Response at completion of therapy
CR	5
nPR	4
PR	0
SD	0
PD	0

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

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

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 chemoimmunotherapeutic 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-naïve 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.

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