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N9986: a phase II trial of thalidomide in patients with relapsed chronic lymphocytic leukemia

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Abstract

We enrolled 28 eligible patients with relapsed chronic lymphocytic leukemia (CLL) to a phase II study of single agent thalidomide (200 mg/d, with dose escalation up to 1000 mg/d over 60 days). The median age was 66 years and 71% were males. Study participants received a median of 2 (range 1–7) prior treatment regimens and 61% had Rai stage 3–4 disease at enrollment. Grade 3 or higher hematologic toxicity was observed in 13 (46%) and 16 (57%) had grade 3 or higher non-hematologic toxicity. Grade 3–4 tumor flare was observed in five (18%) patients. The overall response rate was 11% (3 of 28) with one (4%) complete remission and two (7%) partial remissions. Duration of response for these three responders was 3, 14 and 15 months. Fourteen (50%) patients had stabilisation of disease for a median duration of 8 months (95% CI: 7–16 months). Median time to progression for all 28 patients was 7.3 months. Although thalidomide appears to have modest clinical activity in pretreated/relapsed CLL primarily based on reduction of the absolute lymphocyte count, in our opinion the toxicity profile precludes it from more active investigation in CLL.

Keywords

CLL; treatment; relapsed; thalidomide; angiogenesis

Introduction

First line therapy for patients with chronic lymphocytic leukemia (CLL) has evolved to employ combinations of chemotherapeutic agents along with monoclonal antibodies. These new treatments have resulted in very high overall response rates (ORR) and complete responses (CR) for previously untreated CLL. Despite the improved efficacy of these regimens, a majority of patients still relapse and require salvage therapy [1–3]. A limited number of therapeutic options are available for salvage therapy, particularly after patients become refractory to purine nucleoside analogues and alkylating agents. New drugs with non-overlapping mechanisms of action are needed to treat relapsed patients. Candidate compounds for clinical investigation have primarily employed monoclonal antibodies (alemtuzumab, rituximab) or chemotherapeutic compounds believed to target biologic processes thought to be integral to CLL disease progression (e.g. anti-sense agents for Bcl-2). To develop more targeted treatment approaches, we and others have postulated that signalling via angiogenic cytokines and neovascularisation are related to CLL progression [4–8]. Based on this observation, clinical testing of anti-angiogenic therapies for patients

with relapsed CLL appears warranted. Thalidomide is a drug with pleiotropic activities but is known to be at least an inhibitor of angiogenesis, and we believed that its potential ability to interrupt both vascular endothelial growth factor (VEGF) induce CLL B cell survival as well as to reduce neovascularisation was sound rationale for testing this drug in CLL [9]. Thus, we initiated a phase II trial for relapsed/refractory CLL in 2001 and now report the results of that study.

Patients, materials and methods

Clinical trial sites and patient eligibility

This was a phase II, multi-centre clinical trial conducted in the North Central Cancer Treatment Group (NCCTG). The clinical trial was designed to determine the efficacy and toxicity of thalidomide in patients with relapsed B-CLL, and to explore the correlation between alterations in vascular growth factors and bone marrow angiogenesis patterns with thalidomide treatment. The eligibility criteria required patients to have received prior treatment for CLL and have active, relapsed/refractory disease requiring treatment according to the criteria of the National Cancer Institute (NCI) – sponsored CLL Study Group [10]. Patients were permitted to have had up to three prior chemotherapy regimens but individuals who had received prior allogeneic bone marrow transplant were excluded. Patients were at least 18 years old, with no active second malignancy, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. The protocol was reviewed and approved by the Institutional Review Board at each treating site.

Study design and treatment plan

After giving written informed consent, eligible patients received a treatment of 200 mg thalidomide P.O. daily as a single dose at bed time. The dose was then increased by 200 mg every 2 weeks, as tolerated, up to 1000 mg/day in the first 60 days. Thalidomide was given for up to a maximum of 12 cycles (1 cycle = 28 days). While patients were assessed for clinical response during the first 6 months of treatment on a monthly basis, after 6 months of treatment, patients with a clinical response [CR, nodular partial response, partial response (PR)] or stable disease continued on the therapy for another six cycles. Treatment was discontinued in cases of progressive disease or excessive toxicity (grade 2 rash or neurologic adverse events that do not resolve to grade 1 or recur after dose reduction, grade 2 seizures, grade 2 thrombosis or embolism, or intolerance to 50 mg/day of thalidomide). Patients who developed grade 3 tumor flare upon initiation of thalidomide were instructed to hold treatment and were monitored weekly. Treatment was restarted at 50 mg thalidomide per day once the flare subsided. Toxicity was graded using the Common Toxicity Criteria (v. 2) of the NCI. There was no routine use of prophylaxis for venous thromboembolism.

Criteria for response

Responses were evaluated according to NCI Working Group criteria [10]. Bone marrow biopsy was collected at baseline and repeated after 6 and 12 months of treatment or at the time of progression. Patients meeting clinical criteria for a complete remission (CR) had an additional bone marrow collected 2 months after criteria for response were documented. At the completion of therapy, patients were then followed and observed at 3-month intervals for up to 5 years or until documented progression.

Statistical design and analysis

A two-stage analysis was conducted to assess the ORR to treatment. Individuals obtaining a CR, nPR or PR on two consecutive evaluations, at least 2 months apart, were considered to have had an objective response. The trial was designed to test the null hypothesis that the true ORR is 5%. The smallest ORR that would imply that this regimen warranted further

study was 20%. Assuming a one-sided level of significance of 0.1, an initial sample size of 37 eligible patients was calculated to provide a 90% power to detect at least a 15% difference in ORR. For patients who achieved a response, duration of response was defined as the time from the date at which the patient's objective status is first noted to be a CR, nPR or PR to the earliest date progression is documented. Stabilisation of disease was defined as an objective status of stable for at least 2 months after registration. The distributions of overall survival, duration of response and time to progression were estimated using the method of Kaplan–Meier.

Results

Patient demographics

Overall, 28 patients were enrolled from 12 NCCTG sites between January 2001 and July 2003 at which time the study was closed due to slow accrual. All the 28 patients were eligible and are included in the clinical outcome analyses. Patient characteristics are presented in Table I. The median age of study participants was 66 years (range, 54–83 years), with 13 (46%) patients being 70 years or older. Twenty patients (71%) were males. The majority of patients (17 of 28; 61%) had stage 3 or 4 disease by Rai criteria at study entry [11]. The study population was pre-treated, with a median of two prior treatment regimens (range, 1–7). Twenty-four (86%) patients had received prior purine analogue based treatment and 24 (86%) patients had received prior alkylating agents (e.g. cyclophosphamide, chlorambucil), while 20 had been treated with both agents in previous treatments. No patient had ever received alemtuzumab as prior therapy. The median time from last dose of prior treatment to registration was 8 months (range, 1–57 months).

Toxicity and tolerability

At the time of this report, all patients have completed active treatment. Twenty-five patients (89%) discontinued treatment early for the following reasons: disease progression (five patients, 18%), refusing further treatment (two patients, 7%), adverse event (11 patients, 39%), alternate treatment (three patients, 11%), and other (four patients, 14%). More specifically, the 11 patients who went off study for adverse events went off for tumor flare (four patients), hematologic adverse events (two patients), non-hematologic adverse events (two patients), or both hematologic and non-hematologic adverse events (three patients). The three patients who went off study for alternate treatment discontinued therapy for the following reasons: one for physician discretion, one for increase in lymphadenopathy and absolute lymphocyte count (ALC) but not at levels that were clearly indicating progression, and one for hemolytic anemia requiring prednisone. The four patients that discontinued treatment early due to 'other' reasons were removed from therapy for what was believed to be clinical progression but was later determined to be tumor flare. While on treatment, 15 patients (54%) had the dose of thalidomide held or modified with the most common reasons being tumor flare ($n = 7$), hospitalisation ($n = 3$), neurologic ($n = 3$), somnolence/sedation ($n = 3$), dermatitis ($n = 2$) and fatigue ($n = 2$).

Patients received a median of 2.5 cycles of treatment (range 1–24 cycles), with two patients receiving beyond 12 months of treatment utilising commercially supplied thalidomide. The highest tolerated dose for individual patients ranged from 100–1000 mg/day (median 400 mg/day). Two patients were titrated up to 1000 mg/day. Twelve patients were dose-reduced to 50 mg/day at some point during treatment due to adverse events but nine of those patients were later re-escalated to higher dose levels.

Overall, 17 (61%) patients had a grade 3 or higher hematologic adverse events and 18 (64%) patients had a grade 3 or higher non-hematologic adverse event (regardless of perceived

attribution). Focussing only on those adverse events deemed at least possibly related to treatment, 13 (46%) patients had a maximum of grade 3 or higher hematologic toxicity and 16 (57%) had a grade 3 or higher non-hematologic toxicity. Four patients (14%) had grade 3 tumor flare and one patient (4%) had grade 4 tumor flare at a median dose of 200 mg/day (range 100–200 mg/day). The frequency and severity of grade 3 or higher toxicities are shown in Table II. For the five patients who experienced grade 3 or higher tumor flare, one was removed from study and the other four underwent dose modification.

Eleven patients discontinued the treatment due to following adverse events: four due to tumor flare, two non-hematology AEs (a grade 3 GI bleed and possible aspiration pneumonia, and a grade 3 neuropathy-sensory), two hematology AEs (a thrombocytopenia and a recurrent neutropenia/thrombocytopenia), and three both hematology and non-hematology AEs (an anemia and orthostasis with pneumonia and two with multiple toxicities).

Response to therapy

Of the 28 eligible patients, one (4%) patient attained a CR and two (7%) patients a PR (ORR = 11%; 95% CI: 2–28%). Of the three patients who responded to treatment with a CR or PR, the time to first documentation of any response (i.e. Clinical Complete Response or PR) was 28, 29 and 406 days. The duration of response among these three patients was 14, 3 and 15 months, respectively. The patient with complete response was stage 1 and the two patients with PR were stage 1 and 4 at the time of registration. None of the three responding patients had tumor flare. In addition to the confirmed responses, 14 (50%) patients had stabilization of disease for a median duration of 8 months (95% CI: 7–16 months). ALC value declined during treatment for 22 of the 28 (79%) eligible patients, of whom 15 had a ≥50% decline (median drop in ALC was $20.15 \times 10^9/L$ [range, 1.71–142.9]).

The median follow-up on living patients is 59 months (range, 1.5–76 months). At the time of these analyses, 17 (61%) patients have died and 23 (82%) have progressed. The median OS from registration was 48.3 months (95% CI: 26.9–62.3 months) and the median TTP was 7.3 months (95% CI: 6.4–14.2 months) for all patients.

Discussion

This present study was the first clinical trial to evaluate the efficacy of thalidomide for treatment of relapsed/refractory CLL. In a cohort of pretreated patients, single-agent thalidomide led to a decrease in ALC in 79% of patients and to a complete or partial remission in 11% of patients. We believe that the higher number of patients with stable disease in this treatment approach is largely due to the decrease in absolute lymphocyte count. Thus, in the 14 patients with stable disease, there was a greater than 50% decrease in their absolute lymphocyte count although the percentage decrease did vary considerably. Responses were durable for 14 months in two of the three patients who achieved a response. Treatment was associated with 46% of patients having grade 3 or 4 hematologic toxicity and 57% having grade 3 or 4 non-hematologic toxicity attributed to study medication. Importantly, our patient cohort does represent a relatively unfavorable CLL cohort to treat: patients received a median of two prior therapies, over half the patients had an unmutated immunoglobulin heavy chain variable region status and one-third of patients were CD38 positive (see Table I), all factors that predict for more aggressive resistant disease.

Although this is the first study to evaluate the efficacy of single-agent thalidomide in patients with CLL, several recent studies have evaluated thalidomide in combination with purine analogues for patients with previously untreatable CLL. Chanan-Khan *et al.* was able to combine thalidomide with fludarabine for previously untreated patients with CLL and

observed a 100% overall responses (55% CR) [12]. Acceptable toxicity was observed in this study which used similar doses of thalidomide to our single-agent thalidomide trial. The toxicities in the Chanan-Khan *et al.* study was similar to ours with fatigue, constipation and peripheral neuropathy [12]. A more recent trial combined thalidomide along with oral fludarabine and cyclophosphamide [13] for previously treated CLL but reported it to not be as effective as the former trial of thalidomide and fludarabine [12]. This is likely due to the heavily pretreated cohort of CLL in this latter trial. Finally, another trial conducted by Furman *et al.*, found that thalidomide alone or in combination with fludarabine was able to generate hematologic improvement and decrease in lymph node size in previously treated patients with CLL [14].

As our trial was completed, several trials have evaluated the efficacy of the thalidomide derivative, lenalidomide, in patients with CLL. Lenalidomide appears to be more potent than thalidomide with response rates of 25–41% in two phase II studies [15,16]. Similar to our observations with thalidomide, tumor flare reactions were frequently observed with use of lenalidomide in patients with relapsed CLL [16,17] and appears to be a side effect of immunomodulatory drugs in patients with CLL. Although some have speculated flare reaction may be a marker of the immune stimulatory affects associated with response, none of the three responders in our thalidomide trial had a tumor flare reaction. The etiology of the flare is unclear but could be related to the ability of these drugs to enhance the immune system [18,19]. From our study we would recommend that if thalidomide is to be used as single agent in CLL treatment that it be used at a starting dose of 50 mg per day and only slowly build up to higher doses such as 200–400 mg per day. If a flare still occurs we would suggest discontinuing the drug and likely not attempt to resume its use.

In summary, we observed single-agent activity with use of thalidomide in patients with relapsed/refractory CLL. We believe this is justified based primarily on the ability of this oral drug to decrease the ALC in almost 80% of our heavily pretreated CLL cohort and to decrease the ALC by over 50% in 15 of these patients. However, thalidomide treatment was associated with substantial side effects and appears less active than lenalidomide for patients with previously treated CLL.

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Table I

Patient characteristics.

Characteristics	N (%)
Age	
Median (range)	65.5 (54, 83)
Gender	
Female	8 (29)
Male	20 (71)
Rai stage	
1	6 (21)
2	5 (18)
3	5 (18)
4	12 (43)
No. of prior treatments	
Median (range)	2 (1, 7)
Best responses to prior treatment	
Complete response	8 (29)
Partial response	17 (61)
Stable	3 (11)
Weight loss in previous 6 months	
None	15 (54)
5% of body weight	3 (11)
Not applicable	10 (36)
Fever	
No	28 (100)
Night sweats	
Yes	4 (14)
No	24 (86)
Hemorrhage	
Yes	1 (4)
No	27 (96)
Infection	
No	28 (100)
Bone marrow pattern at baseline	
Diffuse	1 (4)
Nodular	4 (14)
Interstitial	11 (39)
Nodular and Interstitial	12 (43)
FISH	
17p-	2 (10)
11q-	1 (5)
+12	3 (15)

Characteristics	N (%)
13q-	10 (50)
Normal	4 (20)
Missing	8
IgV _H mutation status	
Mutated	7 (47)
Unmutated	8 (53)
Missing	13
CD38	
Negative	18 (72)
Positive	7 (28)
Missing	3

FISH, fluorescence *in situ* hybridisation.

Table II

Toxicity (side effects considered to be at least possibly related to treatment).

Toxicity	Grade 3	Grade 4
Anemia	2 (7)	1 (4)
Dyspnea	1 (4)	1 (4)
Fatigue	7 (25)	0 (0)
Febrile neutropenia	1 (4)	0 (0)
Neutropenia	2 (7)	7 (25)
Pneumonitis	1 (4)	0 (0)
Thrombocytopenia	6 (21)	1 (4)
Tumor flare	4 (14)	1 (4)

Values in parentheses represent percentage.