Original Article

Interim Report of A Phase 2 Clinical Trial of Lenalidomide for T-Cell Non-Hodgkin Lymphoma

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BACKGROUND: Novel therapies are needed to improve outcomes in T-cell lymphomas. The authors report the interim results of a prospective multicenter trial evaluating lenalidomide in T-cell lymphomas. **METHODS:** Patients with recurrent and refractory T-cell lymphomas other than mycosis fungoides and untreated patients ineligible for combination chemotherapy were prescribed oral lenalidomide (25 mg daily) on Days 1 to 21 of each 28-day cycle until disease progression, death, or unacceptable toxicity. The primary endpoint was overall response rate. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety. The 2-stage design allows for up to 40 patients. **RESULTS:** At the time of this interim analysis, 24 patients were enrolled in this study, and 23 were evaluable for response. The median age was 65 years. The overall response rate was 7 (30%) of 23; all were partial responses. Two patients had stable disease for $\geq$5 cycles. Responses were seen in anaplastic, angioimmunoblastic, and peripheral T-cell unspecified histologies. Median PFS was 96 days (range, 8-696+ days). Median OS was 241 days (range, 8-696+ days). The most common grade 4 adverse event was thrombocytopenia (33%). The most common grade 3 adverse events were neutropenia (21%), febrile neutropenia (17%), and pain not otherwise specified (17%). Rash correlated with response to therapy (P=.003). **CONCLUSIONS:** In patients with recurrent and refractory T-cell lymphomas, oral lenalidomide monotherapy has clinical activity, and toxicity is consistent with the known safety profile of lenalidomide. Further study of lenalidomide in these diseases is warranted. ***Cancer*** **2010;116:4541–8.** © *2010 American Cancer Society.*

KEYWORDS: T-cell lymphoma, antineoplastic agents, clinical trial, phase 2.

T-cell lymphomas are a diverse and often aggressive group of non-Hodgkin lymphomas. Most subtypes of T-cell lymphoma are derived from mature T cells and are collectively called peripheral T-cell lymphomas (PTCLs). This group of aggressive T-cell lymphomas is characterized by biological diversity, relative rarity of the disease, and a poor clinical prognosis. Conventional chemotherapy provides 5-year survival in the range of 30% or less for most types of PTCL.[1-7] Anaplastic lymphoma kinase-positive anaplastic large cell lymphoma (ALCL) has proven to be an exception, with significantly longer survival than other forms of PTCL.[8-10] The tendency of PTCL to recur has prompted several studies into high-dose chemotherapy and stem cell transplant for recurrent and refractory disease. In general, these studies have found that long-term survival remains in the range of 40% for chemosensitive disease, with predictably better survival in ALCL.[11-14] The prognosis for patients with T-cell lymphomas that are either ineligible for or have developed disease recurrence after high-dose chemotherapy remains poor.[14,15] Novel therapeutic approaches are needed to further improve outcomes in T-cell lymphomas.

Lenalidomide (Revlimid) is an immunomodulatory agent that has demonstrated clinical efficacy in several hematologic malignancies. Lenalidomide has several hypothesized mechanisms of action, including direct cytotoxicity to tumor cells,[16-18] and immunomodulatory effects such as cytokine modulation[19] and enhanced natural killer and T-cell function.[20,21] In addition, lenalidomide alters the tumor cell microenvironment to discourage the growth of tumor cells and

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inhibit the mitogenic signaling that supports tumor cells in the bone marrow, both by overcoming the protective role of bone marrow stromal cells[17,22,23] and through antiangiogenic properties.[23-25]

Lenalidomide has proven efficacy in the treatment of several hematologic malignancies, including chronic lymphocytic leukemia,[26] multiple myeloma,[27] and myelodysplastic syndrome.[28,29] Preliminary results of a phase 2 trial of lenalidomide in cutaneous T-cell lymphoma have shown clinical activity,[30] and a phase 2 trial has recently demonstrated clinical activity of lenalidomide monotherapy in recurrent or refractory aggressive B-cell non-Hodgkin lymphoma.[31] We report the interim results of a prospective phase 2 multicenter trial evaluating the safety and efficacy of oral lenalidomide monotherapy in recurrent and refractory noncutaneous T-cell lymphomas.

MATERIALS AND METHODS

Patients

The study was designed in accordance with the general ethical principles outlined in the Declaration of Helsinki.

Key inclusion criteria were age $\geq$18 years, histologically proven T-cell lymphoma (excluding cutaneous T-cell lymphoma/mycosis fungoides), with recurrent/refractory disease after at least 1 line of chemotherapy or untreated patients with contraindications to chemotherapy (no restriction on number of prior therapies), allowing prior radiotherapy or autologous or allogeneic stem cell transplant, at least 1 measurable lesion $\geq$2 cm on imaging or clinical examination, World Health Organization performance status of $\leq$2 at study entry, absolute neutrophil count $\geq 1.0 \times 10^9$/L, platelet count $\geq 75 \times 10^9$/L, serum creatinine $\leq$200 μM/L, total bilirubin $\leq$2 $\times$ the upper limit of normal, and aspartate aminotransferase and alanine aminotransferase $\leq$2 $\times$ the upper limit of normal or $\leq$5 $\times$ the upper limit of normal if hepatic metastases are present. Women of childbearing potential must have had a negative serum or urine pregnancy test within 10 to 14 days and again within 24 hours of starting study drug. In addition, sexually active women of childbearing potential must have agreed to additional pregnancy testing throughout the study and to commit to continued abstinence from heterosexual intercourse or begin 2 acceptable methods of birth control 4 weeks before initiation of study drug, during therapy and any breaks in therapy, and for 4 weeks after the last dose of study drug. Men must have agreed not to father a child and to use a condom with partners of child-bearing potential even after successful vasectomy. Key exclusion criteria are cutaneous T-cell lymphoma/mycosis fungoides histologies, pregnant or lactating women, the development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs, and any prior use of lenalidomide.

Study Design

This open-label, single-arm, multicenter Canadian phase 2 clinical trial was designed to assess the overall response rate (ORR) to lenalidomide for patients with T-cell lymphoma. The primary endpoint is ORR as defined using the International Working Lymphoma Response Criteria.[32] The secondary endpoints are overall survival (OS), progression-free survival (PFS), and safety.

Patients were treated with oral lenalidomide (25 mg once daily) on Days 1 to 21 of every 28-day cycle. Treatment was continued until there was evidence of progressive disease, intolerable side effects, patient choice to withdraw, or death. Administration of lenalidomide was instructed to be in the morning, at approximately the same time each day. Patients were provided with enough lenalidomide for each 21-day cycle. Patients were instructed to maintain a diary to record drug administration, and were asked to bring any unused study drug to the research center at their next visit. Research personnel recorded the number of used and unused study drug capsules at each visit, to document treatment compliance.

Dose modifications were predefined and followed by the treating physician. These include dose modifications for grade 3 neutropenia associated with a fever, grade 4 neutropenia, grade $\geq$3 thrombocytopenia, grade $\leq$3 nondesquamating rash, grade 2 sinus bradycardia or other cardiac arrhythmias, grade 2 or 3 allergic reaction, grade $\geq$3 venous thrombosis/embolism, hyperthyroidism or hypothyroidism, and any other grade $\geq$3 nonhematologic toxicity assessed as lenalidomide related. Lenalidomide treatment was discontinued for any grade desquamating rash, grade 4 nondesquamating rash, grade $\geq$3 sinus bradycardia or other cardiac arrhythmias, or grade 4 allergic reaction.

Supportive care and concomitant therapy, including transfusions of blood and blood products, antibiotics, antiemetics, erythropoietic agents, and filgrastim (granulocyte colony-stimulating factor), were allowed at the discretion of the investigator. Concomitant use of sargramostim (granulocyte-macrophage colony-stimulating factor) and other anticancer therapies, including radiation, thalidomide, or other investigational agents, was not

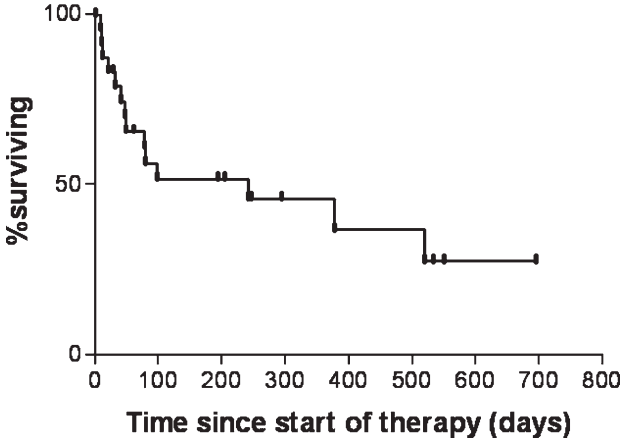

Figure 1. Overall survival is shown.

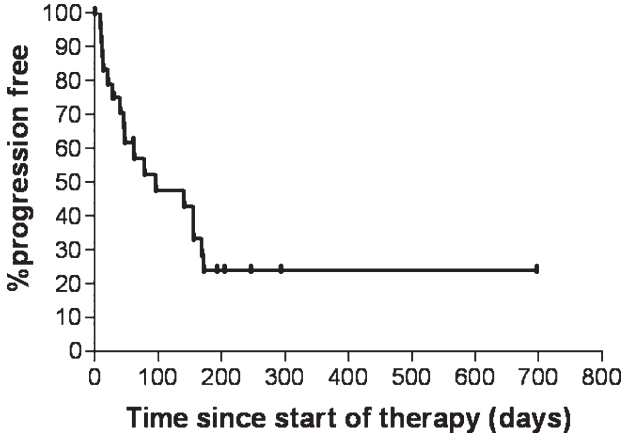

Figure 2. Progression-free survival is shown.

permitted. Use of any other experimental drug or therapy within 28 days of baseline was prohibited. Corticosteroid use was allowed in palliative doses (maximum dose, dexamethasone 4 mg orally 4× daily or equivalent) to treat nausea or peritumoral edema; however, corticosteroid use in higher doses or as an antineoplastic agent was prohibited. Prophylactic anticoagulation or antiplatelet therapy was not required on study, but consideration was given as deemed appropriate by the treating physician.

Response and Safety Assessments

Study visits were performed on Day 1 of every 28-day cycle of treatment. Target and nontarget lesions were assessed by computed tomography and/or magnetic resonance imaging at baseline, and every 3 treatment cycles thereafter. Bone marrow core biopsy was repeated only to confirm a complete remission, and only if the pretreatment bone marrow biopsy showed evidence of lymphoma. Response and progression were evaluated using the International Working Lymphoma Response Criteria.[32] Patients who discontinued treatment for any reason were followed for toxicity for at least 30 days, and underwent a safety assessment approximately 30 days after the last dose of study drug. In addition, off study evaluations were performed every 3 months to obtain follow-up data on PFS and OS.

Safety evaluations included adverse events, vital signs, and hematology and serum chemistry profiles every 28 days. Hematology profiles were done weekly during Cycle 1, on Days 1 and 15 of Cycles 2 and 3, and then on Day 1 of subsequent cycles unless more frequent assessments were clinically indicated. Serum thyroid function tests were performed at screening, at the end of Cycle 3, and every 3 cycles thereafter. For women of child-bearing potential, a pregnancy urine or serum test was done 10 to 14 days prior and again within 24 hours of initiation of therapy. In this population, pregnancy testing was repeated weekly for the first 4 weeks, then monthly if menstruation was regular or every 2 weeks if it was irregular.

Statistical Analysis

The primary endpoint is the ORR, defined as the proportion of patients assessable for response whose best response was either a partial response (PR) or a complete response (CR). Secondary endpoints are PFS, OS, and the incidence of grade 3 or 4 hematologic or nonhematologic toxicities as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

The study has a 2-stage design, with a goal of enrolling a total of 40 patients. Stage 1 has accrued 22 patients, and the remainder continue to be enrolled in stage 2. The alpha level of the design is .04, and the power is 0.9. If <4 of 40 patients responded, this trial was to be considered evidence that lenalidomide is inactive in the population studied.

Response rates and the occurrence of grade 3-4 toxicities are expressed as percentages. Kaplan-Meier curves are used to characterize OS (Fig. 1) and PFS (Fig. 2). Categorical variables are compared using Fisher exact test. Survival distributions are compared using the log-rank

Table 1. Patient Demographics and Baseline Disease Characteristics (N=24)

Characteristic	No. of Patients	%
Age, y		
Median	65	
Range	42-91	
Men	21	88
Time from diagnosis to lenalidomide, mo		
Median	13	
Range	1-84	
Time from last treatment to lenalidomide, mo		
Median	8	
Range	1-48	
No. of prior treatment regimens		
0	4	16
1	10	41
2	5	20
3	4	16
4	1	4
Type of prior treatment		
Combination chemotherapy, at least once	20	83
Stem cell transplantation	3	12
Refractory to last treatment	5	21
Ann Arbor stage at enrollment		
1	2	8
2	2	8
3	6	25
4	14	58
Histology		
Anaplastic large cell lymphoma	5	20
Angioimmunoblastic T-cell lymphoma	7	29
Enteropathic-type T-cell lymphoma	1	4
Hepatosplenic T-cell lymphoma	1	4
Peripheral T-cell lymphoma, unspecified	10	41
ECOG performance status		
0	5	20
1	10	41
2	7	29
3	2	8

ECOG indicates Eastern Cooperative Oncology Group.

test. Multivariate survival analysis uses Cox regression. Results reported are based on data available on November 1, 2008.

RESULTS

Patient Baseline Characteristics

From September 2006 to November 2008, at the time of this interim analysis, 24 patients were enrolled at 5 centers in Canada. Patient demographics and baseline disease characteristics are summarized in Table 1. The median age was 65 years. Eastern Cooperative Oncology Group performance status was 0-1 (n = 15), 2 (n = 7), and 3 (n = 2). The histology was PTCL unspecified (n = 10), angioimmunoblastic lymphoma (n = 7), anaplastic large cell lymphoma (n = 5), enteropathic T-cell lymphoma (n = 1), and hepatosplenic gamma/delta lymphoma (n = 1). The median time from the completion of previous therapy to initiation of lenalidomide was 8 months (range, 1-48 months). The median number of prior therapies was 1 (range, 0-4). Twenty (83%) patients had received at least 1 prior treatment with combination chemotherapy, 3 (12%) had undergone prior stem cell transplantation, and 5 (21%) were refractory to their last therapy. Four patients were previously untreated and, in the opinion of the treating physician investigator, not candidates for combination chemotherapy.

Safety

The most common adverse events were fatigue, gastrointestinal, and hematological. Table 2 summarizes all adverse events reported in $\geq$10 % of patients. The most common grade 4 adverse event was thrombocytopenia (33%), and the most common grade 3 adverse events were neutropenia (21%), febrile neutropenia (17%), pain not otherwise specified (17%), dyspnea (13%), muscle weakness (13%), and pneumonitis (13%). Table 3 summarizes all grade 3 and 4 adverse events.

Four (17%) patients underwent a total of 6 dose reductions. Three dose reductions were for neutropenia, 1 was for febrile neutropenia, 1 was for diarrhea, and 1 was for a generalized maculopapular rash. The patient dose reduced because of a rash was subsequently titrated back up to full dose without further dose reductions required.

Reasons for discontinuing therapy on study were disease progression (n = 11), death (n = 6), and intolerance (n = 4). At current assessment, 3 patients are still on treatment.

Fourteen patients have died on study to date, 8 of whom died after discontinuing lenalidomide. Eleven deaths were attributed to disease progression. Two patients died of infection, 1 of pneumonia on Cycle 1 and the other of a lung abscess on Cycle 3. One remaining death was attributed to a small bowel obstruction complicated by perforation.

Response

At the time of the interim analysis, 24 patients were enrolled in this study, and 23 were evaluable for response. The patient excluded from response evaluation was on treatment but had not yet reached the first response

Table 2. Adverse Events Reported in ≥10% of Patients (N = 24)

Adverse Event	No. of Patients	%
Fatigue	13	54
Constipation	10	42
Anorexia	8	33
Diarrhea	8	33
Neutropenia	7	29
Thrombocytopenia	7	29
Dizziness	7	29
Insomnia	6	25
Pruritis	6	25
Rash	6	25
Back pain	5	21
Muscle weakness	5	21
Peripheral edema	5	21
Nausea	5	21
Infection	5	21
Cough	4	17
Dry skin	4	17
Dyspnea	4	17
Anemia	4	17
Febrile neutropenia	4	17
Pain abdominal	3	13
Fever	3	13

Table 3. All Grade 3 and 4 Adverse Events (N = 24)

Adverse Event	Grade 3		Grade 4	
	No.	%	No.	%
Thrombocytopenia	2	8	8	33
Neutropenia	5	21	0	0
Dyspnea NOS	3	13	1	4
Febrile neutropenia	4	17	0	0
Pain NOS	4	17	0	0
Pneumonitis	3	13	1	4
Fatigue	2	8	1	4
Muscle weakness	3	13	0	0
Allergic reaction	2	8	0	0
Anorexia	2	8	0	0
Dehydration	2	8	0	0
Pruritis	2	8	0	0
Acute gout	1	4	0	0
Anemia	1	4	0	0
Cognitive disturbance	0	0	1	4
Diarrhea	1	4	0	0
Dizziness	1	4	0	0
Insomnia	1	4	0	0
Lymphopenia	1	4	0	0
Pulmonary consolidation	1	4	0	0
Rash NOS	1	4	0	0
Renal failure	1	4	0	0
Respiratory failure	0	0	1	4
Seizure	0	0	1	4

NOS indicates not otherwise specified.

evaluation at the time of the analysis. The ORR was 7 of 23 (30%; Table 4). All 7 responders achieved a PR (PR = 30%), no patients achieved a CR, and 2 patients had stable disease (SD) for ≥5 cycles. The median OS (OS) was 241 days (range, 8-696+ days). The median PFS was 96 days (range, 8-696 days). Among the 9 patients with SD or better, median time on treatment was 172 days, median PFS was 168 days, and median OS has not yet been reached with 241 to 696 days of follow-up. Mean time to response was 65 days (range, 29-87 days). Histologic subtypes found to achieve objective responses were anaplastic large cell lymphoma (ORR, 40%), angioimmunoblastic T-cell lymphoma (ORR, 29%), and PTCL unspecified (ORR, 33%). Patients who responded to lenalidomide treatment had a median of 1 prior line of treatment (range, 0-3), with no previously transplanted patients responding to treatment. Two of the responders had been refractory to their last treatment before lenalidomide. The median Ann Arbor stage of responders was stage 4 at enrollment (range, 1-4).

The development of a skin rash was common among patients responding to treatment. Of the 6 patients in this trial who developed a rash (grade 1, n = 3; grade 2, n = 2; grade 3, n = 1), 5 achieved a PR. In every case, the rash developed during the first cycle of lenalidomide treatment. The sixth patient who developed a rash did so in the second cycle of treatment and achieved SD, which continues at the time of this analysis after 24 cycles of treatment. Two patients with no rash responded to treatment, both achieving a PR. Fisher exact test was used to assess the relationship of rash to treatment response, and the results suggest a significant relationship ($P = .003$).

Several other baseline patient characteristics were assessed in relation to treatment response. None of the variables analyzed correlated with response, including age ≤60 years, Eastern Cooperative Oncology Group performance status <2, Ann Arbor stage 1 or 2, histology subtype, time from completion of prior therapy to the start of lenalidomide ≤3 months, and number of lines of therapy before lenalidomide <2.

Two patients achieved SD. The first of these patients had SD for 5 cycles before disease progression. This patient had received 1 prior treatment regimen with CHOP (Cytoxan, hydroxyrubicin, Oncovin, prednisone) chemotherapy. The second patient remains on lenalidomide therapy after 24 cycles and has achieved SD. This patient had received multiple prior treatment regimens, including systemic prednisone, CHOP chemotherapy, prophylactic intrathecal methotrexate and cytarabine, and weekly systemic methotrexate. Both of these patients have PTCL unspecified histology and had stage 4 disease at enrollment.

Table 4. Response of Patients Receiving Lenalidomide Treatment by Histology (N = 23)

Histology	No.	CR	PR	SD	PD	ORR, %
Anaplastic large cell lymphoma	5	0	2	0	1	40
Angioimmunoblastic T-cell lymphoma	7	0	2	0	2	29
Enteropathic-type T-cell lymphoma	1	0	0	0	0	0
Hepatosplenic T-cell lymphoma	1	0	0	0	0	0
PTCL unspecified	9	0	3	2	3	33
All histologic subtypes	23	0	7	2	6	30

CR indicates complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; PTCL, peripheral T-cell lymphoma.

DISCUSSION

The response rates of oral lenalidomide monotherapy in T-cell lymphoma are comparable to those of other monotherapies previously tested. The nucleoside analogue gemcitabine has shown efficacy in phase 2 trials in recurrent and refractory T-cell lymphomas with CR rates of 8% to 20% and ORR of 60% to 69%.[33,34] The CR rate of the histone deacetylase inhibitor romidepsin was 8% and the ORR 30% in a phase 2 trial of recurrent and refractory PTCL.[35] Another phase 2 study in a similar group of noncutaneous T-cell lymphomas found denileukin diftitox, an interleukin-2–diphtheria toxin fusion protein, to have a CR rate of 22% and an ORR of 48%.[36] Recently, a CR rate of 12% and an ORR of 35% have been described for lenalidomide monotherapy in aggressive B-cell non-Hodgkin lymphoma.[31] Although lenalidomide therapy in the current interim analysis has not resulted in CR, small patient numbers in the studies discussed make direct comparison difficult. Strategic combinations of lenalidomide with agents shown to achieve CRs may further improve responses while capitalizing on complementary mechanisms of action.

The results demonstrate a marked difference in outcome between responders and nonresponders in this study. Given the design limitations of a phase 2 trial, we cannot conclude whether the improved outcome seen in responders is because of favorable underlying disease biology or the treatment. However, it is possible that lenalidomide may have provided meaningful palliation of T-cell lymphoma for a subset of patients in this study.

With a median number of 1 prior therapy (range, 0-4), and only 12% of patients previously undergoing stem cell transplant, the majority of patients enrolled in this trial were clearly not felt to be well suited for aggressive chemotherapy or stem cell transplant by their treating physicians. Younger patients who had been treated aggressively and whose disease was demonstrably refractory to multiple therapies including transplantation were not well represented in this trial. Effectively, this was a study of palliative oral therapy in older, nontransplant candidates.

The median time from diagnosis to lenalidomide treatment is relatively short at 13 months, and the median Ann Arbor stage at enrollment was stage IV (range, I-IV). These patient characteristics may reflect both the tendency for T-cell lymphomas to recur after primary treatment, and the lack of standard and effective treatment strategies in recurrent and refractory T-cell lymphoma.

Among patients responding to treatment, 2 were Ann Arbor stage I or II, and 5 were stage III or IV. It is encouraging that responses were seen among 2 patients who were refractory to their prior therapy.

A relationship between response to lenalidomide and the development of a skin rash is suggested by the results. Single-agent lenalidomide has been reported to cause rash in about 30% of patients in various studies.[31,37-39] To our knowledge, rash has not previously been reported as predictive of response to lenalidomide treatment in other hematological malignancies. The early onset of rash among responders in this study is intriguing, and suggests that rash could be an early predictor of response. The first month of treatment with lenalidomide has previously been identified as the most common time of rash onset in general among multiple myeloma and amyloidosis patients.[37] The mechanism of lenalidomide-induced rash remains unclear. Characteristic rashes have been found with other agents, such as erlotinib and cetuximab when treating various solid malignancies, and in some cases the severity of rash has been associated with improved survival.[40,41]

Lenalidomide has proven to be a well-tolerated drug, with clinical efficacy in a variety of malignancies both as monotherapy and in combination. It has an acceptable safety profile alone or when combined with a variety of other agents, including dexamethasone,[27] melphalan,[42] and rituximab.[43] Lenalidomide, by virtue of its

oral dosing and tolerable side effect profile, also lends itself to the setting of maintenance therapy after remission induction, and its use in this fashion is being actively investigated. Further investigations therefore are warranted within this indication.

CONFLICT OF INTEREST DISCLOSURES

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