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ORIGINAL REPORT

Phase II Trial of the Oral Mammalian Target of Rapamycin Inhibitor Everolimus in Relapsed or Refractory Waldenström Macroglobulinemia

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ABSTRACT

Purpose
The phosphatidylinositol 3-kinase/mammalian target of rapamycin (mTOR) signal transduction pathway controls cell proliferation and survival. Everolimus is an oral agent targeting raptor mTOR (mTORC1). The trial's goal was to determine the antitumor activity and safety of single-agent everolimus in patients with relapsed/refractory Waldenström macroglobulinemia (WM).

Patients and Methods
Eligible patients had measurable disease (immunoglobulin M monoclonal protein > 1,000 mg/dL with > 10% marrow involvement or nodal masses > 2 cm), a platelet count more than 75,000 × 10^6/L, a neutrophil count more than 1,000 × 10^6/L, and a creatinine and bilirubin less than 2 × the laboratory upper limit of normal. Patients received everolimus 10 mg orally daily and were evaluated monthly. Tumor response was assessed after cycles 2 and 6 and then every three cycles until progression.

Results
Fifty patients were treated. The median age was 63 years (range, 43 to 85 years). The overall response rate (complete response plus partial remission [PR] plus minimal response [MR]) was 70% (95% CI, 55% to 82%), with a PR of 42% and 28% MR. The median duration of response and median progression-free survival (PFS) have not been reached. The estimated PFS at 6 and 12 months is 75% (95% CI, 64% to 89%) and 62% (95% CI, 48% to 80%), respectively. Grade 3 or higher related toxicities were observed in 56% of patients. The most common were hematologic toxicities with cytopenias. Pulmonary toxicity occurred in 10% of patients. Dose reductions due to toxicity occurred in 52% of patients.

Conclusion
Everolimus has high single-agent activity with an overall response rate of 70% and manageable toxicity in patients with relapsed WM and offers a potential new therapeutic strategy for this patient group.

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INTRODUCTION

Waldenström macroglobulinemia (WM) is a distinct B-cell lymphoproliferative disorder characterized by bone marrow infiltration with lymphoplasmacytic cells, along with demonstration of an immunoglobulin M (IgM) monoclonal gammopathy.[1-4] The overall incidence of WM is approximately 3 per million persons each year.[5-7] Despite continuing advances in the therapy of WM, the disease remains incurable, thereby necessitating the development and evaluation of novel therapeutics.[3,8,9]

Tumorigenesis results from synergistic interactions of a network of signal transduction processes, including multiple oncoproteins and tumor suppressors such as Ras, Myc, PKB/Akt, HER-2/neu, p53, and PTEN.[10-12] Overexpression of Akt plays an important role in the progression of hematologic malignancies. The phosphatidylinositol-3-kinase (PI3K) pathway is important to cell survival by its effects on cell proliferation and apoptosis.[13-17] The PI3K/Akt/mTOR pathway is regulated at several critical junctures.[18] One of these involves the mammalian target of rapamycin (mTOR) itself. This kinase exists in mutually exclusive complexes with

either the rapamycin-sensitive regulatory associated protein of TOR (Raptor) or rapamycin-insensitive companion of TOR (Rictor).[19-21] The rapamycin analogs temsirolimus and everolimus are now approved agents for the treatment of renal cell carcinoma.[22,23] Our preclinical studies in lymphoma and multiple myeloma cell lines and primary samples have demonstrated that mTOR inhibition with rapamycin has a significant antiproliferative effect on malignant B cells.[24,25] Clinical trials of temsirolimus for mantle-cell lymphoma and other B-cell non-Hodgkin's lymphomas demonstrated overall response rates of 40%.[26-28]

We have previously demonstrated that Akt, a key member of the PI3K pathway upstream of mTOR is constitutively activated in malignant B cells from the bone marrow of patients with WM.[29] Incubation of these cells in vitro with rapamycin leads to significant cytotoxicity and induction of apoptosis in WM cell lines and patient samples (unpublished data).

These clinical and laboratory studies provided the rationale to perform a phase II clinical trial using single-agent everolimus (Afinitor; Novartis Pharmaceuticals, East Hanover, NJ) to test the efficacy and safety of this agent in patients with relapsed or relapsed/refractory WM.

PATIENTS AND METHODS

This phase II study was conducted through a collaboration of the Mayo Clinic Cancer Center and Dana-Farber Cancer Institute and was approved by both institutional review boards. Patients were eligible for this trial if they had previously received therapy and had experienced relapse or were refractory to their last treatment. Proof of relapse was required by a biopsy within 6 months before enrollment. Patients were required to have symptomatic disease that warrants therapy based on the consensus panel recommendations for therapy in WM.[30,31]

There was no limit on the number of prior therapies. Patients were required to be ≥18 years old and have measurable disease. Measurable disease was defined as at least one lesion with a single diameter of greater than 2 cm by computed tomography or bone marrow involvement with greater than 10% malignant cells and quantitative IgM monoclonal protein greater than 1,000 mg/dL. Patients were to have a life expectancy of more than 3 months; Eastern Cooperative Oncology Group performance status of 0, 1, or 2; absolute neutrophil count more than $1,000 \times 10^6$/L; platelets more than $75,000 \times 10^6$/L; hemoglobin more than 8 g/dL; serum creatinine less than 2 × the upper limit of normal (UNL); serum bilirubin less than 2 × UNL (if total bilirubin > 2 × ULN then a direct bilirubin of <1.5 × UNL was acceptable); AST ≤ 3 × ULN (≤ 5 × ULN if liver involvement is present). Patients could not have known HIV infection.

Patients were treated with a dose of 10 mg of everolimus orally in the fasting state. Treatment was daily, and 4 weeks was considered one cycle. A CBC was performed each week during the first cycle and with each subsequent cycle. If the platelet count was more than $40,000 \times 10^6$/L and the absolute neutrophil count more than 1000×10^6/L and there were no grade 3 or 4 nonhematologic toxicities (National Cancer Institute Common Toxicity Criteria version 3.0), the full dose of everolimus was prescribed for the next cycle. Patients who did not meet the re-treatment criteria had the dose held until recovery and followed by a stepwise dose modification to 5 mg daily, 5 mg every other day, and 5 mg every third day. Patients were not to receive prophylactic WBC growth factors to maintain dosing, but could receive them at physician discretion if neutropenia developed. Erythropoietin treatment for anemia was also permitted at physician discretion.

Patients were restaged for tumor response after two and six cycles and every three cycles thereafter. Responses for WM were categorized using the Consensus recommendations for response.[30,32] However, progression was

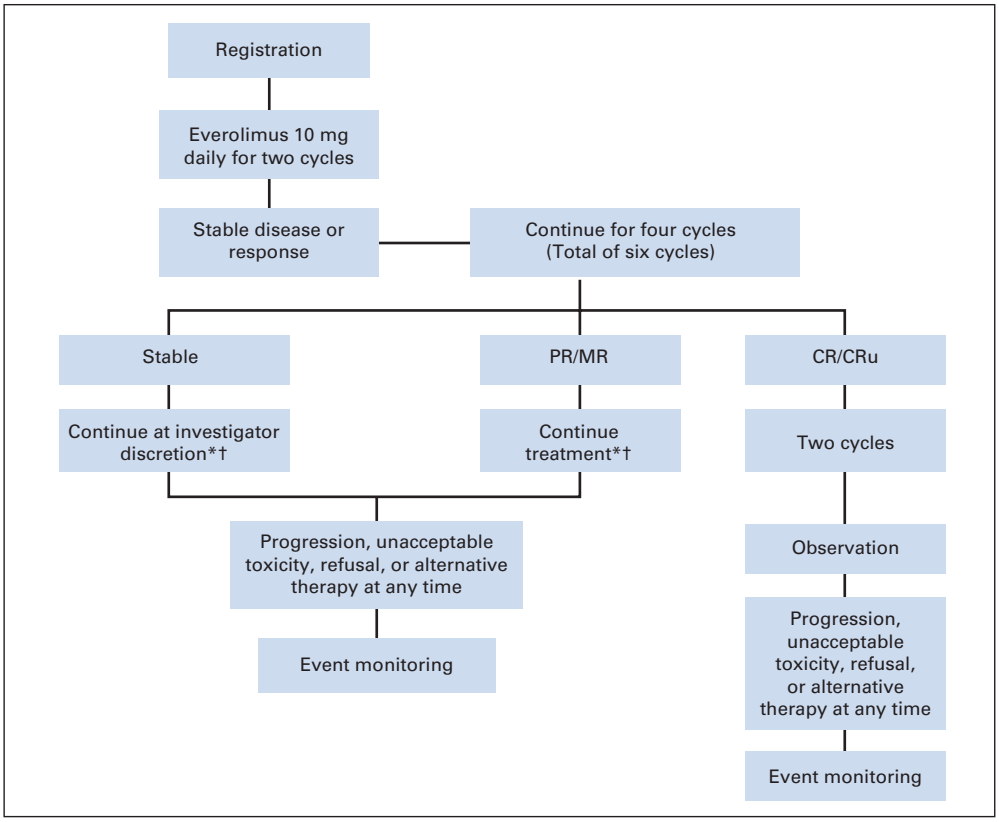

Fig 1. CONSORT diagram. (*) Patients who subsequently obtain complete remission (CR)/CR unconfirmed (CRu) receive two additional cycles and follow the schema for CR/CRu. (†) If discontinued per physician discretion where patient is still responding and has not refused follow-up or gone to other treatment, follow in observation. Patients with macroglobulinemia and who obtain a minor response should follow the schema as a partial response (PR). One cycle = 4 weeks. MR, minimal remission.

measured as a confirmed 25% increase in the monoclonal protein from baseline and not from nadir. Patients who progressed or had unacceptable toxicity at any time went off study. Patients with stable disease or better after six cycles continued treatment per physician discretion until progression or toxicity.

Adverse events were graded using the National Cancer Institute Common Toxicity Criteria (version 3.0). Attributable toxicity was defined as an adverse event classified as being possibly, probably, or definitely related to study treatment.

Statistical Design

This phase II study used a one-stage three-outcome design[32a] to assess the efficacy and safety of everolimus in patients with WM. A response was defined to be either a complete remission (CR) or partial remission (PR). Minimal response (MR) was also recorded based on the International Consensus recommendations. Twenty-seven evaluable patients were required to test the null hypothesis that the true response rate for this regimen is at most 5% versus the alternative hypothesis that the true response rate is 20% or greater. The study had 82% power, with a 4% type I error rate. A patient was considered evaluable for response if they were eligible and received treatment. At the time of the final analyses, a total of four or more responses were required in the first 27 evaluable patients to indicate that this regimen warrants further evaluation in this patient population. The response rate was estimated by the number of responses divided by the number of evaluable patients. A 95% exact binomial CI for the true response rate was calculated, assuming that the number of responses was binomially distributed. On the basis of promising early results and to allow access to everolimus, additional patients with WM were accrued to this study for a total of 50 eligible patients. This allowed us to better assess the response rate and toxicity profile of everolimus in patients with WM. The decision rule was not modified, so power was not calculated for 50 patients. Including these additional patients reduces the maximum width of the exact binomial CI for the true response rate from 0.39 to 0.29.

Duration of response (DR) was defined as the time from the date of documented response to the date of progression. Time to progression (TTP) was defined as the time from the date of registration to the date of progression. Patients who died without disease progression were censored at the date of their last evaluation. If a patient died without documentation of disease progression, the patient was considered to have had disease progression at the time of death unless there was sufficient documented evidence to conclude that progression did not occur before death. Progression-free survival (PFS) was defined as the time from the date of registration to the date of progression or death due to any cause. Patients who were still receiving treatment at the time of these analyses were censored at the date of their last evaluation. Overall survival (OS) was defined as the time from the date of registration to the date of death resulting from any cause. The distributions of these time-to-event end points were each estimated using the Kaplan-Meier method.[33] The Wilcoxon rank sum test was used to evaluate the relationship between response status and patient characteristics (age, baseline hemoglobin, and so on).

RESULTS

Patient Characteristics

A total of 51 patients were enrolled onto this trial from April 2006 to August 2008 (see CONSORT diagram in Fig 1). One patient never received treatment and was classified as a cancel, leaving 50 patients eligible for analysis (Table 1). All but two patients (96%) had received prior rituximab-based therapy and 64% of patients had received prior alkylator based therapies. Fifty percent of the patients were intermediate or high risk on the basis of the international scoring system for WM.[34]

Table 1. Baseline Characteristics

Characteristic	No.	%
Age, years		
Median	63	
Range	43-85	
Sex, male	42	84
Performance status		
0	33	66
1	13	26
2	4	8
International scoring system for WM*		
Low	11	50
Intermediate	7	32
High	4	18
Baseline IgM level, mg/dL		
Median	3,320	
Range	323-7,410	
Baseline serum M protein, g/dL		
Median	2.0	
Range	0.2-10.5	
Baseline hemoglobin, g/dL		
Median	11.5	
Range	8.7-17.4	
Grade 0	9	18
Grade 1 (≥ 10g/dL but less than normal)	32	64
Grade 2 (8 to < 10 g/dL)	9	18
Baseline platelet count, 10^9/L		
Median	247	
Range	75-419	
Bone marrow percent involvement†		
Median	50	
Range	0-90	
β_2-microglobulin > 3.0 mg/dL*	12	55
"B" symptoms	22	44
Nodal disease	36	72
No. of extranodal sites		
0-1	38	76
≥ 2	12	24
No. of prior therapy treatments		
Median	3	
Range	1-11	
1	12	24
2	10	20
3	5	10
4	9	18
≥ 5	14	28
Type of prior therapy		
Rituximab	48	96
Alkylator (including cyclophosphamide, chlorambucil CHOP, CVP)	32	64
Purine nucleoside analog (including fludarabine, cladribine, pentostatin)	16	32
Bortezomib	9	15
Others (including thalidomide, sildenafil, imatinib, interferon, alemtuzumab, radioimmunotherapy, dexamethasone)	20	40
Stem-cell transplantation	3	6

Abbreviations: WM, Waldenström macroglobulinemia; IgM, immunoglobulin M; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone.

*Twenty-eight patients are missing β_2-microglobulin and international scoring system for WM.

†Two patients are missing bone marrow percent involvement.

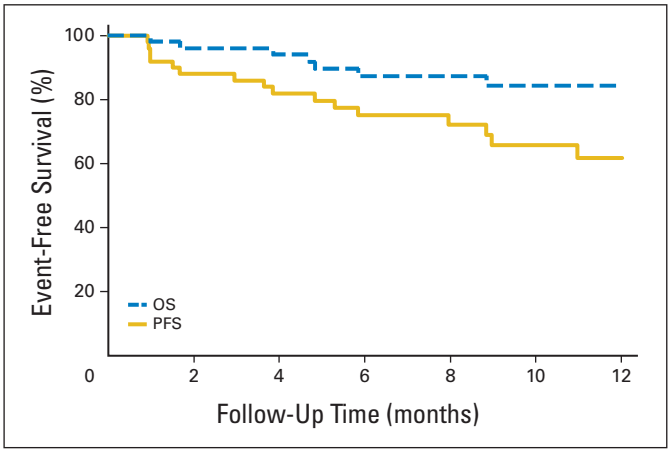

Fig 2. Kaplan and Meier curve of progression free-survival (PFS) and overall survival (OS) in 50 patients with relapsed Waldenström macroglobulinemia treated with single-agent everolimus.

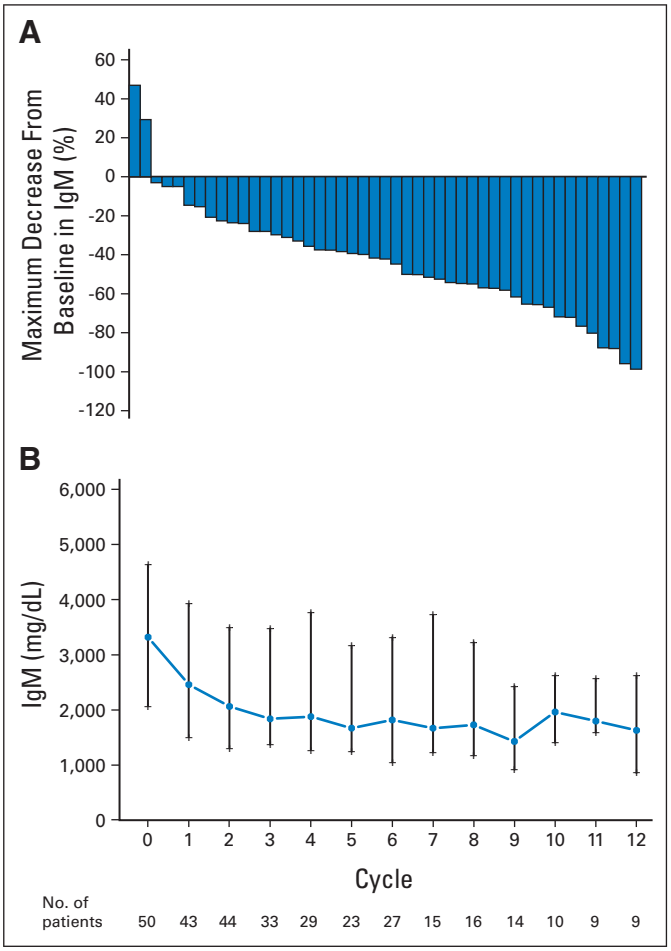

Fig 3. (A) Maximum percent decrease from baseline in immunoglobulin M (IgM) over all cycles in response to everolimus per patient. (B) Median and interquartile range for IgM values in response to everolimus per each cycle.

Clinical Outcomes

Of the 50 patients who received therapy, 42% (21 of 50 patients; 95% CI, 26% to 55%) of patients achieved a PR; there were no CRs. In addition, 28% of patients (14 of 50 patients) achieved an MR, for an overall response rate of 70% (95% CI, 55% to 82%). Stable disease occurred in 16% of patients (eight of 50 patients), and 8% (four of 50 patients) experienced disease progression on therapy without response (primary progression). Three patients went off study before the first response evaluation and were considered nonresponders. One of these died and two refused further therapy. The median TTP, DR, PFS, and OS for the entire study population have not been reached. The estimated PFS at 6 and 12 months is 75% (95% CI, 64% to 89%), and 62% (95% CI, 48% to 80%), respectively (Fig 2).

The 21 patients who achieved a PR responded after a median of 2 months (range, 1 to 10 months) of treatment. The median DR for these patients has not yet been reached, and 16 of these patients remain in response after a median follow-up of 6.6 months (range, 1.0 to 18.2+ months). There was no association between response status and age, hemoglobin level at baseline, IgM level at baseline, or β_2-microglobulin level at baseline.

All but two patients had a decrease in their serum IgM (Figs 3A and 3B). The hemoglobin initially decreased, likely as a result of the myelosuppressive effect of everolimus, but then increased steadily with subsequent cycles after the antitumor effect became evident (Fig 4). Patients with lymphadenopathy also had responses (Fig 5).

Twenty-one patients remain on therapy after a median of 7.3 months (range, 4.1 to 25.0 months) of treatment; 29 patients have discontinued therapy with a median time to discontinuation of active treatment of 7.3 months (95% CI, 4.5 to 11.0 months). To date, 26% of patients (13 of 50 patients) have experienced disease progression, and 14% (seven of 50 patients) have died. Four of the deaths were due to progressive WM. Three deaths, one each due to sepsis, pneumonia, and congestive heart failure, were assessed to be unrelated to everolimus. The median follow-up for the patients who remain alive is 11.5 months (range, 3.2 to 30.4 months).

Per the original protocol, progression was defined as a greater than 25% increase in IgM over baseline on two measurements within a 1-month period. We also examined an alternative definition of progression, based on more recent criteria that define progression as a greater than 25% increase over the lowest recorded IgM value on two consecutive measurements.[35] There were 14 patients who fit this second definition for progression while on active treatment after a median of 5.8 months (range, 1.0 to 17.8 months). Four of these patients experienced disease progression on the same day by both definitions. One patient experienced disease progression 112 days earlier using the lowest recorded value compared with baseline. Nine of these patients have not experienced disease progression with continued everolimus dosing by an increase from baseline a median of 99 days (range, 0 to 279 days) after having a greater than 25% increase over the lowest recorded value. In fact, two of these patients have returned to a status of response.

Safety and Tolerability

Grade 3 or higher toxicities (adverse events considered at least possibly related to everolimus) were observed in 56% of patients (28 of 50 patients; Table 2). There were 21 grade 3 and seven grade 4 toxicities. Sixteen percent of patients developed thrombocytopenia that was either grade 3 or grade 4. It should be recalled that patients could enroll on the trial with grade 1 thrombocytopenia, and patients continued full dosing as long as the platelet count was

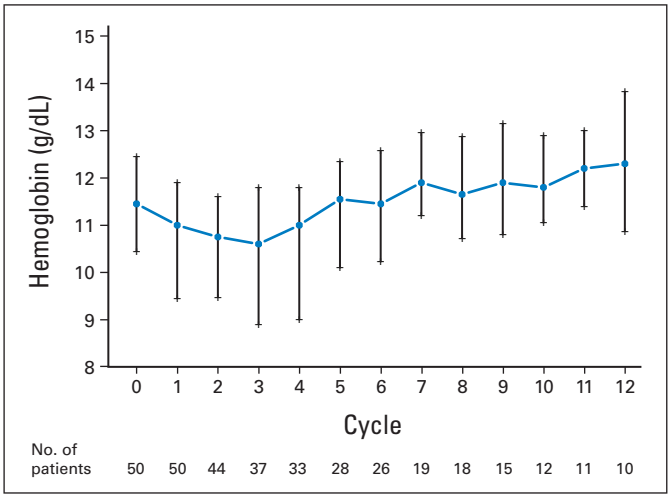

Fig 4. Median and interquartile range for hemoglobin values in response to everolimus per each cycle. The lowest hemoglobin value per patient for each cycle was used for this analysis.

at least 40,000 $\times$ 10^6/L on day 1 of each cycle. This likely explains the level of thrombocytopenia observed on this trial. Pulmonary toxicity did occur on this trial and was manageable. One patient developed pulmonary infiltrates, cough, and mild shortness of breath beginning at cycle 2 of everolimus consistent with grade 2 pulmonary toxicity. The study drug was held for 1 month with complete resolution of his symptoms without the need for oxygen or corticosteroid therapy. Another patient developed grade 2 cough and dyspnea during cycle 4 and went off study. His symptoms completely resolved in 2 weeks without any treatment. In addition, three patients (6%) had grade 3 pulmonary toxicity (pleural effusion and dyspnea, n = 1; dyspnea, n = 2). The patient with the pleural effusion also had pulmonary infiltrates, shortness of breath, and cough. These symptoms developed after cycle 4 of everolimus. Bronchoscopy was negative for tumor or infection; therefore, the symptoms were assumed to be due to everolimus toxicity, and the drug was discontinued. No corticosteroids or oxygen therapy were required, and he completely recovered in 3 months.

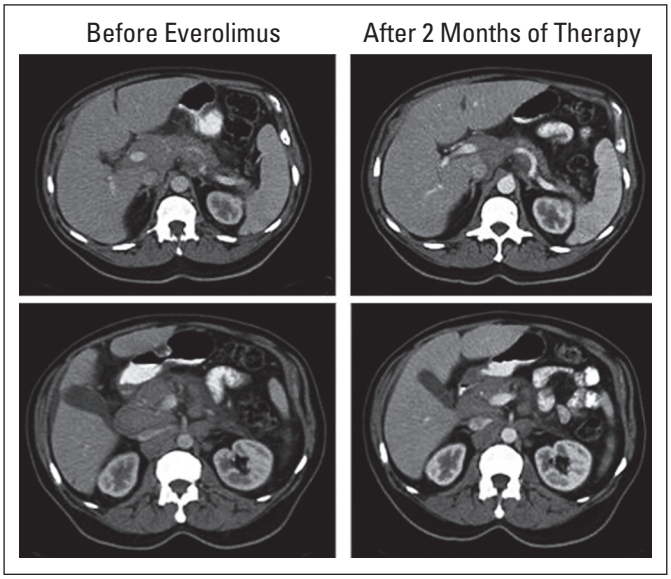

Fig 5. Computed tomography scan before and after two cycles of everolimus showing a significant decrease in the retroperitoneal lymph nodes after therapy. The patient also had a more than 60% reduction in the immunoglobulin M paraprotein after two cycles of therapy.

Table 2. All Grade 3 and 4 Toxicities (adverse events at least possibly related) to Everolimus

Toxicity	Grade 3		Grade 4	
	No.	%	No.	%
Hematologic				
Anemia	8	16	1	2
Leukopenia	8	16	2	4
Neutropenia	6	12	1	2
Thrombocytopenia	6	6	5	10
Infection/febrile neutropenia				
Pneumonia	1	2		
Upper airway infection	1	2		
Sepsis	1	2		
Metabolic/laboratory				
Hypercholesterolemia	2	4		
Hyperglycemia	2	4		
Hypertriglyceridemia	1	2		
Hypoglycemia	1	2		
Hyponatremia	1	2		
Pulmonary				
Dyspnea	2	4		
Pleural effusion with dyspnea	1	2		
Constitutional symptoms				
Fatigue	4	8	1	2
Gastrointestinal				
Diarrhea	3	6		
Mucositis, oral ulcers	4	8		
Maximum overall grade	21	42	7	14

NOTE. Maximal overall toxicity grade refers to the number of patients that had the respective grade toxicity across all toxicity types.

Across all patients, the median dose of everolimus received per month on study was 280 mg both in responding patients and those that did not respond. Fifty-six percent of patients (28 of 50 patients) had dose reductions or treatment delays. Dose reductions due to toxicity occurred in 52% of patients (26 of 50 patients). Dose delays occurred in 30% of patients (15 of 50 patients) and were due to cytopenia (n = 4), pneumonia (n = 3), mucositis (n = 2), diarrhea (n = 2), and in one patient each, for rash, sore throat, pulmonary infiltrates, and pulmonary fibrosis. Patients were able to receive a median of two cycles of everolimus at full dose (range, one to 27 cycles). Eighty-two percent of patients (41 of 50 patients) received 10 mg daily for at least the first cycle of treatment, 10% of patients (five of 50 patients) required dose reductions in cycle 1, and 8% of patients (four of 50 patients) went off study during cycle 1 (two patients refused further therapy due to toxicity, one refused without a reason, and one patient withdrew consent and elected hospice care). Two additional patients went off study after completing cycle 1 because of disease progression and death on study. Of the 39 patients who completed cycle 1 at the full dose level and continued treatment, 21 patients eventually required a dose reduction in subsequent cycles, and 13 patients had the treatment delayed because of either adverse events

or hospitalization. Of the 26 patients who had dose reductions, 21 patients were reduced to 5 mg daily and five patients were reduced to 5 mg every other day. Responses were maintained after being dose reduced, and in seven patients, a treatment response (two PRs and five MRs) occurred after dose reduction to 5 mg daily.

DISCUSSION

Major advances in the treatment of patients with both lymphoma and plasma cell malignancies have occurred in recent years.[36] Current therapies used in the upfront or relapsed settings include alkylator agents (eg, chlorambucil), nucleoside analogs (cladribine or fludarabine), and the monoclonal antibody rituximab.[37-41] Although the overall response rate (ORR) is high with initial therapy, in the salvage setting the ORR is in the range of 30% to 40%, with a median response duration of 1 year or less.[38,42] The use of fludarabine or alkylating agents in combination therapy in these patients induces high response rates, but these regimens have significant toxicity in older adults.[30,43] The use of bortezomib as a single agent in WM has been tested in two phase II clinical trials in relapsed WM.[44,45] Chen et al[44] treated 27 patients with bortezomib and determined a clinical benefit rate of 78% including MR, with major responses (PR or better) observed in 44% of patients. Sensory neuropathy occurred in 74% of patients (20 of 27 patients), including five patients with grade 3. The neuropathy typically occurred after two to four cycles of therapy. Studying other novel therapeutic agents that have less toxicity and that target specific signaling pathways in WM is warranted.

WM is a distinct disease that necessitates the development of agents tailored specifically for this particular disorder. We have previously shown that WM tumor cells harbor constitutive activation of Akt.[29] On the basis of this and preclinical testing of everolimus in WM cell lines and patient samples, we tested the activity of this agent in patients with relapsed or relapsed and refractory disease.

The ORR (CR + PR+ MR) with everolimus in this study was 70%, and an additional 16% of patients had stabilization of their disease while receiving therapy. The median DR and PFS have not yet been reached in this study population. Everolimus thus represents one of the more potent therapeutic agents in relapsed WM. Tumor responses to everolimus were durable and tended to be apparent after 2 months of therapy. This is encouraging because the median DR with single agents such as rituximab or bortezomib in patients with relapsed or refractory WM is approximately 12 months or less.[44-47] In our study, 62% of patients were alive and remain progression free at 12 months.

The tolerability of oral everolimus proved acceptable, with manageable toxicities. Patients who developed pulmonary toxicity can be managed by stopping the agent until the symptoms clear and then restarting at a lower dose. It is always prudent to rule out infection or tumor involvement of the lung before attributing the symptoms to drug toxicity. In general, responding patients can be treated for long periods of time with the daily everolimus after individualized dose adjustments. In future studies, it would be reasonable to follow the dosing plan from this study by initiating single-agent everolimus at the 10-mg daily dose with dose reductions to 5 mg daily or 5 mg every other day. Alternatively, patients could be initiated at the 5-mg daily dose and increase to 10 mg daily as tolerated. Additional studies to clarify the optimal dose are required. Patients who experience toxicities in the first cycle should be encouraged to remain on drug at reduced doses, because in this study, patients who had their dose reduced maintained their responses at the lower dose, and seven responses occurred at 5-mg daily doses.

This level of single-agent antitumor activity for an oral agent now warrants further studies in new, untreated WM, and especially in combination with other active agents or as maintenance. The lack of CRs with everolimus in these patients with relapsed or relapsed/refractory WM suggests that some of the lymphoplasmacytic cells might be resistant to mTOR inhibition. Further studies to understand mechanisms of mTOR resistance in these patients will help to rationally combine other agents with mTOR inhibitors to enhance the response.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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