A Phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma

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Everolimus is an oral antineoplastic agent that targets the raptor mammalian target of rapamycin (mTORC1). The phosphatidylinositol 3-kinase/mTOR signal transduction pathway has been demonstrated to be activated in tumor samples from patients with Hodgkin lymphoma (HL). The goal of this trial was to learn the antitumor activity and toxicity of everolimus in patients with relapsed/refractory HL. Patients were eligible if they had measurable disease, a platelet count >75,000, and an absolute neutrophil count >1,000. Patients received everolimus 10 mg PO daily. Dose reductions were allowed. Response was assessed after two and six cycles and then every three cycles until progression. Patients could remain on drug until progression or toxicity. Nineteen patients were enrolled. Median age was 37 years (range, 27–68). Patients had received a median of six prior therapies (range, 3–14) and 84% had undergone prior autologous stem cell transplant. The ORR was 47% (95% CI: 24–71%) with eight patients achieving a PR and one patient achieving a CR. The median TTP was 7.2 months. Four responders remained progression free at 12 months. Patients received a median of seven cycles of therapy. Of the 19 patients, one remains on therapy at 36 months; the others went off study because of progressive disease (16), toxicity (1), and death from infection (1). Four patients experienced a Grade 3 or higher pulmonary toxicity. Everolimus has single-agent activity in relapsed/refractory HL and provides proof-of-concept that targeting the mTOR pathway in HL is clinically relevant. Am. J. Hematol. 85:320–324, 2010. © 2010 Wiley-Liss, Inc.

Introduction

Hodgkin Lymphoma (HL) is diagnosed in ~8,500 new patients each year in the US [1]. HL is curable with frontline therapy in a high percentage of patients. Many of the patients that fail initial therapy can be salvaged with high-dose therapy and stem cell transplant (SCT) [2,3]. However, despite these impressive treatment advances, at least 15% of patients fail these treatments and require additional therapy. There is a need for new agents for this important patient population. A pathologic hallmark of HL is the Reed Sternberg cell. Substantial research has been devoted for understanding the molecular pathways that drive the proliferation of this malignant cell. The PI3K/Akt/mTOR pathway has become an important focus for cancer therapeutics [4–6] and is regulated at several critical junctures [7]. One of these involves the mammalian target of rapamycin (mTOR). This kinase exists in mutually exclusive complexes with either Raptor (regulatory associated protein of TOR, mTORC1) or Rictor (rapamycin-insensitive companion of TOR, mTORC2).

Rapamycin (sirolimus), a macrolide antibiotic [8], is the parent drug of the class of mTOR inhibitors and was approved as an oral immunosuppressant to prevent acute rejection in solid organ transplantation in 1999 [9]. Sirolimus binds to the immunophilin FK506-binding protein 12 (FKBP12) with the resulting complex directly inhibiting mTOR. This inactivation of mTOR results in G1 cell cycle arrest or apoptosis. mTOR inhibitors have demonstrated activity against lymphoma cell lines in vitro [10]. Although there is an extensive human experience with rapamycin with organ transplantation, there has been limited experience with rapamycin as an anticancer agent. Three analogs of rapamycin—temsirolimus, everolimus, and deforolimus [11]—are currently in clinical trials. Initial results demonstrate that mTOR inhibitors are well tolerated and may induce prolonged stable disease and tumor regressions in cancer patients. Temsirolimus (Torisel™; Wyeth) is an ester of rapamycin that is available as an intravenous or oral formulation. The US FDA approved temsirolimus for renal cell carcinoma based on demonstrated antitumor activity at a dose of 25 mg IV weekly [12,13]. Single-agent temsirolimus has shown an overall response rate (ORR) of ~40% with a median duration of response and time to progression of 6 months in two trials for relapsed mantle cell non-Hodgkin lymphoma (MCL) [14,15]. A randomized Phase III trial in relapsed MCL demonstrated a higher ORR with temsirolimus compared to standard chemotherapy, although the ORR in that trial was only 22% [16]. Everolimus (Affinitor™, Novartis) is an oral mTOR inhibitor that is approved in Europe as an immunosuppressive agent for solid organ transplantation and in the US for relapsed renal cell carcinoma [17]. A Phase I trial in hematological malignancies demonstrated safety of everolimus at a dose of 10 mg daily [18].

HL cells have been demonstrated to have activation of the PI3K pathway [19,20] and may be susceptible to inhibition of this pathway. Constitutively active NF-kB promotes cell survival and proliferation in HL cell lines [21], and TSC/mTOR signaling activates NF-kB survival signaling [22].

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TABLE I. Patient Characteristics (n = 19)

Characteristic	Number (%)
Age, years	
Median	37
Range	27–68
Sex, male	10 (53)
Performance status	
0	4 (21)
1	12 (63)
2	3 (16)
Lymphoma stage at study entry	
1,2	3 (16)
3,4	16 (84)
Disease type	
Classical HL	19
Prior stem cell transplant	16 (84)
B-Symptoms	1 (5)
Number of extranodal sites	
0–1	11 (58)
≥2	8 (42)
Number of prior therapy treatments	
Median (range)	6 (3–14)
Type of prior therapy	
Radiotherapy	14 (74)
Stem cell transplant	16 (84)

The Akt-mTOR-4EBP1 pathway has been demonstrated to be constitutively active in HL cell lines [19]. Two studies have examined the effects of mTOR inhibition in HL. Everolimus downregulated the truncated isoform of transcription factor CCAAT enhancer binding protein B in HL cell lines, resulting in inhibition of constitutive NF-kB survival signaling [20]. Temsirolimus induced cell cycle arrest and was followed by autophagy in HL cell lines, suggesting a class effect with mTOR inhibitors [23].

On the basis of this preclinical work and the excellent toxicity profile of everolimus in previous studies, we performed this Phase II trial of single-agent everolimus in patients with relapsed HL who had already undergone or were deemed ineligible for SCT.

Patients and Methods

A two-stage, Phase II study was conducted to assess the proportion of patients with rare lymphomas, including relapsed or refractory HL, who achieved a partial response (PR) or better after treatment with single-agent everolimus. This study was conducted through the Mayo Clinic Cancer Center and was approved by the Mayo Clinic Institutional Review Board. Patients were eligible if they had previously received therapy and had relapsed or were refractory to their last treatment. There was no limit on the number of prior therapies. Patients were required to have failed or be ineligible for SCT. The relapse was required to have been biopsy proven within 6 months of enrollment. Patients were to be ≥18 years old, have measurable disease by CT or MRI with at least one lesion >2 cm diameter, have a life expectancy of >3 months; ECOG performance status < 2; absolute neutrophil count (ANC) > 1,000× 10(6)/L; platelets > 75,000× 10(6)/L; hemoglobin > 8 g/dL; serum creatinine < 2× the upper limit of normal (ULN); serum total bilirubin < 2 ULN (or direct bilirubin of <1.5 UNL); aspartate aminotransferase (AST) ≤ 3 × ULN (≤5 × ULN if liver involvement is present). The HL patients represented a planned subset of a broader cohort of patients including uncommon diseases often not enrolled in clinical trials because of their rarity, including posttransplant lymphoproliferative disorders, CNS lymphoma, and peripheral T-cell lymphoma; only the HL patients are included in this report.

Patients received 10 mg of everolimus orally in the fasting state daily; 4 weeks was considered one cycle. A CBC was performed weekly during the first cycle and on Day 1 of each subsequent cycle. At the time of retreatment, the full dose of everolimus was prescribed if the platelet count was >40,000 × 10(6)/L, the ANC > 1000× 10(6)/L, and there were no Grade 3 or 4 nonhematological toxicities (NCI Common Toxicity Criteria version 3.0). Patients who did not meet the retreatment criteria had the dose held until recovery, followed by a stepwise dose modification to 5 mg daily, 5 mg every other day, and 5 mg every third day. Patients could receive white blood cell growth factors if neutropenia developed. Erythropoietin treatment for anemia was permitted.

Patients were restaged for response after two and six cycles and every three cycles thereafter. Responses were categorized using the International Workshop Criteria [24]. Patients who progressed or had unacceptable toxicity at any time discontinued therapy. Patients with stable disease after six cycles continued treatment at physician discretion. Patients who had a CR on Cycle 6 or later were to receive two additional cycles and then could either discontinue everolimus or continue at physician discretion. Patients with PR after six cycles continued until progression or toxicity.

Statistical design. This Phase II study used a modified two-stage Simon design [25] to assess the efficacy and tolerability of everolimus in patients with uncommon lymphomas, where the modification is that accrual was not suspended for the Stage I analysis. Thirty-seven evaluable patients were required to test the null hypothesis that the true ORR for this regimen is at most 5% versus the alternative hypothesis that the true ORR is 20% or greater. The study had 90% power, with a 9% Type I error rate. A patient was considered evaluable for response if they received treatment. The response rate was estimated by the number of responses divided by the number of evaluable patients. A 95% binomial confidence interval for the true ORR was calculated.

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 registration to the date of progression. Patients who had not yet progressed were censored at the date of their last evaluation. Time to discontinuation of active treatment was defined as the time from registration to the date the patient discontinued treatment. 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 registration to death from any cause. The distributions of these time-to-event endpoints were estimated using the Kaplan-Meier method [26]. Toxicity was defined as an adverse event classified as being possibly, probably, or definitely related to study treatment.

Results

Patient characteristics. A total of 41 patients were enrolled within the uncommon lymphoma group of which 17 patients with HL were enrolled from August 2005 to May 2007 (Table I). An additional two patients with HL were enrolled in a compassionate use extension of this protocol. These 19 patients are the focus of this analysis. The median time from diagnosis of HL to enrollment was 3.5 years (range, 1–26.5), and the median TTP from last therapy was 4 months (range, 1–26).

Clinical outcomes. The ORR was 47% (9/19; 95% CI: 24–71%) with eight PR and one CR. (Fig. 1). Eight additional patients had stable disease and two progressed by the first assessment, one with prior mTOR inhibitor exposure. These results met the study design criteria for success at both the interim and final analysis time points. Tumor responses occurred relatively rapidly, with a median time to response for responders of 3.6 months (range, 2.1–19.3). Four responses occurred after two cycles, one response after three cycles, and four after six cycles. Fifty percent (8/16) of the patients with a history of a prior SCT responded. The median DR for the responders (CR/PR) was 7.1 months (95% CI: 3.9–14.8) and four responders remained progression free at 12 months.

Overall, 16 patients have had disease progression and eight patients have died (Fig. 2). Six patients died from disease progression. One patient died without documented disease progression due to streptococcal pneumonia while on study and one patient died from unknown causes after going off study and receiving additional therapy elsewhere. The median follow-up on living patients was 24.0 months (range, 2.1–35.8 months). The median TTP for all patients was 7.2 months (95% CI: 5.9–9.5 months); the median PFS was 6.2 months (95% CI: 5.9–9.5 months); and the median OS from study entry was 25.2 months (95% CI: 13.0 months–upper CL not yet available).

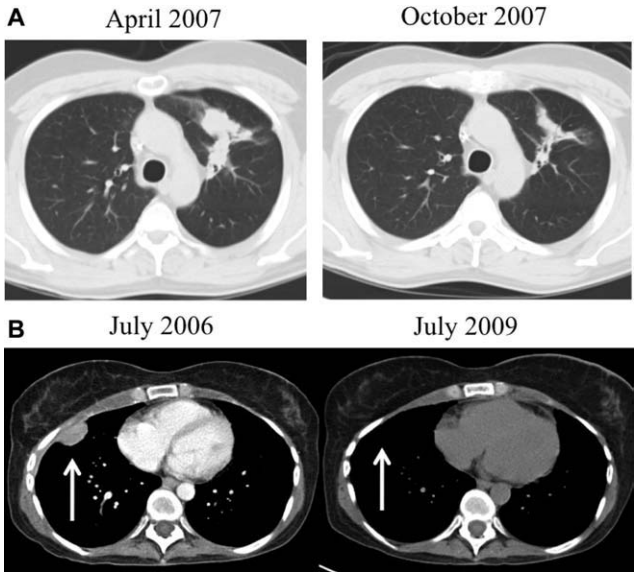


Figure 1. Computed tomography scans of two patients with relapsed Hodgkin lymphoma who responded to single-agent everolimus. (A) Patient with left lung parenchymal relapsed HL who obtained a partial response to everolimus. He had a 10-month time to progression. (B) Patient with right chest wall involvement has experienced a complete response to everolimus. She has been on study for 36+ months.

Safety and tolerability. Eleven patients experienced a Grade 3 or higher hematologic adverse event (six Grade 3 and five Grade 4) and 11 patients experienced a Grade 3 or higher nonhematologic adverse event (eight Grade 3, two Grade 4, and one Grade 5). Focusing on adverse events at least possibly attributable to the study therapy, 10 patients experienced a Grade 3 or higher hematologic toxicity (six Grade 3 and four Grade 4) and six patients experienced a Grade 3 or higher nonhematologic toxicity (five Grade 3 and one Grade 4). Grade 3 or 4 anemia, neutropenia, and thrombocytopenia occurred in 32, 5, and 32% of patients, respectively.

Fourteen patients (74%) had at least one Grade 3/4 toxicity at least possibly related to everolimus. Although most patients experienced toxicity, as described in Table II, the incidence of most of these complications was low and they were manageable with dose reductions. Thrombocytopenia was the cause of most dose reductions and was rapidly reversible with drug delays of typically 1 week. One patient experienced Grade 3 respiratory tract infection. Three patients had Grade 3 pulmonary toxicity (two with dyspnea and one with pleural effusion) and one patient had Grade 4 pulmonary toxicity (pneumonitis). One additional patient experienced Grade 5 pneumonia felt to be unrelated to study treatment.

Patients received a median of 7 months (range, 2–36+) of therapy. Eighteen patients have discontinued treatment for reasons of disease progression (16), inability to restart drug within the limits of the protocol due to development of pneumonia (1), and death from infection (1). One patient remains on study at 3+ years of therapy. The median time to discontinuation of treatment was 5.8 months.

Ten patients (53%) had dose reductions or treatment delays. Dose reductions occurred in eight patients and were due to thrombocytopenia (5), neutropenia (1), rash (1), infection (1), and pulmonary infiltrates (1). Treatment delays occurred in seven patients and were due to thrombocytopenia (4), neutropenia (1), dyspnea (1), diarrhea (1), pneumonia (1), and inability to pick up study drug on schedule (1). All patients completed at least one cycle of therapy and 95% (18/19) of patients tolerated 10 mg daily for the entire first treatment cycle. The median number of cycles at 10 mg daily was five (range 1–20). Of the 16 patients who received more than one cycle at the full dose level, five eventually required a dose reduction.

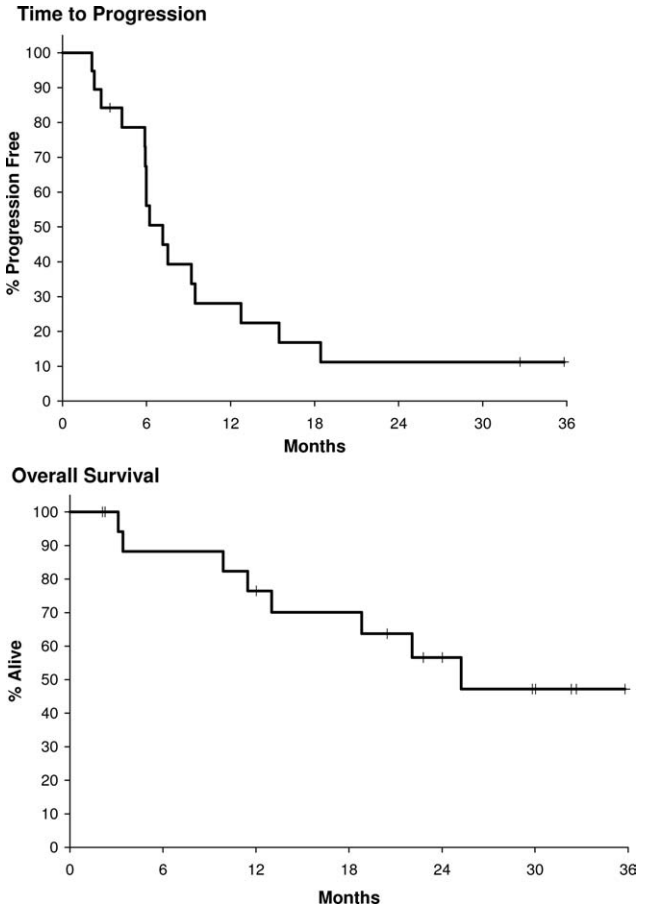


Figure 2. Time to progression and overall survival in 19 eligible patients treated with single-agent everolimus.

TABLE II. Grades 3 and 4 Toxicity (Adverse Events Considered at Least Possibly Related to Everolimus) Observed in 74% (14/19) of Patients

	Grade		
Toxicity	3	4	Total (%)
General			
Rash/Desquamation	1	0	1 (5)
Weight loss	1	0	1 (5)
Hematologic			
Anemia	6	0	6 (32)
Leukopenia	1	0	1 (5)
Neutropenia	1	0	1 (5)
Thrombocytopenia	2	4	6 (32)
Infection			
Myocarditis	1	0	1 (5)
Respiratory tract infection	1	0	1 (5)
Pulmonary			
Effusion–Pleural	1	0	1 (5)
Dyspnea	2	0	2 (10)
Pneumonia	1	1	2 (10)

Discussion

There remains an unmet need for new agents for patients with relapsed or refractory HL; patients who are

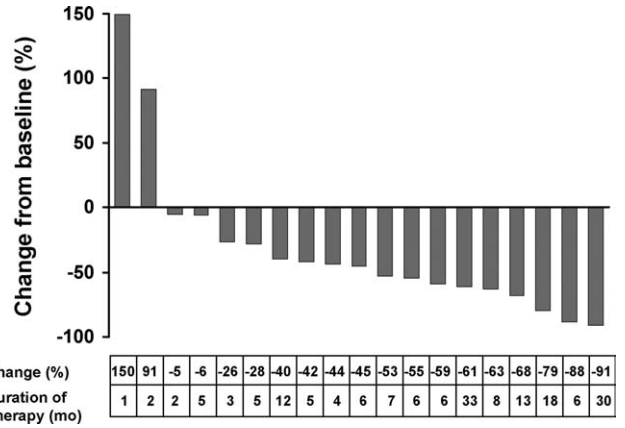
not eligible for transplant or who relapse afterward have a particularly poor prognosis. The rationale to test mTOR inhibitors in HL is based on studies that demonstrate activation of the PI3K pathway in these tumors [19,20]. In the patients with HL, our Phase II trial of everolimus demonstrated a 47% ORR providing proof-of-concept that the mTOR pathway is an important survival pathway for HL cells. This is the first report of the antitumor activity of mTOR inhibitors in relapsed HL. The results are particularly encouraging because of the poor prognostic features of this group of patients. Not only were they heavily pretreated (median six prior therapies), but the median TTP from their most recent therapy was only 4 months and all but one patient had progressed within a year of their prior therapy. These results in HL are similar to the ORR found with mTOR inhibitors for relapsed mantle cell lymphoma [14–16] and relapsed Waldenstrom's macroglobulinemia (WM) [27] and higher than the 18% ORR reported for relapsed small lymphocytic lymphoma [28].

Everolimus and other mTOR inhibitors are generally well tolerated. Some patients in this study were able to tolerate everolimus for years. The majority of patients tolerated everolimus at 10 mg daily for the first cycle but subsequent dose reductions to 5 mg was common; however, the median number of cycles of treatment at full dose was five. The need for dose reductions likely reflects the heavily pretreated nature of these patients. The Phase I/II study of Yee et al. [18], which tested the 5 and 10 mg doses, recommended the 10-mg dose for future studies. Their study only had four patients with NHL (all mantle cell), and no patient responded. The recommended dose from a Phase I trial in children was 5 mg/m^2 [29]. We would recommend subsequent single-agent trials start with 10 mg daily with the option for dose reductions.

mTOR inhibitors can produce hyperlipidemia, especially hypertriglyceridemia that often requires intervention if the patient remains on everolimus for prolonged periods of time. In this study, only 3 of the 19 patients developed Grade 2 hyperlipidemia, and no patients developed Grade 3 or 4 hyperlipidemia. Cardiac transplant patients who are on mTOR inhibitors to prevent rejection also develop hypertriglyceridemia. Celik et al. [30] demonstrated in a small study that this toxicity could be partially treated or controlled with omega-3 fatty acid supplementation at a level of 4 g/day. We did not include omega-3 FA supplements in our trial.

We observed an 11% incidence of Grade 3 dyspnea, a rate similar to that found in other studies with everolimus [31] or temsirolimus [16,32]. Pulmonary symptoms from these drugs are difficult to distinguish from tumor or infection, and both must be ruled out first. The initial presentation is usually asymptomatic interstitial pulmonary infiltrates on CT scans performed while assessing tumor response. We did not reduce or discontinue everolimus unless the patient developed symptoms such as cough or dyspnea on exertion.

Although the ORR in relapsed HL is encouraging, many patients do not respond and responders eventually progress on treatment. As noted in the waterfall cascade of response to therapy (Fig. 3), many patients who do not achieve a PR or CR still may have reductions in tumor size. It is notable that patients with stable disease remained without progression on everolimus for prolonged periods. The encouraging ORR, the ability to induce stable disease, and the novel mechanism of action suggest that combinations of everolimus with other agents may be even more effective. For example, everolimus has antitumor activity in a mouse model of acute lymphoblastic leukemia and was synergistic with vincristine [33]. We have demonstrated



Change (%)	150	91	-5	-6	-26	-28	-40	-42	-44	-45	-53	-55	-59	-61	-63	-68	-79	-88	-91
Duration of Therapy (mo)	1	2	2	5	3	5	12	5	4	6	7	6	6	33	8	13	18	6	30

Figure 3. Maximum change in sum of the products of measurable lesions from baseline in 19 eligible patients treated with single-agent everolimus. The duration of time (in months) that the patient was on study is included in the table demonstrating that patients can obtain clinical benefit for prolonged periods of time even if they do not achieve a partial or complete response.

synergy of mTOR inhibitors with histone deacetylase inhibitors leading to a trial of this combination for patients with relapsed HL [34].

The promising activity of mTOR inhibition also has implications for adjuvant therapy in lymphoma. Armand et al. [35] found that patients with NHL or HL who underwent GVHD prophylaxis with sirolimus after reduced-intensity allogeneic SCT had an improved survival relative to patients who received prophylaxis with a calcineurin inhibitor plus methotrexate. This finding suggests a potential role for mTOR inhibition in preventing lymphoma relapse and adjuvant trials of single-agent mTOR inhibitors are ongoing with NHL.

Other novel therapeutic agents have been investigated for the treatment of HL. Monoclonal antibodies to cell surface proteins have been investigated in heavily pretreated patients with HL. Rituximab, an anti-CD20 monoclonal antibody, has been reported to produce a 22% (5/22) ORR with a median DR of 7.8 months in patients with relapsed nodular sclerosing HL [36]. Rituximab in combination with gemcitabine produced an even higher ORR of 48% (16/33) with a median failure-free survival of 2.7 months (range, 0.9–18.3) [37]. Because of the constitutive activation of NF-kB in HL, proteosome inhibition with bortezomib was investigated; however, this agent showed no antitumor activity as a single agent and no compelling synergy in combination studies [38–40].

CD30 is a cell surface protein expressed on Reed Sternberg cells that is thought to play a role in survival and proliferation [41]. In a single agent Phase II trial, the unconjugated anti-CD30 antibody showed only a 12% (6/51) ORR in patients with HL and ALCL [42]. A subsequent study was closed early because of unexpected pulmonary toxicity when this unconjugated CD30 antibody was combined with a gemcitabine-based chemotherapy regimen [43]. An auristatin E conjugated anti-CD30 antibody has demonstrated an ORR of 46% (13/28) with seven CR in a Phase I trial for patients with relapsed CD30-positive lymphoma including patients with relapsed HL [44]. This agent has now moved to Phase II testing.

This study of everolimus for relapsed HL in heavily pretreated patients has demonstrated significant single-agent activity and provides the rationale to study this class of agents in future trials both alone and in combination with other agents.

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