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Journal

Clinical Lymphoma Myeloma & Leukemia, 20(7)

ISSN

2152-2650

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Publication Date

2020-07-01

DOI

10.1016/j.clml.2020.02.006

Peer reviewed

HHS Public Access

Author manuscript

Clin Lymphoma Myeloma Leuk. Author manuscript; available in PMC 2021 October 21.

Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2020 July ; 20(7): 453–458. doi:10.1016/j.clml.2020.02.006.

A Phase I study of Everolimus and Bendamustine in Patients with relapsed/refractory lymphoid hematologic malignancies

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Abstract

Purpose: Everolimus and bendamustine both have single-agent activity against lymphoid hematologic malignancies. We examined this combination in a group of heavily pretreated patients with non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL) and multiple myeloma (MM).

Patients and methods: In this phase 1 trial, 18 patients (8 with NHL, 6 with MM and 4 with HL) were treated with bendamustine 90 mg/M^2 on days 1 and 2 and everolimus from 5 to 10 mg daily on a 28-day cycle, for up to four cycles.

Results: Adverse events (AEs) were generally mild and mostly hematologic in nature. The most frequent grade 3/4 AEs were lymphopenia (61%), thrombocytopenia (22%), leukopenia (22%), neutropenia (17%) and fatigue (17%). Overall response rate (ORR) varied by malignancy: diffuse large B-cell lymphoma (DLBCL), 20%; HL, 50%; MM, 80%; indolent lymphomas, 100%. The maximal tolerated dose of everolimus was determined to be 7.5 mg daily.

Conclusion: The combination of everolimus and bendamustine appeared to be well-tolerated and relatively efficacious.

Micro abstract

This is the first study to examine the combination of everolimus and bendamustine in the treatment of lymphoid hematologic malignancies. Eighteen patients with relapsed/refractory lymphoma and multiple myeloma were treated. Toxicities were mainly hematologic. Response rates varied by malignancy from 20–100%.

Introduction

Treatment options in relapsed/refractory lymphomas and multiple myeloma have expanded dramatically in recent years. As an example of this, over 20 new medications have been

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Conflicts of interest page

Rasmus Hoeg: No conflicts of interest

Julian Davis: No conflicts of interest

approved by the FDA for the treatment of non-Hodgkin lymphoma (NHL) and multiple myeloma in the last ten years[1,2]. Moreover, multiple new drugs are being tested in clinical trials. Given the plethora of novel agents, a major challenge is how to best rationally combine these agents in a way that optimizes efficacy and minimizes toxicity.

Bendamustine and everolimus have both shown efficacy in lymphoma and multiple myeloma. Bendamustine currently has a well-established role in the therapy of hematologic malignancies. In combination with rituximab, it is used as first line therapy against chronic lymphocytic leukemia[3] and low-grade lymphomas[4], and it is used as later line therapy for many hematologic malignancies[5,6].

Conversely, everolimus has a less defined role in the treatment of hematologic malignancies. Its fellow mammalian target of rapamycin (mTOR) inhibitor, temsirolimus, has been the more studied agent. It has proven activity in relapsed mantle cell lymphoma, both as a single agent and in combination with rituximab[7,8]. Temsirolimus is approved for the treatment of relapsed/refractory mantle cell lymphoma in the EU, but is not approved by the FDA. Similarly, everolimus is not FDA approved for any hematologic malignancy, but has demonstrated single-agent activity in relapsed/refractory hematologic malignancies. In a phase II study by Bennani et al[9] of single-agent everolimus in heavily pre-treated follicular lymphoma, the overall response rate (ORR) was 61. Everolimus has also been shown to be active as a single agent in relapsed/refractory Hodgkin's lymphoma[10] and multiple myeloma[11].

The combination of everolimus and bendamustine has not previously been studied in any cancer. To our knowledge, only one other study has examined the combination of bendamustine and an mTOR inhibitor. Hess et al[12] found that the combination of bendamustine, temsirolimus and rituximab was well-tolerated and resulted in a 91% ORR in patients with previously treated mantle cell lymphoma. The responses appeared to be durable (19-month PFS of 67%).

Both bendamustine and everolimus are well-tolerated as single agents and have mostly non-overlapping toxicities, two of the primary tenets that rationalize their combination. Based on their mechanism of action, there is hope that they can act synergistically. The mTORC1 pathway is known to promote protein synthesis and cell proliferation and can be overexpressed in cancer cells[13]. One important role of p53 is to suppress the mTORC1 pathway[14]. Bendamustine induces DNA damage via alkylation, thus activating p53, leading to cell cycle arrest and apoptosis. Everolimus' mechanism of action is downstream from p53, inhibiting mTOR and its positive effects on protein synthesis and cell survival. Lu et al[15] demonstrated the synergy of bendamustine and everolimus in a multiple myeloma cell line. Based on their independent anti-neoplastic mechanisms of action and mostly non-overlapping toxicities, we hypothesized that the combination of bendamustine and everolimus would prove a feasible, efficacious therapy for relapsed/refractory lymphoid hematologic malignancies. To study this, we designed a phase I trial to assess the safety and preliminary efficacy of the combination of everolimus and bendamustine in patients with relapsed lymphoma and multiple myeloma.

Methods

Patients

Adult (age ≥ 18) patients with relapsed/refractory lymphoid malignancies that included Hodgkin's lymphoma (HL), follicular lymphoma (FL), mantle cell lymphoma (MCL), diffuse large b-cell lymphoma (DLBCL) and multiple myeloma (MM), were eligible. There was no limit to lines of prior therapy, including autologous stem cell transplantation. Patients needed to have measurable disease upon enrollment. Patients were required to have adequate bone marrow reserve (absolute neutrophil count (ANC) > 1,000/mm3, platelet count > 50,000/mm3), normal renal and hepatic function (creatinine clearance of 40mL/min, total bilirubin < 2 times upper level of normal, INR < 2.0 and AST/ALT < 3 times upper level of normal). Eastern Cooperative Oncology Group (ECOG) performance status of 2 or better was required. Patients with CNS lymphomas as well as patients with significant heart, lung, liver, gastrointestinal, infectious or endocrine diseases were excluded from the study.

Study Design

This was a prospective, single-arm dose-escalation, open-label phase I trial to study the safety, efficacy and establish the maximum tolerated dose (MTD) of everolimus and bendamustine. Bendamustine was administered at 90 mg IV daily on days 1 and 2 of a 28-day cycle. Rituximab was allowed for CD20 positive disease and was given at 375 mg/m^2 on day one of each cycle. Everolimus was given at 5, 7.5 or 10 mg daily and was increased using a standard 3+3 design. Patients received up to four cycles of therapy. Follow up was 30 days after last therapy. The primary outcome was to determine toxicity and maximum tolerated dose (MTD). The secondary outcome measure was to determine efficacy.

The trial was approved by the University of California Davis Institutional Review Board in accordance with the Declaration of Helsinki and registered under ClinicalTrials.gov identifier NCT02240719.

Safety

Toxicities were recorded at each visit and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03[16]. Dose-limiting toxicity (DLT) was defined as: any grade 3 or 4 non-hematologic toxicity; grade 4 neutropenia lasting > 5 days, any grade 4 thrombocytopenia, and grade 3 thrombocytopenia with bleeding or requirement for platelet transfusion. Patients were taken off study at time of progression of their disease, or if they experienced prolonged grade 3 or 4 AEs (any non-hematologic AE lasting > 3 weeks) or any delay of therapy by > 4 weeks due to hematologic AEs).

Response Criteria

Response assessments were performed after cycles 2 and 4. Lymphoma response was assessed using 2007 Cheson IWG response criteria[17]. Multiple myeloma response was assessed per 2016 IMWG criteria[18].

Statistics

Demographics, safety, and tolerability outcomes are reported in qualitative terminology. No direct comparisons were made among the dosing regimens or across tumor types.

Efficacy analyses were performed using all evaluable patients, defined as all patients who received at least one dose of study drug, and who followed up for efficacy evaluation. The safety assessment, similarly, was performed using the entire evaluable study population, defined as all enrolled patients who received at least one dose of study drug and had at least one safety assessment.

Results

Patient characteristics

From September 2014 to October 2017, 18 patients were enrolled on the trial. The hematologic diagnoses were DLBCL (5 patients), MM (6 patients), HL (4 patients), FL (2 patients) and MCL (1 patient). Patients had received a median of four prior lines of therapy. No patients had received bendamustine or any mTOR inhibitor previously. Eight (44%) patients had progressed and two (11%) had stable disease while receiving their previous line of therapy, whereas the remaining eight patients (44%) had progressed off therapy prior to entering the study. Patient demographics and baseline disease characteristics can be found in Table 1.

Safety

Six patients completed all four planned cycles of everolimus and bendamustine. One patient completed three cycles, six patients completed two cycles, and five patients completed only one cycle. Of all subsequent cycles (i.e. cycle two and beyond), 17/26 cycles (65%) were delivered on time. The remaining cycles were delayed by a mean of 14 days (range, 3 – 23 days). The majority of the grade 3 and 4 AEs were hematologic: lymphopenia (11 patients; 61%); thrombocytopenia (4 patients; 22%) and neutropenia (3 patients; 17%). The only grade 3 non-hematologic AEs were fatigue (3 patients; 17%), diarrhea (1 patient; 6%) and hypokalemia (1 patient; 6%). No grade 4 non-hematologic AEs occurred. All AEs occurring with greater than 20% frequency, as well as all grade 3 and 4 AEs, are shown in table 2. One patient was taken off study due to an AE (grade 3 diarrhea lasting > 3 weeks). One death occurred in the follow up period: a patient developed a subdural hematoma and eventually passed away due to complications. This happened in the setting of progressive lymphoma and severe thrombocytopenia. The latter worsened after coming off study and was not felt to be secondary to the trial drugs.

Four dose-limiting toxicities (DLTs) occurred. At dose level 1 (everolimus 5 mg daily), one patient had grade 3 fatigue as well as symptomatic grade 4 thrombocytopenia. At dose level 2 (everolimus 7.5 mg daily), one patient developed grade 3 diarrhea. At dose level 3 (everolimus 10 mg daily), one patient developed grade 3 fatigue, grade 3 hypokalemia and grade 4 thrombocytopenia and another patient developed grade 3 fatigue. Based on the “3+3” (see figure 1) dose-escalation schema, the MTD was determined to be 7.5 mg.

Efficacy

All 18 patients completed at least one cycle of therapy. Six patients completed all four planned cycles. Reasons for premature discontinuation (n=12) were progressive disease (n=5), physician discretion (n=4), AEs (n=2) and patient choice (n=1). This latter patient completed cycle 1 but withdrew from the study before response assessment.

Clinical activity was seen across multiple lymphoid malignancies and at all dose levels tested. The ORR for multiple myeloma was 80% (n=5), HL 50% (n=4) and DLBCL 20% (n=5), and indolent NHL 100% (n=3, 2 FL and 1 MCL). These results are summarized in Table 3.

Discussion

This is the first study assessing the safety and efficacy of everolimus and bendamustine in patients with relapsed or refractory lymphoid hematologic malignancies. Eighteen heavily pre-treated lymphoma and multiple myeloma patients (the majority of whom had undergone autologous stem cell transplantation) were enrolled and treated. The combination had an acceptable safety profile. The most common side effects were hematologic, resulting in dose delays (35% of doses were delayed, by a mean of two weeks). Only a third (6/18) of the enrolled patients completed the planned four cycles of therapy. Of the 12 patients taken off study, nine (75%) were taken off due to progression or physician choice, rather than drug toxicity, reflecting the very sick patient population. Four DLTs occurred across the three dose levels. We determined that the MTD of everolimus when given with standard dose bendamustine was 7.5 mg daily. The frequent dose delays and hematologic toxicities suggest that a reduced dose of bendamustine may be warranted for some patients at increased risk for cytopenias.

The response rate appeared highest in patients with multiple myeloma and indolent non-Hodgkin lymphoma. These are diseases in which bendamustine already has a defined role, making it difficult to ascertain the effect of adding everolimus to bendamustine in our small sample. A critique of our study, in addition to the small sample size, is the variability in prior lines of therapy. The indolent lymphomas had only seen 1–3 lines of prior therapy compared to 4–10 lines for patients with MM.

Our study adds to the available literature of mTOR inhibitors used to treat hematologic malignancies, in combination with other agents. An open question is whether bendamustine is the ideal partner to an mTOR inhibitor.

Several chemotherapies and novel agents have been combined with mTOR inhibitors in various hematologic malignancies. Fenske et al[19] combined temsirolimus with bortezomib in the treatment of various non-Hodgkin lymphomas. As in our study, the main toxicities were hematologic. Particularly, thrombocytopenia was pronounced, leading to a study amendment reducing the dose of temsirolimus. Similarly, Hill et al[20] showed that a combination of everolimus and bortezomib was found to cause frequent thrombocytopenia and dose delays when used against various NHLs. Overall response rates were moderate in both studies.

Le Guill et al[21] combined temsirolimus with either R-CHOP, R-FC of R-DHA in the treatment of relapsed mantle cell lymphoma. The combination of temsirolimus and R-CHOP appeared feasible, whereas the combination of temsirolimus and R-FC and R-DHA, respectively, appeared too toxic. Inwards et al[22] combined temsirolimus with rituximab and cladribine in the upfront treatment of MCL in elderly patients. The combination appeared feasible and the ORR was high at 94%.

Perhaps the most impressive results have been achieved when combining an mTOR inhibitor with chemoimmunotherapy for the treatment of DLBCL. Johnston et al[23] combined everolimus and R-CHOP in the treatment of DLBCL and found a 96% response rate and 100% three year survival. Witzens-Harig et al[24] added temsirolimus to R-DHAP salvage chemoimmunotherapy therapy in relapsed/refractory DLBCL. The combination was felt to be safe and feasible. Median OS had not been reached at two years, which compares favorably with historical cohorts[25].

With the available literature, we are left with an impression that mTOR inhibitors given in combination with various therapies add efficacy compared with historical data. Across the studies, including ours, myelosuppression appears to be the main toxicity. The ideal partner of an mTOR inhibitor remains unknown. To date, no randomized study has examined the combination of an mTOR inhibitor and any chemotherapy or novel agent in the treatment of a hematologic malignancy. The combination of everolimus and bendamustine deserves further study, but as it has never been described outside our relatively small series, larger single-arm studies are warranted before a randomized design can be justified.

Acknowledgements

The study was funded in part by Novartis Pharmaceuticals, Inc. and the UC Davis Paul Calabresi Career Development Award for Clinical Oncology as funded by the National Cancer Institute/National Institutes of Health through grant #5K12-CA138464 (ASR)

Brian A. Jonas:

Consulting/advisory role for AbbVie, Amgen, Celgene, GlycoMimetics, Jazz, Pharmacyclics, and Tolero. Travel support from AbbVie, Amgen, and GlycoMimetics. Research funding to his institution from AbbVie, Accelerated Medical Diagnostics, AROG, Celgene, Daiichi Sankyo, Esanex, Forma, Genentech/Roche, GlycoMimetics, Incyte, LP Therapeutics, and Pharmacyclics.

Joseph Tuscano:

Research funding from Abvie, Celgene, Genenetech, Pharmacyclics, Novartis, Spectrum, and Takeda. Honoraria from Celgene, Amgen and Seattle Genetics

Aaron Rosenberg:

Speakers bureau for Jansenn, Millenium-Takeda. Research funding from Amgen. Advisory board for Amgen and Karyopharm. Honorarium: Celgene. Research

Mehrdad Abedi:

Speakers Bureau for Celgene, Takeda, Genentech, Gilead and BMS.

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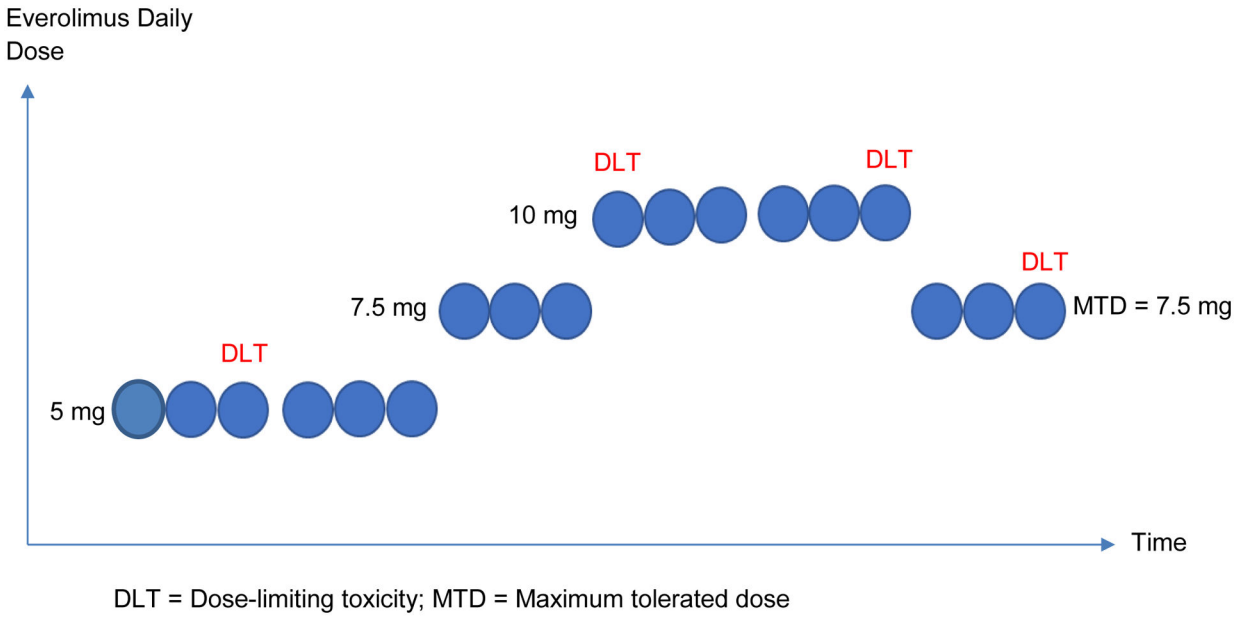

Figure 1.
Illustration of "3+3 schema"

Table 1.

Patient characteristics (n = 18)

Age, years	
Median [range]	62 [22 – 73]
Male, n (%)	15 (83%)
Prior Therapy, n	
Median [range]	4 [1 – 11]
Malignancy, n (%)	
DLBCL	5 (28%)
FL	2 (11%)
HL	4 (7%)
MCL	1 (5%)
MM	6 (33%)
ECOG PS, n (%)	
0	5 (28%)
1	11 (61%)
2	2 (11%)

Abbreviations: DLBCL = diffuse large b-cell lymphoma; FL = follicular lymphoma; HL = Hodgkin's lymphoma; MCL = mantle cell lymphoma; MM = multiple myeloma

Table 2.

Treatment-related adverse events (CTCAE)

CTCAE	Toxicity	Any Grade, N (%) in ≥ 20% of patients	Grade 3 – 4, N (5)
Blood and lymphatic system disorders	Lymphopenia	12 (67%)	11 (61%)
	Thrombocytopenia	11 (61%)	4 (22%)
	Leukopenia	10 (56%)	4 (22%)
	Anemia	8 (44%)	1 (6%)
	Neutropenia	7 (39%)	3 (17%)
Cardiac disorders	Tachycardia	5 (28%)	-
Gastrointestinal disorders	Nausea	8 (44%)	-
	Diarrhea	-	1 (6%)
Investigations	AST increased	5 (28%)	-
	ALKP increased	4 (22%)	-
Metabolism and nutrition disorders	Anorexia	6 (33%)	-
	Hypokalemia	-	1 (6%)
General disorders	Fatigue	10 (56%)	3 (17%)
Nervous system disorders	Subdural hematoma, leading to cerebral edema, encephalopathy and death	-	1 (6%)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; AST = aspartate aminotransferase; ALKP = alkaline phosphatase

Table 3.

Response per patient, organized by diagnosis

Diagnosis	Patient sex or diagnosis group	Age, years	Number of prior therapies**	Best response / ORR (CR+PR) per diagnosis, %	Prior stem cell transplantation
HL	M	22	3	PD	-
	F	27	11	PR	Allogeneic
	M	49	4	CR	Autologous
	M	36	5	PD	-
	All patients			*50%*	
MM	M	74	4	NA*	Autologous
	M	66	9	PR	Autologous
	M	67	6	VGPR	Autologous
	M	60	10	PD	Autologous
	M	73	5	PR	Autologous
	F	62	5	PR	Autologous
	All patients			*80%*	
MCL	M	67	2	CR	Autologous
	All patients			*100%*	
FL	M	51	1	CR	-
	M	73	3	CR	-
	All patients			*100%*	
DLBCL	M	61	4	PD	-
	F	59	3	DLT	-
	M	70	3	PD	-
	M	66	3	PD	Autologous
	M	61	4	PR	Autologous
	All patients			*20%*	

* The patient withdrew from the study after cycle 1 and refused follow-up.

** Including autologous or allogeneic stem cell transplantation.

Abbreviations: M = Male; F = Female; ORR = overall response rate; CR = complete response; PR = partial response; PD = progressive disease; NA = non-applicable; VGPR= very good partial response; DLT = dose-limiting toxicity