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Therapy with bortezomib plus lenalidomide for relapsed/ refractory mantle cell lymphoma: Final results of a phase II trial (CALGB 50501)

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Abstract

CALGB designed a phase II trial of lenalidomide+bortezomib for relapsed/refractory mantle cell lymphoma (MCL). Induction therapy was lenalidomide (days 1-14) plus bortezomib (days 1/4/8/11), every 21 days for eight cycles. Complete and partial responders (CR, PR) received maintenance lenalidomide (days 1-14) and bortezomib (days 1/8), every 21 days. Primary endpoint was overall response rate; secondary endpoints were CR rate, progression-free- (PFS), event-free- (EFS), and overall survival (OS). Fifty-three eligible patients, median age 67 years, were accrued. Median number of cycles received was 4 (range, 1-82). Median follow-up is 46 (range, 12-67) months. Best response was CR (n=8, 15%), PR (n=13, 25%). 5/8 CR and 4/13 PR patients received maintenance therapy. Of responders, 6 CR/1 PR patients remain in remission at a median of 3.2 years. Thirty-three (62%) patients have died. One-year PFS, EFS, OS are 40%, 25%, and 68%, respectively. This combination will not be pursued further at this dose/schedule.

Keywords

mantle cell lymphoma; bortezomib; lenalidomide

Introduction

Mantle cell lymphoma represents approximately 6% of non-Hodgkin lymphomas (NHL), and has increased in incidence over the past several decades [1,2]. The clinical course is

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aggressive in most patients, although more indolent in others [3]. Most patients present with advanced stage disease, with a predilection for extranodal, especially gastrointestinal, involvement. The majority of patients respond to initial therapy, but remission duration is typically short (1.5-3 years) [4,5]. Despite improved progression-free survival (PFS) rates with bendamustine-rituximab therapy and prolonged remission durations reported with rituximab maintenance, there is no plateau in PFS with any approach [6]. Median overall survival (OS) is three to six years with standard chemotherapy approaches, and fewer than 15% of patients are long-term survivors [4,7]. Although stem cell transplantation (SCT) remains a treatment option both in first remission and at relapse, it is not curative in the majority of patients, and many are not SCT candidates due to age and co-morbidities.

Standard therapy for patients with relapsed or refractory disease, especially for those who are not candidates for SCT or have relapsed following SCT, may include lenalidomide or bortezomib, both with response rates ranging from 30% to 53% [8-16]. Nevertheless, responses are brief, with eventual death from progressive disease. Based on these findings, the Cancer and Leukemia Group B (now part of the Alliance for Clinical Trials in Oncology) designed a phase II trial of bortezomib plus lenalidomide therapy for patients with relapsed or refractory mantle cell lymphoma (CALGB 50501). Data from myeloma trials with this combination revealed manageable toxicities, even in an older, heavily pretreated, patient population [17].

Patients and Methods

Eligibility

Eligibility criteria included histologically documented mantle cell lymphoma, which was CD5+, CD23-, and cyclin D1+, either on initial biopsy or at time of relapse; at least one prior regimen; measurable progressive or refractory disease following initial therapy; prior autologous, but not allogeneic, SCT was allowed; age ≥ 18 years; no corticosteroids within two weeks prior to study entry, except for maintenance therapy for a non-malignant disease; no prior radio-immunotherapy within 12 months of study entry; no $>$ grade 3 peripheral neuropathy within a month prior to study entry; Eastern Cooperative Oncology Group performance status 0-2; left ventricular ejection fraction $>45\%$ by MUGA or echocardiogram; no known central nervous system involvement by lymphoma; no history within three months of study entry of deep venous thrombosis or pulmonary embolus; no NYHA Class III or Class IV congestive heart failure at study entry; and no known positivity for hepatitis A, B or C. HIV-positive patients were eligible. Required laboratory data included: absolute neutrophil count (ANC) $\geq 1000/\text{mL}$, or $>500/\text{mL}$ if marrow involvement; platelet count $\geq 75,000/\text{mL}$; creatinine $\leq 1.5 \times$ upper limit of normal (ULN), unless attributable to lymphoma; estimated creatinine clearance $\geq 30 \text{ mL/minute}$; total bilirubin $\leq 2 \times$ ULN in the absence of a history of Gilbert's disease; negative urine or serum HCG. Each participant signed an IRB-approved, protocol-specific informed consent in accordance with federal and institutional guidelines.

Induction therapy consisted of bortezomib, 1.3 mg/m^2 IV, days 1, 4, 8, 11, and lenalidomide, 20 mg po qd, days 1-14, administered every 21 days for eight cycles (Figure 1). Patients were restaged at three and six months. After completion of the six month

induction therapy, patients with complete or partial remission (CR, PR) went onto maintenance therapy [18]. For those patients with stable or progressive disease as best response to induction therapy, protocol therapy was discontinued. Maintenance therapy consisted of bortezomib, 1.3 mg/m² IV, days 1,8, and lenalidomide, 15 mg po qd, days 1-14, given every 21 days as long as tolerable and patient remained in remission. In September 2009, the protocol was modified to have separate, instead of concomitant, dose reduction schedules for each agent. The bortezomib dose was reduced for neuropathy-related adverse events, and the lenalidomide dose was modified for therapy-related myelosuppression. Prophylactic aspirin or low molecular weight heparin was recommended for patients at high risk of thrombotic complications.

Objectives

The primary objective of this study was to determine the overall response rate (ORR) (CR +PR) to bortezomib plus lenalidomide therapy. Secondary objectives were to determine the CR rate, PFS, event-free survival (EFS), and OS.

Data Management

Data collection and statistical analyses were conducted by the Alliance (CALGB) Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies. All analyses were based on data collected through February 28, 2014.

Statistics

The study was planned to accrue 49 patients via a two-stage design with a futility stopping. We considered an ORR of 45% as inadequate to pursue the regimen further, and an ORR of 65% of strong interest. Nineteen patients were treated in the first stage. If nine or fewer responded, the study was to be stopped, with the conclusion that study therapy was not efficacious. Otherwise, the study continued to the second stage to accrue an additional 30 patients. If 28 or more patients of the cumulative 49 responded, then the study therapy was accepted for further investigation. This two-stage design had a type I error rate of 5% if the true ORR was 45%, and 85% power if the true ORR was 65%. Accounting for the two-stage design, the ORR was estimated using the method of Jung and Kim [19], the confidence interval was calculated by the method of Jennison and Turnbull [20], and the p-value for ORR was calculated by the method of Jung et al. [21]. The sample size was calculated to include a potential 10% ineligibility rate.

PFS was defined as the time to disease progression or death from any cause; EFS was the time to early termination of study therapy due to severe toxicity, disease progression, or death from any cause; OS was time to death or last follow-up. The distributions of these time-to-event outcomes were estimated using Kaplan-Meier curves [22].

Results

This study was activated on November 15, 2007 and closed on July 7, 2011, with a final accrual of 54 patients. One patient was deemed ineligible due to prior bortezomib therapy

and was removed from all analyses. The baseline characteristics for the 53 eligible patients are shown in Table I. Median age was 67 (range, 39-83) years; 83% were male. Relapsed disease was present in 89% (n=47) of patients; 6 (11%) had refractory disease. The Mantle Cell Prognostic Index (MIPI) score was low in 43% and high in 21% of patients. Known extranodal disease was present in 53% of patients (including gastrointestinal tract [n=13], head and neck region [n=9], lung [n=2]).

Previous Treatments

Fifty-two patients received prior chemotherapy, with the number of regimens ranging from 1 to 5. Thirty-one of the 52 (60%) received one prior regimen, 13 (25%) received two, six (12%) received three, and one each (2%) received four and five regimens. Fifty patients (94%) received prior immunotherapy, primarily rituximab (n=46), with a single patient each receiving 17 AAG, idiotype vaccine, TRU 016, and rituximab/GM-CSF/interleukin. Fourteen patients (26%) received prior radiotherapy. Twenty-one patients (40%) had undergone a prior autologous SCT.

Treatment Administration and Efficacy (Figure 2)

The median number of cycles administered was 4 (range, 1 to 93). One patient remained on treatment in CR as of last follow-up in February 2014, having received 93 cycles of therapy. Twenty-two patients (41.5%) discontinued protocol therapy due to disease progression (n=21) or non-response to treatment (n=1). Treatment was discontinued in 17 (32.1%) patients for treatment-related toxicities, in 4 (7.6%) for patient refusal to continue treatment, in one (1.9%) for increasing peripheral blood lymphocyte count interpreted as progressive disease (PD), treatment-related death (1 [1.9%]), physician decision (1 [1.9%]), and receipt of other non-protocol therapies in 6 patients (7.6%). One of these six patients began other treatment (i.e., radiation therapy) due to symptoms of presumed progression, which was later determined to be a lenalidomide flare reaction.

The best response for the 53 eligible patients was 8 CR (15.1%), 13 PR (24.5%), 8 (15.1%) stable disease, 17 PD (32.1%); 7 (13.2%) were taken off therapy after one cycle and were inevaluable for response. The overall response rate was 39.6% (90% CI, 34-68%). Two CR patients discontinued protocol therapy after cycles 4 and 7 due to adverse events; one CR refused maintenance therapy. Of the 5 CR patients who went on to receive maintenance therapy, 2 discontinued therapy after cycles 9 and 10 due to adverse events, one went onto SCT after cycle 9, one progressed after 52 cycles and one remains on maintenance therapy (93 cycles). Six of the 8 CR patients remain in remission, including four who discontinued protocol therapy after cycles 7, 8, 9 and 10. Only two CR patients had prolonged maintenance therapy, of which one remains.

Four of the 13 PR patients received maintenance therapy. Reasons for discontinuation of protocol therapy included adverse events (n=3) after cycles 2, 5 and 6, refusal (n=2) after cycles 4 and 6, PD (n=2) after cycle 8, and receipt of SCT (n=2) after cycles 4 and 8. Only the patient who went onto SCT after 4 cycles remains in remission. Of the remaining 4 partial responders, 2 developed PD after cycles 24 and 53, one discontinued protocol therapy due to an increased lymphocyte count after cycle 18, and one refused further therapy after

cycle 26. Only this latter patient was in remission at last follow-up. One patient in PR after induction therapy achieved a CR while on maintenance therapy, before developing PD after cycle 53 of therapy. Only 6 of 21 responders underwent prolonged maintenance therapy (18 to 82 total cycles, including the eight induction cycles), and two of these remain in remission.

Ten patients discontinued protocol therapy after only one cycle (the 7 inevaluable patients, and 3 others with PD). An additional 7 patients had PD after 2 cycles of therapy, and 5 more after 3 treatment cycles.

Median follow-up period of the enrolled cohort is 46 (range, 12-67) months. The median follow-up interval in the 20 patients still alive is 3.2 (range, 1.1-5.0) years. Of responders, 6 CR/1 PR patients remain in remission at a median of 3.2 years. Median PFS, EFS, and OS are 7, 4.3, and 26 months, respectively (Figure 3). Thirty-three (62%) patients died, one related to treatment, 30 due to progressive disease, and two due to other causes (fungal sinusitis, metapneumonic virus infection with septic shock and acute renal failure). The MIPI risk group was marginally associated with PFS ($p=0.069$, hazard ratio=1.42), but not EFS ($p=0.112$, HR=1.37). However, the association of the MIPI risk category with OS was strong ($p=0.0003$, HR=2.24). The presence of extra-nodal disease was not significantly associated with PFS, EFS or OS.

Safety and tolerability

Adverse events are summarized in Table II. Although grade 3/4 sensory neuropathy occurred only in 8% of patients, 36% experienced grade 2 sensory neuropathy. Autonomic neuropathy, manifest as orthostatic hypotension, occurred in 17% of patients. There was no grade 4 anemia or leukopenia, but 21% of patients had reversible grade 4 thrombocytopenia. Although 21% of patients had grade 3/4 neutropenia, infections were not common, and only one patient had febrile neutropenia.

Discussion

The optimal treatment approach for relapsed/refractory mantle cell lymphoma patients is not known, and clinical trials are a preferred option for such patients. Several drugs have recently received FDA approval for this indication. Bortezomib monotherapy for relapsed/refractory mantle cell lymphoma achieves overall response rates of 30-47%, with the majority being PRs [9-12, 23]. The FDA approval of bortezomib for this population was based upon a phase II trial in 141 patients for which the ORR was 33% (8% CR), with median response duration of 9.2 months and median time to progression of 6.2 months [12]. The most common grade 3/4 toxicities were peripheral neuropathy (13%), fatigue (12%), and thrombocytopenia (11%). The addition of rituximab and dexamethasone to bortezomib therapy for relapsed/refractory mantle cell lymphoma resulted in an ORR of 81% (CR 44%), and median PFS and OS of 12.1 and 38.6 months, respectively [24].

Thalidomide and lenalidomide also have activity in mantle cell lymphoma, with the latter approved by the FDA based upon a report of 134 heavily pre-treated (including prior bortezomib) relapsed/refractory mantle cell lymphoma patients who received single agent

lenalidomide at a dose of 25 mg days 1-21 of a 28-day cycle (13-16, 25). The ORR was 28% (8% CR), with median remission duration of 16.6 months (16, 26). A phase II trial of induction lenalidomide (25 mg) followed by maintenance lenalidomide (15 mg, both days 1-21 of a 28-day cycle) in responding patients with relapsed/refractory mantle cell lymphoma was reported by Eve et al, with an ORR of 31%, and median response duration and PFS of 22.2 and 3.9 months, respectively [27]. Similar to our trial, 11 of 26 patients (42%) received less than two cycles of therapy due to progressive disease (n=5), adverse events (n=4), and withdrawal of consent (n=2). Grade 3/4 toxicities included neutropenia (62%), thrombocytopenia (42%), and infection (39%). Eleven patients received at least one cycle of maintenance therapy. After a median follow-up of 23.3 months, the median PFS and OS of the maintenance cohort were 14.6 months and not reached, respectively. Single agent rituximab therapy in relapsed/refractory mantle cell lymphoma patients results in an ORR of 37% and median response duration of 1.2 years [28]. In a phase II trial in relapsed/refractory mantle cell lymphoma patients, rituximab-thalidomide induction therapy, followed by maintenance thalidomide, resulted in an ORR of 81% (CR, 31%), with median PFS of 20.4 months and estimated three-year OS of 75% [25]. Although the role of maintenance rituximab following R-CHOP as initial treatment has been suggested, data supporting its benefit in the relapsed/refractory setting are lacking [29]. Last, in a phase I/II trial of recurrent mantle cell lymphoma patients (n=52) reported by Wang et al, lenalidomide-rituximab therapy resulted in a 58% ORR (CR 33%), with median PFS of 14 months [30].

Perhaps the most active chemoimmunotherapy regimen for relapsed/refractory patients has been bendamustine-rituximab (BR) with ORR of 75-95% (CR 42-60%), with median response duration and PFS of 19 and 30 months, respectively [31, 32]. In a phase III trial in which relapsed/refractory patients were randomized to temsirolimus or the investigator's choice, an improved ORR (22% versus 2%), PFS (4.8 versus 1.9 months), and a trend toward longer OS (10.9 versus 5.8 months) were seen with temsirolimus, although the results were not sufficient for FDA approval [33].

The ORR of 40% in our trial was disappointing, especially given the single agent response rates previously reported. The lower than anticipated response rate may potentially be related to inadequate lenalidomide dosing (initial dose 20 mg/day, with subsequent reductions based upon toxicities), initial simultaneous dose reductions in both agents for toxicity, and the limited amount of protocol therapy administered in 37% of our patients related to disease progression and tolerability issues (median number of cycles received was 4). In addition, 40% of patients had relapsed/refractory disease following autologous SCT. Bortezomib-related neurologic (sensory, autonomic) toxicities were common, resulting in dose reductions and removal from protocol therapy. The use of subcutaneous bortezomib could potentially make this combination less toxic and result in fewer dose reductions. Unfortunately due to small numbers, we could not assess the impact of maintenance therapy in our trial. However, this sort of maintenance therapy may not be deliverable, and case-by-case decisions with regard to the option of maintenance may need to include its impact on quality of life. Based upon our findings, future studies with this dose and schedule of bortezomib plus lenalidomide are not warranted.

Recently, the Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, has become a treatment option for relapsed/refractory mantle cell lymphoma patients, with FDA approval based on a phase II trial with an ORR of 68% (21% CR) [34]. The estimated median response duration and PFS were 17.5 and 13.9 months, respectively, with an 18-month OS of 58%. The most common side effects were mild diarrhea, fatigue, and nausea; grade 3/4 myelosuppression was uncommon. Idelalisib, which targets the delta isoform of the PI3-kinase pathway, has likewise shown activity in this population [35]. These agents will clearly form the basis of future therapeutic strategies for this disorder.

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Figure 1. Treatment Plan

Figure 2. CONSORT Diagram: CALGB 50501

Figure 3. Survival Parameters in the Study Population (95% confidence limits in parentheses)

Table I
Baseline Patient Characteristics

Characteristic	
Age, years	
Median (Range)	67 (39-83)
	n (%)
Race	
White	49 (92.4%)
Black	2 (3.8%)
Hispanic	2 (3.8%)
Male	44 (83.0)
Relapsed Disease	47 (88.7%)
Refractory Disease	6 (11.3%)
Ann Arbor Stage	
II	1 (1.9%)
III	10 (18.9%)
IV	42 (79.2%)
B-symptoms	11 (20.8%)
ECOG Performance Status	
0	33 (62.3%)
1	19 (35.8%)
2	1 (1.9%)
Elevated LDH	17 (32.1%)
MIPI	
Low	23 (43.4%)
Intermediate	19 (35.8%)
High	11 (20.8%)
Extra-nodal Disease	
No	25 (47.2%)
Yes	28 (52.8%)

Table II

Adverse Events (N=53)

Grade of Adverse Event								
2- Mod			3-Severe		4-LifeThr		5-Lethal	
	n	(%)	n	(%)	n	(%)	n	(%)
Hematologic Adverse Events								
Blood/Bone Marrow								
Hemoglobin	10	(19%)	4	(8%)	0	(0%)	0	(0%)
Leukocytes (total WBC)	11	(21%)	3	(6%)	0	(0%)	0	(0%)
Lymphopenia	4	(8%)	7	(13%)	1	(2%)	0	(0%)
Neutrophils/granulocytes (ANC/AGC)	9	(17%)	9	(17%)	2	(4%)	0	(0%)
Platelets	10	(19&percent;)	7	(13&percent;)	11	(21&percent;)	0	(0%)
SUMMARY								
Maximum Hematologic AE	16	(30%)	14	(26%)	12	(23%)	0	(0%)
Non-Hematologic Adverse Events								
Hypotension	5	(9%)	4	(8%)	0	(0%)	0	(0%)
Fatigue (asthenia, lethargy, malaise)	9	(17%)	11	(21%)	0	(0%)	0	(0%)
Weight loss	6	(11%)	1	(2%)	0	(0%)	0	(0%)
Rash/desquamation	5	(9%)	2	(4%)	0	(0%)	0	(0%)
Anorexia	7	(13%)	2	(4%)	0	(0%)	0	(0%)
Constipation	6	(11%)	0	(0%)	0	(0%)	0	(0%)
Diarrhea	5	(9%)	4	(8%)	1	(2%)	0	(0%)
Nausea	9	(17%)	1	(2%)	0	(0%)	0	(0%)
Infection								
Febrile neutropenia	0	(0%)	1	(2%)	0	(0%)	0	(0%)
Infection with normal ANC	5	(9%)	1	(2%)	0	(0%)	1	(2%)
Infection with unknown ANC	3	(6%)	1	(2%)	0	(0%)	0	(0%)
Phosphate serum-low	4	(8%)	1	(2%)	0	(0%)	0	(0%)
Muscle weakness	4	(8%)	2	(4%)	0	(0%)	0	(0%)
Dizziness	5	(9%)	2	(4%)	0	(0%)	0	(0%)

	Grade of Adverse Event					
	2- Mod		3-Severe		4-LifeThr	5-Lethal
	n	(%)	n	(%)	n	(%)
Neuropathy: motor	3	(6%)	5	(9%)	0	(0%)
Neuropathy: sensory	19	(36%)	4	(8%)	0	(0%)
Pain	5	(9%)	2	(4%)	0	(0%)
Dyspnea (shortness of breath)	3	(6%)	5	(9%)	0	(0%)
Thrombosis/thrombus/embolism	0	(0%)	3	(6%)	0	(0%)
SUMMARY						
Maximum Non-Hematologic AE	6	(11%)	32	(60%)	6	(11%)
					1	(2%)
SUMMARY						
Maximum Overall AE	4	(8%)	29	(55%)	17	(32%)
					1	(2%)