Beaven et al., J Clin Trials 2012, 2:3
DOI: 10.4172/2167-0870.1000120

Journal of Clinical Trials
ISSN: 2167-0870

Research Article Open Access

Bortezomib Combined with Rituximab, Fludarabine, Mitoxantrone, and Dexamethasone (R-VFND) for the Treatment of Relapsed/Refractory Follicular Lymphoma

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Abstract

Background: Pre-clinical data suggests that bortezomib may have a suppressive effect on B-cell lymphoma 2 (bcl-2), an anti-apoptotic protein over expressed in follicular lymphoma; therefore, the addition of bortezomib to standard chemotherapy may improve the treatment of follicular lymphoma. We conducted this prospective, single-arm, open-label phase II trial of bortezomib combined with rituximab, fludarabine, mitoxantrone, and dexamethasone (R-VFND) to evaluate the efficacy and safety of this regimen in patients with relapsed/refractory advanced follicular lymphoma.

Methods: Twelve patients with relapsed or refractory stage III or IV follicular lymphoma were treated with bortezomib 1.6 mg/m^2 day 1 and day 8 in combination with R-FND (rituximab 375 mg/m^2 day 1, fludarabine 25 mg/m^2 iv days 1, 2, and 3; mitoxantrone 10 mg/m^2 iv day 2; and dexamethasone 20 mg/m^2 p.o. days 1, 2, 3, 4, and 5). Cycles were repeated every 28 days for a maximum of 8 cycles. Cycles were held for grade 3-4 cytopenias and patients were withdrawn if drug was held for more than 2 weeks.

Results: Of 11 evaluable patients, 7 had a response (64%) with 4 complete responses (CR) (36%). Two patients remain in CR after 43 months: one after four cycles with no further treatment, the other after three cycles followed by allogeneic hematopoietic stem-cell transplant. Cytopenias were significant: 55% of patients had grade 3-4 neutropenia and 55% had grade 3-4 thrombocytopenia. Four patients (36%) withdrew early due to hematologic adverse events and one patient (9%) due to neuropathy.

Conclusion: The addition of bortezomib to R-FND for treatment of follicular lymphoma resulted in a high response rate, but it was not clearly higher than what is expected from R-FND and the cytopenias were severe. Therefore, while bortezomib's role in the treatment of follicular lymphoma remains to be fully defined, we find it hard to justify further trials with this fludarabine based combination and suggest future studies focus on alternative combinations.

Keywords: Bortezomib; Rituximab; Fludarabine; Mitoxantrone; Dexamethasone; FND; Follicular lymphoma

Introduction

Follicular lymphoma accounts for 20-25% of all cases of non-Hodgkin lymphoma (NHL) [1,2]. Median patient age at diagnosis is 59, and most patients present with advanced disease [3], requiring multiple regimens to control their disease over time. Though rituximab has significantly improved outcomes for patients, it is still not curative, and median survival is approximately 10 years from diagnosis [4,5].

Treatment options for follicular lymphoma range from a watch and wait approach to stem cell transplant. Although there are many options, eventually patients become refractory to therapy; therefore, it is imperative that research continues into new and more effective chemotherapy and alternative modalities.

Bortezomib, a small molecule reversible proteasome inhibitor, is an FDA approved therapy for multiple myeloma that, due to its effects on Bcl-2 (B-cell lymphoma 2), is of increasing interest in the treatment of lymphoma. Bcl-2 is an anti-apoptotic protein that is frequently over expressed in follicular lymphoma due to the t(14;18) translocation, which moves the bcl-2 gene adjacent to the immunoglobulin heavy chain locus [6]. Bortezomib has been found to induce apoptosis in cells that expressed bcl-2 [7], making follicular lymphoma cells an ideal target. A phase II study of single agent bortezomib in patients with relapsed/refractory follicular lymphoma had a response rate of 58%, with a median event-free survival of 8.5 months [8].

The combination of Fludarabine, Mitoxantrone, and Dexamethasone (FND) for the treatment of follicular lymphoma was first reported in a Phase I study published by McLaughlin in 1994 [9]. Subsequent studies showed response rates of 69%-94% in heavily pre-treated populations [10,11]. The addition of rituximab has further improved these results with response rates of 92% and 3-year failure free survival of 77% [12]. *In vitro* data has shown an increased cytotoxic effect when bortezomib is combined with fludarabine for the treatment of chronic lymphocytic leukemia (CLL) [13]. Based on these promising data, we added bortezomibto a chemoimmunotherapy backbone of rituximab, fludarabine, mitoxantrone, and etoposide (R-VFND) in a prospective, single-arm, open-label phase II trial to evaluate the efficacy and safety of this regimen in patients with relapsed/refractory advanced follicular lymphoma.

Materials and Methods

Patient selection

Patients with relapsed/refractory follicular lymphoma after at least one prior regimen were eligible if they had Eastern Cooperative Oncology

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Received July 10, 2012; **Accepted** August 18, 2012; **Published** August 21, 2012

Citation: Sung AD, Rizzieri D, Li Z, Beaven AW (2012) Bortezomib Combined with Rituximab, Fludarabine, Mitoxantrone, and Dexamethasone (R-VFND) for the Treatment of Relapsed/Refractory Follicular Lymphoma. J Clin Trials 2:120. doi:10.4172/2167-0870.1000120

Group (ECOG) performance status 0-2; aspartate aminotransferase, alanine aminotransferase, and total bilirubin < 3 times the upper limit of normal unless thought to be secondary to underlying lymphoma; and platelet count >50,000 and absolute neutrophil count (ANC) > 1,000 unless thought to be secondary to bone marrow involvement by lymphoma. Patients with prior exposure to bortezomib were excluded, as were patients with grade 2 or higher peripheral neuropathy; Stage IV or V chronic kidney disease (glomerular filtration rate <30); myocardial infarction within 6 months of enrollment; cardiac ejection fraction <35%; New York Heart Association Class III or IV heart failure; HIV positive status; pregnancy or lactating; or hypersensitivity to any drugs in the protocol. Informed consent was obtained from every patient prior to enrollment and the study was approved by the institutional review board of Duke University Medical Center and registered on www.clinicaltrials.gov, identifier NCT00510887.

Drug administration

This was a phase II efficacy study of the combination ofrituximab, bortezomib, fludarabine, mitoxantrone, and dexamethasone (R-VFND) in patients with relapsed/refractory follicular lymphoma. Drugs were administered on the following schedule: rituximab 375 mg/m^2 iv day 1; bortezomib 1.6 mg/m^2 iv days 1 and 8; fludarabine 25 mg/m^2 iv days 1, 2, and 3; mitoxantrone 10 mg/m^2 iv day 2; and dexamethasone 20 mg/m^2 p.o. days 1, 2, 3, 4, and 5. Cycles were repeated every 28 days for a maximum of 8 cycles. Patients were evaluated after every two cycles with re-staging computed tomography scan (CT) and bone marrow biopsy if known involvement, or sooner if clinically warranted. All patients received prophylaxis against pneumocystis pneumonia. Use of growth factor support was at the discretion of the treating physician.

Dose reductions were employed for grade 4 hematologic toxicity, febrile neutropenia, or other severe non-hematologic toxicities. Up to two dose reductions were allowed: first incidence: bortezomib 1.3 mg/m^2 iv, fludarabine 18 mg/m^2 iv, mitoxantrone 8 mg/m^2 iv; second incidence: bortezomib 1.0 mg/ m^2 iv, fludarabine 14 mg/ m^2 iv, mitoxantrone 6 mg/m^2 iv; third incidence: patient taken off study. Standard bortezomib dose modifications were followed for episodes of neuropathy. If patients experienced grade 3 hematologic toxicity, chemotherapy was held until platelet >50,000 or ANC >1,000. For non-hematologic toxicities, drug was held until toxicity resolved to at least a grade 1. If drug was held for more than 2 weeks, patients were withdrawn from the study.

Endpoints

The primary endpoint for this study was the overall response rate to the R-VFND combination in patients with relapsed/refractory follicular lymphoma. Response was graded using the standardized criteria current at the time the study was conducted [14]. As such, we define complete response (CR) as normal lymph nodes on CT (all lymph nodes <1.5 cm) and no evidence of bone marrow involvement; CR unconfirmed (CRu) as ≥ 75% decrease in the sum of the products of the greatest diameter (SPD) of lymph node masses and normal or indeterminate bone marrow; partial response (PR) as ≥ 50% decrease in the SPD of lymph node masses; relapse/progression as new or enlarging (≥ 50%) lymph nodes; and stable disease as none of the above.

The secondary objective was to evaluate the safety of this regimen. Toxicities were graded using the National Cancer Institute (NCI) Common Toxicity Criteria (CTCAE) version 3.0 and are presented here in table format.

Results

Patients

Between January 2007-2010, twelve patients were enrolled (Table 1) before the study was stopped due to slow accrual. The median age was 59 years (range 39-72) and 67% were male. All patients had stage III (25%) or stage IV (75%) disease. Patients were diagnosed a median of 7 years prior to enrollment (range 0.7-13.8) and had received a median of 4 therapies (range 1-8), including two patients who had high-dose therapy followed by autologous stem cell rescue. Seven patients (58%) had grade 1 thrombocytopenia at enrollment and one (8%) had grade 2 thrombocytopenia. One patient (8%) had grade 1 neutropenia at enrollment and two (17%) had grade 2 neutropenia. Although 11 (92%) patients had received prior vincristine, no patients had neuropathy at baseline.

Response

Patients received a median of 3.5 cycles of R-VFND (range 1-6) (Table 2). Eleven patients had at least one re-staging event after receiving study drug and are evaluable for response; the 12th patient received 1 cycle of R-VFND and was then immediately lost to follow

Patient	Age	Gender	Stage	Previous therapies*	Time from diagnosis (years)
1	71	M	III	R-CHOP	3.8
2	52	M	III	R-CHOP, ICE, R-MTX/araC, auto, R-gem/ox	1.5
3	60	M	IV	R-PC	2.1
4	49	M	IV	R-CHOP	2.5
5	57	F	IV	CHOP f/b R, R, zevalin, R-F	8.3
6	51	M	IV	CHOP, R, bexaar, R-FD	8.4
7	65	M	IV	Cy, CHOP-R, bexaar, R, R-F, R-ESHAP	13.8
8	39	M	IV	R-CHOP	0.7
9	65	F	IV	R-CHOP + XRT, R-CHOP	10.1
10	46	M	IV	R-CHOP, F x2, R-ICE	8.3
11	69	F	III	CVP, R, R-galiximab, zevalin	7.4
12	56	F	IV	R-CHOP, R, zevalin, R-ICE, DHAP, auto, R-EPOCH, gem/navelbine, MTX/araC	6.5

*R = rituximab; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; ICE = ifosfamide, carboplatin, etoposide; MTX/araC = methotrexate, cytarabine; auto = high dose therapy followed by autologous stem cell rescue; gem/ox = gemcitabine, oxaliplatin; PC = pentostatin, cytoxan; F = fludarabine; FD= fludarabine, dexamethasone; Cy = cyclophosphamide; ESHAP = etoposide, methylprednisolone, cisplatin, cytarabine; CVP = cyclophosphamide, vincristine, prednisone; DHAP = dexamethasone, cisplatin, cytarabine; EPOCH = etoposide, prednisone, vincristine, doxorubicin, cyclophosphamide; gem/navelbine = gemcitabine, navelbine

Table 1: Patient characteristics.

up. Seven of the eleven (64%) evaluable patients had a response with 4 CR/CRu (36%) and 3 PR (27%). Two patients are still in CR, both at 43 months from start of therapy. One completed 4 cycles of R-VFND before stopping due to the development of grade 2 neuropathy. This subject remains in a CR without further treatment 40 months after stopping study drug. The other patient achieved a CR with 2 cycles of R-VFND and received a third cycle before proceeding to allogeneic hematopoietic stem-cell transplant; this patient also remains in a CR 4 years later. The two remaining patients who obtained a CR/ CRu both progressed at 9 months. After a median follow up of 37.6 months (range 10.6-48.0), four patients are still alive, three of whom went on to receive further therapy including the above patient who had an allogeneic hematopoietic stem-cell transplant.

Toxicity

This regimen resulted in profound myelosuppression leading to dose reductions or patients being withdrawn from study (Table 3). Twelve patients received at least one dose of study drug, but 1 patient was lost to follow up after day 8 while she was doing well and so is not evaluable for toxicity analysis. Five of the eleven evaluable patients (45%) were withdrawn from the study due to an adverse event. Two patients (18%) were withdrawn due to prolonged neutropenia, one (9%) due to thrombocytopenia, one (9%) due to both thrombocytopenia and neutropenia, and one (9%) due to painful neuropathy. Two patients (18%) had one protocol driven dose reduction and one patient (9%) had two dose reductions, all due to grade 4 neutropenia. In addition, the day 8 dose of bortezomib was omitted due to cytopenias in 8 of 34 (24%) cycles administered.

Overall, seven patients (64%) had a grade 3-4 hematologic toxicity. Six patients (55%) had grade 3-4 neutropenia, though there were no episodes of febrile neutropenia. Six patients (55%) developed grade 3-4 thrombocytopenia without clinically significant bleeding. Despite the use of prior vincristine in almost all patients, only one developed a painful grade 2 neuropathy. This patient was removed from the study per investigator discretion, although protocol driven withdrawal criteria were not met.

Two patients (18%) developed additional malignancies during treatment or in follow up. One patient was diagnosed with non-small cell lung cancer (NSCLC) and withdrawn from the study after the fourth cycle. On review of the patient's radiographic imaging, it is likely that this cancer was present prior to enrollment. A second patient, who had received four prior treatment regimens, was diagnosed with acute myeloid leukemia almost two years after completing four cycles of R-VFND.

Discussion

The addition of bortezomib to R-FND resulted in significant hematologic toxicities without improvement in response rates. Fifty five percent of patients had grade 3-4 neutropenia and 55% had grade 3-4 thrombocytopenia, compared to 47% and 35% respectively in a trial of FND by Crawley et al. [11]. While only one patient (8%) in our study had significant neurotoxicity, 24% of day 8 bortezomib doses were held for cytopenias. These cytopenias may be due in part to heavy pretreatment or advanced disease: 75% of our study population had grade 1-2 neutropenia or thrombocytopenia at enrollment. No patient was able to finish all 8 planned cycles.

As a result of these cytopenias, 36% of our patients withdrew prematurely versus 10-18% of patients in prior FND trials [11,12,10]. However, it is worth noting differences in trial design: in our study, patients were withdrawn if the next cycle was delayed by more than 2 weeks for grade 3-4 neutropenia or thrombocytopenia; in contrast, prior FND trials allowed delays of 35 days [11,12]. In addition, the earlier FND/R-FND studies preemptively reduced cycle 1 doses of FND by 20% in subjects considered at high risk of cytopenias due to advanced age or in those who were heavily pretreated, something that was not allowed in our R-VFND trial. Therefore, it is not surprising that the number of patient withdrawals for toxicities was higher in the current protocol than in prior FND/R-FND trials. This is important because dose intensity affects efficacy. In the initial FND study, the median time to PR was 2 cycles and CR was 5 cycles [10]. However, patients in the current trial only received a median of 3.5 cycles of therapy. This may explain why the overall response rate with R-VFND is only 64% compared to reports of 69-97% with FND or R-FND [11,12,10]. Consistent with this, all 7 subjects (64%) on our trial who received 3 or more cycles of R-VFND had at least a PR. It is likely that if the current trial had allowed more prolonged duration of cytopenias, the rate of withdrawal would have been lower, possibly leading to a higher response rate.

Patient	Cycles	Reason for stopping	Best Response	Duration of response (months)	Follow up (months)	Alive at follow up (cause of death)
1	1	progression	progression	NA	6.7	no (progression)
2	2	investigator decision (R-bendamustine)	stable	NA	10.6	yes
3	6	neutropenia	CRu	9.2	19.0	no (unk)
4	4	NSCLC	PR	3.7*	12.4	no (unk)
5	4	neurotoxicity	CR**	43.0	43.0	yes
6	3	investigator decision (allo-BMT)	CR**	42.7***	42.7	yes
7	1	progression	progression	NA	6.8	no (progression)
8	4	neutropenia	CRu	8.7	32.0	yes
9	1	lost to follow up	unknown	NA	NA	NA (unk)
10	4	progression	PR	3.4	7.5	no (unk)
11	4	neutropenia and thrombocytopenia	PR	4.6****	26.4	no (AML)
12	1	thrombocytopenia	stable	NA	2.4	no (unk)

*developed NSCLC at 3.7 months; no evidence of disease progression at that time
**still in CR
***Patient achieved CR after 2 cycles and went to allo-BMT at 3.1 months
****developed AML at 4.6 months; no evidence of disease progression at that time

Table 2: Treatment Response.

Toxicity	Number (percent of patients)
Cytopenia, any grade	10 (91%)
Cytopenia, grade 3 or 4	7 (64%)
Thrombocytopenia, any grade	9 (82%)
Thrombocytopenia, grade 3 or 4	6 (55%)
Neutropenia, any grade	9 (82%)
Neutropenia, grade 3 or 4	6 (55%)
Neuropathy, any grade	1 (9%)*
Dose reduction	4 (36%)**
Bortezomib held	8 (73%)

*grade 2 neuropathy
**Three patients required one dose reduction (two for cytopenia, one for creatinine elevation) and one required two dose reductions (both times for cytopenia)

Table 3: Toxicities.

Similar studies combining bortezomib with other cytotoxic chemotherapies have also failed to demonstrate significant benefit. Studies of the addition of bortezomib to rituximab [15], R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) [16], R-CVP (rituximab, cyclophosphamide, vincristine, prednisone) [17], or bendamustine [18] all resulted in increased cytopenias with only minor increases in response rates.

Limitations of this study include the stringent withdrawal criteria for cytopenias, single-arm design, and small sample size. As noted above, less stringent withdrawal criteria may have allowed more patients to receive more drugs potentially leading to increased response rates. Additionally, the single-arm design requires us to compare our study to FND/R-FND trials in the literature with minor differences in the study population and trial design. Finally, our study only enrolled 12 patients, subjecting it to bias from the outcomes of a few patients. Nonetheless, the fact that so many patients had toxicity supports the validity of our findings that hematologic toxicity is profound with this combination.

In summary, the addition of bortezomib to R-FND resulted in grade 3 or 4 cytopenias in 64% of patients, leading to discontinuation in 36%. Although one patient did extremely well and is in a continued CR almost 4 years since receiving R-VFND, we find it hard to justify further trials with this combination given the high incidence of myelosuppression and without clear evidence of improved response rates. Despite the promising pre-clinical data and success in other hematologic malignancies like multiple myeloma, this study failed to show an advantage with bortezomib plus fludarabine for treatment of follicular lymphoma. Therefore, while bortezomib's role in the treatment of non-Hodgkin lymphoma remains to be fully defined, we find it hard to justify further trials with this fludarabine based combination and suggest future studies focus on alternative combinations.

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