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A phase I/II study of the pan Bcl-2 inhibitor obatoclax mesylate plus bortezomib for relapsed or refractory mantle cell lymphoma

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Abstract

Obatoclax, a BH3 mimetic inhibitor of anti-apoptotic Bcl-2 proteins, demonstrates synergy with bortezomib in preclinical models of mantle cell lymphoma (MCL). This phase I/II study assessed obatoclax plus bortezomib in patients with relapsed/refractory MCL. Twenty-three patients received obatoclax 30 or 45 mg plus bortezomib 1.0 or 1.3 mg/m², administered intravenously on days 1, 4, 8 and 11 of a 21-day cycle. In phase I, the combination was feasible at all doses. Obatoclax 45 mg plus bortezomib 1.3 mg/m² was selected for phase II study. Common adverse events were somnolence (87%), fatigue (61%) and euphoric mood (57%), all primarily grade 1/2. Grade 3/4 events included thrombocytopenia (21%), anemia (13%) and fatigue (13%). Objective responses occurred in 4/13 (31%) evaluable patients (three complete and one partial response). Six patients (46%) had stable disease lasting ≥ 8 weeks. Obatoclax plus bortezomib was feasible, but the synergy demonstrated in preclinical models was not confirmed.

Keywords

Lymphoma and Hodgkin disease; chemotherapeutic approaches; drug resistance; obatoclax; bortezomib; mantle cell

Introduction

Outcomes in patients with mantle cell lymphoma (MCL) have improved due to dose-intensive strategies [1] and the development of novel therapies in the relapsed/refractory setting [2]. However, high-dose chemotherapy and autologous stem cell support (HDC-

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ASCS) approaches may not be applicable in approximately 30–50% of patients due to the advanced age of the population with MCL (median age at diagnosis is approximately mid- to late 60s) [3]. Most patients with MCL respond to induction therapy but relapse eventually, even after HDC-ASCS as front-line consolidation. Furthermore, in the relapsed setting, patients with MCL may develop chemotherapy resistance and subsequently experience very poor outcomes, emphasizing the need to develop novel options in this setting.

Considerable progress in the understanding of the biology of MCL over the last two decades has revealed a great diversity among patients with MCL with regard to disease course (indolent versus aggressive), and has highlighted a number of key oncogenic pathways as suitable for novel targeted therapy. The genetic and molecular mechanisms involved in MCL pathogenesis combine a deregulation of the cell cycle and survival pathways with a high level of chromosome instability that seems related to disruption of the DNA damage response pathway [4]. As consequence of the landmark t(11;14)(q13;q32) translocation, MCL is characterized by persistently high aberrant expression of cyclin D1, which regulates progression through the G1 cell cycle checkpoint (reviewed in [5–7]). However, cyclin D1 deregulation alone appears insufficient to induce neoplastic transformation in B cells; instead, it may provide a proliferative stress that facilitates secondary genetic mutations leading to lymphomagenesis [8,9]. Genes encoding the Bcl-2 family of apoptosis regulators are also deregulated in MCL [10,11], and may act together with cyclin D1 to increase the threshold for apoptosis. Anti-apoptotic members of the Bcl-2 family (A1, Bcl-2, Bcl-w, Bcl-xL and Mcl-1) directly inhibit the pro-apoptotic Bcl-2 proteins BAK and BAX. When these anti-apoptotic proteins bind with any of a third subgroup of Bcl-2 family members containing only BAX homology domain 3 (BH3), including Noxa and PUMA, the cell is sensitized to apoptotic cues. Pharmacologic manipulation of this pathway might increase cell susceptibility to apoptosis after exposure to genotoxic or biologic agents (e.g. monoclonal antibodies).

Four targeted therapies are currently approved for use in patients with relapsed or refractory MCL: the mammalian target of rapamycin (mTOR) inhibitor temsirolimus in Europe [12], and the proteasome inhibitor bortezomib, the immunomodulatory agent lenalidomide and the Bruton's tyrosine kinase inhibitor ibrutinib in the United States [13–15]. The activity of single-agent bortezomib in relapsed or refractory MCL has been demonstrated in five phase II studies, with objective response rates (ORRs) ranging from 29% to 50% [16–20]. The multicenter PINNACLE trial ($n = 155$) confirmed the activity of bortezomib, with an ORR of 33% and complete response (CR) rate of 8%. While the median duration of response (DOR) was 9.2 months for all patients, the median DOR was not reached in patients who achieved CR or unconfirmed CR (CRu) after a follow-up period of 27 months [17]. On the other hand, most of the patients treated with bortezomib eventually progressed, stressing the need to combine bortezomib with other agents to improve outcomes. Interestingly, preclinical studies in MCL models have shown that bortezomib induces cellular accumulation of the anti-apoptotic Bcl-2 protein Mcl-1 in MCL cells, which may promote resistance to apoptosis [21,22]. However, bortezomib treatment may also be associated with increased levels of a pro-apoptotic, cleaved form of Mcl-1, and the balance of these effects

on apoptosis remains to be elucidated [23,24]. Therefore, the efficacy of bortezomib in MCL may be improved by the addition of a modulator that targets Bcl-2 anti-apoptotic proteins, particularly Mcl-1.

Obatoclax mesylate (GX15-070MS) is a small-molecule BH3 mimetic that antagonizes anti-apoptotic members of the Bcl-2 family of proteins, including Mcl-1, Bcl-xL and Bcl-w, but has minimal interaction with Bcl-2 [25,26]. In preclinical studies, BH3-only mimetics have shown some single-agent antineoplastic activity [27–31]; however, their greatest clinical value may lie in their ability to lower the apoptotic threshold and act in an additive/synergistic manner with other cancer treatments [28]. In MCL cell lines and primary cells, bortezomib treatment induces accumulation of Mcl-1, which is no longer degraded by the proteasome; obatoclax synergizes with bortezomib in a sequence-independent manner to inhibit Mcl-1 accumulation and increase its interaction with the BH3 protein Noxa, thus allowing BAX to induce apoptosis [31]. Given that obatoclax is a pan-Bcl-2 inhibitor capable of modulating several anti-apoptotic proteins, including Mcl-1, we hypothesized that the addition of obatoclax may improve bortezomib efficacy.

This phase I/II study was designed to determine the maximum tolerated dose (MTD) of obatoclax in combination with bortezomib and to evaluate the efficacy and safety of this combination regimen in patients with relapsed or refractory MCL.

Methods

Study design

This open-label dose-escalation study was conducted from 14 November 2006 to 20 March 2009 at three centers in the United States. The study was conducted in accordance with the principles of the Declaration of Helsinki, in a manner consistent with International Conference on Harmonisation and Good Clinical Practice guidelines, and adherent to local, state and federal regulations. The study protocol was reviewed and approved by the respective institutional review boards. All patients provided written informed consent prior to enrollment. This trial was registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00407303) (NCT00407303).

The phase I portion of the study followed the standard 3 + 3 dose-escalation scheme, in which 3–6 patients were enrolled in each of three sequential dose levels (Table I). The starting and escalation doses for obatoclax were chosen based on the similarities of pharmacokinetic exposure across the doses, and for ease of preparation and administration. Also, preclinical evidence suggests that obatoclax is a potent inhibitor of CYP1A2, 2C19 and 3A4 isoenzymes (involved in bortezomib metabolism), but has been administered at a 60 mg dose with tolerable toxicities. Therefore, the initial dose of bortezomib was reduced to 1.0 mg/m² (recommended dose 1.3 mg/m²) and obatoclax to 30 mg to decrease the potential for CYP interaction and provide an adequate safety margin. Upon determination of the MTD, up to 23 additional patients were to be enrolled in the phase II portion of the study to further evaluate the safety and efficacy of this combination in patients with relapsed MCL.

Patients

Eligible patients were at least 18 years old with pathologically confirmed MCL (by cyclin D1 expression or evidence of t(11;14) translocation by fluorescence *in situ* hybridization [FISH]) that relapsed or progressed after antineoplastic therapy including at least one anthracycline- or mitoxantrone-based regimen and at least one rituximab-based regimen. Patients were allowed a maximum of four prior lines of therapy for entry into the phase I portion of the study and a maximum of two prior lines of therapy for entry into the phase II portion. Patients were required to have at least one measurable or assessable site of disease that had not been previously irradiated (or had grown since previous irradiation), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, no unresolved adverse events (AEs) of grade ≥ 2 severity from previous treatment and adequate organ function (defined as absolute neutrophil count $\geq 1000/\text{mm}^3$, platelet count $\geq 50\,000/\text{mm}^3$, total bilirubin of no more than the upper limit of normal [ULN], alanine aminotransferase no more than 1.5 times ULN, and creatinine within normal institutional limits or a calculated creatinine clearance of $\geq 50\text{ mL/min/1.73 m}^2$). Patients were excluded if they received cytotoxic chemotherapy or radiotherapy within 3 weeks, antibody therapy within 4 weeks, or radioimmunoconjugates or antibody–drug conjugates within 10 weeks before study initiation; had disease progression within 3 months of their last dose of bortezomib (if previously treated with bortezomib) or within 6 weeks of their last dose of rituximab; a history of a seizure disorder or central nervous system (CNS) and/or leptomeningeal lymphoma; uncontrolled concurrent illness (including symptomatic neurologic illness, clinically significant active systemic infection or evidence of human immunodeficiency virus-1 infection, symptomatic congestive heart failure, uncontrolled angina pectoris, cardiac arrhythmia, significant pulmonary disease/hypoxia or a psychiatric disorder that would limit compliance with study medications). Patients previously treated with bortezomib were excluded in the phase II portion of the study only.

Treatment

Obatoclax was administered as a 3 h intravenous (IV) infusion followed by bortezomib administered as a bolus IV injection on days 1, 4, 8 and 11 of a 21-day treatment cycle. Three sequential doses were chosen for investigation: obatoclax 30 mg plus bortezomib 1.0 mg/m^2 , obatoclax 30 mg plus bortezomib 1.3 mg/m^2 and obatoclax 45 mg plus bortezomib 1.3 mg/m^2 (Table I). Three patients were initially enrolled at each dose level. If no dose-limiting toxicities (DLTs) were reported in these patients for at least 3 weeks (through and including cycle 1 day 21 assessments), enrollment continued at the next dose level; if a DLT was documented, the cohort was expanded to six patients. Dose escalation was stopped if two or more patients developed a DLT during the first cycle at a given dose level. DLTs were defined as grade ≥ 3 infusion-related neurologic AEs, grade ≥ 3 non-hematologic toxicity not ameliorated by symptomatic-directed therapy, grade 4 neutropenia of any duration with fever, grade 4 neutropenia without fever lasting at least 7 days or grade 4 thrombocytopenia.

The dose used in the phase II study was to be the highest dose level at which no more than one of six patients experienced a DLT, although the final dose selection was also to take into consideration any delayed or cumulative toxicities. Patients were treated with obatoclax and

bortezomib for up to 12 cycles or four cycles beyond a CR, whichever was less, or until disease progression, unacceptable toxicity or investigator/patient decision.

In the event of a DLT, stable or responding patients were permitted to continue on treatment at a reduced dose once the DLT had resolved to grade 2. For DLTs attributed to myelosuppression or peripheral neuropathy, the dose of bortezomib was to be reduced from 1.3 to 1.0 mg/m². A second dose reduction of bortezomib to 0.75 mg/m² was allowed for persistent peripheral neuropathy following the initial dose reduction. If DLTs occurred at the first dose level (1.0 mg/m²) or recurred following dose reduction, bortezomib was discontinued. Obatoclax could be continued as a single agent if bortezomib was discontinued due to persistent peripheral neuropathy. In the event of infusional DLTs (e.g. CNS symptoms), obatoclax was discontinued on days 4 and 11. For all other DLTs, the dose of obatoclax was reduced to the previously evaluated dose level. If treatment was delayed for > 28 days from the date of the last dose received, the patient was removed from the study.

Prophylaxis with H1 and H2 blockers was recommended prior to each dose of obatoclax to prevent cytokine release syndrome, which has been reported to occur during infusion [32]. Antiemetic prophylaxis was permitted for acute nausea or vomiting. Full supportive care measures were permitted to treat any emerging DLTs, although the use of corticosteroids was allowed only if other treatments were ineffective, because corticosteroids could potentially confound assessments of efficacy.

Assessments

Patients were regularly monitored for emerging AEs. Physical and neurological examinations, vital signs, body weight, ECOG performance status and serum chemistries were documented at baseline, on days 1 and 8 of cycle 1 and on day 1 of every subsequent cycle, and at the time of treatment discontinuation. Complete blood counts were assessed at baseline, prior to each dose and at treatment discontinuation. Other assessments included chest X-ray at baseline, every two cycles during treatment and at the end of therapy; electrocardiogram at baseline, pre-dose and following bortezomib administration on days 1 and 11 of cycles 1 and 3, and at discontinuation; and brain magnetic resonance imaging and pulmonary function tests at baseline and as clinically indicated. AE severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Tumor evaluations were conducted by computed tomography scans at baseline, every 6 (±1) weeks during treatment (i.e. every two cycles) and 30 days following the last treatment dose. Response assessments were determined by the site investigators based on International Working Group criteria [33].

Statistical analysis

The intent-to-treat (ITT) population included all patients in the safety population who received any amount of study drug. The efficacy-evaluable (EE) population included those patients who received study drug and underwent at least one response assessment.

Statistical analysis was not performed on data from the phase I portion of the study. The phase II portion was designed to detect a true CR/CRu rate of 28% versus an unsuccessful rate of 8% [17] with an alpha level of 0.05. Phase II enrollment occurred in two stages: 14 patients were enrolled in stage 1; if two or more CR/CRu occurred, the trial was to proceed to stage 2 and enroll an additional nine patients for a total of 23 patients. At least five patients with CR/CRu out of the 23 patients enrolled were required to conclude that the CR rate was significantly greater than 8% with over 80% confidence, and that the confidence intervals (CIs) for the true CR rate include 28%.

AEs were summarized across dose levels using descriptive statistics. The disease response rate (best response of CR, partial response [PR] or stable disease [SD]) and ORR (defined as CR or PR) were calculated with the associated two-sided 95% exact binomial CI for the efficacy population. Kaplan–Meier analysis was to be used to estimate survival rates for the duration of disease response, duration of objective disease response, duration of CR, time to progression and progression-free survival.

Role of the funding source

Teva Pharmaceuticals contributed to the development of obatoclox, the analysis and interpretation of data, and the writing of the report, and supported the decision to submit the paper for publication.

Results

Disposition and patient characteristics

Twenty-four patients were enrolled in the study; however, one patient with a rapidly progressing blastoid variant in leukemic phase died prior to receiving any treatment. Twenty-three patients received at least one dose of study treatment and were included in the safety/ITT population: three patients each at dose levels 1 and 2, and 17 patients at dose level 3. Due to slow enrollment and no clear evidence of efficacy, the study was closed prior to completing the first stage of the phase II enrollment. Six patients had no post-baseline efficacy assessment and were unevaluable for efficacy; five of the six patients discontinued due to disease progression after baseline assessment and one patient was excluded for QTc 450 ms. An additional four patients were excluded from the EE population due to protocol violations, specifically, having received more than four prior therapies. All were listed as having five prior therapies; however, in one patient, fludarabine, cyclophosphamide and rituximab followed by rituximab maintenance was listed as two separate therapies, and in another patient, ifosfamide, carboplatin and etoposide followed by high-dose cyclophosphamide prior to transplant was listed as two separate therapies. The final EE population comprised 13 patients who received any amount of study drug and had at least one post-baseline response assessment. None of the 23 patients completed all 12 cycles of treatment; the most common reason for study discontinuation was disease progression (52%) (Table II). Two patients discontinued the study due to AEs, including peripheral neuropathy, abdominal distension, abdominal pain, fatigue and weight loss in one patient; and fatigue and peripheral neuropathy in another patient. One additional patient with a blastoid MCL variant in leukemic phase with a high white blood cell count (82 000) died before the 30-day

follow-up visit due to disease progression approximately 3 weeks following the last dose of study treatment.

Demographics and baseline disease characteristics of the study population are listed in Table III.

Dose escalation and selection of phase II dose

No DLTs were reported during cycle 1 in the first three patients enrolled at dose level 1 (obatoclax 30 mg + bortezomib 1.0 mg/m²). Per protocol, the dose was then escalated and three patients were enrolled at dose level 2 (obatoclax 30 mg + bortezomib 1.3 mg/m²). During cycle 1, grade 3 streptococcal bacteremia and grade 4 anemia were observed in one patient in this cohort; these events resolved in 2 days and 38 days, respectively, and the patient subsequently discontinued study treatment due to disease progression. No other DLTs were reported at this dose level and enrollment continued at dose level 3 (obatoclax 45 mg + bortezomib 1.3 mg/m²). At dose level 3, one patient experienced grade 4 thrombocytopenia on day 16, which resolved in 17 days without study drug dose adjustment. Per DLT dosing criteria, three additional patients were enrolled at dose level 3 and none experienced DLTs; dose level 3 was chosen for further study. Enrollment continued at dose level 3 to include a total of 17 patients, and two additional patients experienced DLTs at this dose: one patient experienced grade 3 right lower extremity edema and scrotal edema on day 16; both events resolved in 5 days and the patient subsequently discontinued the study due to disease progression; the other experienced grade 3 thrombocytopenia on day 8, which worsened to grade 4 and resolved 35 days after the initial onset without adjustment in study treatment.

Safety

The number of cycles administered and duration of treatment are summarized in Table II. AEs are summarized in Table IV. Seventeen (74%) patients experienced at least one AE that was grade 3 or greater in intensity, the majority of which were hematologic, including thrombocytopenia (21%), anemia (11%) and fatigue (13%). Fifteen infections were reported in seven patients, including grade 3 infection (unspecified) in two patients; grade 3 pneumonia in two patients; and grade 4 urinary tract infection, grade 3 catheter-related infection, grade 3 clostridial infection, grade 3 enterocolitis, grade 3 sepsis and grade 3 streptococcal bacteremia in one patient each.

Two patients died on study or within 30 days of receiving study drug, one due to a subdural hematoma before receiving the first dose of study drug and the other due to disease progression/blast crisis occurring 3 weeks after the last dose of study drug. Eighteen additional serious AEs were reported in 12 (52%) patients: two at dose level 1 and 16 at dose level 3. Six patients experienced 12 serious AEs that were considered to be related to treatment; these included: (1) grade 3 sensory and motor peripheral neuropathy at dose level 1, cycle 4, which progressed to grade 4 and resulted in discontinuation of bortezomib; (2) grade 3 angioedema at dose level 1, cycle 4, which was characterized by facial and lip swelling and shortness of breath, managed with IV steroids and H1/H2 blockers, and resolved within 24 h; (3) grade 3 sepsis (dose level 3, cycle 3) and hyperbilirubinemia (cycle

4), which was managed with supportive care and dose delays; sepsis was ruled out by negative blood cultures and serum bilirubin returned to normal by cycle 6; (4) four events of grade 3 hypersensitivity (dose level 3, cycle 1), which resolved with supportive care and ultimately were prevented with dose and infusion rate reduction and premedication with IV lorazepam, famotidine, diphenhydramine and oral acetaminophen; (5) grade 1 facial edema (dose level 3, cycle 5) involving the eyelid and cheek without pain, itching or drainage; the patient was hospitalized as the swelling worsened over a 3-day period and was treated with dexamethasone, famotidine and diphenhydramine, with resolution noted after 9 days; and (6) grade 4 urinary tract infection and grade 3 infectious enterocolitis (dose level 3, cycle 6), which required intensive care admission and dopamine and antibiotic therapy; study drugs were stopped permanently at the time of hospitalization.

Dose reductions for either study drug were required in a total of six patients (26%). Obatoclax was reduced in two patients, one due to grade 3 hypersensitivity (serious AE as described above) (dose reduced from 45 mg to 40 mg) and one due to grade 3 somnolence (dose reduced from 45 mg to 30 mg). Bortezomib was reduced (from 1.3 mg/m² to 1.0 mg/m²) in four patients due to peripheral neuropathy; one of these patients required further reduction to 0.75 mg/m². Two additional patients discontinued treatment due to peripheral neuropathy (no patients with dose reduction discontinued treatment due to AEs). Dose delays due to AEs were reported in seven patients (30%): two patients in dose level 1 (grade 2 peripheral neuropathy; grade 3 angioedema, grade 1 upper respiratory tract infection); one patient in dose level 2 (grade 2 diarrhea, grade 3 thrombocytopenia); and four patients in dose level 3 (grade 3 hyperbilirubinemia; grade 1 dizziness; grade 1 hiccups, grade 3 infection; and grade 3 muscle weakness).

Efficacy

The majority of patients (61%) had stage IV disease and had received a median of 2 (range 1–8) previous treatment regimens (Table III). Of the 13 patients included in the EE population, four (31%; 95% CI, 9–61%) achieved an objective response, including two patients (15%) with CR at dose level 1, one patient with CRu at dose level 2 and one patient with PR at dose level 3 (Table V). One of the two patients with CR at dose level 1 had received prior bortezomib. An additional six patients (46%) achieved SD (maintained for 8 weeks) that lasted a median of 4 months (95% CI, 1.7–6.1 months). Objective responses were corroborated by a reduction in lymph node sum of product diameter at dose levels 1 and 2 (Table V). In a preplanned efficacy analysis in the safety/ITT population ($n = 23$), an objective response was reported in five patients (22%; two CR, one CRu and two PR), with an additional eight patients (35%) achieving SD for a median of 4 months (95% CI, 1.7–6.1 months). In the subset of patients treated with prior bortezomib ($n = 7$ in the safety/ITT population), three (43%) achieved SD, two experienced disease progression as a best response and two were unevaluable. Two of the four patients excluded from the EE population for having received 4 prior therapies achieved SD with obatoclax (one received five cycles of treatment and the other received seven cycles); one patient progressed and received two cycles; and one patient achieved PR and received seven cycles.

Patients were followed until 30 days after receipt of their last dose; the median duration of follow-up was 3.1 months (range 0.1–7.4 months). At the time of last follow-up, all responders remained relapse-free; thus, the median duration of response had not been reached. The estimated median duration of stable disease among the seven evaluable patients with SD was 4 months (95% CI, 1.7–6.1 months); at the time of analysis, four of seven evaluable patients with SD in the EE population demonstrated disease progression. Estimated median progression-free survival was 5.2 months (95% CI, 1.4 months– not reached).

Discussion

In this phase I/II study, combination treatment with obatoclax and bortezomib was determined to be feasible in patients with relapsed or refractory MCL. The highest planned dose regimen (obatoclax 45 mg plus bortezomib 1.3 mg/m²) demonstrated a manageable toxicity profile but showed only PR or SD in the few evaluable patients. Approximately 20% of patients experienced grade 3 or 4 myelosuppression, mainly thrombocytopenia, at this dose and all events were resolved with appropriate administration of supportive care or delayed treatment. Grade 3 and 4 non-hematologic events were infrequent. Most patients experienced grade 1 or 2 infusion-related CNS toxicity, including somnolence, euphoria and/or dizziness. These events are consistent with the AE profile reported with single-agent obatoclax [32,34,35]. CNS events were manageable with dose reduction or delay of obatoclax; additional medication was administered to relieve dizziness in some cases. Peripheral neuropathy, which is commonly reported with bortezomib [16,17], did not appear to be exacerbated by obatoclax and was typically manageable by dose reduction. However, bortezomib discontinuation was necessary in two patients.

In the EE population, the combination regimen produced an ORR of 31% (23% CR/CRu); an additional 46% of patients achieved SD for a median of 4 months. In the safety/ITT population, the ORR was 22% (13% CR/CRu), with an additional 35% achieving SD for a median of 4 months. Treatment response was not clearly associated with dose; in fact, all CRs were reported in patients treated at the lower dose levels (potentially reflecting longer treatment exposure). The addition of obatoclax does not appear to increase ORR when compared with historical observations of bortezomib alone [16–20]. However, the contribution of obatoclax to the activity of this combination is difficult to establish due to the non-comparative design and small size and short follow-up period of the trial. Also, approximately half of the patients were not evaluable for efficacy due to disease progression after baseline assessment, or were considered not eligible upon review based on the number of prior therapies, further limiting the interpretation of observed responses. Larger studies would be needed to determine whether the response rate associated with the combination of obatoclax plus bortezomib exceeds that for bortezomib alone.

Although obatoclax and other BH3 mimetics have demonstrated synergy with proteasome inhibitors in previous studies, the data do not confirm superior activity *in vivo* over bortezomib alone, which might be explained by dependence on treatment schedule [29]. Furthermore, in one preclinical study, addition of a BH3 mimetic (AT-101) was found to have a synergistic effect with one proteasome inhibitor (carfilzomib) and an antagonist

effect with another (bortezomib) [30]. These studies suggest that dose and schedule may be important factors in determining efficacy [29,30].

Another approach to reduce treatment resistance may be to combine BH3 mimetics, or to reformulate existing ones. A preclinical study in MCL cells showed that targeting both Bcl-2 and Mcl-1 is necessary to overcome resistance [36], but neither obatoclax nor other BH3 mimetics have shown a high affinity for both Bcl-2 and Mcl-1 at physiologic concentrations [25,37–39]. Taken together, these findings suggest that novel combinations and dose schedules for obatoclax may potentially improve outcome in future studies.

Conclusions

The findings of this study suggest that obatoclax in combination with bortezomib is tolerable, but antitumor activity in patients with relapsed/refractory MCL cannot be substantiated. Our study did not confirm the promising preclinical observations seen with the combination of bortezomib and obatoclax, illustrating the difficulty of exporting results from preclinical models into clinical trial design. Further exploration of obatoclax supported by preclinical models is ongoing, with cytotoxic regimens and/or other biologics (bortezomib or rituximab) in lymphomas, multiple myeloma and solid tumors. A better understanding of schedule-dependence issues as well as the contributions of Bcl-2 proteins to resistance might help to consolidate the rationale of future trials with obatoclax as well as other Bcl-2 inhibitors, given the central role of anti-apoptosis mechanisms developed by cancer cells.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I

Phase I dose-escalation scheme.

Dose level	Obatoclox dose	Bortezomib dose [*]
1	30 mg	1.0 mg/m ²
2 [†]	30 mg	1.3 mg/m ²
3 [†]	45 mg	1.3 mg/m ²

* Bortezomib was administered after obatoclox.

[†] If dose-limiting toxicity (DLT) was attributable to myelosuppression and peripheral neuropathy, the dose level was repeated with bortezomib dose reduced to 1.0 mg/m². Dose escalation of obatoclox was permitted to continue if DLT did not recur at the reduced bortezomib dose. A second dose reduction of bortezomib to 0.75 mg/m² was permitted if peripheral neuropathy persisted after initial dose reduction.

Table II

Patient disposition and study drug exposure.

	Dose level 1 (<i>n</i> = 3)	Dose level 2 (<i>n</i> = 3)	Dose level 3 (<i>n</i> = 17)	All patients (<i>n</i> = 23)
Patients evaluable for safety [*] , <i>n</i>	3	3	17	23
Patients evaluable for efficacy [†] , <i>n</i>	3	2	8	13
Median treatment cycles administered, <i>n</i> (range)	6 (6–6)	6 (1–8)	2 (1–8)	4 (1–8)
Median duration of treatment, months (range)	3.8 (3.6–3.8)	3.8 (0.2–5.5)	1.1 (0.3–5.7)	2.7 (0.2–5.7)
Reasons for study discontinuation, <i>n</i> (%)				
Disease progression	0	2 (67)	10 (59)	12 (52)
Adverse event	1 (33)	0	1 (6)	2 (9)
Patient refusal	0	0	2 (12)	2 (9)
Investigator decision	0	0	3 (18)	3 (13)
Other	2 (67)	1 (33)	1 (6)	4 (17)

^{*} Patients who received any study treatment (intent-to-treat population).

[†] Patients with at least one post-baseline response assessment and without any major protocol violations.

Table III

Demographics and baseline disease characteristics.

	Dose level 1 (n = 3)	Dose level 2 (n = 3)	Dose level 3 (n = 17)	All patients (n = 23)
Male, n (%)	3 (100)	2 (67)	11 (65)	16 (70)
Median age, years (range)	67 (60–81)	64 (44–74)	64 (42–80)	64 (42–81)
Race, n (%)				
White	2 (67)	2 (67)	16 (94)	20 (87)
African American	1 (33)	0	1 (6)	2 (9)
Hispanic	0	1 (33)	0	1 (4)
ECOG performance status, n (%)				
0	2 (67)	0	6 (35)	8 (35)
1	1 (33)	3 (100)	11 (65)	15 (65)
Disease stage at enrollment, n (%)				
I	1 (33)	0	0	1 (4)
II	0	1 (33)	2 (12)	3 (13)
III	2 (67)	1 (33)	2 (12)	5 (22)
IV	0	1 (33)	13 (76)	14 (61)
Median time since diagnosis, months (range)	29.5 (13.4–44.7)	60.2 (6.3–83.8)	38.2 (3.0–140.8)	38.2 (3.0–140.8)
Median prior chemotherapy or experimental regimens, n (range)	2 (1–3)	2 (1–6)	2 (1–8)	2 (1–8)
Prior bortezomib treatment, n (%)	1 (33)	1 (33)	5 (29)	7 (30)
Patients refractory to last treatment, n (%)	0	2 (67)	5 (29)	7 (30)
Prior radiation, n (%)	0	1 (33)	5 (29)	6 (26)

ECOG, Eastern Cooperative Oncology Group.

Table IV

Adverse events (AEs) occurring in 15% of patients treated with obatoclax + bortezomib ($n = 23$).

AE, n (%)	All grades	Grade 3	Grade 4
Hematologic events			
Thrombocytopenia	10 (44)	1 (4)	4 (17)*
Anemia	9 (39)	2 (9)	1 (4)
Neutropenia	4 (17)	0	1 (4)
Non-hematologic events			
Somnolence	20 (87)	1 (4)	0
Fatigue	14 (61)	3 (13)	0
Euphoric mood	13 (57)	0	0
Diarrhea	11 (48)	1 (4)	0
Nausea	11 (48)	2 (9)	0
Vomiting	10 (44)	0	0
Peripheral neuropathy	10 (44)	0	1 (4)
Dizziness	8 (35)	1 (4)	0
Rash	8 (35)	0	0
Cough	7 (30)	0	0
Abdominal pain	6 (26)	1 (4)	0
Constipation	6 (26)	0	0
Peripheral edema	6 (26)	2 (9)	0
Hypomagnesemia	6 (26)	0	0
Headache	6 (26)	0	0
Ataxia	5 (22)	1 (4)	0
Confusion	5 (22)	2 (9)	0
Stomatitis	4 (17)	0	0
Weight loss	4 (17)	1 (4)	0
Dehydration	4 (17)	1 (4)	0
Hyperglycemia	4 (17)	1 (4)	0
Pruritus	4 (17)	0	0
Hypotension	4 (17)	1 (4)	0

* Two of these patients had thrombocytopenia at baseline (one grade 1 and one grade 3).

Table V

Best response observed in patients treated with obatoclax and bortezomib (efficacy-evaluable population, $n = 13$).

	Dose level 1 ($n = 3$)	Dose level 2 ($n = 2$)	Dose level 3 ($n = 8$)	All patients ($n = 13$)
Objective response rate [*] , % (95% CI)	67 (9–99)	50 (1–99)	13 (1–53)	31 (9–61)
Disease response rate [†] , % (95% CI)	100 (29–100)	100 (16–100)	63 (25–92)	77 (46–95)
Best response, n (%)				
Complete remission (CR)	2 (67) [‡]	0	0	2 (15)
Complete remission unconfirmed (CRu)	0	1 (50)	0	1 (8)
Partial response (PR)	0	0	1 (13)	1 (8)
Stable disease [§] (SD)	1 (33)	1 (50)	4 (50)	6 (46)
Progressive disease	0	0	3 (38)	3 (23)
Median (range) lymph node SPD, cm ²				
Baseline	9.8 (3.24 to 22.29)	35.1 (21.62 to 48.51)	26.1 (6.49 to 54.57)	21.6 (3.24 to 54.57)
Cycle 3 (change from baseline)	−3.3 (−5.62 to −0.99)	−4.3 (−11.53 to 2.9)	10.3 (0.16 to 50.53)	0.3 (−11.53 to 50.53)
Cycle 5 (change from baseline)	−1.7 (−7.5 to 1.23)	−5.9 (−17.66 to 5.95)	−4.1 (−8.52 to 0.35)	−1.7 (−17.66 to 5.95)
Last evaluation (change from baseline)	−1.7 (−7.5 to 1.23)	−6.5 (−18.89 to 5.95)	1.8 (−21.73 to 50.53)	−1.7 (−21.73 to 50.53)

CI, confidence interval; SPD, sum of product diameters.

* Includes CR, CRu and PR.

† Includes CR, CRu, PR and SD.

‡ Includes one patient who received prior bortezomib.

§ Defined as SD lasting ≥ 8 weeks.