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A phase II study of obatoclox mesylate, a Bcl-2 antagonist, plus topotecan in relapsed small cell lung cancer

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Abstract

Introduction—We previously reported data on the safety, tolerability, and recommended phase II dose of obatoclox mesylate in conjunction with topotecan in patients with advanced solid tumor malignancies. Preliminary efficacy data suggested activity in patients with recurrent small cell lung cancer (SCLC). Based on these data, we performed a phase II study of obatoclox mesylate plus topotecan in patients with relapsed SCLC to assess efficacy.

Methods—This was an open-label, single-arm, phase II extension of obatoclox mesylate plus topotecan in patients with relapsed SCLC. Obatoclox mesylate was given intravenously (IV) at a dose of 14 mg/m² on days 1 and 3 with IV topotecan at 1.25 mg/m² on days 1–5 of an every 3-week cycle. The primary end-point of this study was overall response rate.

Results—Nine patients with recurrent SCLC were enrolled into the first stage of the study. Patients received a median of 2 cycles of treatment. All patients were evaluable for the primary end-point of overall response. There were no partial or complete responses. Five patients (56%) had stable disease. The remaining four patients (44%) developed progressive disease. The most common grade 3 or 4 adverse events included thrombocytopenia (22%), anemia (11%), neutropenia (11%), and ataxia (11%).

Conclusion—Obatoclox mesylate added to topotecan does not exceed the historic response rate seen with topotecan alone in patients with relapsed SCLC following the first-line platinum-based therapy.

Keywords

Obatoclox mesylate; Topotecan; Small cell lung cancer (SCLC); Apoptosis

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Conflict of interest statement

The authors disclose the following potential conflicts of interest: Lee M. Krug, consultant for Poniard Pharmaceuticals; Mark G. Kris, consultant for GlaxoSmithKline; Charles M. Rudin, consultant for Genentech, OSI Pharmaceuticals, and Syndax.

1. Introduction

Small cell lung cancer (SCLC) is an aggressive subtype of lung cancer that accounts for 13% of lung malignancies diagnosed in the United States, with some 35,000 new cases diagnosed in 2009 [1,2]. It exhibits a higher growth fraction and an earlier time to metastasis when compared to non-small cell lung cancer (NSCLC). Approximately two-thirds of patients with SCLC present with disease that exceeds the boundaries of feasible thoracic radiation, which, in conjunction with chemotherapy, provides the sole chance for long-term disease-free survival in patients with limited-stage SCLC (LS-SCLC). For patients with extensive-stage SCLC (ES-SCLC), chemotherapy with cisplatin and etoposide yields response rates of up to 70%, though virtually all patients will relapse, with fewer than 5% of patients alive after 2 years [3]. Topotecan remains the only FDA-approved drug in the second-line setting [4,5].

The dearth of effective treatments for patients with recurrent or ES-SCLC is a reflection of the minimal progress that has been made in the intervening two decades since the identification of platinum plus etoposide as an active regimen [6]. The inability for standard cytotoxic chemotherapy to provide a cure despite a high rate of initial efficacy intimates at the emergence of resistance mechanisms. Pre-clinical data identified a shift in the balance of apoptosis as a potential cause of this clinical observation, based in part on expression studies in which Bcl-2 was found to be over-expressed in a majority of SCLC tumors and experiments that showed enhanced apoptosis in SCLC cell lines following knockdown of Bcl-2 by anti-sense oligodeoxynucleotides [7–10]. Beyond this, overexpression of Bcl-2 may also facilitate the growth of SCLC tumors driven by oncogenic proteins such as Myc that would otherwise succumb to the homeostatic mechanisms of programmed cell death [11].

Obatoclax mesylate is a small-molecule BH3-mimetic that exhibits binding affinity for a range of Bcl-2 family members, including Bcl-2, Bcl-XL, and Mcl-1. Disruption by obatoclax of the dimerization between these anti-apoptotic factors and pro-apoptotic proteins such as Bax and Bak presumably contributes to its cytotoxic effects across a range of solid tumor cell lines and xenograft models [12–14]. Additional studies pointed towards synergy with conventional cytotoxic chemotherapy [13,14].

We previously reported data assessing the safety and tolerability of obatoclax mesylate given in conjunction with topotecan in patients with advanced solid tumor malignancies [15]. Forty patients were enrolled into our phase I study, six of whom were diagnosed with relapsed SCLC. Of these six, two developed partial responses to therapy and the other four, stable disease. Two of five patients experienced a dose-limiting toxicity (DLT) at the 20 mg/m² dose level, with one episode of grade 3 somnolence and speech impairment and one episode of febrile neutropenia. This rate was sufficient to declare the 20 mg/m² dose the maximum-tolerated dose. No DLTs were experienced at 14 mg/m² on days 1 and 3, which was ultimately declared the recommended phase II dose. Based on these data, we performed a phase II extension study of obatoclax mesylate plus topotecan in patients with relapsed SCLC to determine the efficacy of this regimen.

2. Materials and methods

2.1. Study design and treatment plan

This study was the phase II extension of a combined phase I/II, open-label, single-arm trial of obatoclax mesylate plus topotecan. Patients with advanced solid tumors for whom topotecan was an appropriate therapy were enrolled into the phase I portion to determine the maximum-tolerated dose (MTD), which was previously reported [15]. Patients with relapsed

SCLC were enrolled into the phase II extension study, reported here. Obatoclax mesylate was given intravenously (IV) over 3-h at the previously determined recommended phase II dose of 14 mg/m² on days 1 and 3 of an every 3-week cycle. Topotecan was administered at 1.25 mg/m² IV on days 1–5 of an every 3-week cycle. Growth factor support with pegfilgrastim (Neulasta) was provided on days 6, 7, or 8. Because of an associated hypersensitivity reaction marked by the rapid onset of severe pain, patients received pre-medication with dexamethasone 10 mg IV, diphenhydramine 50 mg IV, and ranitidine 50 mg IV before each dose of obatoclax mesylate. Patients also underwent serial neurologic examinations during and for at least 1-h after the completion of the obatoclax infusion in light of the characteristic and transient neurologic side-effects reported during phase I studies. A 3-h infusion of obatoclax was selected based on data which showed fewer dose-limiting toxicities (DLTs) versus a 1-h infusion [16,17]. Standard anti-emetics (palonosetron or dolasetron) were given before each dose of topotecan.

Treatment continued until the time of disease progression, limitation from an intercurrent illness, unacceptable adverse event, consent withdrawal, or a treatment delay of ≥ 22 days due to toxicity. Participating centers included Memorial Sloan-Kettering Cancer Center and The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. Obatoclax mesylate is manufactured by GeminX, Biotechnologies, Inc. and was provided for this study by the Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute. Topotecan (GlaxoSmithKline) was obtained from commercial sources.

The protocol for this study was reviewed and approved by the Institutional Review Boards (IRB) at both Memorial Sloan-Kettering and Johns Hopkins University. All patients were required to sign informed consent prior to treatment initiation.

2.2. Response assessment

The primary end-point of this study was overall response rate as defined by Response Evaluation Criteria In Solid Tumors (RECIST) v1.0. Patients underwent CT imaging after every 2 cycles (6-weeks) of treatment. Patients with stable disease or a partial or complete response were allowed to continue. Confirmation of stable disease or response was required with a repeat CT scan performed a minimum of 4 weeks after the preceding scan. Overall response was defined as the best response from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since treatment initiation). Best response assignment required achievement of both measurement and confirmation criteria.

2.3. Adverse event assessment

Patients were evaluated for toxicity on day 1 of each 3-week cycle by history, physical examination, and blood work (complete blood count and complete metabolic panel). Adverse events were characterized and graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Toxicity leading to deferral of treatment required a subsequent re-evaluation on day 8 for dose adjustment or continued deferral until day 15. Based on investigator assessment of the toxicity experienced, the doses of either obatoclax mesylate or topotecan were reduced as per a pre-planned schema. Treatment delay of ≥ 22 days led to withdrawal of the patient from the study. Due to the known transient neurologic side-effects during the infusion of obatoclax mesylate, patients were also monitored with serial neurologic examinations during and for at least 1-h after completion of drug infusion.

2.4. Patient selection

Patients ≥ 18 years of age with histologically or cytologically confirmed SCLC with disease progression after one prior platinum-based regimen were eligible. Patients with treated brain

metastases were eligible. Patients with progressive brain metastases, however, or leptomeningeal involvement, a history of a seizure disorder, or any other neurologic dysfunction outside of peripheral neuropathy were excluded due to the neurologic side-effects associated with obatoclox mesylate. Patients with uncontrolled intercurrent illnesses and patients who were pregnant were also excluded from this study.

A 4-week hiatus since the last administered chemotherapy or radiation treatment was required prior to the initiation of the study regimen. Prior treatment with a Bcl-2 inhibitor was an exclusion criterion. Patients were required to have an ECOG performance status 1 (Karnofsky Performance Status 70%) and normal organ and marrow function defined by a leukocyte count 3000/ μ L, absolute neutrophil count 1500/ μ L, platelets 100,000/ μ L, total bilirubin within institutional normal limits, AST and ALT 2.5 times institutional upper limit of normal, and a creatinine clearance 60 mL/min/1.73 m².

All patients signed informed consent prior to enrollment onto the study.

2.5. Biostatistics

The primary end-point of this study was overall response rate. A Simon two-stage design with an unacceptable response rate of 10% and a desirable response rate of 30% with $\alpha=0.05$ and $\beta=0.20$ was utilized. These cut-offs were based on historic response rates associated with single-agent topotecan in the second-line setting, and these parameters took into account a mix of patients with sensitive and refractory relapse. Two or more responses were needed in the first cohort of 10 patients to exceed the criterion for unacceptable response. The cohort could then be expanded by an additional 19 patients to a total of 29 patients. Six or more responses in the final cohort of 29 patients were needed to declare the regimen worthy of further study.

3. Results

3.1. Patients

Nine patients were enrolled between September 2008 and March 2010. Patient characteristics are summarized in Table 1. While enrollment of 10 patients was planned for the initial stage of the study, the absence of a response following accrual and evaluation of nine patients obviated the need to expand to the second stage. All patients were treated and assessed in an identical manner.

Overall, three patients had sensitive disease (disease progression greater than three months after completion of the first-line chemotherapy) and six had refractory disease. Two of the nine patients (22%) were initially diagnosed with LS-SCLC. Both patients achieved a complete response to the first-line therapy and were classified as having sensitive disease. Seven patients (78%) were diagnosed with ES-SCLC at presentation. The overall response rate to first-line chemotherapy was 66% (five partial, two complete).

3.2. Tumor response

All nine patients were evaluable for the primary endpoint of best overall response by CT imaging (Table 2). Five patients (56%) had stable disease (SD) while four patients (44%) developed progressive disease (PD) during treatment. Of the five patients with SD, two had platinum-sensitive disease (both with an initial diagnosis of LS-SCLC) and the other three platinum-refractory disease. There were no partial (PR) or complete (CR) responses as per RECIST. One patient developed an unconfirmed partial response after the second cycle of treatment, with a subsequent appearance of new lesions following the fourth cycle.

At a median follow-up of 8 months, all patients had developed progressive disease. The median number of administered cycles of obatoclox mesylate plus topotecan was two (range 2–6). The median progression-free survival was 2 months (range 2–5 months). PFS for the two patients with recurrence of LS-SCLC was 4 months and 2 months. The longest PFS was 5 months in a patient with platinum-refractory ES-SCLC.

3.3. Adverse events

The most common adverse event (AE) group was neurologic, with the most frequent AEs including somnolence (89%) and ataxia (56%), all but one episode of which was grade 2 or less. As had been previously described, obatoclox mesylate is associated with a transient constellation of symptoms including ataxia, mood disturbance, and somnolence that occurs during drug infusion and that abates within 1–2 h after administration of the drug. One patient experienced grade 3 ataxia, which was the only grade 3 or 4 neurologic AE. No persistent neurologic AEs were experienced by any patient.

Non-hematologic toxicities occurred at rates of between 11 and 44%, including fatigue (44%), nausea (33%), constipation (11%), mucositis (11%), and dizziness (11%). All non-hematologic toxicities were grade 2 or less. Hematologic toxicities were relatively uncommon including anemia (22%), thrombocytopenia (22%), and leukopenia and neutropenia (11%).

Grades 3 and 4 toxicities (other than neurologic) were similarly infrequent, occurring in three patients (33%) (Table 3). Hematologic toxicities were the most severe. Both episodes of thrombocytopenia were grade 4. The episode of leukopenia/neutropenia was grade 3, as was the episode of anemia. Packed red blood cell and platelet transfusion support were required for the episodes of anemia and thrombocytopenia.

A reduction in the dose of obatoclox mesylate was required in two patients, one in response to grade 4 thrombocytopenia that did not resolve by day 8 of the fourth cycle of treatment and the other in response to QTc prolongation on EKG with a subsequent, likely unrelated, episode of lone atrial fibrillation at the end of the first cycle. The dose of obatoclox mesylate was reduced to 10 mg/m² for the former patient and the dosing interval of obatoclox mesylate extended to days 1 and 4 for the latter.

Two patients (22%) were taken off study due to adverse events, including the one patient with grade 4 thrombocytopenia following dose-reduction of obatoclox mesylate. The second patient had an antecedent history of cluster headaches which had been difficult to manage and required care by a neurologist. A flare of his headaches occurred at the beginning of the fourth cycle which, while deemed to be unrelated to treatment, required withdrawal from the study to facilitate further management of this.

4. Discussion

For patients with recurrent SCLC, little in the way of meaningfully effective therapy following first-line platinum-based chemotherapy or chemoradiation exists. Topotecan, approved by the FDA in 2007, yields response rates of between 6 and 24% and a median overall survival gain of approximately 3 months versus best supportive care (BSC) [4,18,19]. We previously reported the results of a phase I study of the BH3 mimetic obatoclox mesylate given in conjunction with IV topotecan in patients with advanced solid tumor malignancies, noting two partial responses among six patients with recurrent SCLC.

No partial or complete responses were observed in this phase II trial. SD was the best response in five patients (56%). Neither best response nor PFS appeared to correlate with

prior platinum-sensitivity or initial stage at diagnosis, though the sample sizes were small. The patients enrolled onto this study had predominantly platinum-refractory disease. Prior studies have shown response rates to topotecan as low as 7–10% in this population and a PFS of about 4 months [4,5]. The absence of any responses among the nine patients studied and median PFS of 2 months is thus not inconsistent with the efficacy of topotecan administered alone. Based on these findings, we conclude that the addition of obatoclox mesylate at 14 mg/m² on days 1 and 3 of any every 3-week cycle to topotecan does not improve upon the effectiveness of single-agent topotecan in patients with relapsed, platinum-refractory SCLC.

We reviewed the characteristics of the two patients who developed a PR to the study regimen in our phase I trial. One patient held an initial diagnosis of LS-SCLC and attained a PR with sequential chemoradiation that included six cycles of cisplatin + etoposide. Prophylactic cranial irradiation (PCI) was given, though the patient developed a solitary brain metastasis 16 months after diagnosis that was treated with resection and whole brain radiation therapy (WBRT). Recurrent disease did not develop for another 9 months thereafter. The other patient was diagnosed with ES-SCLC and attained a CR following 5 cycles of cisplatin + etoposide. The patient developed recurrent disease 1 year later and was treated sequentially with doxorubicin and irinotecan. Neither patient was treated with obatoclox mesylate at the recommended phase II dose of 14 mg/m² on days 1 and 3. One patient was treated at 14 mg/m² on day 1 and the other at 20 mg/m² on day 1. Each patient received the pre-planned total of 4 cycles of therapy, withdrawing from the study after expressing a desire for a treatment break rather than because of progressive disease. The disease durations of these patients prior to enrollment onto the phase I trial were 26 months and 21 months. This relatively long natural history may have reflected an underlying tumor biology predictive of a response to the treatment received.

While not apparent based on our data, we do note that higher doses of obatoclox mesylate may be associated with greater clinical activity [20]. In a phase Ib dose finding study of obatoclox plus carboplatin and etoposide in patients with ES-SCLC, Chiappori et al. achieved an MTD of 30 mg/m² for obatoclox, when infused over 3 h on days 1–3. DLTs characterized by myelosuppression were reached in two previously treated patients, leading to the subsequent exclusion of this group for safety. The MTD for obatoclox in treatment-naïve patients was 45 mg/m² on days 1–3, with a recommended phase II dose of 30 mg/m². Preliminary efficacy data using this regimen in 12 untreated patients with ES-SCLC showed an ORR of 100%, which is higher than what one would expect from carboplatin + etoposide alone.

It is worth noting that the phase II dose utilized by Chiappori et al. is the highest achieved to date. A phase I dose finding study of single-agent obatoclox in patients with previously treated advanced solid tumors or lymphoma, for example, yielded an MTD of 20 mg/m² when given weekly over 3 h, which is similar to the MTD reached by us [17]. These patients were heavily pre-treated, however, with a median number of prior regimens totaling 3.5–5, depending on the cohort. If higher doses of obatoclox are needed before clinical activity is seen, then the aggregate data suggest that the ideal setting may be in those patients who have not yet been treated, and in whom higher doses of obatoclox can be achieved.

Studies testing the efficacy of two other BH3 mimetics in SCLC have been reported recently. A phase IIa study of ABT-263, an oral compound based on ABT-737 with binding affinity for a number of Bcl-2 family members, has completed accrual in patients with relapsed SCLC at a dose of 325 mg daily following a 7-day lead in at 150 mg daily to minimize treatment-related thrombocytopenia [21]. Of the 39 patients enrolled, one had a PR, nine have had SD, and 21 developed disease progression. The median PFS was 1.7

months. A phase I study of ABT-263 in combination with cisplatin and etoposide is currently ongoing.

AT-101 is an oral inhibitor of multiple Bcl-2 family members as well as an inducer of the pro-apoptotic proteins noxa and puma. It is currently under evaluation in a phase II trial of patients with platinum-sensitive ES-SCLC. With 15 of 42 patients enrolled, no objective responses have been reported [22]. AT-101 has also been studied in combination with cisplatin and etoposide in patients with advanced solid tumors, with efforts under way to determine the efficacy of this regimen in treatment-naïve ES-SCLC patients [23]. The previously mentioned phase Ib study of obatoclast plus carboplatin and etoposide in untreated patients with ES-SCLC has led to a randomized phase II study of carboplatin plus etoposide with or without obatoclast, which has now completed accrual [24].

Correlative studies to characterize the expression of the Bcl-2 family members were planned as part of this trial, based on the premise that obatoclast mesylate would be most effective in tumors overexpressing Bcl-2 and perhaps less effective in tumors that downregulated the expression of pro-apoptotic partners such as Bax and Bak. To facilitate enrollment, however, prospective collection of tumor tissue adequate for immunohistochemical (IHC) analysis of protein expression was not mandated, with insufficient material collected by the close of the study to perform meaningful testing. While pharmacodynamic studies to confirm the on-target effect of obatoclast mesylate were not performed, the pharmacokinetics of the recommended phase II dose do correlate with AUC values that lead to antitumor activity in pre-clinical mouse models [12].

It is important to note that, until recently, the mechanism of action of the BH3 mimetics was assumed to involve direct activation of the intrinsic apoptotic pathway through sequestration of the Bcl-2 family members, this based on the high binding affinities that these drugs have to the various Bcl-2 family members and the *in vitro* identification of end-products of mitochondrial damage following treatment. This assumption may be flawed, however. Experiments by Vogler et al. demonstrated that while a number of BH3 mimetics, including obatoclast mesylate, AT-101, chelerythrine, and EM20-25 do have single-agent cytotoxicity in murine fibroblasts, Jurkat T-cells, and primary CLL cells, ABT-737 alone exhibits a dependence on key components of the intrinsic apoptotic pathway, including Bax, Bak, and caspase 9 which, when deficient, abrogate the efficacy of ABT-737 [25]. While the other BH3-mimetics do not appear to require these prototypical elements of the intrinsic pathway for activity, they nevertheless do generate products of mitochondrial damage, such as cleaved caspase 3 and cytosolic cytochrome *c* which, while suggestive of apoptosis, are not specific for it, as evidenced by the divergent ultrastructural cell death phenotypes produced by each. Indeed, early evidence for the varying mechanisms of action of these compounds was hinted at in their characteristic side effect profiles, with obatoclast mesylate leading to neurologic toxicity, ABT-737 to thrombocytopenia, and gossypol to male infertility.

While these data suggest that markers of apoptosis may prove to be inaccurate predictors of efficacy, save in the case of ABT-263, they do not argue against the potential effectiveness of these agents in cancer therapy. For now, however, the therapeutic efficacy of the BH3-mimetics in the treatment of recurrent SCLC has yet to be realized. Based on the current study, obatoclast mesylate does not appear to add efficacy to topotecan in patients who have progressed following the first-line platinum-based chemotherapy. Further characterization of the mechanisms of action of BH3 mimetics may help to identify settings in which efficacy is boosted.

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Table 1Patient demographics and characteristics ($N=9$).

Characteristic	Patients	
	<i>N</i>	%
Age		
Median	61	
Range	49–69	
Sex		
Female	7	78
KPS		
Median	80	
Range	70–90	
Initial stage at diagnosis		
Limited stage	2	22
Extensive stage	7	78
Duration of disease (months)		
Median	8.5	
Range	2.5–18.2	
First-line treatments		
Etoposide + cisplatin or carboplatin	7	78
PCI	4	44
WBRT	1	11
Surgery + adjuvant chemotherapy	1	11
Thoracic radiation	1	11
Response to first-line treatment		
CR	2	22
PR	4	44
SD	2	22
PD	1	11
Platinum sensitivity		
Sensitive	3	33
Refractory	6	67
Brain metastases	1	11

Table 2Best overall response by RECIST ($N=9$).

Response	Patients	
	<i>N</i>	%
CR	0	0
PR	0	0
SD	5	56
PD	4	44

Table 3

Grades 3 and 4 adverse events ($N = 9$).

Adverse event	<u>Grade 3</u>		<u>Grade 4</u>	
	<i>N</i>	%	<i>N</i>	%
Neurologic				
Ataxia	1	11	0	0
Hematologic				
Anemia	1	11	0	0
Leukopenia	1	11	0	0
Neutropenia	1	11	0	0
Thrombocytopenia	0	0	2	22