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A phase 1 safety study of veliparib combined with cisplatin and etoposide in extensive stage small cell lung cancer: A trial of the ECOG-ACRIN Cancer Research Group (E2511)

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Abstract

Objectives—Veliparib (V) potentiated therapeutic efficacy of cisplatin (C) and etoposide (E) in preclinical models of SCLC. We conducted this phase 1 study to establish the safety of the combination in human subjects.

Materials and Methods—The study employed the 3+3 dose escalation design to establish the safety and recommended phase 2 dose (RP2D) of V when combined with fixed doses of C (75mg/m² on D1) and E (100mg/m² on D1-3) in a 21-day cycle. The starting dose of V was 60mg (bid D1-7) with plan to escalate to 100mg (D1-7) or de-escalate to 40mg (D1-7) depending on the dose limiting toxicity (DLT) experience during cycle 1. Patients with treatment-naïve, extensive stage SCLC were included.

Results—The study enrolled 9 patients: M/F (4/5); median age (60); White/African American (8/1). V was tolerated at the 60mg (DLT in 0 of 3 patients) and 100mg dose (DLT in 1 of 6 patients; grade 5 cardiac failure). Veliparib at 100mg in combination with standard doses of C and

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E was established as the RP2D. Grades 3-5 adverse events irrespective of attribution during cycle 1 included: dehydration (1), diarrhea (1), fatigue (1), febrile neutropenia (1), heart failure (1), leukopenia (6), lymphopenia (1), nausea (2), neutropenia (8), respiratory failure (1) and thrombocytopenia (2). Investigator-assessed efficacy outcome in 7 evaluable patients were stable disease in 2/7 (28.6%), partial response in 4/7 (57.1%) and complete response in 1/7 (14.3%) patients.

Conclusions—This study demonstrated the safety of combining veliparib with cisplatin and etoposide in previously untreated SCLC patients.

Keywords

small cell; veliparib; PARP; phase I

1. Introduction

It is estimated that more than 30,000 new patients will be diagnosed with small cell lung cancer (SCLC) in the US in 2014 [1]. Approximately 65% of all cases of SCLC will present with the extensive stage category of the disease, which at present has no curative treatment option. Platinum plus etoposide doublet chemotherapy remains the established frontline regimen in the North American patient population with no significant improvement in outcomes in two decades [2-4]. While SCLC remains very sensitive to this frontline platinum doublet with objective tumor response in 50-70% of treated patients, the majority of such patients eventually progress and die of the disease [4, 5]. Salvage therapy strategies for relapsed disease using various classes of agents have met with repeated failures [6]. Improved survival for SCLC patients will require the incorporation of novel biologically rational anticancer agents that improve on the efficacy of platinum-based chemotherapy without increasing treatment-related toxicities.

Poly (ADP) ribose polymerase (PARP) is a family of enzymes that catalyze the addition of ADP-ribose to a variety of cellular molecules including DNA, histones and nonhistone proteins [7]. PARP is involved in DNA damage repair, primarily through the base excision repair mechanism [7, 8]. SCLC showed the highest expression of PARP among all histologic subtypes of lung cancer, suggesting a biologically relevant role for this protein in this disease [9]. Limited experience in early phase studies also suggests modest single agent efficacy of a PARP inhibitor in previously treated SCLC patients [10]. We previously showed in *in vitro* and *in vivo* models of SCLC that veliparib has limited activity as a single agent but significantly potentiated the cytotoxicity of standard chemotherapy agents currently employed in the clinic to treat SCLC including cisplatin, carboplatin and etoposide[11].

It is anticipated that clinical translation of this observation will result in improved outcome for SCLC patients. We therefore conducted this phase I study as a lead-in step to establish the optimal dose and safety of veliparib when combined with cisplatin and etoposide as part of a phase I/II clinical study in patients with newly diagnosed with extensive stage SCLC. This established regimen will also be applicable to other stages of SCLC as well as other

neuroendocrine cancer types where the combination of platinum and etoposide is standard therapy.

2. Materials and Methods

2.1 Patient selection

The study was conducted as a multicenter phase I study across a limited number of institutions belonging to the ECOG/ACRIN cooperative group. Salient eligibility criteria included: age of 18 years or above with pathologically confirmed SCLC or large cell neuroendocrine NSCLC, not pregnant and not breastfeeding if a female of childbearing potential, extensive stage SCLC or stage IV (AJCC 7th edition) if large cell neuroendocrine NSCLC; measurable disease by RECIST 1.1 criteria, ECOG performance status 0 or 1; and acceptable organ function. Due to a suspected increased risk of seizures in patients with brain metastasis enrolled on other ongoing studies of veliparib at the time of study initiation, patients with CNS metastases were excluded from this study. Also, patients who had received prior chemotherapy for their diagnosis of SCLC were not eligible. The study was conducted under a prospective clinical trial protocol approved by the respective IRB of the participating institutions. All participants provided a written informed consent prior to undergoing any protocol-mandated procedures. The study was registered at www.clinicaltrials.gov (NCT01642251) and the detailed protocol will be made available on the clinicaltrials.gov reporter website.

2.2 Dose selection and escalation strategy

The study employed the standard 3+3 dose escalation de-escalation design to test three possible doses of veliparib (40mg, 60mg and 100mg bid on days 1 to 7 of the cycle) in combination with fixed, standard doses of cisplatin (C, 75mg/m² on day 1) and etoposide (E, 100mg/m² on days 1, 2 and 3). Eligible patients were enrolled in sequential cohorts of three patients to test the defined doses. The starting dose of veliparib was 60mg with plan to either escalate to the higher dose level of 100mg if dose limiting toxicity (DLT) in <33% of patients or to de-escalate to 40mg dose if DLT was observed in ≥33% of treated patients. DLT was defined during the first cycle only and the following toxicities, graded according to the standardized NCI CTCAE version 4.0 criteria constituted DLT on the study: grade 4 thrombocytopenia, grade 4 anemia, grade 4 neutropenia, grade 3 neutropenia with persistent fever (febrile neutropenia) for more than 7 days, grade 4 fever and neutropenia (febrile neutropenia) of any duration and grade ≥3 non hematologic toxicity of any duration that is not an expected toxicity of CE regimen (excluding alopecia, lab values that did not warrant clinical intervention and any grade ≥3 electrolyte abnormality that resolved within 24 hours). All hematologic toxicities must have resulted in a delay of more than 14 days in initiating cycle 2 to be considered a bona fide DLT. Prophylactic growth factor support was not allowed during the DLT assessment period in cycle 1. In the absence of intolerable toxicity, disease progression or withdrawal of consent, patients received a maximum of 4 cycles using the same dose as primarily assigned without inpatient dose escalation. Restaging scan was obtained after every two cycles of treatment.

2.3 Statistical considerations

The study plan required DLT in 0/3 or 1/6 in order to escalate to the next dose level. With this design, the probability of dose escalation for different rates of true DLT 10%, 20%, 30%, 40%, and 50% were estimated as 91%, 71%, 49%, 31% and 17%, respectively. Patient demographics, tumor characteristics and toxicity experienced were summarized using descriptive statistics only. Response assessment performed by local investigators without central confirmation was classified according to RECIST 1.1 criteria as complete response, partial response, stable disease or progressive disease. Overall survival was measured as time from enrollment to death from any cause, and patients not experiencing an event were censored at their last date of follow-up.

3. Results

This phase I study opened to accrual on September 28, 2012 and concluded on July 23, 2013. Nine patients were enrolled: three patients at dose level 1 and six patients at dose level 2.

3.1 Patient demographics and disease characteristics

The median age was 60 years, four of the nine patients enrolled were male, and all patients were of non-Hispanic ethnicity. All patients had extensive SCLC except one patient who had large cell neuroendocrine cancer. Full details of patient demographics and tumor characteristics are presented in Table 1.

3.2 Toxicities and dose-limiting toxicity assessment

Three patients were treated at the starting dose of veliparib (60mg bid on days 1-7) along with cisplatin and etoposide. There was no DLT observed among the three patients. The dose of veliparib was therefore escalated to the next level of 100 mg bid for seven days along with the same fixed doses of cisplatin and etoposide as in the starting cohort. One of the first three patients at this dose level experienced DLT with grade 3 febrile neutropenia, grade 4 neutropenia, grade 4 thrombocytopenia, grade 4 respiratory failure, and grade 5 heart failure. Due to the observed DLT in one of the first three patients, an additional cohort of three patients was treated at the same dose level. There was no further DLT experienced at this dose level. With one of 6 patients treated experiencing DLT, this dose of veliparib (100mg bid on days 1-7) was established as the maximum administered dose and the phase II recommended dose to be employed in the follow-on randomized phase II trial of this triplet versus standard doublet of cisplatin and etoposide. Neutropenia and fatigue were the most frequent treatment emergent toxicities during cycle 1. The frequency and grade of neutropenia improved significantly during cycle 2 when growth factor was allowed. The overall dose intensity was 83% for the nine enrolled patients. Six patients completed a total of 4 cycles of veliparib plus chemotherapy as planned (100% DI); one patient each completed only one cycle (25% DI), two cycles (50% DI), and three cycles (75% DI). The full details of toxicities by dose cohort for treatment cycles 1 and 2 and overall across all cycles, are presented in Tables 2, 3 and 4, respectively.

3.3 Preliminary efficacy

At the time of this analysis, seven of the nine patients enrolled had died. Unconfirmed response classification by the local investigators according to RECIST 1.1 criteria showed 1 patient with complete response (14.3%), 4 with partial responses (57.1%), and 2 patients with stable disease (28.6%). Reasons for treatment discontinuation included death on study (1), withdrawal of consent (1), disease progression (1) and completion of a maximum four cycles of combination therapy as prescribed by the study (6). The median overall survival was 9.0 months (95% CI: 4.8-not reached).

4. Discussion

New treatment options are of great necessity in the management of patients with SCLC due to the limited benefit and minimal survival impact of currently available agents. We previously showed in preclinical SCLC models that the PARP inhibitor, veliparib, potentiated standard chemotherapy agents that are employed in the clinical management of patients with SCLC[11]. We therefore conducted this phase I study to establish the safety of the combination of veliparib, cisplatin and etoposide in patients with extensive stage SCLC as part of a combined phase I/II study designed to evaluate for potential improved efficacy of this regimen over standard chemotherapy alone. Previous phase I combination studies of veliparib and cytotoxic chemotherapy reported intolerable hematologic toxicity as dose limiting leading to either very low doses of the PARP inhibitor or significant reduction in the standard doses of the cytotoxic agents.[12, 13] When combined with topotecan, veliparib was tolerable at a very low dose of 10mg along with a reduced dose of topotecan at 0.6mg/m² due to hematological toxicities.[13] The established dose of the combination regimen significantly compromised the dose intensity of topotecan by more than 50% of the standard dose. A much higher dose of veliparib of 60mg once daily was safely combined with metronomic cyclophosphamide in previously treated patients [14]. We were able to combine veliparib at a much higher dose of 100 mg twice daily without any reduction in the standard doses of cisplatin and etoposide. The target maximum dose of 100mg twice daily for veliparib was chosen based on the prior demonstration of the safety of this dose when combined with full doses of platinum-based doublet chemotherapy[15]. This flat dose also compares favorably to the human equivalent dose (2mg/kg or 120mg daily for a 60kg man) of veliparib based on the dose of 25mg/kg required for optimal antitumor efficacy in murine xenograft models of SCLC[11].

The success of our study in combining veliparib with cytotoxic agents where other studies had failed in the past could be attributed to several factors related to patient selection and study design. We enrolled previously untreated patients who are more likely to have adequate bone marrow reserve thereby making them less susceptible to the possible additive hematologic toxicity of PARP inhibition and chemotherapy. The impact of prior exposure to marrow toxic chemotherapy on the tolerability of PARP inhibitors was previously recognized, especially when combined with other cytotoxic agents. In a phase I clinical trial of olaparib combined with cisplatin and gemcitabine, the regimen could not be delivered in heavily pretreated patients but was well tolerated in patients with limited prior exposure to marrow-toxic agents [16]. Similarly, in a phase I clinical trial of veliparib combined with

carboplatin and gemcitabine, the regimen could not be delivered in heavily pretreated patients but was well tolerated in patients with limited prior exposure to marrow-toxic agents. Another important consideration is our careful definition of the criteria for dose limiting toxicity on the study. The rate of grade 3 or 4 neutropenia and thrombocytopenia with cisplatin and etoposide in untreated SCLC is 60-80% and 15-20%, respectively, in contemporary studies that evaluated this regimen [3, 17]. In addition, due to the high rate of febrile neutropenia (>20%) with this doublet chemotherapy regimen, prophylactic growth factor administration is standard of care in line with the guidelines issued by professional groups such as ASCO, EORTC and NCCN [18]. Since this rate already exceeds the acceptable rate of hematologic toxicity in the standard 3 + 3 dose escalation scheme and the use of prophylactic growth factor could mask possible additive hematologic toxicity of veliparib when combined with the chemotherapy regimen, we prohibited the use of growth factors during the DLT assessment period in cycle 1 and required that hematologic toxicity should result in treatment delay in order to be considered a DLT.

Our well-considered strategy is consistent with the recent guidelines issued by the NCI CTEP task force on the conduct of phase I clinical trials of agents with possible overlapping toxicities.[19] We were able to successfully demonstrate that the addition of veliparib did not significantly increase the severity of the expected hematologic toxicities from cisplatin and etoposide. Eight of the nine treated patients proceeded with cycle 2 treatment without significant delay. Recent review of phase I studies of targeted biologic agents revealed significant heterogeneity in the criteria for DLT and that the need for treatment delay and reduced dose intensity were less likely to be incorporated in the definition of DLT. The use of alternative DLT definitions and clearly defined DLT assessment windows are some of the strategies proposed to address these challenges [19, 20]. Although we only evaluated this combination in a limited number of patients, the 3+3 design is one of the most frequent escalation strategies employed in phase I drug testing while DLT assessment in cycle 1 is predictive of tolerability in later trials [21]. Additional independent safety assessment of the defined RP2D will be conducted in the first 30 enrolled patients in the ongoing randomized phase II study of the regimen versus standard cisplatin etoposide regimen.

In conclusion, this phase I study established the safety and tolerability of the combination of veliparib, cisplatin and etoposide. The study design and the outcome will be relevant for future development of veliparib and other PARP inhibitors currently in development. This important study serves as the lead-in step on the E2511 study, a randomized clinical trial comparing the 3-drug regimen to the standard doublet chemotherapy in newly diagnosed extensive stage SCLC.

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- PARP inhibitor potentiated DNA damaging agents in preclinical models of SCLC.
- The combination of veliparib, cisplatin and etoposide was safe in untreated SCLC
- The recommended phase II dose (RP2D) of this combination regimen is now established
- Veliparib (100mg bid), cisplatin (75mg/m²) and etoposide (100mg/m²) is the RP2D

Table 1

Patient Demographics and Disease Characteristics

Variable	Category	Total
Sex	Female	5
	Male	4
Age	Median	60
	Range	51-78
ECOG performance status	0	2
	1	7
Race	Black	1
	Caucasian	8
Ethnicity	Hispanic	0
	Non Hispanic	9
Pleural effusion	Yes	4
Brain Metastases	No	9
Weight loss	>5% in the last 6 months	0
Histology	SCLC	8
	LCNEC	1

Table 2

Treatment-emergent toxicity irrespective of attribution in cycle 1 (n=9)

Toxicity	Dose Level 1				Dose Level 2				Total
	Grade				Grade				
	1,2	3	4	5	1,2	3	4	5	
Alopecia					2				2
Anemia	1				4				5
Chills					1				1
Constipation					1				1
Dehydration						1			1
Depression					1				1
Diarrhea					1	1			2
Dysgeusia					1				1
Fatigue	1				4	1			6
Febrile neutropenia						1			1
Fever					1				1
Headache					1				1
Heart failure								1	1
Hypokalemia	1								1
Leukopenia	2	1			1	3	2		9
Lymphopenia					1		1		2
Mucositis oral					1				1
Nausea	3				2	2			7
Neutropenia	1		2			1	5		9
Thrombocytopenia	1				2	1	1		5
Respiratory failure							1		1
Sore throat					1				1
Vomiting	1				1				2

Table 3

Treatment-emergent toxicity irrespective of attribution in cycle 2 (n=8)

Toxicity	Dose Level 1				Dose Level 2				Total
	Grade				Grade				
	1,2	3	4	5	1,2	3	4	5	
Alopecia					3				3
Anemia	2				4				6
Constipation					2				2
Dysgeusia					1				1
Fatigue	1				2	1			4
Flushing					1				1
Hypokalemia		1							1
Hyponatremia							1		1
Infusion related reaction	1				1				2
Leukopenia	3				2				5
Nausea					2	1			3
Neutropenia	1	1				1			3
Peripheral neuropathy					1				1
Thrombocytopenia					3				3
Skin hyperpigmentation	1								1
Tinnitus	1								1
Vomiting					2				2

Table 4

Treatment-emergent toxicity irrespective of attribution for all cycles (n=9)

Toxicity	Dose Level 1 (n=3)				Dose Level 2 (n=6)				Total
	Grade				Grade				
	1,2	3	4	5	1,2	3	4	5	
Alopecia					4				4
Anemia	2				6				8
Chills					1				1
Constipation					3				3
Dehydration						1			1
Depression					1				1
Diarrhea					1	1			2
Dysgeusia					2				2
Fatigue	1				4	2			7
Febrile neutropenia						1			1
Fever					1				1
Flushing					1				1
Headache					1				1
Heart Failure								1	1
Hypokalemia		1							1
Hyponatremia							1		1
Infusion related reaction	1				1				2
Leukopenia	2	1			1	3	2		9
Lymphopenia					1		1		2
Mucositis					1				1
Nausea	3				2	3			8
Neutropenia	1		2			1	5		9
Peripheral neuropathy					1				1
Respiratory Failure								1	1
Thrombocytopenia	1				3	1	1		6
Skin hyperpigmentation	1								1
Sore Throat					1				1
Tinnitus	1								1
Vomiting	1				3				4