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A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation — An NRG Oncology/Gynecologic Oncology Group study ☆

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HIGHLIGHTS

- Veliparib has single-agent activity among germline BRCA1/2 mutation carriers.
- Adverse events were observed but generally mild and managed conservatively.
- Responses were observed among platinum-sensitive and -resistant recurrent disease patients.

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ABSTRACT

Background. Veliparib is a potent small molecule inhibitor of PARP-1/2, which is cytotoxic in tumor cells with deficiencies in *BRCA1* or *BRCA2*. We studied the clinical activity and toxicity of veliparib in ovarian cancer patients carrying a germline *BRCA1* or *BRCA2* mutation (*gBRCA*).

Methods. Eligibility included three or fewer prior chemotherapy regimens, measurable disease and no prior use of a PARP inhibitor. Veliparib was administered at 400 mg orally BID with one cycle being 28 days. The two-stage Simon design was capable of detecting a 25% response probability with 90% power while controlling alpha = 10% (at a 10% assumed null response probability).

Results. The median age of the 50 eligible patients was 57 years (range 37–94) and 14, 18, and 18 patients had 1, 2, and 3 prior therapies respectively. Thirty patients (60%) were platinum-resistant. The median number of cycles administered was 6 (1–27). There was one grade 4 thrombocytopenia. Grade 3 adverse events were: fatigue (n = 3), nausea (2), leukopenia (1), neutropenia (1), dehydration (1), and ALT (1). Grade 2 events >10% were: nausea (46%), fatigue (26%), vomiting (18%), and anemia (14%). The proportion responding was 26% (90% CI: 16%–38%, CR: 2, PR: 11); for platinum-resistant and platinum-sensitive patients the proportion responding was 20% and 35%, respectively. The most common reason for treatment discontinuation was progression (62%). Twenty-nine patients are alive; two with SD remain on veliparib. The median PFS is 8.18 months.

☆ This trial was registered at clinicaltrials.gov (NCT01540565).

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Conclusions. The single agent efficacy and tolerability of veliparib for BRCA mutation-associated recurrent ovarian cancer warrants further investigation.

1. Introduction

Synthetic lethality was first described by the American geneticist Calvin Bridges in 1922 who noted when crossing fruit flies that certain non-allelic genes were lethal only in combination [1]. His colleague Theodore Dobzhansky coined the term 20 years later [2], and in 1997 Hartwell et al. proposed exploiting this phenomenon as an anti-cancer strategy [3]. Clinically, one of the more developed synthetic lethality programs has been the administration of poly-(ADP-ribose) polymerase (PARP) inhibitors in patients carrying a mutation in the tumor suppressor genes, *BRCA1* or *BRCA2* [4]. The BRCA1 and BRCA2 proteins both function in the performance of error-free repair of double-strand DNA breaks through homologous recombination [5]. Loss of functional protein via germline or somatic mutation leads to increased reliance on more error prone DNA repair mechanisms, promoting carcinogenesis. The loss of homologous recombination DNA repair in ovarian carcinomas associated with *BRCA1* or *BRCA2* mutations leads to increased sensitivity to platinum-based agents and longer survival [6]. Preclinically, it was observed that cells lacking functional *BRCA1* or *BRCA2*, were up to 1000 fold more sensitive to PARP inhibition than wild type cells [7,8]. The exact mechanism by which this synthetic lethality is leveraged is not completely understood, but likely occurs due to the functionality of PARP in repairing single strand defects as well as, release of governance over error-prone non-homologous end joining (NHEJ) pathways leading to more frequent mitotic catastrophe and cellular death [9].

Clinically, evidence of tumor response has been documented in several clinical settings among germline BRCA mutation carriers, including treatment of measurable breast or ovarian metastases as well as, secondary maintenance in patients with ovarian carcinoma responding to platinum [10–15]. Veliparib (ABT-888) is a novel small molecule agent that inhibits PARP-1 and PARP-2 at nanomolar concentrations [16]. It has good oral bioavailability and crosses the blood–brain barrier. In syngeneic and xenograft tumor models, veliparib potentiates temozolomide, platinum compounds, cyclophosphamide, and radiation [16].

In the clinical arena veliparib has been predominantly studied in combination with cytotoxic chemotherapy. In the I-SPY2 breast cancer trial, the combination of veliparib and carboplatin graduated with the triple-negative signature [17]. As documented for other PARP inhibitors, objective responses were observed and indicated further clinical investigation. However, limited information exists regarding the efficacy of single agent veliparib. A single-agent phase I study demonstrated the maximum tolerated dose to be 400 mg BID [18–20]. In light of these findings and the strong preclinical and clinical rationale, we conducted an open label, phase II, multi-centered clinical trial to evaluate veliparib in a population of BRCA mutation-carrying women with recurrent ovarian cancer. Herein, we demonstrate that veliparib met prespecified efficacy parameters warranting further clinical investigation.

2. Methods

2.1. Patients

Eligible patients had histologic documentation of primary ovarian, fallopian tube, or primary peritoneal cancer by central pathology review [Gynecologic Oncology Group (GOG) Pathology Committee] and carried a deleterious mutation in *BRCA1* or *BRCA2* (confirmation was required via clinical report, BRCAnalysis, Myriad Genetics, Salt Lake City, UT). Up to 3 prior cytotoxic regimens were allowed. GOG performance status 0–2 was allowed for one previous regimen; 0–1, for 2–3 regimens. Prior biological therapy was allowed. All patients were required to have measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST 1.1), have discontinued prior chemotherapy (≥3 weeks) and hormonal therapy (≥1 week) before registration, and recovered from effects of recent surgery, radiotherapy, or chemotherapy [21]. Other eligibility and ineligibility are presented in the Supplemental Methods. All patients signed approved informed consent in accordance with federal, state, and local requirements and provided authorization, permitting release of personal health information.

2.2. Treatment

Enrolled patients received veliparib 400 mg orally BID until progression or intolerance. One cycle equaled 28 days. Dose modifications were allowed (300 mg BID and 200 mg BID) for toxicity. Patients were to take veliparib 12 h apart; dosing delays of ≥4 h were skipped. Veliparib could be taken with or without food but patients were cautioned about agents inhibiting CYP1A2 or CYP3A4. A pill calendar was kept by the patient and reviewed at each visit, as were concomitant medications. As nausea was an anticipated side effect, patients were instructed on the use of anti-emetics.

2.3. Toxicity

Toxicity was monitored before each treatment cycle, with adverse events defined and graded according to Common Terminology Criteria for Adverse Events (version-4). Veliparib was held up to a maximum of 3 weeks for grade 3–4 hematological or non-hematological toxicity. Continuation with dose reduction was allowed if there was recovery to grade 0–1. Grade 2 or greater peripheral neuropathy required reduction of one dose level and delay of subsequent therapy until resolution to grade 0–1 for a maximum of 3 weeks. In addition, veliparib could be held and/or reduced for grade 2 toxicity not adequately controlled by concomitant medication and/or supportive care. It was anticipated patients could have nausea and diarrhea with veliparib limiting dose compliance. As such, investigators were allowed to reduce the dose of veliparib within a treatment cycle for persistent grade 1–2 toxicity. Dose reduction was preferred to dose delay. However, patients experiencing a treatment-related dose delay of ≥3 weeks or intolerable toxicity at the lowest dose (200 mg PO BID) were removed from study. No dose escalations were allowed. Treatment was planned until disease progression or adverse events prohibited further therapy.

2.4. Evaluation criteria

All patients had measurable disease and were evaluated for clinical efficacy using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1 [21]. Target lesions were to be ≥1 cm in longest diameter by computed tomography or magnetic resonance imaging, ≥2 cm by chest X-Ray, or ≥1 cm by physical exam using calipers, except lymph nodes, which were to be ≥1.5 cm on the short axis [22]. CA-125 information was collected, but was not used as a criterion for progression. However, patients achieving a complete clinical response of measurable disease had to additionally have a normalized CA-125, if it was elevated upon study entry. Assessment was performed at baseline, every other cycle for the first six months, and every three months thereafter until documentation of disease progression was obtained or as clinically indicated.