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A final report of a phase I study of veliparib (ABT-888) in combination with low-dose fractionated whole abdominal radiation therapy (LDFWAR) in patients with advanced solid malignancies and peritoneal carcinomatosis with a dose escalation in ovarian and fallopian tube cancers☆

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HIGHLIGHTS

- Combining PARP inhibition with radiation potentiates DNA damage in tumor cells.
- This effect may be enhanced in those with an underlying DNA damage deficiency.
- Combining PARP inhibition with radiation can be tolerable.
- A single response was observed in a platinum-sensitive, BRCA-mutation + patient.

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ABSTRACT

Background. The combination of low-dose radiation therapy with PARP inhibition enhances anti-tumor efficacy through potentiating DNA damage. We combined low-dose fractionated whole abdominal radiation (LDFWAR) with ABT-888 in patients with peritoneal carcinomatosis with a dose escalation in ovarian and fallopian cancer patients (OV).

Methods. Patients were treated with veliparib, 40–400 mg orally BID on days 1–21 of 3 28-day cycles on 6 dose levels. Dose levels 5 and 6 included only OV patients. LDFWAR consisted of 21.6Gy in 36 fractions, 0.6 Gy twice daily on days 1 and 5 for weeks 1–3 of each cycle. Circulating tumor material and quality of life were serially assessed.

Results. 32 pts were treated. Median follow-up was 45 months (10–50). The most common treatment-related grade 3 and 4 toxicities were lymphopenia (59%), anemia (9%), thrombocytopenia (12%), neutropenia (6%), leukopenia (6%), nausea (6%), diarrhea (6%), anorexia (6%), vomiting (6%) and fatigue (6%). The maximum tolerated dose was determined to be 250 mg PO BID. Median PFS was 3.6 months and median OS was 9.1 months. In OV patients, OS was longer for platinum-sensitive patients (10.9 mo) compared to platinum-resistant patients (5.8 mo). QoL decreased for all groups during treatment. Germline BRCA status was known for 14/18 patients with OV cancers, 5 of whom were BRCA mutation carriers. One objective response (3%) was observed.

Conclusion. ABT-888 plus LDFWAR is tolerable with gastrointestinal symptoms, fatigue and

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myelosuppression as the most common toxicities. The single observed objective response was in a germline BRCA mutated, platinum-sensitive patient.

1. Introduction

We previously reported the results of a phase I study combining low-dose whole fractionated abdominal radiation (LDFWAR) with veliparib (ABT-888) in patients with advanced solid tumors and peritoneal carcinomatosis [1]. The rationale for this approach was good preclinical evidence that, PARP inhibitors may act as sensitizing agents for DNA-damaging modalities such as chemotherapy and radiotherapy beyond their well-established anti-tumor effect in cancers with BRCA mutations [2–10]. In addition, it had been demonstrated in prior early phase clinical trials that the combination of LDFWAR with chemotherapy in patients with small bowel cancers, pancreatic cancer and ovarian cancer was well tolerated [11,12]. Therefore, using the same dosing of LDFWAR as previously published, we anticipated our proposed combination to have manageable toxicity. Consistent with this previously established data, a maximum tolerated dose (MTD) was not reached in our original study, which consisted of 22 patients with peritoneal carcinomatosis of varying origins including colorectal cancer, peritoneal mesothelioma, pancreatic cancer, gastric cancer, appendiceal cancer, small bowel cancers and cholangiocarcinoma.

No objective responses were observed during the original trial. However, there was durable stabilization of disease (≥24 weeks) in 7 of 22 patients, 4 of whom had ovarian or fallopian tube cancers (OV). At the time of the initial analysis, it was noted that the patients in the OV subset had a median OS of 17.5 months. BRCA mutation carrier status was known for only half the patients in this cohort. Somatic BRCA mutation status was unknown. We hypothesized that the OV subset of patients were plausibly the most likely to be afflicted with a homologous recombination deficit (HRD), and therefore may have been the most sensitive to the combination of PARP inhibition and DNA-damaging radiotherapy.

The original protocol was amended and the study was reopened with two additional dose levels (DL5 and DL6) for patients with advanced ovarian or fallopian tube cancers. In this follow-up manuscript, we report the final, complete results of our phase I study.

2. Patients and methods

2.1. Study design

The primary objective was to assess the safety profile of veliparib and LDFWAR in patients with peritoneal carcinomatosis. Secondary objectives included disease response and quality of life (QoL) assessment. Analysis of γ-H2AX levels in serial circulating tumor cell (CTC) and circulating endothelial cells (CEC) were exploratory objectives. Germline BRCA status for OV patients in DL 1–4 was collected as available by chart review. Patients in DL5 and DL6 were specifically queried about germline BRCA mutational status. Assessment for somatic BRCA mutations was not performed.

2.2. Eligibility criteria

Eligible patients in DL1-DL4 had an unresectable or metastatic solid tumor malignancy with the presence of peritoneal carcinomatosis documented either via imaging, operative notes, clinical notes or symptoms. Measureable disease was not required as an eligibility criterion. Any number or prior treatments was permitted. Extra-abdominal disease was permitted so long as peritoneal disease was dominant. Patients in DL5-DL6 had to have advanced peritoneal, ovarian or fallopian tube cancers.

Patients had adequate organ function, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 and a life expectancy of >3 months. Exclusion criteria included prior treatment with PARP inhibition, prior abdominal radiation therapy (prior pelvic radiation was acceptable as long as there was no overlap between radiation fields), previous malignant bowel obstruction (except if at diagnosis) or uncontrolled ascites. The protocol was approved by the institutional review boards of the participating institutions, and written informed consent was obtained from all patients prior to performing study-related procedures in accordance with federal and institutional guidelines.

2.3. Drug/radiotherapy administration

Veliparib was provided by the Cancer Therapy Evaluation Program (CTEP) through a Clinical Trials Agreement between Abbott Laboratories and the NCI Division of Cancer Treatment and Diagnosis. Patients were treated with veliparib by mouth in 6 escalating doses [dose levels (DL) 1–4: 40 mg PO BID (DL1), 80 mg PO BID (DL2), 120 mg PO BID (DL3), 160 mg PO BID (DL4), 250 mg PO BID (DL5) and 400 mg PO BID (DL6)]. Patients received veliparib on days 5–21 of the first 28-day cycle and on days 1–21 of the subsequent 2 cycles. LDFWAR was delivered using anterior and posterior open fields, in two daily fractions of 60 cGy on days 1 and 5 (minimum 4 h between fractions) for weeks 1–3 of each cycle, with posterior kidney shielding used to keep kidney doses <20 Gy. The field borders were as follows: superiorly 1 cm above the dome of the diaphragm at the patient's maximum comfortable expiration and inferiorly either at the inferior border of the obturator foramina or 2 cm below the lowest extension of disease. Lateral borders extended at least 2 cm beyond skin. In some cases and extended source to skin distance (SSD) was needed to cover the entire area. Radiation treatment was standardized between the participating centers.

The trial was amended during the initial accrual period to allow ovarian/fallopian tube cancer patients who had obtained substantial benefit from the treatment to continue on single-agent veliparib at a dose of 400 mg PO BID until progression of disease at the discretion of the principal investigator. These patients were required to either have a germline BRCA mutation or a strong family history of BRCA-associated malignancies.

We enrolled successive cohorts of 3 patients each using a standard 3 + 3 design [13]. Dose escalations occurred no sooner than 4 weeks after the last patient on the dose level had begun therapy. DLTs were defined as any grade 4 toxicity; any grade 3 toxicity with the exception of nausea, vomiting or diarrhea that improved to grade ≤2 within 3 days of receiving maximal medical support and any grade 3 electrolyte abnormality that did not correct to grade ≤2 within 48 h. Asymptomatic lymphopenia or leukopenia of any grade was not considered to be a DLT.

2.4. On-study evaluation and safety assessment

Patients underwent a complete clinical assessment and imaging at baseline. Patients had weekly physical exams, adverse event (AEs) evaluation, and laboratory studies. Response was assessed every 8 weeks by CT with intravenous contrast and using RECIST 1.1 criteria [14].

QoL was measured by the European Organization for the Research and Treatment of Cancer core quality of life questionnaire, QLQ-C30 at baseline and every 2 cycles.

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